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Patterns of Lipid Lowering Therapy, Adherence and Up-titration in Older Adults

By

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Patterns of Lipid Lowering Therapy, Adherence and Up-titration in Older Adults

To the Faculty of the University of Houston, College of Pharmacy:

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DEDICATION

To the women in my life – my grandmother and mother for their unwavering support

Table of Contents

1 Preface

This project was conceptualized based on my prior work with statins over a period of 3 years (2015 -2018), which includes (a) understanding the utilization of statin and non-statin therapies based on the 2013 ACC/AHA guideline using the National Ambulatory Medical Care Survey (NAMCS) data; (b) identifying patterns of adherence to statins using group-based trajectory modeling; (c) assessment of the risk of major adverse cardiovascular events in patients on statins with uncontrolled LDL-C values.

The proposal was developed in October 2018 and defended in December 2018. The data required for the study was provided by Cigna HealthSpring in Houston.

This document is organized starting with an Executive Summary which provides an overview of the entire study. The study had three aims each of which is written as a manuscript with the intent of submission for publication. The three manuscripts follow the summary with a conclusion section towards the end with the major takeaways from each aim.

2 Executive Summary

2.1 Background and rationale

Cardiovascular (CV) diseases are one of the leading causes of death in adults in the United States and are associated with a significant economic burden costing $200 billion each year which includes the cost of lost productivity.[1,2] Additionally the US population is aging and increasing age is a risk factor for CV events. In 2014, 14.5% of the US population was aged 65 or older.[3] Much of the chronic disease burden results from known risk factors which need to be effectively addressed to improve health outcomes.[4] High levels of low-density lipoprotein cholesterol (LDL-C) has been associated with the development of CV diseases.[5] Several classes of lipid lowering therapies (LLT) are available for reduction of LDL-C levels. Of the available LLT, statins have been the main stay of therapy for several decades and have been recommended in the clinical practice guidelines as the primary pharmacologic agents for LDL-C lowering. In recent years, new classes of drugs have become available in addition to existing agents now available as generic drugs, allowing more options for patient treatment.[6] Results from recent clinical trials have also demonstrated that lower LDL-C values reduce the risk of CV events, with unprecedented mean values of 30 mg/dl achieved in these trials.[7,8]

2.1.1 Current guidelines for LDL-C management

The 2018 American College of Cardiology and American Heart Association (ACC/AHA) guidelines identified patient groups that benefit from statin treatment; 1) secondary atherosclerotic cardiovascular disease (ASCVD) prevention 2) primary severe hypercholesterolemia i.e. LDL-C ≥190 mg/dl; 3) diabetes and age 40-75 years or 4) primary prevention of ASCVD. There is scarcity of evidence regarding the benefits of LLT in patients aged 75 years and above. For these patients, the ACC/AHA 2018 guidelines suggest continuing a statin if the patient is already tolerating a

statin, initiation of a moderate intensity statin for secondary prevention and not starting a statin for primary prevention based on patient risk, frailty and preferences.[6] The publication of new trial results, the availability of new therapy and the increasing prevalence of older adults using LLT coupled with less evidence regarding benefit in patients >75 make it pertinent to understand the current patterns of use of LLT in older adults.

2.1.2 Lipid lowering therapy management

Patients on LLT may have treatment modifications due to reasons ranging from adverse events to goal achievement or even formulary changes. If a patient does not achieve goal LDL-C reduction, a physician may up-titrate i.e., increase the potency of the LLT with an intention to lower LDL-C incrementally. On the other hand, LLT may be down-titrated or switched due to various reasons including but not limited to poor tolerability, attainment of lipid goals, or introduction of a new therapy into the regimen. Failure to intensify LLT in patients who have not achieved the goal LDL-C reduction could result in suboptimal LDL-C lowering in patients. Often times, the term *clinical inertia* has been used to characterize the failure of providers to modify therapy based on guidelines when the patients have suboptimal responses from existing medications.[9,10] Even though clinical inertia appears to be physician behavior, it may actually result from various physician, patient or system related factors. As the evidence generated since the publication of recent trials emphasizes up-titration of LLT to achieve lower LDL-C, an understanding of the factors that predict treatment up-titration in older adults is important. The focus again is older adults as they are more prone to adverse events from statins but are also at a higher risk of CV events.

2.1.3 The role of adherence in management of therapy

Medication adherence is an important factor which affects achievement of the maximal therapeutic effect from the LLT.[11,12] Management of therapy via switching, medication up-titration or down-

titration may include a window of repeated exposure to the healthcare system. This could include lipid testing, physician and pharmacy visits allowing opportunities for patient education and clarification which in turn may positively impact a patient's adherence. Studies evaluating the relationship between medication adherence and treatment up-titration for chronic conditions have inconsistent results.[13-15]

Although there is some evidence that treatment modification can potentially affect adherence, there were no studies specifically assessing the association of LLT up-titration with change in medication adherence. Both up-titration and medication adherence however, affect the cumulative exposure of the patient to the drug which affects disease control and management. It is therefore important to determine what effect treatment up-titration has on adherence and whether it could compromise or enhance the ability to attain treatment goals.

2.2 **Objectives**

Aim 1: To describe the real-world treatment patterns and characteristics of patients on lipid lowering therapy in a Medicare Advantage Plan. This was a descriptive aim to understand the current patterns of LLT in clinical settings.

Aim 2: To identify the sociodemographic and clinical predictors of treatment up-titration in older adults on lipid lowering therapy with a subgroup analysis in patients with uncontrolled LDL-C values at baseline (LDL-C $\geq$ 70 mg/dl in patients with ASCVD).

Hypothesis: There is variation in the up-titration of LLT across patient sociodemographic and clinical factors.

Aim 3: Measure changes in adherence to lipid lowering therapy over time after treatment up-titration.

Hypothesis: Up-titration of lipid lowering therapy affects subsequent LLT adherence.

2.3 **Main findings**

The study aims 1 and 2 had 14,360 patients using LLT. Most of them (99%) were on monotherapy and using statins (99%). Non-statin use was 2.1% either as monotherapy or as a combination. A majority of the LLT users were prevalent users (92.6%), i.e. they had some LLT use in the 1-year pre-index period. Prevalent users had fewer changes, interruptions and discontinuations as compared to new users. In a subgroup analysis of patients ≥ 75 years of age as compared to patients aged 65-74, it was observed that older patients were more likely to be on stable therapy, i.e. have fewer changes, up- and down-titrations. Switching, interruption and discontinuation of therapy was not significantly different between patients aged 65 - 74 and patients ≥ 75 years.

Predictors of treatment up-titration included younger age groups, having low income subsidization for pharmacy, hypertension and pre-index down-titrations. Patients with higher CMS risk score, ASCVD, prevalent users and patients with pre-index up-titration were less likely to receive treatment up-titration in the follow-up period. In the subgroup of patients with ASCVD and with LDL-C values ≥ 70 mg/dl, increasing LDL-C value was associated with increased likelihood of up-titration. Differences in the subgroup from the overall cohort included increased likelihood to up-titrate among patients with diabetes and among patients who were adherent (proportion of days covered for LLT ≥ 0.8) at baseline.

In the evaluation of the relationship between treatment up-titration and adherence, it was found that patients with no changes in the pre-index period had overall higher mean (SE) adherence measured as proportion of days covered (PDC) of 0.88 (0.12) but it decreased to 0.86 (0.16) in the follow-up period. Patients with an up-titration had a pre-PDC of 0.72 (0.26) and patients with other

changes such as down-titration and switching had a pre-index mean PDC of 0.62 (0.27). In the model which evaluated the change in PDC over time, there was a decrease in monthly PDC for all the three study groups (no change, up-titration, and other changes) pre-index but all the groups had a significant increase in the PDC each month after the index date. The PDC for the no change group changed from a mean decrease by 1.4% each month to an increase by 0.3% each month after the index date. Similarly the PDC change was 1.1% decrease pre-index which changed to an increase of 1% each month for the group which had an up-titration at the index date. Lastly for the group which had other changes on or prior to the index date, the change in PDC each month pre-index was a 0.9% decrease and it shifted to a mean increase of 1.9% each month post index date.

2.4 **Summary**

Older adults on lipid lowering therapy were more likely to be stable users with fewer treatment changes, but new users had greater interruptions and discontinuations requiring more care for these high risk patients. Older patients, prevalent users, and patients with a higher risk score (indicating sicker patients) were less likely to receive treatment up-titration. High risk conditions for CV events like diabetes and hypertension were associated with an increased likelihood of up-titration. This cohort of patients was being prescribed LLT in accordance with recommendations from the guidelines. Both up-titration as well as other treatment changes were associated with an improvement in adherence to LLT indicating that regular monitoring of patients by providers may act as an effective intervention to counter the decline in adherence seen with chronic medications over time.

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3 Manuscript 1

3.1 Title: Patterns of lipid lowering therapy use among older adults

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3.2 Abstract

Background: The prevalence of both cardiovascular events and patients aged ≥ 65 years is increasing. High values of low density lipoprotein cholesterol (LDL-C) and increasing age are risk factors for cardiovascular events. There have been new therapies available in the recent years as well as an increased evidence through literature and guidelines to ensure that patients with risk factors for cardiovascular events are prescribed lipid lowering therapy (LLT) and are adherent to it to maintain LDL-C goals. The objective of this study was to describe the current LLT use as well as treatment modification among adults ≥ 65 years.

Methods: A retrospective analysis of administrative claims data between January 2016 and May 2018 was conducted to identify older adults using LLT. Patients were required to be continuously enrolled for one year pre-index as well as one year follow-up and changes in LLT in both these periods were identified. The treatment episodes that were measured included interruption of therapy, intensity changes, dose changes, treatment augmentation, switching and discontinuation. A subgroup analysis of treatment patterns among patients ≥ 75 years of age was also performed and compared to patients aged 65-74 years as there is limited recommendation for LLT use in patients aged 75 years and above.

Results: There were 14,360 patients (mean age 73 years, 57.6% female) with a LLT who were included in the study of which 99% of patients were on statin monotherapy and further 99% of them were using statins. Overall non-statin therapy use either as monotherapy or combination was 2.1%. There were significant differences among new and prevalent users of therapy in the cohort (92.5% prevalent users). Among prevalent users 57.4% had no changes in the follow-up period, 13.6% interrupted therapy and 6.6% discontinued. Among new users 25% patients had no changes,

47.9% interrupted therapy and 21.9% discontinued therapy. Patients 75 years and older had fewer changes including both up-titrations and down-titration as compared to patients < 75 years of age.

Conclusion: This study represents the most recent patterns of LLT use in older adults. Most of the patients in the sample were on monotherapy and on statins with low non-statin use. Older adults were more likely to be prevalent users on stable therapy but the new users among them were more likely to discontinue and interrupt therapy representing an opportunity to improve care for these patients.

3.3 **Introduction**

Cardiovascular diseases are the leading cause of death in adults aged 40-65 as well as in adults above 65 years of age.[1] Low density lipoprotein (LDL-C) has been implicated as a risk factor for cardiovascular events and LDL-C lowering has proven beneficial in prevention and recurrence of cardiovascular events.[2,3] 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors i.e. statins have been the mainstay of lipid lowering therapy (LLT) for several decades, although there have been new therapies for LDL-C reduction approved in the past few years. The guideline approved LDL-C lowering non-statin drug classes include cholesterol absorption inhibitors (ezetimibe), bile acid sequestrants and proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors.[4] Over 25% of adults older than 40 years of age were reported to be on a statin in a nationally representative data in the years 2012-2013.[5,6] These results are prior to the 2013 American College of Cardiology/American Heart Association (ACC/AHA) guidelines which expanded the eligibility of patients recommended to be on a statin by shifting the focus on patient groups that would benefit from statin based on their risk factors rather than LDL-C values. [2]

PCSK9 inhibitors are the newest class of LLT which were approved by the FDA in 2016 as an add-on to statins. At the same time ezetimibe, a cholesterol absorption inhibitor also became available as a generic drug in the US from December 2016. Completion of large-scale randomized clinical trials including FOURIER, ODYSSEY OUTCOMES and IMPROVE-IT have demonstrated cardiovascular risk reductions with mean LDL-C levels achieved in these trials as low as 30mg/dl.[7-9] The new trial results and newer therapies available were incorporated in the recent publication of the 2018 ACC/AHA guidelines for cholesterol management.

The current 2018 ACC/AHA guidelines identify patient management groups for statin therapy which include (a) patients with atherosclerotic cardiovascular disease (ASCVD) (b) patients with severe hypercholesterolemia (LDL-C ≥ 190mg/dl) (c) patients aged 40-75 with diabetes mellitus and (d) primary prevention adults aged 40 -75 years with an intermediate 10 year ASCVD risk.[4] For patients over 75 years of age, the guidelines recommend continuation of LLT in patients with ASCVD or diabetes who are already on therapy. However initiation of therapy is recommended only after a discussion of risk and benefits of treatment, and after taking into account patient frailty and preferences.[4]

Older adults are especially vulnerable to cardiovascular events and the consequences may be more severe in older adults.[10] A meta-analysis of 28 randomized controlled trials (RCTs) found that statins reduced vascular events irrespective of age which includes patients > 75 years.[11] Studies have reported a steady increase in use of statins between 2007 and 2016 among older adults[12] and similar tolerability of statins among patients > 75 as compared to less than 75 years of age.[13] However, there is limited literature identifying utilization of LLT in older adults in the recent years. Even among the adult population there have been studies evaluating the use of statins or a particular LLT only, or of LLT in specific subgroups such as patients with diabetes, ASCVD or

myocardial infarction. There is considerable literature evaluating the impact of the 2013 ACC/AHA guidelines on statin use but using data from years 2013 -2015.[14-16](fox 2017) For instance, Okerson et al. and Tran et al. found no change in statin treatment rates following the 2013 guideline changes while Pokharel et al. found an increase in the use of higher intensity statins but also concluded that the trend was present prior to guideline publication. [14-16] Due to the potential of bias, most studies have focused on understanding utilization among new users of any LLT.[17-20] There is a need to evaluate the use of both statin and non-statin LLT among all older adults, not limiting to a certain risk group and by using current data which would reflect clinical practice since the availability of new therapies and publication of their trial results.

Similar to other chronic diseases, in the real-world setting, LLT may undergo interruptions, switching, dose adjustments, reduction or augmentation of therapy.[19,21,22] These modifications correspond to factors such as side effects or poor tolerance of LLT, need for additional LDL-C lowering, achievement of LDL-C threshold and formulary changes. LLT modifications are common and can impact adherence and LDL-C goal achievement.[21] Treatment patterns in older adults are likely to differ from their younger counterpart due to differences in guideline recommendations, increased medication complexity, and altered metabolism in older adults. Thus, in addition to LLT use, assessing treatment patterns in older adults is needed to understand the current clinical practice and treatment landscape.

The objective of this study was (a) to describe the utilization of different guideline recommended LLTs and their combinations in older adults (b) identify the modifications in LLT in older adults (age ≥ 65 years) as well as in the subgroup of patients aged 75 years or older.

3.4 **Methods**

3.4.1 Study design and data description

A retrospective cohort study was performed using administrative claims data from a regional Medicare Advantage Plan between January 1, 2016 and May 30, 2018. The data included patient health plan enrollment information, patient demographics, medical claims from outpatient visits and pharmacy claims. The medical files included diagnostic information in the form of ICD-10-CM codes and procedure information as CPT codes. The pharmacy records contained information about drug names, fill dates, dosage information and days supplied for each prescription.

3.4.2 Patient selection

This study identified patients with a prescription of any guideline recommended LLT between January 2017 and June 2017. This five month duration was the identification period for patients and it ensured the availability of two year data for all patients to implement the study design. The date of the first prescription in the identification period for each patient was identified as the index date. The one year period prior to the index date was the pre-index period. As this study intended to identify patterns of LLT, patients with conditions which affect LLT use including cirrhosis, rhabdomyolysis and end stage renal disease (ESRD) in the pre-index period were excluded from the study. Patients without continuous enrollment in the plan during the pre-index period as well as patients under the age of 65 were excluded from the study. As patients were followed-up for one year after the index date, patients without continuous enrollment in the follow-up period were also excluded from the study.

3.4.3 Study measures

3.4.3.1 Identification of baseline therapy

The type of LLT used by the patients was identified on the index date and was referred to as baseline therapy. The guideline recommended LLT classes evaluated in this study included statins,

ezetimibe, bile acid sequestrants and PCSK9 inhibitors. Some of these therapies are prescribed in combination, mainly with statins to provide additional LDL-C lowering. Patients could therefore be on multiple drugs on the index date. Any LLT which was refilled before the index date but had days supply overlapping with the index date was included to identify concurrent therapy use. Additionally, as shown in Figure 1(a), a baseline therapy identification period of 45 days following the index date was used to identify all the overlapping prescriptions. Any therapy overlap with the index drug, of 14 days or greater within the 45-day period was considered as combination therapy. This definition was selected after evaluating overlap definitions from literature and performing an analysis on 30 patients from our cohort to identify which definition would have the least misclassification of patient therapy [23-26]. Patients on three or more drugs in the baseline identification period were excluded from the study (n=28). Patients concurrently using two drugs from the same LLT class were excluded from the study. Figure 1(b) represents the study design and the baseline identification period.

3.4.3.2 LLT use type

Patients without any LLT prescriptions in the pre-index period were classified as new users of LLT.[19] Patients with prior LLT claims were classified as prevalent users. As new users would not have any pre-index treatment patterns and were expected to be different as compared to patients already on LLT, all treatment modifications were stratified by LLT user type.

3.4.3.3 Treatment modifications

The first treatment modification in the pre-index as well as follow-up period closest to the index date was identified as presented in Figure 1. The treatment modifications captured in the study are defined below

Interruption of therapy: defined as a gap of ≥ 90 days without any LLT following the end of days of supply from the previous claim.[19]

Dose intensification: this modification could only occur with statin medications based on their classification in the ACC/AHA guidelines. The guidelines identify statins as being low, moderate and high intensity statins based on the drug and its daily dose.[4] Intensification was the escalation in the intensity (low to moderate, moderate to high, or low to high) of the refilled statin.

Dose increase: defined as increase in daily dose of the LLT. If a change for a statin drug was identified as an intensification, then the same change was not considered as a dose increase.

Treatment augmentation (add-on): use of a new LLT with continued use of the previous LLT. Continuous use was captured as a subsequent fill of the index LLT after starting the new LLT.

Switching: at least one claim for a LLT other than the index drug(s) without continued use of the previous therapy. The date of the first claim for the new therapy was the treatment modification date. Switching in the follow-up period was evaluated in further detail as (a) switching from a statin to another statin and (b) switching from a statin therapy to a non-statin therapy or vice versa.

Intensity reduction: Similar to intensification, this modification could only occur with statin treatment and was defined as a reduction in intensity (moderate to low, high to moderate, or high to low) between consecutive claims for the statin.

Dose decrease: defined as decrease in the daily dose of the therapy that the patient was using at baseline. A decrease in intensity of statin was not considered as a dose decrease.

Treatment discontinuation: defined as the complete discontinuation of therapy in the follow-up period.

In the patterns mentioned above, specifically intensity changes, dose changes and switching which required discontinuation of previous therapy and initiation of a new therapy, the previous therapy could either be discontinued prior to or within 90 days after initiation of the new therapy. As most LLT are filled as 90 day refills, a 90-day cutoff was used in the treatment pattern definitions.

Measure of treatment up-titration and down-titration: The treatment modifications including intensification of the statin, increase in the dose and therapy augmentation were combined in to a composite measure identified as treatment up-titration because all these modifications aimed to increase the potency of the LLT taken by the patient. Similarly treatment down-titration was a combination of statin intensity reduction and dose decrease.

3.4.4 Statistical analysis

All baseline demographics and comorbidities were identified for patients in the pre-index period in order to describe the characteristics of the cohort. Chi-square tests were used to compare the treatment modifications among new and prevalent users as well as the subgroup ≥ 75 years of age as compared to 65-74 year old patients. The treatment mapping algorithms and descriptive statistics were analyzed using Statistical Analysis Software, version 9.4 (SAS Institute Inc., Cary, NC).

Subgroup analysis

All treatment modifications were evaluated in patients ≥ 75 years of age and compared using descriptive statistics with patients 65-74 years of age.

3.5 Results

There were 34,506 patients with any lipid lowering therapy use between January 2016 and May 2018 identified by the Medicare Advantage Plan. Of these 23,112 patients had a LLT prescription

between January and May 2017. Figure 2 represents the flow chart of patient attrition based on the exclusion criteria after which 14,360 patients were included in the final cohort.

The mean age of the sample was 73 (SD: 6.07) with 35% patients aged 75 years and above. There were 8,265 (57.6%) females and 6,269 (43.7%) had low-income subsidy. Table 1 presents the baseline demographics and comorbidities in the cohort.

3.5.1 Baseline LLT therapy use

From the study cohort, 14,222 (99%) patients were on monotherapy at baseline and only 138 (1%) were identified as being on a combination of two drugs. A majority (99%) of the monotherapy patients were on statins and a majority of combination users (99.3%) were concurrently using a statin with a non-statin. Triglyceride lowering agent use was also identified in 1,203 (8.4%) patients in the pre-index period. Prevalent users comprised 92.6% of the study sample. LLT use at the baseline (or index therapy) is described in Table 2.

3.5.2 Therapy modifications in the pre-index period

Figure 3 represents the treatment modifications of patients in the pre-index and follow-up period. The treatment modification closest to the index date for each patient in the pre-index period was identified. As the first prescription for new users of LLT was on the index date, the pre-index treatment modifications were only evaluated among the prevalent users (13,298 patients). There were 8,648 (65%) patients without a change in therapy in the pre-index period. Of the prevalent users, 4.7% of patients had an interruption of therapy, switching was observed in 3.8% patients, 11.2% had an up-titration and 5.3% had a down-titration. As the index date at the end of the pre-index period was based on a LLT refill, there were no discontinuations in the pre-index period.

3.5.3 Therapy modifications in the follow-up period

Therapy modification in the follow-up period, as presented in Figure 3 were stratified for new and prevalent users of LLT. There were significantly greater number of patients among the new users who had interruption of therapy (47.9% in new users vs 20.2% in prevalent users) as well as up-titrations (15.6% vs 12.4%) when compared to prevalent users of LLT.

Greater proportion of patients among the prevalent users (57.4% vs 25%) had no change in therapy in the one year follow-up. The treatment modifications in the follow-up period were evaluated in greater detail to provide insight into therapy changes as shown in Figure 4.

3.5.4 Subgroup analysis among patients aged 75 years and older

The pre-index and follow-up changes compared between patients aged 65-74 and patients aged 75 years and above are presented in Table 3. There were a greater proportion of patients above 75 years of age without changes in LLT therapy in the pre-index as well as follow-up period. Similarly, pre-index and follow-up up-titrations were significantly lower in older patients. There were no differences in treatment interruption and discontinuations among the stratified age groups.

3.6 Discussion

This retrospective claims database analysis assessed the real-world use of different LLT and their combinations and also evaluated the LLT treatment patterns in older adults. The study also compared the treatment changes in patients aged 75 and older as compared to older adults aged 65-74 years because the evidence regarding LLT use is the lowest in patients aged 75 years and over.

Statins were used by 99% of patients either as monotherapy or as a part of a combination. Moderate intensity statins were the most commonly prescribed (60.4 %) and their use was more common in the subgroup aged 75 and over. This aligns with the ACC/AHA guidelines for cholesterol management which recommend patients >75 years be prescribed a moderate intensity statin unless

they are already taking a high intensity statin without tolerability issues.[4] Despite the availability of newer therapies and the higher risk of statin intolerance in the older adults, [27,28] non-statin therapies were used by only 2.1% of patients. Bittner et al. studied the use of ezetimibe in Medicare beneficiaries and found that the utilization of ezetimibe peaked in 2007 and was 4.6% at the end of 2011,[29] indicating higher use of statin therapy in this study cohort.

There were 143 patients using simvastatin 80 mg daily, the use of which has been limited by the FDA in 2011 due to increased risk of muscle-related adverse events.[30] We therefore assessed if there were of myalgia or myopathy for these patients in the study period, and did not find any such claims suggesting this therapy may be well-tolerated by them. Among patients on combination therapy, patients were pre-dominantly on a combination with a high or moderate intensity statin. This pattern is consistent with the guidelines which suggest up-titrating a patient to a maximally tolerated statin before addition of non-statin therapies. During evaluation of the baseline treatment, 66 patients were found to be using multiple statins concurrently. Use of multiple statins simultaneously has not been mentioned in the guidelines, and further research is needed to understand the prevalence of and reasons of multiple statin use.

This study enhances the understanding of lipid management in older adults by describing patterns of LLT modifications over a period of two years in both new and prevalent users and not limiting to a certain risk group. Of the prevalent users, 5,881 (44.2%) patients did not have any treatment changes, interruption and discontinuation in the entire pre-index and follow-up period indicating that a majority of the patients were on stable lipid lowering therapy.

This study evaluated interruption in therapy and discontinuations as separate modifications in therapy. The number of patients who either interrupted or discontinued therapy was 23.9% in the overall sample. However, the rates of interruption, discontinuation as well as up-titration were

significantly higher in the new users of statins as compared to prevalent users. The treatment patterns among new users were consistent to a new-user study by Simpson et al. which found that interruption occurred in 46.9% patients with re-initiation in 27.4% of them. Older adults initiating a statin are likely to be on other medications and may be at a higher risk of adverse events. Special attention to new users should be provided to ensure that patients do not have any adverse consequences, understand the importance of the new LLT and take medications as prescribed.

Quek et al. performed a retrospective claims-based study of LLT modifications and created an algorithm to group changes into possible statin intolerance or ineffectiveness based on up to two treatment modifications in the follow-up. Dose escalation and add-on were patterns grouped into possible statin ineffectiveness whereas discontinuations, interruption followed by re-initiation, switching to a non-statin were classified as possible intolerance.[31] This study mapped treatment modifications in an equal detail, but among both, new and prevalent users but made no hypothesis about reasons for modifications. Similar to Quek et al. 75% of new users in this study had at least one treatment modification. Understanding reasons for treatment modifications can provide valuable insight into treatment practices and require further research.

This study has several strengths and unique contributions. The study was performed in the years 2016 - 2018 and therefore provides an update to the existing evidence regarding treatment patterns. The study was not limited to new users, a certain type of LLT or a certain risk group and therefore provides a representation of LLT use in the older adult population.

3.7 **Limitations**

This study has several limitations arising from the use of secondary databases and conducting observational research. The data was obtained from a regional health plan and therefore the generalizability of results may be limited to patients of a similar demographic. The cohort was

drug-based i.e. only information of patients on LLT was available. Therefore estimates regarding prevalence of older adults who were on LLT could not be determined. The comorbidities were identified from one year of administrative claims from outpatient visits only. Diagnostic information from hospitalization claims was not available which may have resulted in missing diagnostic information. Use of liver function tests and other information which affects use of statins and other LLT but is not available in administrative databases could not be evaluated. Similarly, the reason for the treatment modifications and discontinuation could not be captured. This was a descriptive study and no causal relationships can be established. Lastly, the inclusion requirements of continuous enrollment, use of lipid lowering therapy, exclusion of certain comorbidities could have resulted in a healthier cohort on stable LLT.

3.8 **Conclusion**

This was a descriptive study aimed at evaluating the landscape of LLT use at a time where the new clinical data as well as updated guidelines have established the importance of statins among all age groups. The study demonstrated that older adults on LLT are more likely to be prevalent users, but still undergo management of therapy to maintain LDL-C values and corresponding cardiovascular risk. While certain patterns point towards guideline concordant prescribing of LLT there are lingering concerns that should be addressed. Understanding the current treatment landscape is helpful for the providers and health plans to understand the existing gaps and realize the potential of the available LLT. Future research is needed to evaluate the impact of these changes on medication adherence as well as achievement of recommended LDL-C thresholds.

3.9 **References**

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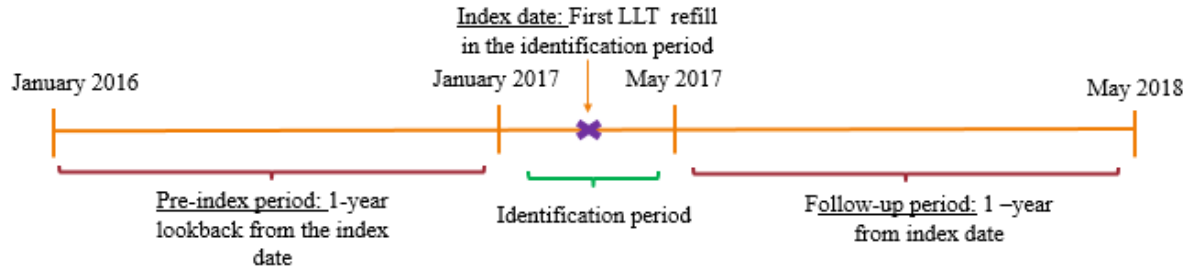
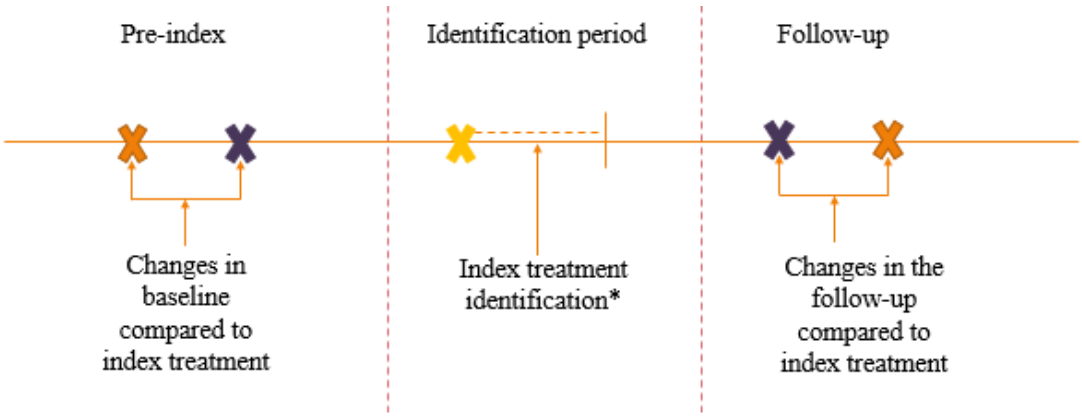
3.10 Figures and tables

Figure 1. Representation of (a) study design and (b) baseline treatment identification

1(a)



1(b)



*14 days overlap in 45 days to be identified as a concomitant LLT taken with the index drug

Figure 2. Flow chart of final cohort derivation

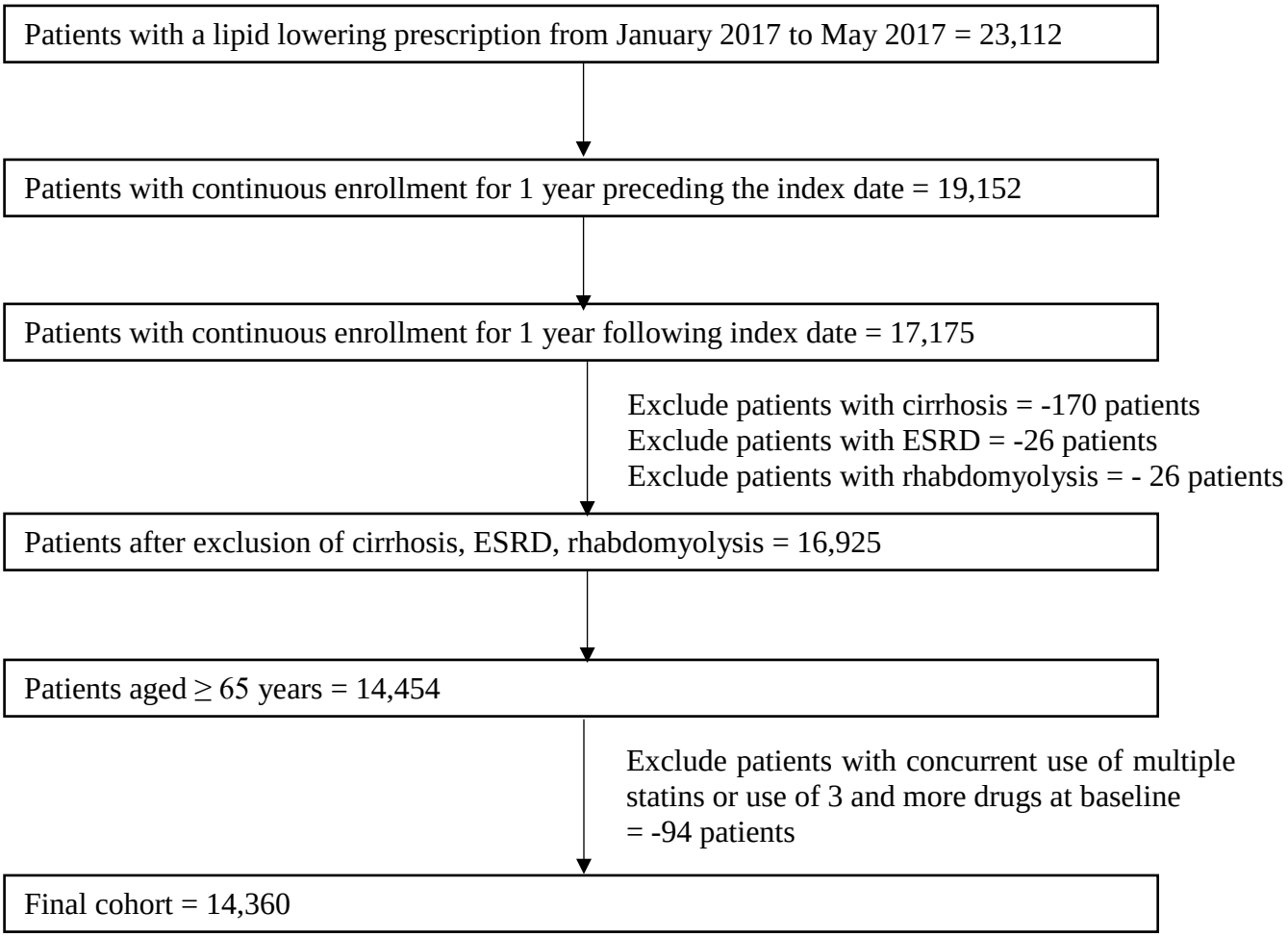


Figure 3. Treatment modifications in the pre-index and follow-up period

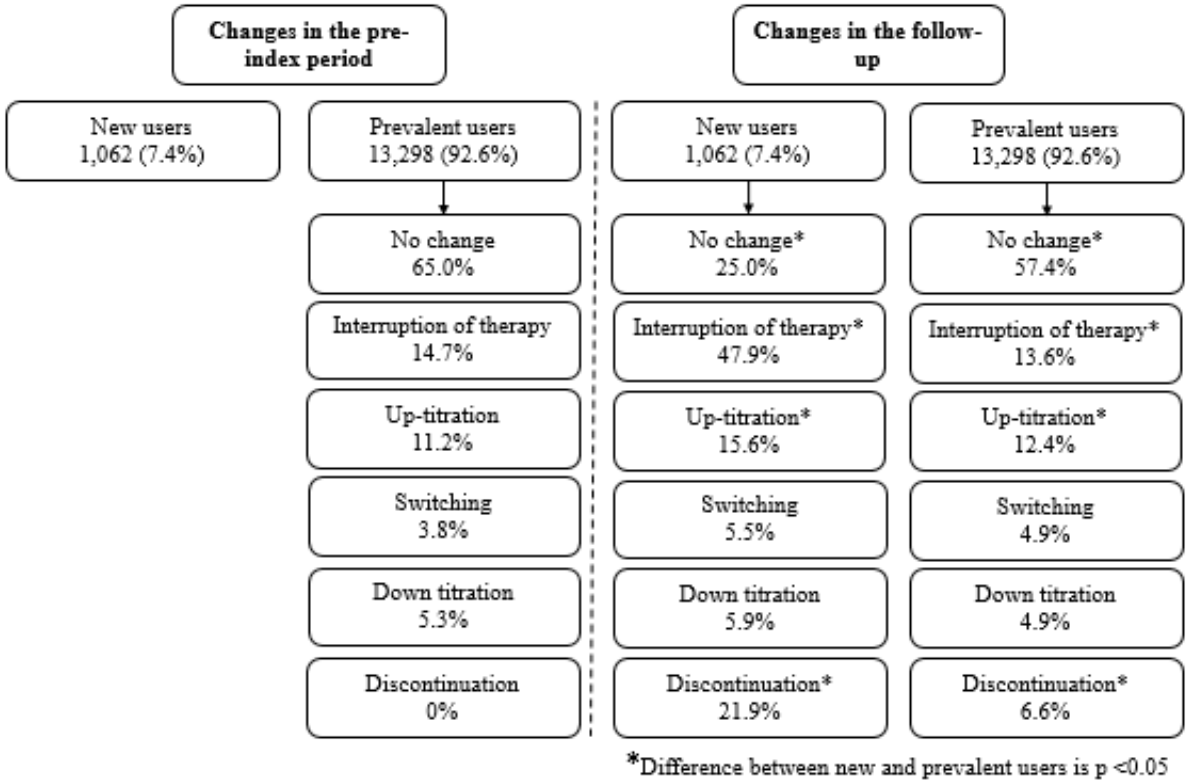


Table 1. Baseline demographics and clinical characteristics of the entire sample

Variable	N	%
Age, *Mean (SD)*	73 (6.07)	
Age groups		
65-69	5,036	35.1%
70-74	4,329	30.2%
75-79	2,689	18.7%
80 and above	2,306	16.1%
Female	8,265	57.6%
Low income subsidy	6,269	43.7%
Presence of comorbidities		
Atherosclerotic cardiovascular disease (ASCVD)	12,005	83.6%
Hyperlipidemia	9,381	65.3%
Hypertension	8,084	56.3%
Diabetes	6,333	44.1%
Chronic kidney disease	3,503	24.4%
Congestive heart failure	1,481	10.3%
Inflammatory conditions	261	1.8%
Obesity	1,521	10.6%
Myalgia	190	1.3%
Myopathy	4	0.0%
Dementia	448	3.1%
CMS Risk score, Mean (SD)	1.31	0.94

Table 2. Baseline statin therapy in the sample (N=14,360)

Lipid lowering therapy type		**N (%)**
Monotherapy		**N = 14,222 (99%)**
Statins		**14,062 (98.9%)**
	Low-intensity	2,077 (14.8%)
	Moderate-intensity	8,495 (60.4%)
	High-intensity	3,490 (24.8%)
Non-statins		**160 (1.1%)**
	Ezetimibe	124 (77.5%)
	PCSK9 inhibitors	2 (1.3%)
	Bile-acid sequestrants	34 (21.3%)
Two drug combination therapy		**N = 138 (1%)**
Statin and non-statin		
Low intensity statin	Ezetimibe	10 (7.3%)
	PCSK9 inhibitors	0
	Bile-acid sequestrants	1 (0.7%)
Moderate intensity statins	Ezetimibe	58 (42.3%)
	PCSK9 inhibitors	0
	Bile-acid sequestrants	16 (11.6%)
High intensity statin	Ezetimibe	44 (32.1%)
	PCSK9 inhibitors	1 (0.7%)
	Bile-acid sequestrants	8 (5.8%)
Non-statin and non-statin		
Ezetimibe	Bile-acid sequestrants	1 (0.7%)

Table 3. Pre-index and follow-up treatment patterns in patients 75 years of age and above as compared to patients aged between 65 -74 years

Variable	Age under 75 (n = 9,365)	Age ≥ 75 (n = 4,995)	p-value
Prevalent user	8,641 (92.3%)	4,657 (93.2%)	0.0355
Pre-index treatment modifications among prevalent users*			
Interruption of therapy	1,275(14.8%)	676 (14.5%)	0.7097
No change	6,181 (71.5%)	3,681 (79.0%)	<0.0001
Pre-index up titration	1,351 (15.6%)	447 (9.6%)	<0.0001
Pre-index down-titration	648 (7.5%)	288 (6.2%)	0.0047
Pre-index switch	461 (5.3%)	241 (5.1%)	0.6938
Follow-up treatment modifications among all user types			
Interruption of therapy	1,360 (14.5%)	727 (14.6%)	0.9582
Discontinuation	709 (7.6%)	404 (8.1%)	0.2695
No change	4,974 (53.1%)	2,924 (58.5%)	<0.0001
Up titration	1,351 (14.4%)	465 (9.3%)	<0.0001
Down-titration	480 (5.1%)	243 (4.9%)	0.4964
Switch	490 (5.2%)	232 (4.6%)	0.1248

*As new users cannot have pre-index treatment modifications, all pre-index modifications are reported only among prevalent users

4 Manuscript 2

4.1 Title: Predictors of lipid lowering therapy up-titration among older adults

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4.2 Abstract

Background: Recent results from clinical trials and newly updated guidelines emphasize lipid lowering for cardiovascular risk reduction, which may require more treatment up-titrations to achieve lower low density lipoprotein cholesterol (LDL-C) values. However older adults are more likely to suffer adverse effects of statins but are also at a greater risk for cardiovascular events. Thus understanding the predictors of LLT up-titration among older adults in the current real-world setting is important.

Objective: To evaluate the patient level predictors of LLT in older adults as well as specifically in high risk older adults with atherosclerotic cardiovascular disease (ASCVD) and LDL-C values ≥ 70 mg/dl.

Methods: Patients aged 65 years and older and using a LLT between January and May 2017 were identified from a regional Medicare Advantage plan. Patterns of LLT use in these patients were captured in the one year prior to as well as one year following the index date. Baseline and clinical characteristics of the patients were measured in the one year pre-index period. Multivariable logistic regression models identified the predictors of LLT up-titration in the follow-up period. A subgroup analysis was specifically performed in patients with ASCVD and pre-index LDL-C values ≥ 70 mg/dl.

Results: There were 14,360 patients included in this study and 4,708 had ASCVD and an LDL-C value ≥ 70 mg/dl. Older age, higher CMS risk score, ASCVD, prevalent use of statins were associated with lower likelihood of treatment up-titration. Having low income subsidy, hypertension, pre-index down-titrations were associated with higher likelihood of up-titrations. In the uncontrolled LDL-C subgroup, important differences from the overall sample were that

diabetes and being adherent to LLT were associated with increased likelihood of treatment up-titration. Higher LDL-C value was also associated with higher odds of up-titration in the follow-up.

Conclusion: Patients with high risk comorbidities and higher LDL-C values were more likely to get up-titrated. Older and sicker patients were less likely to get up-titrated. Older adults in this health plan were being treated with consideration to patient demographics, cardiovascular risk factors and baseline treatment use.

4.3 **Background**

There has been an increased emphasis on lowering of low density lipoprotein cholesterol (LDL-C) for the reduction of cardiovascular risk.[1] The Adult Treatment Panel III cholesterol guidelines published in 2001 recommended a goal of < 100 mg/dl for patients with coronary heart disease, with lifestyle changes recommended to patients with LDL-C between 100 – 129 mg/dl and drug therapy to patients with LDL-C ≥ 130 mg/dl.[2] The 2013 American College of Cardiology/American Heart Association (ACC/AHA) guidelines did not mention specific LDL-C thresholds but the updated 2018 ACC/AHA guidelines recommend a LDL-C threshold of 70 mg/dl for considering up-titration of medication in patients with atherosclerotic cardiovascular diseases (ASCVD), which is lower than the previous standard.[3] The current ACC/AHA guidelines also align with recommendations from 2016 European Society of Cardiology, [4] and the 2017 American Association of Clinical Endocrinologists and American College of Endocrinology (AACE) guidelines.[5] This emphasis is reinforced by the availability of new lipid lowering therapies (LLT) as well as several existing statins and non-statins such as rosuvastatin and ezetimibe being available as generic drugs at lower cost to achieve LDL-C goals.

Achievement of the intended benefit from LLT may be affected by many patient and physician level factors.[6-8] Physician level factors include lack of knowledge about practice guidelines or lack of time.[6-9] Failure to intensify treatment by providers in patients not within LDL-C thresholds can be characterized as clinical inertia.[10] However, there are patient level factors such as poor adherence, age, statin intolerance and preferences which can affect a patient's likelihood to receive up-titration.

The older adult (age ≥ 65 years) population in United Stated is increasing. It is projected to increase from 46 million in 2014 to over 98 million by 2060 and account for almost 24% of the US population.[11,12] Up-titrations in older adults involves additional considerations as compared to younger patients. First of all, the LLT use and modifications in adults > 75 years of age is not fixed as the guidelines recommend that initiation of therapy in patients with ASCVD should account for "the potential of risk reduction, adverse effects, drug-drug interactions, as well as patient frailty and patient preferences".[3] A reason that the guidelines are not very clear is the lack of evidence for adults > 75 years due to their under representation in the existing clinical trials.[13] Patients over 75 years of age are still at a high risk of cardiovascular diseases and a cardiovascular event may be far more serious in older compared to younger patients.[14]

At the same time, older adults are also more susceptible to adverse events and toxicities from LLT. For example, older adults are at higher risk of adverse events such as liver test abnormalities and statin associated muscle symptoms as well as have lower adherence and higher discontinuation rate with high-intensity statins as compared to moderate intensity statins.[15] Other considerations for older adults include lower life expectancy, presence of comorbidities, altered pharmacokinetics, and cognitive factors.[16,17] Polypharmacy which is associated with adverse clinical consequences is another concern associated with up-titration LLT in older adults.[18] Thus

the emphasis on aggressive LDL-C lowering through pharmacotherapy may not be a preferred approach for older adults.

With the dynamic landscape around LLT it is important to understand what patient factors determine treatment up-titration in older adults in the current clinical setting. The questions which need to be answered are, “are patients at high risk being up-titrated?” or “is there a lower rate of up-titration in frail patients or patients at high risk of adverse events from therapy?” Thus the objective of this study is to identify predictors of treatment up-titration in older adults on LLT.

4.4 Methods

4.4.1 Data source and study design

This retrospective study used administrative claims data from a Medicare Advantage Plan in Texas to identify the predictors of LLT treatment up-titration in older adults. The Medicare Advantage data predominantly contains adults over 65 years of age. Data from January 2016 to May 2018 was used to obtain a 2 year study period for all patients. Information regarding patient enrollment, baseline demographics, pharmacy and medical claims were available in the data. Laboratory tests and results were also available for a subgroup of patients. Pharmacy files included drug names as well as National Drug Codes (NDC), generic names, date of refilling the prescription, quantity dispensed and length of supply. Medical claims included information regarding the date of service, diagnostic codes (International Classification of Diseases, Tenth Revision, Clinical Modification [ICD-10-CM] codes), and procedure codes (Current Procedural Terminology codes).

4.4.2 Study sample

Patients with a LLT refill between January and June 2017 (identification period) were identified. Index date was defined as the first prescription of any LLT in the identification period. LLT refilled

before the index date, having overlapping supply with the index refill and belonging to a LLT class other than the index refill were considered as concomitant therapy. Similarly, use of another LLT with an overlap of 14 days within the first 45 days of the index date was also evaluated as a potential combination therapy (described in greater detail in the methodology of Manuscript 1). For example, if a patient had a refill of a statin on the index date and a 90-day refill of ezetimibe 30 days before the index date, the resulting 60 day overlap with the index drug would be considered as combination LLT. Patients with multiple concurrent statin use identified in this period, as well as patients on 3 or more LLT at the same time were excluded. As this study intended to focus on older adults, only patients aged 65 years and above were included. The one year period prior to the index date was the pre-index period during which the covariates were measured. For patients who had LLT use in the pre-index period (prevalent users), the pre-index LLT modifications were also captured. This study excluded patients with a diagnosis of either end stage renal disease (ESRD), cirrhosis, or rhabdomyolysis because the presence of these co-morbidities influences the likelihood of LLT modification. Patients were followed for a 1-year period after the index date to identify the outcome, i.e. treatment up-titration. Inclusion in the cohort required continuous eligibility in the pre-index and follow-up period. Figure 1 represents the stepwise implementation of the study inclusion criteria.

Patients with an LDL-C test in the 180-days prior to the index date were included in a separate subgroup analysis. The LDL-C measurement closest to the index date was used. If the patient had a treatment up-titration between the LDL-C test date and index date, then the patient was excluded from the subgroup analyses.

4.4.3 Medication use and modification variables

Lipid lowering therapies: The guideline recommended LDL-C lowering therapies evaluated were statins, ezetimibe, bile acid sequestrants and PCSK9 inhibitors.

Outcome: The outcome variable was LLT up-titration in the 1 year follow-up period. Treatment up-titration was a composite measure for the occurrence of either statin intensity increase, LLT dose increase or add-on treatment. Each of these modifications are described below:

Statin intensification: this modification could only occur with statin medications based on their classification in the ACC/AHA guidelines. The guidelines identify statins as being low, moderate and high intensity statins based on the drug and its daily dose [3]. Intensification was the escalation in dose intensity (low to moderate, moderate to high, or low to high) between consecutive claims for the statin.

Dose increase: defined as increase in the daily dose of LLT. Even though statins could have dose increases, if a change for a statin drug was identified as an intensification, then the same change was not considered as a dose increase.

Add-on: defined as the use of a new LLT with continued use of the previous LLT.

Pre-index treatment modifications: Treatment up-titration as well as down-titration were also measured in the pre-index period for prevalent users of LLT, i.e. for patients having LLT use in the period before the index date. Treatment down-titration was a composite measure of either decrease in the intensity of a statin or decrease in the dose of LLT.

4.4.4 Independent variables as potential predictors of LLT up-titration

Sociodemographic variables: Demographic variables included as predictors were age group, sex and low income subsidy. Age was divided into the groups 65 - 69, 70 - 74, 75 and above. Female

was the reference group in the sex variable. Low income subsidization (LIS) was a binary variable (yes vs no) which determined whether the patients received any extra financial assistance in their pharmacy copayments.

Comorbidities: Presence of ASCVD was defined as the presence of diagnosis for either acute coronary syndrome (ACS), a history of myocardial infarction, stable or unstable angina, coronary or other arterial revascularization, stroke, transient ischemic attack, or peripheral arterial disease [3]. The other comorbidities tested as predictors of treatment up-titration included diabetes, hypertension, hyperlipidemia, dementia and chronic kidney disease (CKD). Known adverse effects of statins, including myalgia and myopathy, were also tested. Obesity and inflammatory conditions are guideline specified risk factors for cardiovascular events which could be identified using claims data and therefore were also tested. The CMS risk score which accounts for medication burden and disease severity was provided in the data from the Medicare Advantage plan and was also considered.

Treatment characteristics: Patients without any LLT in the pre-index period were defined as new users of LLT. Index treatment was categorized as statins, non-statins or combination with statins. Pre-index treatment up-titration and down-titration were also evaluated as predictors of follow-up treatment up-titration.

4.4.5 Statistical analysis

Data were summarized using descriptive statistics. Statistical differences were assessed using Pearson's $\chi 2$ tests for the categorical variables and t-tests for continuous variables. Multivariable logistic regression analysis was used to determine the unique association of the sociodemographic, comorbid, and treatment characteristics with treatment up-titration. The final logistic model was

selected by adding variables one at a time starting with demographic covariates (age group, sex, and low income subsidy) followed by comorbidities added one at a time as well as the CMS risk score. The pre-index treatment modifications were added, followed by treatment characteristics (prevalent vs new user, use of a statin or combination vs non-statin only). The decision to add a variable was made by the authors based on the c-statistic, Akaike Information Criteria (AIC), clinical relevance of the variable and lastly the statistical significance of the variable. Multicollinearity and interaction assessment between the variables was also performed. Statistical Analysis Software, version 9.4 (SAS Institute Inc., Cary, NC) was used for the analyses.

Subgroup analysis: Patients with ASCVD and an LDL-C value ≥ 70 mg/dl were evaluated in the subgroup analysis because they represented older adults at high risk of cardiovascular events and candidates of treatment up-titration. For the LDL-C assessment subgroup, LDL-C was added into the analytic model as a categorical variable, and values between 70 - 99 mg/dl were compared to LDL-C values of 100 mg/dl and above.

4.5 **Results**

The data contained 23,112 patients with a LLT prescription in the identification period. The final cohort after exclusions comprised 14,360 patients (Figure 1). Among these, 1,816 (12.6%) patients had an up-titration in the follow-up period. The baseline characteristics of the cohort are presented in Table 1. More patients receiving an up-titration were in the younger age groups and a greater proportion of them had low income subsidy. Patients receiving an up-titration also had fewer pre-index up-titrations (10% vs 12.9%) and greater pre-index down-titrations (10% vs 6%) as compared to the patients who did not have an up-titration in the follow-up period. There were 6,189 patients with an LDL-C in the 180-day pre-index period of which 4,708 patients had ASCVD and values ≥ 70 mg/dl and were analyzed in the subgroup analysis.

The variables that were tested but not added into the final logistic model were hyperlipidemia, obesity, and number of physician visits. Table 2 presents the predictors of treatment up-titration in the overall sample. Patients in each of the higher age groups (70 - 74 years, 75 - 79 years, 80 years and above) were less likely to receive treatment up-titration as compared to patients aged 65 - 69. Patients having LIS for pharmacy prescriptions were 20% more likely to receive treatment up-titration [OR: 1.19 (95% CI: 1.08 – 1.32)]. Patients with ASCVD were 25% less likely [OR: 0.75 (95% CI: 0.63 – 0.88)] and patients with hypertension were 14% more likely [OR: 1.14 (95% CI: 1.01 – 1.28)] to receive treatment up-titration as compared to patients without those conditions. Patients with higher CMS risk score were less likely to receive treatment up-titration [OR: 0.93 (95% CI: 0.87 – 0.99)]. Up-titration in the pre-index period was associated with lower odds [OR: 0.70 (95% CI: 0.59 – 0.83)] of being up-titrated in the follow-up while down-titration in the pre-index period was associated with higher odds [OR: 1.65 (95% CI: 1.38 – 1.96)] of being up-titrated in the follow-up. Prevalent users of LLT and patients on either statins or combination were less likely to get up-titrated as compared to patients on non-statins only.

Table 3 presents factors associated with up-titration in the specific subgroup with ASCVD and LDL-C values ≥ 70 mg/dl. The rate of up-titration (11.1%) in the subgroup with LDL-C was lower than the overall sample. Among the patients with a recorded LDL-C value ≥ 70 mg/dl, 12.3% had an up-titration. LDL-C group was a significant predictor of treatment up-titration and patients having an LDL-C ≥ 100 mg/dl were 68% more likely [OR: 1.68 (95% CI: 1.39 – 2.04)] than patients with an LDL-C between 70 and 99 mg/dl to receive an up-titration in the follow-up. The similarities with the overall analysis were the association of age, LIS, CMS risk score, pre-index up and down-titration and baseline drug type with the likelihood of receiving an up-titration. However in the subgroup, having diabetes was associated with 22% higher likelihood of receiving

treatment up-titration [OR: 1.22 (95% CI: 1.01 – 1.47)]. Patients who were adherent (i.e. PDC ≥ 0.8) were 42% more likely to receive a treatment up-titration [OR: 1.42 (95% CI: 1.13 – 1.78)].

4.6 **Discussion**

This study identified the predictors of lipid lowering treatment up-titration among older adults in the current clinical setting. The predictors in the overall sample of older adults on LLT were explored following which the predictors in the specific subgroup with higher risk, i.e. ASCVD and higher LDL-C values were identified. The main purpose of understanding treatment up-titrations is the increasing focus on achieving lower LDL-C values which would require up-titrating patients not at goal but would require additional considerations for older adults. We did not find any study identifying the predictors of LLT up-titration among older adults since the changes in the guidelines in 2013.

Increasing age group was found to be associated with a lower likelihood of treatment up-titrations which aligns with both the guidelines and existing literature. As age increases mean LDL-C values decrease, [19] and additional factors such as patient frailty also have to be accounted for. Wang and colleagues found that older patients were also less likely to receive LDL-C testing following a discharge after an acute myocardial infarction.[20] Additionally intensifying treatment may predispose a patient to adverse events like myopathy and rhabdomyolysis which are dose dependent.[21] Rodondi et al. identified that patients older than 65 were more likely to receive appropriate care for poorly controlled dyslipidemia where appropriate care was defined as either receiving therapy modifications or attain control without any modification in 6 months follow-up.[22] Studies evaluating outcomes among older adults receiving up-titration would provide more insight into the appropriateness of this finding of lower treatment titrations with increasing age for patient care.

Presence of ASCVD and prevalent use of LLT was associated with lower treatment up-titrations. This could be due to long-term use of LLT in such patients leading to patients being on stable or maximally tolerated therapy. Patients with higher CMS risk score also had lower odds of receiving an up-titration which could indicate that sicker or more severe patients were less likely to get up-titrated for LLT. These findings are consistent with the philosophy of the 2018 cholesterol guideline of tailoring the lipid lowering therapy to the individual patient by considering benefit versus risk.

Hypertension and diabetes are independent risk factors for cardiovascular events in older adults.[23] Patients in the overall sample with hypertension and patients with diabetes in the subgroup analysis were more likely to receive an up-titration. Melloni and colleagues found that patients who received up-titration during a hospitalization for acute coronary syndrome (ACS) were more likely to have hypertension.[24] Up-titration in patients with diabetes in the subgroup analysis could be attributable to the additional risk factor for cardiovascular events from diabetes [3]. On the other hand, statin use has been associated with incident diabetes which may result in failure to up-titrate among patients without diabetes.[25] Patients with LIS were also more likely to receive up-titration. LIS is provided to patients by the health plan based on the socioeconomic status. Even though the patients with LIS have subsidization for pharmacy drugs, it is unlikely that cost was a reason that LIS and up-titrations were associated because most patients were on statins which are available at a very low copay even without LIS. Socioeconomic status has been associated with poor health literacy, higher risk of multimorbidity, cardiovascular risk and poor adherence.[26,27] These could be possible underlying factors for the patients with LIS receiving more up-titrations. Information on the reason for up-titration can provide information for these patterns which should be evaluated in future studies.

Patients with up-titration in the pre-index period were less likely to receive up-titration in the follow-up period. Down-titrations in the pre-index period were associated with increased odds of follow-up treatment up-titration. The pre-index down-titration could be associated with improved control or poor tolerability in which case the higher likelihood of follow-up up-titration could mean re-challenge or medication management to maintain LDL-C values. Booth and colleagues found that in patients who re-initiate statins after discontinuation, down-titrations and switching were associated with better persistence indicating that the modifications observed in this study could be associated with medication adherence as well.[28] Patients with prior down-titrations who are up-titrated could be re-challenged with the same therapy or another combination. This also highlights that LLT medication management is a dynamic process in which physician visits, LDL-C panels at regular intervals allow opportunities to identify and mitigate risk of cardiovascular events through modification of pharmacotherapy or other approaches.

The interpretation of the study findings does not give rise to any evident non-compliance of the guidelines in the treatment of older adults. This could be due to increased awareness of the guidelines as consistent efforts are being made by managed care plans to educate providers. As the Center for Medicare and Medicaid Services provides a capitated payment per beneficiary to the managed care plans, comprehensive treatment to provide disease management and slow progression are the approaches often used by managed care plans to enhance performance.

4.7 **Limitations**

Use of pharmacy claims data may result in misclassification of LLT use patterns because it captures refill not actual behavior and therefore, some beneficiaries may not actually have taken the medication they refilled. The reasons for treatment up-titration as well as other modifications could not be ascertained from the database. We had laboratory information on a subset of patients

who were tested at certain laboratories reporting results to the managed care plan. Other patients may also have had laboratory tests, but were not captured by the data source as all the laboratories do not report test information to the health plan. Physician level factors which may influence treatment modifications were not available and were not evaluated in the model. This study did not capture potential efforts of the Managed Care plan from which the data was obtained to emphasize guideline directed medical therapy in the physicians. The results therefore need validation from other data sources with older adults to ascertain the generalizability of the results beyond similar health plans.

Despite these limitations, this study provided an insight of the LLT modification practice in older adults and the similarity in results between the overall sample and subgroup analysis indicate a stability in results.

4.8 **Conclusion**

In summary, older patients and patients on stable therapy were less likely to receive up-titration and patients with comorbidities associated with cardiovascular risk are more likely to get up-titrated. Our study contributes to the scientific literature by providing up-to date patient and medication level predictors of treatment up-titration. Characteristics of physician and managed care plans associated with up-titration, as well as patient outcomes, would provide more information regarding the up-titration practices in older adults and inform evidence based care.

4.9 **References**

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4.10 **Figures and Tables**

Figure 1. Derivation of final patient cohort

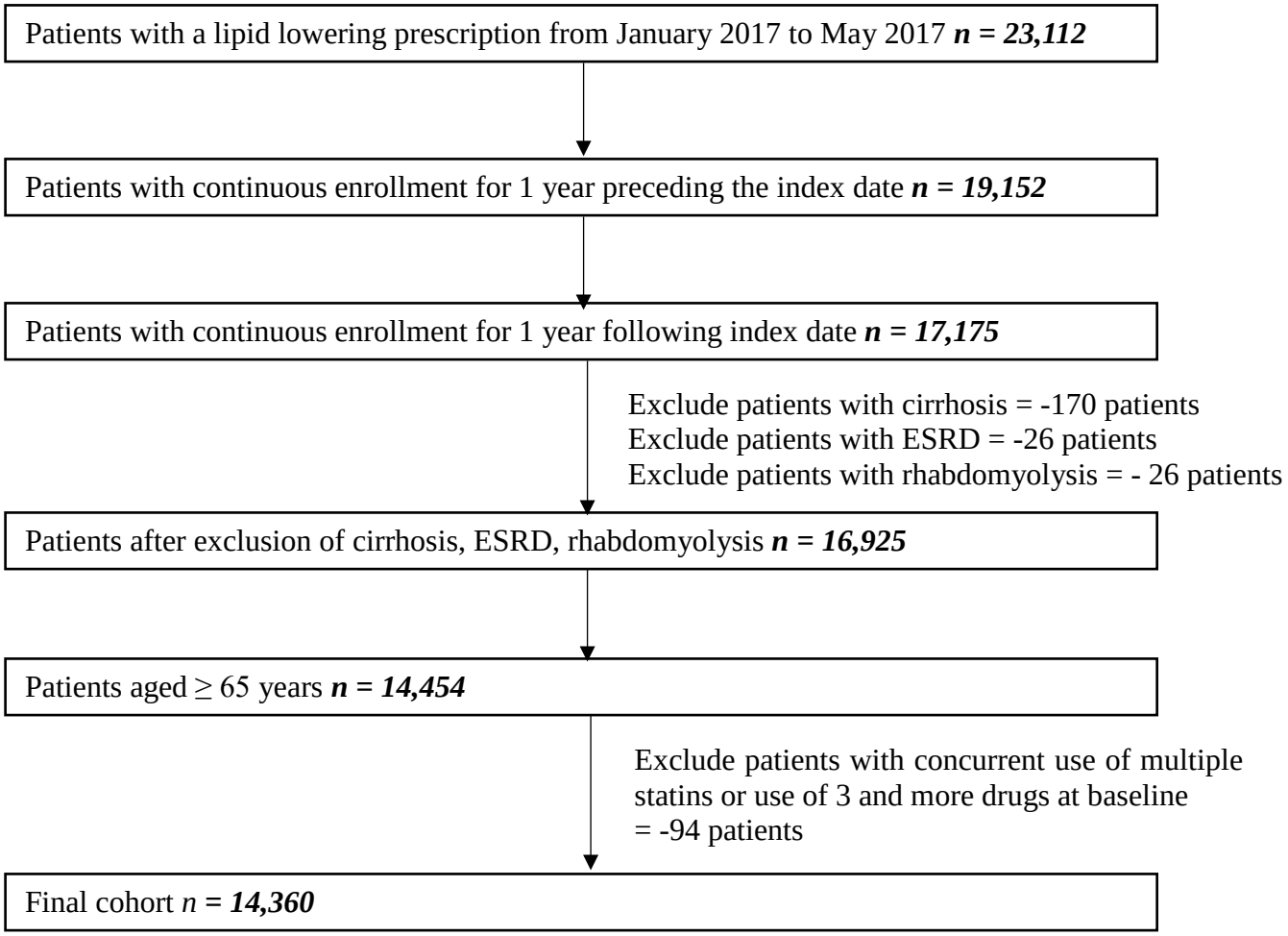

Table 1. Baseline characteristics of patients who received a lipid lowering therapy up-titration versus not.

Variable	Patients without up-titration (n = 12,544)	Patients with an up-titration (n = 1,816)	P-value
Age group			
65 – 69 years	4198 (33.47%)	838 (46.15%)	<.0001
70 – 74 years	3,816 (30.42%)	513 (28.25%)	
75 – 79	2,422 (19.31%)	267 (14.70%)	
80 and above	2,108 (16.80%)	198 (10.90%)	
Female sex	7,198 (57.38%)	1,067 (58.76%)	0.2684
Low income subsidy	5,412 (43.14%)	857 (47.19%)	0.0012
Presence of comorbidities			
ASCVD	10,542 (84.04%)	1,463 (80.56%)	0.0002
Diabetes	5,529 (44.08%)	804 (44.27%)	0.8749
Hypertension	7,057 (56.26%)	1,027 (56.55%)	0.8128
Inflammatory conditions	237 (1.89%)	24 (1.32%)	0.0905
Myalgia	170 (1.36%)	20 (1.10%)	0.3761
Dementia	402 (3.20%)	46 (2.53%)	0.1239
Chronic kidney disease	3,108 (24.78%)	395 (21.75%)	0.0050
CMS Risk score, Mean (SD)	1.32 (1.30)	1.24 (1.20)	0.0002
Hospitalizations in pre-index			
None	9,182 (73.20)	1,352 (74.45%)	0.4321
One	2,103 (16.76)	283 (15.58%)	
More than one	1,259 (10.04)	181 (9.97%)	
Pre-index patterns			
Pre-index up-titration	1,615 (12.87%)	183 (10.08%)	<.0001
Pre-index down-titration	755 (6.02%)	181 (9.97%)	<.0001
Baseline adherence (PDC) >0.80	2,362 (18.83%)	348 (19.16%)	0.7344
Treatment type			
Prevalent vs new user	11,648 (92.86%)	1,650 (90.86%)	0.0024
Pre-index triglyceride use	1,048 (8.35%)	155 (8.54%)	0.7951
Baseline drug type			
Non-statin	134 (1.07%)	40 (2.20%)	<.0001
Statin	12,293 (98.00%)	1,773 (97.63%)	
At least 1 statin	117 (0.93%)	3 (0.17%)	

Table 2. Results of the multivariable logistic regression identifying predictors of lipid lowering therapy up-titration in the overall sample.

Variable	Odds Ratio (95% Confidence Interval)	P-value
Age group		
70 – 74 years vs 65 – 69	0.686 (0.608 - 0.773)	<.0001
75 – 79 vs 65 – 69	0.567 (0.488 - 0.658)	
80 and above vs 65 – 69	0.494 (0.416 - 0.586)	
Female vs male sex	1.039 (0.938 - 1.150)	0.4630
Low income subsidy vs not	1.192 (1.076 - 1.321)	0.0008
Presence of comorbidities		
ASCVD	0.747 (0.632 - 0.883)	0.0006
Diabetes	1.092 (0.974 - 1.224)	0.1313
Hypertension	1.137 (1.008 - 1.283)	0.0364
Inflammatory conditions	0.693 (0.452 - 1.063)	0.0931
Myalgia	0.769 (0.479 - 1.235)	0.2776
Dementia	1.009 (0.735 - 1.386)	0.9539
Chronic kidney disease	0.974 (0.857 - 1.107)	0.6820
CMS Risk score	0.930 (0.874 - 0.989)	0.0202
Hospitalizations in pre-index		
1 vs none	0.966 (0.839 - 1.113)	0.4730
More than 1 vs none	1.095 (0.918 - 1.307)	
Pre-index patterns		
Pre-index up-titration	0.699 (0.591 - 0.826)	<.0001

Pre-index down-titration	1.647 (1.384 - 1.961)	<.0001
Baseline adherence (PDC) >0.80	1.102 (0.970 - 1.253)	0.1369
Treatment type		
Prevalent vs new user	0.778 (0.650 - 0.931)	0.0060
Pre-index triglyceride use	1.003 (0.839 - 1.201)	0.9698
Baseline drug type		
Statin vs non-statin	0.431 (0.299 - 0.620)	<.0001
At least 1 statin vs non-statin	0.068 (0.020 - 0.225)	

Table 3. Results of the multivariable logistic regression in the subgroup of patients with an LDL-C value in the pre-index 180 days ≥ 70 mg/dl

Variable	Odds Ratio (95% Confidence Interval)	P-value
LDL-C group		
71-99 mg/dl vs 100 mg/dl and above	1.681 (1.388 - 2.035)	<.0001
Age group		
70 – 74 years vs 65 – 69	0.712 (0.573 - 0.886)	<.0001
75 – 79 vs 65 – 69	0.654 (0.507 - 0.843)	
80 and above vs 65 – 69	0.483 (0.357 - 0.652)	
Female vs male sex	1.182 (0.978 - 1.429)	0.0832
Low income subsidy vs not	1.339 (1.105 - 1.622)	0.0029
Presence of comorbidities		
Diabetes	1.218 (1.013 - 1.465)	0.0362
Hypertension	1.009 (0.835 - 1.219)	0.9262
Inflammatory conditions	0.654 (0.335 - 1.275)	0.2124
Myalgia	0.615 (0.274 - 1.379)	0.2382
Dementia	0.863 (0.503 - 1.479)	0.5911
Chronic kidney disease	1.033 (0.842 - 1.268))	0.7549
CMS Risk score	0.857 (0.757 - 0.969)	0.0141
Hospitalizations in pre-index		
1 vs none	1.215 (0.968 - 1.525)	0.1085
More than 1 vs none	1.274 (0.952 - 1.707)	
Pre-index patterns		
Pre-index up titration	0.649 (0.482 - 0.874)	0.0044
Pre-index down-titration	2.053 (1.526 - 2.764)	<.0001
Baseline adherence (PDC) >0.80	1.415 (1.125 - 1.780)	0.0030
Treatment type		
Prevalent vs new user	1.154 (0.844 - 1.577)	0.3707
Pre-index triglyceride use	0.808 (0.576 - 1.134)	0.2179
Baseline drug type		
Statin vs non-statin	0.474 (0.282 - 0.796)	0.0061
At least 1 statin vs non-statin	0.105 (0.013 - 0.827)	

5 Manuscript 3

5.1 Title: Does lipid lowering therapy up-titration in older adults impact medication adherence?

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5.2 Abstract

Background: Lipid lowering therapy (LLT) up-titration and adherence improvement both aim to increase the potency of treatment received by the patient thereby augmenting LDL-C reduction. However the impact of LLT modifications on medication adherence is not clear, especially in older adults where additional considerations due to frailty, altered pharmacokinetics and risk of adverse events may affect the response to the up-titrated treatment as well as negatively impact medication adherence. However up-titrtion can also improve adherence by acting as a medication management intervention to the patient and increasing disease awareness and risk management by the patient.

Objective: To identify the impact of treatment up-titration and other modifications (down-titration, switching) on medication adherence in patients on LLT.

Methods: This was a retrospective cohort study conducted in adults ≥ 65 years and enrolled for at least 2 years after their first LLT use between January 2016 and May 2018. Patients were required to have LLT use one year after the first use and were categorized into 3 groups based on their medication refill as: (a) patients with up-titration (UpT) (b) patients with no treatment changes (NoC) (c) patients with other treatment changes (OthC). Adherence to LLT was measured as proportion of days covered (PDC) with a value between 0 – 1 for each month. Piecewise regression with repeated value of monthly PDC as the outcome was used to evaluate the change in monthly adherence prior to as well as following the treatment changes. The covariates added to the analytical model included age, gender, CMS risk score, low income subsidization and chronic comorbidities.

Results: There were 10,038 patients in the final sample. In the first year, all the groups had a decrease in mean PDC each month with the highest decrease of 1.4% for NoC followed by 1.1%

for UpT and 0.9% for OthC groups. The estimate for the piecewise variable was positive and statistically significant indicating that the PDC improved after the first year in all groups. The mean increase in PDC in the second year was 0.3% in the NoC group, 1% for the UpT group and 1.9% for the OthC group. The differences in PDC change were not statistically significant between the UpT and NoC group, but were significant between the OthC and NoC group.

Conclusion: Treatment modifications like switching and down-titration are likely to be performed to address tolerability issues and therefore were associated with the greatest improvement in adherence followed by the up-titration group. The improvement in slope of adherence over time seen with medication management could be interpreted as an intervention. Regular monitoring could prevent the decline in adherence to chronic medications which is observed over time.

5.3 **Introduction**

It has been repeatedly demonstrated that low density lipoprotein cholesterol (LDL-C) is a mutable risk factor for cardiovascular disease, the reduction of which corresponds to reduction of cardiovascular events. [1,2] There is an increased emphasis on LDL-C lowering from the results of the newer clinical trials in which the treatment groups had LDL-C mean values below 50 mg/dl. [3-6]

The 2018 American College of Cardiology and American Heart Association (ACC/AHA) guideline recommended lipid lowering therapies (LLT) include statins, ezetimibe, bile acid sequestrants, ezetimibe and Proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors. Statins are the guideline recommended primary agents for lipid-lowering, but adding a non-statin therapy is reasonable in patients with atherosclerotic cardiovascular diseases (ASCVD) and LDL-C values ≥ 70 mg/dl despite using maximally tolerated statin.[7] The guidelines have differentiated

statins into low-, moderate- and high- intensity based on the expected percentage reduction in LDL-C from their use. In patients who require incremental LDL-C lowering to meet lipid thresholds, the statin dose or intensity can be increased. Alternatively, if the patient is already on the highest intensity statin, or has poor tolerability to a statin, a non-statin drug can be added to the regimen. The dose of the non-statin also can be increased to obtain further LDL-C reduction.

Failure to up-titrate LLT in patients who are not at goal could result in suboptimal LDL-C lowering. Often times, the term clinical inertia has been used to characterize the failure of providers to modify therapy based on guidelines when the patients have suboptimal response from existing medications.[8,9] Even though clinical inertia appears to be physician behavior, it may actually result from various physician, patient or system related factors. Milman et al. have summarized some of the patient and provider factors leading to inertia.[9] Patient factors include older age, lower life expectancy and presence of comorbidities. Provider factors include lack of knowledge about practice guidelines or lack of time.[9] The 2016 ACC decision Pathway stated that when patients do not achieve the expected LDL-C reduction from LLT, medication adherence should be addressed before intensifying treatment.[10] Medication adherence is an important factor which affects achievement of the maximal therapeutic effect from the LLT and achievement of lipid targets. Poor adherence has a negative effect on patient outcomes as well as disease-related costs.[11,12]

Studies have been conducted to assess the relationship between medication adherence and treatment up-titration. Pittman et al. found that non-adherence to statins was associated with an increased likelihood of up-titration.[13] Another study in type 2 diabetes patients found that patients with lowest adherence were less likely to have treatment up-titration.[14] Virani et al. had similar results in a CVD cohort, where non-adherent patients were less likely to be intensified despite elevated LDL-C levels.[15] Hiesler et al. found that poor patient adherence had little impact on

physician's decision to titrate treatment, but the lack thereof was associated with worse outcomes.[16] Improving CV outcomes is a two pronged approach where both ensuring high adherence as well as timely up-titration are important in effectively reducing the risk of adverse outcomes.

Management of therapy which includes switching, medication up-titration or down-titration may include a window of repeated exposure to the healthcare system. This could include lipid testing, physician and pharmacy visits which would allow opportunities for patient education and clarification which in turn may positively impact a patient's adherence. Adherence to medications can be affected by physician-patient communication and an increased contact with physicians.[17] A study in Canada identified physician visits, cholesterol tests, incident myocardial infarction and other CV related hospitalizations as predictors of re-initiation of statin treatment among patients who had interruption of therapy for 90 days or greater.[18]

Older adults are more likely to be on multiple medications, have altered pharmacokinetics, higher risk of medication-related adverse events; therefore up-titration may affect the adherence in older adults differently as compared to the overall adult population.[19] On one hand there is more literature on the importance of LLT in cardiovascular risk reduction in older adults,[20,21] while on the other hand, increased medication complexity is also being associated with increased frailty.[22] As older adults are at high risk for cardiovascular events as well as adverse effects of therapy, understanding the effect of up-titration on adherence in these patients is important.

The literature about the impact of treatment up-titration on adherence and vice versa, as described above, has inconsistent results. Although there is some evidence that treatment modification can potentially affect adherence, we did not find any studies specifically assessing the association of

LLT up-titration with change in medication adherence measured longitudinally. Both up-titration and medication adherence however, affect the cumulative exposure of the patient to the drug which affects disease control and management.

The objective of this study was therefore, to assess the effect of treatment up-titration on change in adherence in older adults on lipid lowering therapy and whether it could compromise or enhance the ability to attain treatment goals.

5.4 Methods

5.4.1 Data source and study design

This study was performed using administrative claims data from a Medicare Advantage Plan in Texas. The database included claims from January 2016 extending to May 2018 and had patient demographic information, pharmacy refills, and medical diagnosis from outpatient visits as ICD-10-CM and CPT codes as well as laboratory tests and results for a subgroup of the sample.

This study used a retrospective cohort design and aimed to capture changes in adherence measured as proportion of days covered (PDC) over time with treatment up-titration.

5.4.2 Inclusion and exclusion criteria and study groups

The study was focused on older adults and only included patients aged 65 and above. The inclusion criteria were based on the study design which is presented in Figure 1. The study period for each patient was two years with a one-year pre-index period and one-year follow-up period for adherence measurement.

The study categorized patients into 3 groups (a) patients with a treatment up-titration at the index date (UpT) (b) patients with no changes on or before the index date (NoC) (c) patients with other treatment changes, i.e. switching or treatment down-titration on or before the index date (OthC).

As shown in Figure 1, in order to operationalize the three study groups, patients were identified at the first LLT refill in the data and were required to have another refill of any LLT at least 360 days after the first but before June 2017. The screening for another refill ensured a 1 year LLT-use for all patients. The index date for patients was the date of treatment up-titration > 360 days after the first LLT use but before June 2017. For patients who did not have a treatment up-titration in this duration, the first refill > 360 days after LLT use but before June 2017 was identified as the index date. Given the one year follow-up requirement and the dates of data availability, May 31 2017 was the last date a patient could be indexed for the study. Once the index date was isolated, patients were required to have 1 year pre-index and 1-year follow-up continuous enrollment.

Patients with a treatment up-titration less than 360 days after the first LLT use were excluded. The reason for this exclusion was to ensure a complete 1-year pre-index period to measure adherence prior to up-titration. As the study intended to measure treatment modifications, patients with co-morbidities such as rhabdomyolysis, end stage renal disease (ESRD) and cirrhosis which affect LLT modifications were excluded. Patients with a combination of LLT were also excluded as some of these patients may not have opportunities to up-titrate further.

5.4.3 Study measures

Treatment up-titration: This was the main exposure of interest and was defined in the study as an increase in the intensity of the statin, an increase in the dose of the LLT, addition of another LLT to an existing regimen. Each of the three measures are defined below:

a. *Statin intensification:* this modification could only occur with statin medications based their classification in the ACC/AHA guidelines. The guidelines identify statins as being low, moderate and high intensity statins based on the drug and its daily dose [7]. Intensification was the escalation

in dose intensity (low to moderate, moderate to high, or low to high) between consecutive claims for the index statin.

b. *Dose increase:* defined as increase in daily dose of the LLT. If a change for a statin drug was identified as an intensification, then the same change was not considered as a dose increase.

c. *Add-on:* use of a new LLT with continued use of the previous LLT.

Other treatment patterns: The control group which could have other treatment patterns included switching and treatment down-titration.

a. *Switching:* defined refill of another LLT the without continued use of the previous therapy.

b. *Treatment down-titration:* This measure was the opposite of treatment up-titration and included decrease in the intensity of statin or dose decrease of the LLT.

5.4.4 Outcome

The outcome was the "monthly change in adherence" which was calculated using PDC ranging from 0 – 1 for each month. The PDC was calculated for 9 months before the index date in monthly intervals. As all patients refilled at the index date and LLT therapies are often refilled as 90 day supplies, the PDC in the 3 months after index date would be close to 1 for all groups. Therefore the study measured PDC after an interval of 90 days from index i.e. from post-index month 4 till the end of 1 year follow-up providing 9 monthly measurements of follow-up PDCs as seen in Figure 1 generating 18 repeated values of PDC which would be assessed as the outcome.

5.4.5 Statistical analysis

Descriptive statistics

T-tests and chi-square tests were used to compare the baseline demographics across the three study groups. The mean value of PDC in the 9 month pre-index and follow-up intervals for each group

were also calculated and the pre-post differences within each group were assessed using paired T-tests.

Mixed model

The hypothesis of the study was that the change in adherence over time would be significantly different after treatment up-titration and the pattern of adherence change in the UpT group would be significantly different than the NoC group. A repeated measures mixed model was applied to compare the change in adherence across the 3 study groups. The outcome of the model were the repeated values of PDC for all the 18 months (9 pre-index and 9 follow-up). The primary independent variables were the study group and the month variable which indicated time and could have values from 1 to 18 for the months in which PDC was evaluated. A piecewise component was added to the model to allow a change in slope at the index date. The piecewise variable or spline added to the model had the value 0 for the months before index date and changed value to 1 for all months after the index date accommodating the change in PDC over time that may occur after up-titration. Interaction terms between (a) month and study group and (b) piecewise variable and study group were added to the model to allow the study groups to have different rates of PDC change. As there were 3 study groups, the change in slope of each group post-index could be compared to pre-index as well as the differences across the study groups could be compared.[23] As the data had repeated observations for each patient, to account for the correlation among variables, a covariance structure had to be specified in the model. The Akaike Information Criterion (AIC) value of the models assuming different covariance matrices was compared and the model with the lowest AIC was used for model building.

Covariates

Even though every patient had pre- and post- measurements and served as their own control, the mixed model controlled for demographic characteristics like age, gender, low income subsidization (LIS) for pharmacy. Presence of comorbidities including ASCVD, diabetes mellitus, hypertension, hyperlipidemia, chronic kidney disease (CKD), congestive heart failure (CHF) and the presence of inflammatory conditions (lupus, rheumatoid arthritis and ankylosing spondylitis) were included in the model. The Center of Medicare and Medicaid Services (CMS) risk score was also added to the model. The CMS risk score accounts for the medication burden and disease severity and was provided for each patient by the health plan as it is calculated from a large pool of beneficiaries. All covariates were measured in the pre-index period and were specified as fixed effects. All analyses were carried out using Statistical Analysis Software, version 9.4 (SAS Institute Inc., Cary, NC).

Subgroup analysis

To further explore whether the changes in adherence after up-titration varied based on patients' baseline adherence or LDL-C values two additional subgroup analysis were performed: (a) Patients with a pre-index mean PDC of < 0.8 (b) Patients with an LDL-C value over 100 mg/dl in the 180-day pre-index period.

5.5 **Results**

There were 31,513 patients identified with at least one LLT refill in the study period of which 13,685 had another refill > 360 days of the first LLT refill and no treatment up-titration between the two dates. After applying all inclusion and exclusion criteria the final cohort, as shown in Figure 2, comprised of 10,038 patients. Of these most (69%) patients had no pre-index changes

(NoC), 23.8% had other treatment changes (OthC) and 7.2% patients had a treatment up-titration (UpT) at the index date.

The baseline characteristics of the three samples are compared in Table 1. Patients in the NoC group were older, fewer of them were female and fewer had LIS as compared to the other two groups. In terms of comorbidities, more patients in the NoC group had ASCVD, hypertension, CKD but had a lower mean CMS risk score. The mean values of PDC in the pre-index and follow-up period for each of the groups are also presented in Figure 3. The mean PDC of the NoC group was highest and its value slightly dropped over the follow-up period. The lowest mean PDC was observed in the group with the OthC group. The UpT and OthC groups showed a significant improvement in the PDC in the follow-up period.

Figure 4 represents the mean monthly PDCs over the 18 month study duration with a vertical line representing the index period. Much similar to the mean PDC values, the graph of NoC group consistently had the highest PDC value over the entire study duration, followed by UpT and OthC group. The differences in the groups were reduced however, in the follow-up period as all the slopes moved closer.

Mixed model results

The unstructured covariance matrix had lowest AIC values as compared to models with compound symmetry, first order autoregressive or autoregressive heterogeneous covariance matrices and was therefore used in the final model. Addition of covariates further lowered the AIC values and the variables in the final model are presented in Table 2 along with the interpretation of beta estimates. The outcome was PDC and therefore has been interpreted as a change in percentage. As the group variable had interaction terms with the month and the piecewise variable, the estimates could not

be interpreted without including the betas from the interaction terms. The p-values for the UpT and OthC in Table 2 are values from the contrast estimates identifying the difference in the estimates between UpT and NoC as well as OthC and NoC groups.

The NoC group was the group with the highest mean PDC at baseline evident from the intercept differences between the groups. All the groups had a small decrease in PDC each month with the highest decrease of 1.4% for NoC followed by 1.1% for UpT and 0.9% for OthC groups. While the change in PDC by month was statistically significant, the difference between the NoC and the UpT group was not significantly different. The estimate for the piecewise variable was positive and statistically significant indicating that the PDC improved after the index date in all groups. The estimates represented in the Table 2 were obtained after adding all interaction terms and also demonstrate an increase in PDC for all groups. For e.g., the PDC slope of the NoC group changed from a decrease by 1.4% each month prior to index to an increase by 0.3% each month after index. The mean monthly increase in PDC was 1% for the UpT group and 1.9% for the OthC group. The differences in PDC change were not significantly different between the UpT and NoC group, but were different between the OthC and NoC group.

The interpretation of the fixed variables were similar to a linear regression model and is presented in Table 2. The covariates increasing age, female sex, low income subsidy, ASCVD were associated negatively with PDC. The presence of comorbidities hypertension and chronic kidney disease were associated with an increase in PDC.

5.5.1 Subgroup analyses

Results from the subgroup analysis can be found in Table 3. In the subgroup with pre-index LDL-C > 100 (n = 1,031), the direction of PDC changes were similar to the overall group. However, the

PDC change after index date were not significantly different in either the UpT group or the OthC group compared to the NoC group indicating similar levels of improvement in adherence among uncontrolled patients at the index refill irrespective of the treatment pattern. On the other hand in the subgroup which was non-adherent (i.e. PDC < 0.8) in the pre-index period (n = 3,479), both the UpT and the OthC groups were significantly different from the NoC group and the magnitude of the PDC changes was greater than the overall sample.

5.6 **Discussion**

This study mapped changes in adherence after treatment up-titration and compared it to patients who had either no changes or other treatment changes. Patients with no treatment changes had the highest PDC in the entire study period, but also had a greater magnitude of decrease over time as compared to the other groups. On the other hand, patients with other changes had the lowest mean PDC but the greatest improvement in PDC over time. All groups had a statistically significant improvement in PDC after the index date. The difference in PDC between the patients who received an up-titration and patients who had no treatment changes was not statistically significant either before or after the index date.

The decrease in PDC over time represents the course of chronic medication-taking behavior and could affect disease management.[24] Patients in the no treatment change group were older, had more comorbidities but still had a lower CMS Risk score indicating lower overall resource utilization. Some studies have found that patients with more medications or comorbidities have been associated with higher adherence.[25] The patient characteristics and adherence patterns of the no change group appear to represent patients on stable lipid lowering therapy.

Patients in the other change group had the lowest adherence but greatest improvement after the index date. This group was characterized by treatment changes like switching and down-titrations, which are more likely to be made to address tolerability, safety, cost and formulary issues or concerns. Simplification of medication regimen has been found to improve medication adherence.[26,27] Thus, these changes are expected to positively impact treatment adherence as compared to up-titration which addresses the need for incremental lipid-lowering. In either cases, it could be expected that the medication management may provide greater opportunities for educational, risk communication and self-management discussions with the healthcare providers, all of which have been proven as effective techniques to improve adherence.[28] Thiebaud et al. found that new statin users who switched were less likely to be compliant which would reduce their ability to achieve treatment benefit.[29] However, they measured both switching and adherence in the same duration. Our study teases out the two parts and shows that switching could be a change resulting from non-compliance rather than the cause.

Poor adherence has been associated with decreased likelihood of treatment up-titration in some studies, [14,15] while other literature shows the opposite effect of adherence on likelihood of up-titration.[13,30] Both up-titration and adherence however, serve the same purpose of help patient receive maximal treatment effect and meet clinical endpoints to reduce cardiovascular risk. In the subgroup analysis of patients who were not controlled at baseline, no such associations were observed. The results of the subgroup analysis were similar to the overall sample, and the patients who did not have any change still had a consistently higher PDC as compared to patients who received an up-titration indicating that adherence is inherent patient behavior and may not affect the physicians' decision to up-titrate LLT.

We also believe this study may have experienced a ceiling effect because the mean PDC of all the groups combined during the pre-index period was 80%, with limited scope for improvement. This was confirmed to a certain extent in the subgroup analysis with mean pre-index PDC <0.8 in which the magnitude of improvement of PDC after the index date was greater in all groups.

Treatment up-titration in older adults is challenging due to multiple considerations such as medication complexity, patient risk and frailty considerations. However, this study showed an increase in adherence in patients after up-titration as compared to before up-titration which was the primary hypothesis of this study. Improvements of different magnitude were seen across all study groups indicating that in this sample of older adults, medication management has the scope of improving adherence.

5.7 **Limitations**

This study was conducted using a Managed Care Plan population database, where adherence to statins is a triple-weighted star measure,[31] and several interventions may be ongoing at provider and patient levels to maintain or improve adherence which impact the study findings and generalizability. The study design requirement of LLT refill at two time points at least 1 year apart may have resulted in a sample with higher mean adherence than is representative of the health plan. None of the patients in the study were new LLT users due to the requirement of pre-index LLT use in the study design, but the number of years the patients were using LLT which affects adherence could not be assessed. The slope of the PDC was affected by the way PDC was measured. The calculation method assumes that patients are adherent till they run out of the medication and then become completely non-adherent, which may not be the case in the real world. Methods to improve PDC calculations can be incorporated to improve the ability of the model to determine changes in adherence over time. The reason for treatment changes was not known. Other

factors such as hospitalization, or diagnosis of a new condition may have led to the treatment change in which case, the change would be a mediator in the pathway rather than the cause for change in adherence. Despite these limitations, this was a unique study that followed patients over time and mapped changes in adherence associated with treatment modifications.

5.8 **Conclusion**

To summarize, this study evaluated if treatment changes, particularly treatment up-titration could affect LLT adherence. The improvement in the slope of adherence over time seen with medication management could be possibly treated as an intervention. There have been a large number of interventions evaluated to improve adherence with only one out of two found to be generally effective. This study attempts to show that regular patient monitoring which includes medication management could be a means of ensuring that patient adherence does not decline over time. More studies however, are needed to understand the duration of this effect and understanding the reasons for the treatment changes.

5.9 **References**

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5.10 **Figures and Tables**

Figure 1. Schematic representation of the study design

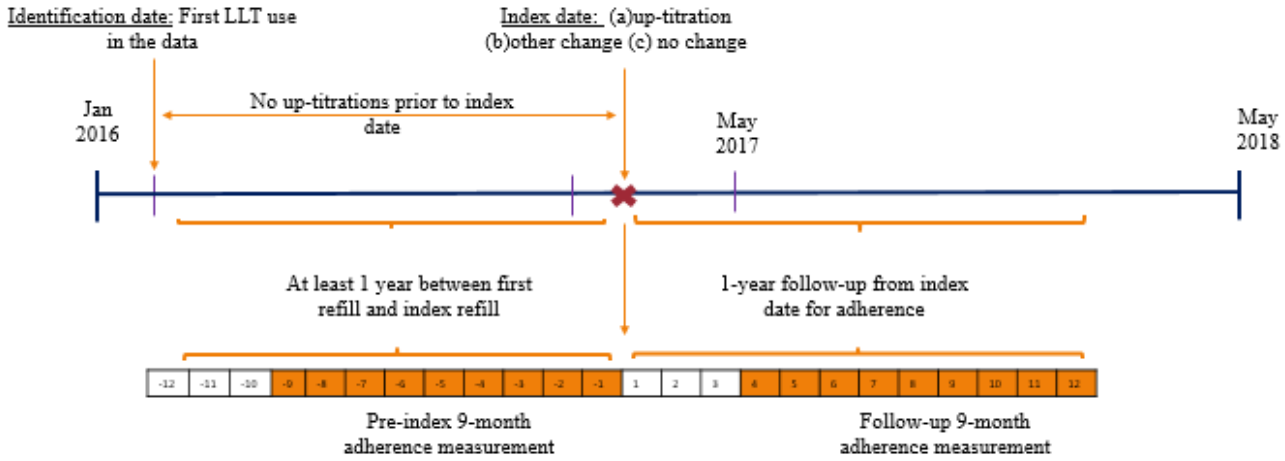

Figure 2. Flow chart of cohort derivation

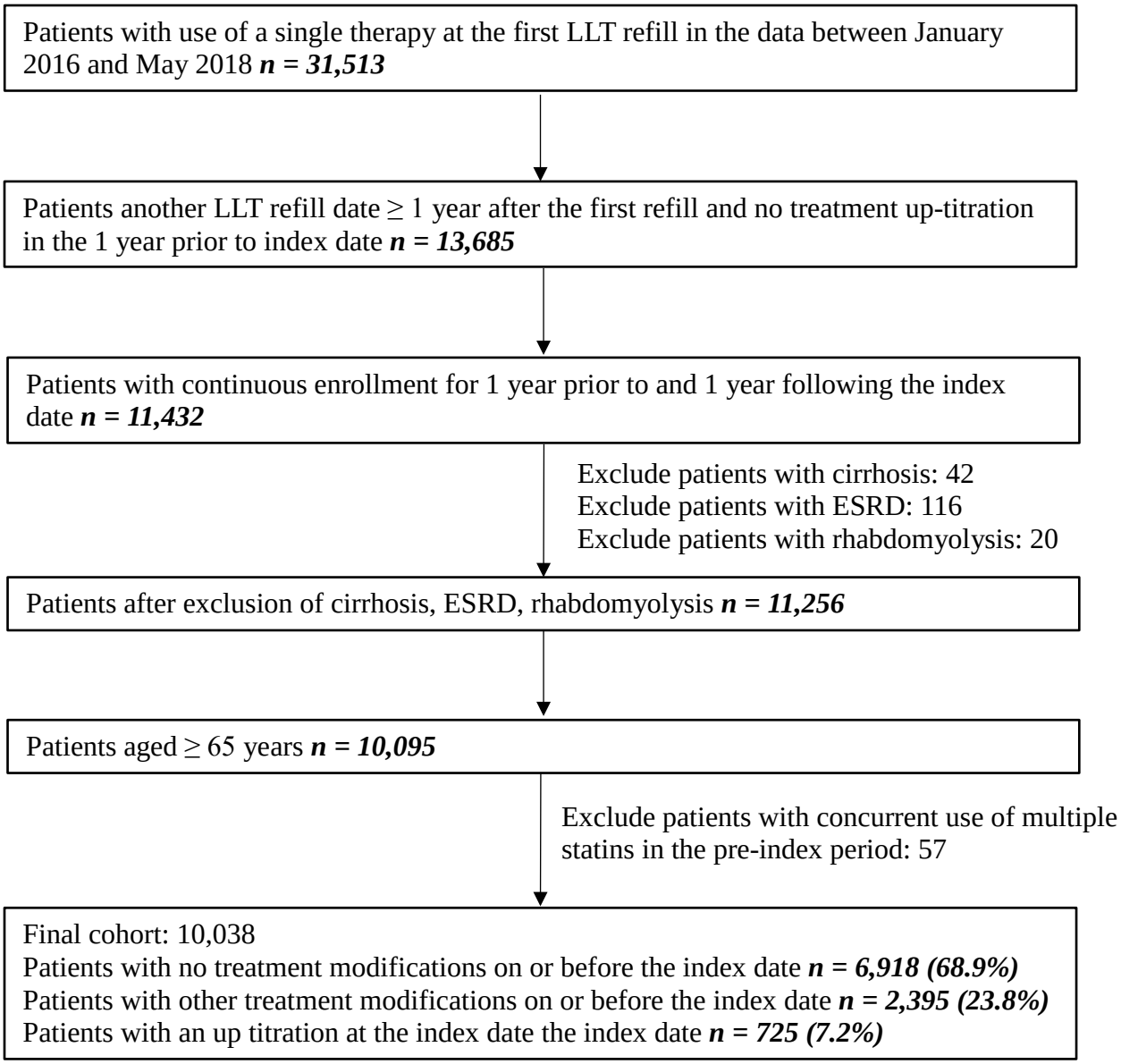

Figure 3. Mean PDC values in the pre-index and follow-up 9 months across the 3 study groups

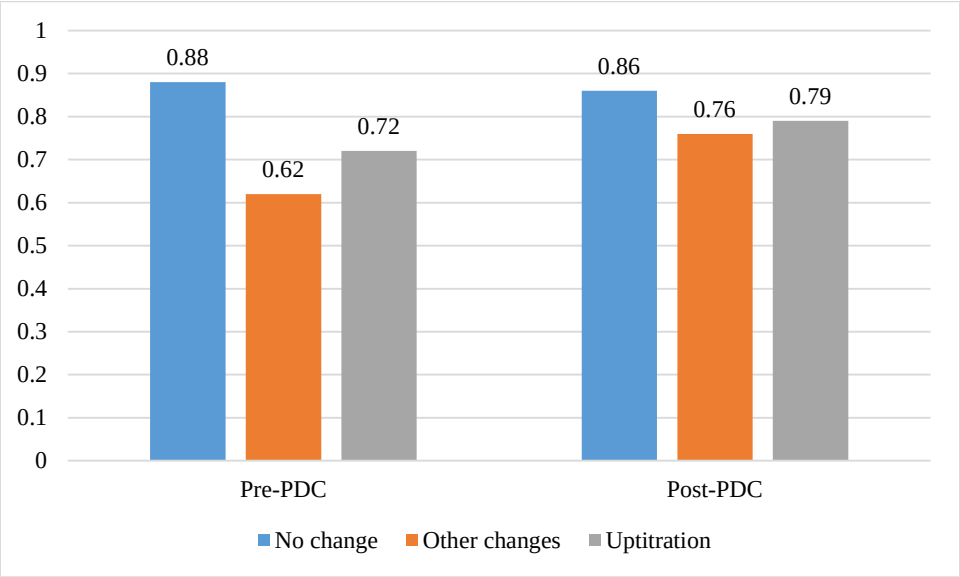

Figure 4. Mean PDC over the study period across the 3 groups with a vertical line at the index

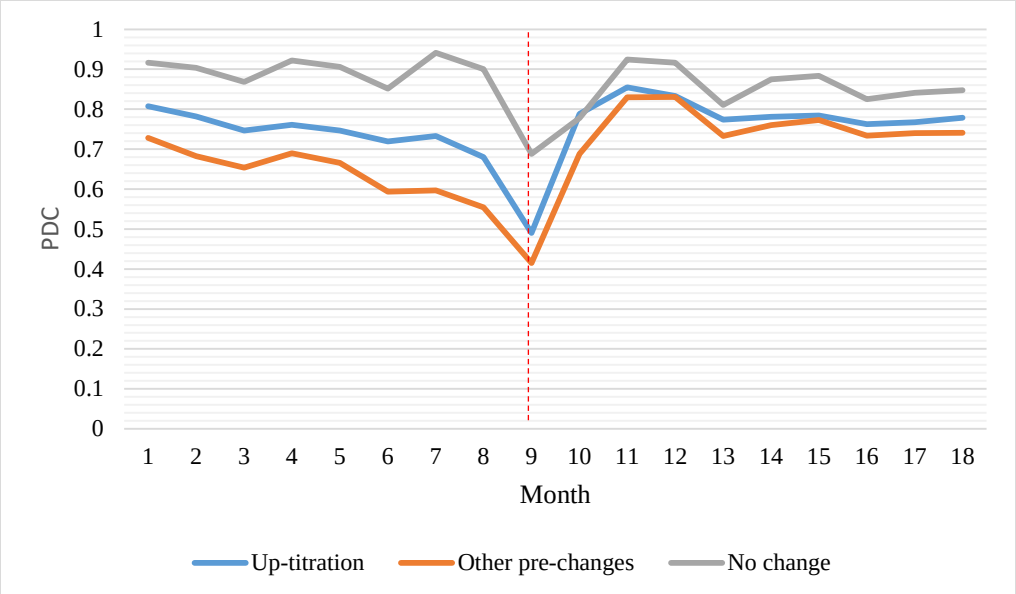

Table 1. Baseline demographic and clinical characteristics of the sample

Variable	Index up-titration (n = 725)	Other pre-index changes (n = 2,395)	No change (n = 6,918)	P-value
Age **(Mean, SD)**	73.99 (5.65)	74.98 (6.34)	75.71 (6.37)	<0.0001
Female gender	433 (59.7%)	1,400 (58.5%)	3,835 (55.4%)	0.0068
Low income Subsidy	337 (46.5%)	1,031 (43.1%)	2,844 (41.1%)	0.0095
Comorbidities				
Atherosclerotic cardiovascular disease	552 (76.1%)	1,949 (81.4%)	5,955 (86.1%)	<0.0001
Hypertension	401 (55.3%)	1,367 (57.1%)	3,962 (57.3%)	0.5976
Diabetes	292 (40.3%)	1,023 (42.7%)	3,156 (45.6%)	0.0027
Hyperlipidemia	459 (63.3%)	1,562 (65.2%)	4,590 (66.4%)	0.1951
Congestive heart failure	74 (10.2%)	269 (11.2%)	769 (11.1%)	0.7312
Chronic kidney disease	177 (24.4%)	550 (23.0%)	1,780 (25.7%)	0.0248
Obesity	65 (9.0%)	239 (10.0%)	755 (10.9%)	0.1553
Inflammatory conditions	11 (1.5%)	47 (2.0%)	130 (1.9%)	0.739
Dementia	28 (3.9%)	79 (3.3%)	232 (3.4%)	0.7484
Myalgia	16 (2.2%)	35 (1.5%)	67 (1.0%)	0.0043
CMS Risk Score **(Mean, SD)**	1.49 (1.09)	1.46 (1.06)	1.42 (0.97)	0.0402
Intensity of statin among statin users				
Low intensity	199 (28.1%)	173 (7.5%)	927 (13.5%)	<0.0001
Moderate intensity	401 (56.6%)	1,467 (63.2%)	4,362 (63.4%)	
High intensity	109 (15.4%)	682 (29.4%)	1,592 (23.1%)	

ASCVD: atherosclerotic cardiovascular disease; CMS: Center for Medicare and Medicaid Services

Table 2. Association between treatment changes and change in PDC

Variables	Parameters	Estimate (SE)	P-value	Interpretation
Intercept terms				
NoC	β_0	1.011 (0.018)	<.0001	Mean PDC of group NoC at time 0 was above 100%
UpT	$\beta_0 + \beta_1$	-0.138 (0.010)	<.0001	Mean PDC of group UpT at time 0 was 86%
OthC	$\beta_0 + \beta_2$	-0.229 (0.006)	<.0001	Mean PDC of group UpT at time 0 was 77%
Slope of adherence in months before index (Month 1 – Month 9)				
NoC	β_3	-0.014 (0.000)	<.0001	Mean PDC decrease for each month was 1.4% for the first 9 months
UpT	$\beta_3 + \beta_4$	-0.011 (0.000)	0.0885	Mean PDC decrease for each month was 1.1% for the first 9 months
OthC	$\beta_3 + \beta_5$	-0.010 (0.000)	<.0001	Mean PDC decrease for each month was 0.9% for the first 9 months
Slope of adherence in months after index (Month 10 – Month 18)				
NoC	$\beta_6 + \beta_3$	0.003 (0.000)	<.0001	The mean PDC slope shifts after the index date with a mean PDC increase by 0.3% each month
UpT	$\beta_6 + \beta_3 + \beta_4 + \beta_7$	0.010 (0.000)	0.1512	The mean PDC slope shifts after the index date with a mean PDC increase by 1% each month
OthC	$\beta_6 + \beta_3 + \beta_5 + \beta_8$	0.018 (0.000)	<.0001	The mean PDC slope shifts after the index date with a mean PDC increase by 1.9% each month
Fixed effect variables				
Age	β_9 to β_{16}	-0.001 (0.00)	0.0148	Fixed effects are interpreted similar to estimates in linear regression. A beta of -0.001 indicates a decrease of PDC by 1% with each unit increase in the fixed-effect variable
Female vs male		-0.013 (0.003)	<0.0001	
LIS vs not		-0.007 (0.003)	0.0208	
ASCVD vs not		-0.021 (0.006)	0.0003	
Diabetes vs not		0.002 (0.003)	0.6513	
Hyperlipidemia vs not		0.007 (0.004)	0.0803	
Hypertension vs not		0.007 (0.003)	0.0462	

Inflammatory conditions versus not		0.003 (0.01)	0.8038	
CKD vs not		0.015 (0.004)	<0.0001	
CHF vs not		0.003 (0.005)	0.6175	
CMS risk score		0.002 (0.002)	0.1765	

NoC: no change; UpT: up titration; OthC: other changes

PDC: proportion of days covered; LIS: low income subsidy: ASCVD: atherosclerotic cardiovascular disease; CMS: Center for Medicare and Medicaid Services; CKD: chronic kidney disease; CHF: congestive heart failure

Table 3. Association between treatment changes and PDC in specific subgroups

		Subgroup with pre-index PDC <0.8		Subgroup with pre-index LDL-C > 100	
Variables	**Parameters**	**Estimate (SE)**	**P-value**	**Estimate (SE)**	**P-value**
Intercept terms					
NoC	β_0	0.856 (0.030)	<.0001	0.953 (0.092)	<.0001
UpT	$\beta_0 + \beta_1$	0.637 (0.019)	<.0001	0.804 (0.028)	<.0001
OthC	$\beta_0 + \beta_2$	0.586 (0.012)	<.0001	0.68 (0.021)	<.0001
Slope of adherence in months before index (Month 1 – Month 9)					
NoC	β_3	-0.034 (0.001)	<.0001	-0.021 (0.002)	<.0001
UpT	$\beta_3 + \beta_4$	-0.019 (0.003)	<.0001	-0.018 (0.004)	0.4297
OthC	$\beta_3 + \beta_5$	-0.016 (0.002)	<.0001	-0.015 (0.003)	0.0444
Slope of adherence in months after index (Month 10 – Month 18)					
NoC	$\beta_6 + \beta_3$	0.03 (0.002)	<.0001	0.01 (0.003)	<.0001
UpT	$\beta_6 + \beta_3 + \beta_4 + \beta_7$	0.059 (0.005)	0.0040	0.02 (0.007)	0.8063
OthC	$\beta_6 + \beta_3 + \beta_5 + \beta_8$	0.06 (0.003)	0.0001	0.023 (0.005)	0.1653

Fixed level covariates are not shown in this table

NoC = No change group; UpT = up-titration group; OthC = other treatment changed

The estimates are mean PDCs and can be interpreted as (beta*100)%

6 Conclusion

The increasing prevalence of older adults with cardiovascular risk and the increased emphasis on lowering of LDL-C for which long term data is not available make it important to understand the current patterns of LLT use in older adults. While it is known that higher levels of LDL-C are associated with higher risk for cardiovascular events, the lower values seen in the recent clinical trials have not been achieved before and their long term effects are not clear. The first aim intended to identify LLT use and found that most patients were on statins monotherapy with moderate intensity statins being the most widely used. In terms of patterns of LLT use it was found that new users were at higher risk of discontinuations and interruptions and require greater attention to ensure appropriate use and adherence to LLT. Adults aged 75 years and above had very few treatment modifications which included both up and down-titrations. The predictors of up-titration in older adults were assessed in Aim 2 and included presence of hypertension, diabetes and pre-index down-titrations. Older and sicker patients were less likely to get up-titrated. The patterns of LLT use as well as predictors of up-titration in these patients were reassuring because no guideline discordant practices could be identified. Risk factors, age and current medication behavior were being accounted for by physicians treating older adults in this health plan. The results also identified cycles of up-titration and down-titration in patients and emphasized that LDL-C management is a dynamic process and any associations between medication use and outcomes should account for these changes.

There is a need to however compare the results of this study with a more generalized sample because the data was obtained from a Medicare Managed Care Plan which focuses on physician education as well as patient adherence. Once this study is performed in another database with older

adults, the generalizability will be well understood, and any difference in results will be able to identify if the practices in this health plan indeed benefit the patients and physician behavior or not.

Lastly in aim 3, this study identified the impact of treatment modifications on medication adherence and found that any modification including up-titration, down-titration and switching had a positive impact on patient adherence. The change in treatment could be viewed as an intervention. Constant monitoring has previously been shown to prevent decline in adherence which is generally seen with chronic medications over time. Regular patient monitoring can prevent the decline in adherence and also provide opportunities to ensure the patient is receiving appropriate treatment and care.

In summary:

- Older adults were more likely to be on a stable therapy but were receiving appropriate LLT and modifications in this health plan. Continued physician education can ensure that the physicians are updated with the guidelines and available therapies to treat the patients.
- Patients who were older and sicker were less likely to be up-titrated, while patients with risk factors, with prior down-titrations and high adherence were more likely to be up-titrated. Physicians were not indiscriminately up-titrating LLT in these patients. Older adults need additional considerations prior to treatment up-titration and aggressive lipid lowering in these patients requires caution.
- Patients who received treatment modifications had improvements in adherence re-emphasizing the importance of monitoring even in patients who have been on stable LLT

for a long time and are not anticipated to have treatment changes. This could prevent the need for external interventions for patients to improve adherence and education.