Drug Benefit Plans for Elderly Under Managed Care and Utilization of Lipid Lowering Agents

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DRUG BENEFIT PLANS FOR ELDERLY UNDER MANAGED CARE
AND UTILIZATION OF LIPID LOWERING AGENTS

BY

SUSAN M. ABUGHOSH

A DISSERTATION SUBMITTED IN PARTIAL FULFILMENT OF THE
REQUIREMENTS FOR THE DEGREE OF
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SUSAN M. ABUGHOSH

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ABSTRACT

Many health maintenance organizations (HMOs) have implemented programs providing varying degrees of annual drug coverage for Medicare beneficiaries enrolled in their plans. Older adult plan members in an HMO operating in central Massachusetts were able to choose among 3 drug benefit options starting January 1, 1994: full coverage for prescription drugs, a maximum of $1000/year in coverage, or no drug coverage. As such, cost containment policies have been shown to affect prescription drug use and other types of health service utilization. The unintended effects of this policy are important to consider. This research investigated the effects of type of drug benefit plan chosen on use of lipid lowering agents (LLA), a group of drugs of well documented benefit for both primary and secondary prevention of coronary heart disease (CHD), which continues to be a leading cause of death in the United States and worldwide.

The objectives of this study were a) to describe LLA utilization during a one-year period, for both prevalent and new users, and to compare this utilization with various patient characteristics including gender, age group, prescriber specialty, comorbidities (CHD, diabetes, hypertension), and choice of drug benefit plan option; b) to examine differences in persistence to LLAs among members of different drug benefit plans; c) to determine the effect of drug plan benefit option on the type of statin drugs, a class of LLAs, prescribed (expensive versus the less expensive statins).

Analyses were performed using 2229 seniors who were continuously enrolled between July 1, 1993 and June 30, 1996 and had a prescription for an LLA. Of these, 1551 were studied to describe the LLA utilization during a one-year period (paper1),
322 to examine persistence to LLA (paper2), and 484 to investigate the type of statin prescribed (paper3).

Statins were the most widely prescribed group of LLAs among both prevalent (61.8%) and new (65.5%) users, and a very low rate of combination therapy was found in both prevalent (1.6%) and new (0.9%) users of LLAs. This may, in part, explain why many patients on LLAs do not reach their target cholesterol levels since combination therapy is more effective than monotherapy in lowering cholesterol levels.

The type of drug benefit plan option did not affect choice among LLAs, but comorbidities, mainly CHD and diabetes, seem to be among the main factors that influenced drug selection, possibly through affecting lipid levels. Patients with CHD were more frequently prescribed statin monotherapy (p<0.0001 in prevalent use; p=0.0028 in new use) and combination therapy (p=0.0467 in prevalent use) and less frequently prescribed bile acid sequestrants (p<0.0001 for prevalent use). Diabetic patients more frequently used fibrates (p=0.0032 for prevalent use), less frequently used bile acid sequestrants (p=0.0007 for prevalent use; p=0.0329 for new use), and niacin (p=0.0336 in prevalent use) compared to nondiabetics.

Other observed differences include: females were more frequently prescribed bile acid sequestrants compared to males (p=0.0213 for prevalent use; p=0.0168 for new use), which could be a result of confounding by diabetes since the significant difference disappeared after restricting the analysis to diabetics or non-diabetics. Cardiologists prescribed bile acid sequestrants more frequently (p=0.0008 for new use) and prescribed fibrates less frequently (p=0.0092 for prevalent use) than
internists, and finally patients aged 65-69 were less frequently prescribed a bile acid sequestrant compared to other age groups (p=0.0006 in prevalent use).

The overall discontinuation rate for LLAs increased with time from 18.3% after 6 months of therapy, to 46.4% at 12 months, to 66.3% at 18 months.

Statin users had better persistence than non-statin users in the bivariate (p=0.0004) and multivariate (HR=0.536; CI=0.375-0.766; p=0.0006) models. In the bivariate models, males had better persistence than females (p=0.0078), and CHD patients had better persistence than non-CHD patients (p=0.0424), but no significant differences with regard to gender or CHD existed after controlling for covariates in the multivariate model. No significant differences existed with plan type in the bivariate model (p=0.3121) or multivariate model (HR= 0.877; CI=0.610-1.260; p=0.4777). Other variables, diabetes, other medications ≥3, age ≥70, were not significantly associated with persistence as well.

There was no significant association between the drug benefit plan option and statin type prescribed (OR=0.654; CI=0.376-1.139; p=0.1335) after controlling for potential confounders including gender, age ≥70, comorbidities (CHD, diabetes, hypertension), and physician prescriber specialty. There were no significant associations with other predictor variables as well.

In sum, research results generally indicate that the policy of drug benefit plan option initiated at the HMO among older adult members did not significantly influence the choice among or persistence to LLAs.
ACKNOWLEDGEMENTS

I dedicate this research to my husband, Hani, for his tireless support and endless devotion gave me the strength to pursue a dream. I thank my caring parents for always believing this was possible. I thank my committee members for their continuous input. Dr. Paul Larrat, my major professor, for his insight and guidance throughout this project and throughout my class-work. Dr. Stephen Kogut was of invaluable assistance in the preparation, analysis, and review of this research, and his input is gratefully acknowledged. I thank him for his enthusiasm and expertise. I thank Dr. Norman Campbell for his valued advice and good humor, and for helping me better understand the healthcare system. I thank Dr. Phillip Clark for giving me the benefit of his knowledge and insight. I thank Dr. Susan Andrade for her astute comments and suggestions that greatly improved this research. Finally, thanks to everyone who introduced me to the intriguing world of research.
PREFACE

This dissertation is organized using the manuscript format. Part 1 consists of three studies that form the main body of the dissertation. Part 2 contains the appendices, which provide details required by the University, but are not usually presented in a published paper.

Part 1 includes the following manuscripts:

Study 1: Drug benefit plans for elderly under managed care: A pharmacoepidemiologic assessment of lipid lowering medication use.

Study 2: Persistence of lipid lowering therapy: Influence of drug benefit plan option on time to discontinuation.

Study 3: Predictors of prescriber’s choice among three statins: Influence of drug benefit plan option.

Part 2 includes the following appendices:

Appendix A. Background and significance
Appendix B. Details of the Methods
Appendix C. Overview of major findings
Appendix D. Kaplan-Meier Survival curves and Log-log Kaplan-Meier survival curves
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PART 1

Part 1 includes the following manuscripts:

Study 1: Drug benefit plans for elderly under managed care: A pharmacoepidemiologic assessment of lipid-lowering medication use.

Study 2: Persistence of lipid-lowering therapy: Influence of drug benefit plan option on time to discontinuation.

Study 3: Predictors of prescriber’s choice among three statins: Influence of drug benefit plan option.
Drug benefit plans for the elderly under managed care: A pharmacoepidemiologic assessment of lipid-lowering medication use.

ABSTRACT:

Background High cholesterol is a major cause of Coronary Heart Disease (CHD). CHD is the leading cause of death in the United States. The beneficial effects of Lipid-lowering Agents (LLA) have been widely demonstrated in both primary and secondary prevention, and the choice among different LLAs is left to the prescriber.

Objective To describe LLA drug utilization patterns in a patient population of Medicare beneficiaries enrolled in managed care; and to determine if these patterns differ by patient characteristics including type of drug benefit plan option.

Methods Descriptive cross-sectional study of 1551 older adult members of an HMO in central Massachusetts who were prescribed LLAs during a 12-moth period. Drug use was categorized into five major classes: statin monotherapy, bile acid sequestrant monotherapy, fibrate monotherapy, niacin monotherapy, and combination therapy. We compared this utilization with different patient characteristics, including gender, age group, prescriber specialty, comorbidities (CHD, diabetes, hypertension), and choice of drug benefit plan option.
Chi-square analyses were used to assess differences in frequencies of the drug regimens utilized with various patient characteristics. This was carried out for both new and prevalent users during the one-year period.

**Results**

Statin monotherapy was the most frequently prescribed LLA in both prevalent (61.8%) and new users (65.5%). Combination therapy was the least prescribed regimen among both prevalent (1.6%) and new users (0.9%).

The type of drug benefit plan option was not significantly associated with any of the drug classes in prevalent or new users.

In prevalent LLA use, patients with CHD used statin monotherapy (p<0.0001) and combination therapy (p=0.0467) more frequently, but used bile acid sequestrants less frequently (p<0.0001) compared to patients without CHD. Diabetic patients used fibrates more frequently (p=0.0032), and used bile acid sequestrants (p=0.0007) and niacin (p=0.0336) less frequently compared to non-diabetics. Females were more frequently prescribed bile acid sequestrants compared to males (p=0.0213), but this difference no longer existed when the analysis was restricted to diabetics or non-diabetics only, indicating a confounding effect of diabetes. Cardiologists prescribed fibrates less frequently than internists and other specialties (p=0.0092), and patients aged 65-69 were less frequently prescribed a bile acid sequestrant compared to other age groups (p=0.0006).

In new LLA use, patients with CHD more frequently used statin monotherapy (p=0.0028). Diabetic patients used bile acid sequestrants less frequently than non-diabetics (p=0.0329). Females were more frequently prescribed bile acid sequestrants
compared to males (p=0.0168), a result that could be confounded by diabetes since the result no longer existed when we restricted the analysis to non-diabetics. The low number of new bile acid sequestrant users with diabetes prevented us from conducting a valid chi-square test among diabetics only. Finally, internal medicine physicians prescribed bile acid sequestrants less frequently than cardiologists and other specialties (p=0.0008).

**Conclusion**  Statins remain the most widely prescribed LLA. A very low rate of combination drug use was found, which can in part explain why many patients on LLAs do not reach their target cholesterol levels. This finding may perhaps help increase the use of combination therapy in the near future. The type of drug benefit plan option did not affect choice among LLAs, but comorbidities, mainly CHD and diabetes, seem to be among the main factors that influenced drug selection, possibly through affecting the lipid levels and lipid profile of these patients.
BACKGROUND

High cholesterol, specifically elevated low-density lipoprotein cholesterol (LDL-C), is a major cause of CHD [1-4], a link that was first made by the Framingham Heart Study [5]. Despite marked declines in mortality during this century [6-8], CHD continues to be the leading cause of death among the US population [9-11], and worldwide [10, 12]. Cardiovascular disease accounts for 950,000 deaths annually in the US including 460,000 from CHD [9]. In 1990, there were 489,171 deaths attributed to CHD [6], and 675,000 patients were discharged from US hospitals with a primary diagnosis of myocardial infarction [13]. Hospitalization for CHD continues to increase [7]. The prevalence of nonfatal CHD among US adults aged 40 and above is reported to be 11.8% [11]. It remains an important disease with significant burden. Estimated yearly costs of CHD for medical treatment and lost wages in the US range between $50 and $100 billion [2, 9, 14].

Twenty-eight percent of US adults over age 20 have hyperlipidemia that warrants treatment [15], based on the National Health and Nutrition Examination Survey (NHANES) III phase 2 data (collected from 1991-1994) and the 1993 National Cholesterol Education Program (NCEP) recommendations that were available at the time of the survey [2]. Since then, the guidelines have been updated in year 2001 [3], but our data coincides with the earlier guidelines [2].

Currently, the American Heart Association estimates that 70 million adults in the US have total cholesterol levels>200mg/dl, and that at least 40% of these individuals have cholesterol levels in excess of 240mg/dl [9,16].
Individuals aged 65 years and older constitute 12% of the US population [17, 18] yet they consume approximately 30% of the prescribed medications [17-19]. By the year 2015, it is estimated that there will be over 45 million individuals aged 65 or older, representing a 31% increase in this age group compared to the 2000 US Census [20]. The aging population, increased prevalence of diabetes and hypertension, and growing number of overweight Americans can explain the persistence of CHD as the leading cause of death [4]. Eighty-five percent of those who die from CHD are 65 years of age or older [9]. Therefore, CHD-related research in this rapidly growing age group is of extreme importance.

Currently, there are 4 major classes of LLAs in use: statins, bile-acid-binding resins, nicotinic acid, and fibrates [10]. Some of these drugs are also used to treat low high-density lipoproteins (HDL) as well [2, 3]. For convenience, the term LLA will be used to denote these drugs, as the majority of patients receive them for cholesterol lowering. The number of adults eligible for lipid-modifying therapy was recently increased in the NCEP Adult Treatment Panel (ATP) III guidelines [3] to more than 65 million [16], many of whom will require drug therapy to achieve target cholesterol levels goals [21].

Statin drugs have assumed a major role in the treatment of LDL-C elevations. They are reversible inhibitors of HMG-CoA reductase. By inhibiting the rate-limiting step in cholesterol biosynthesis, these drugs reduce intracellular cholesterol stores. Increased numbers of LDL receptors are then generated, thereby restoring intracellular cholesterol homeostasis and accelerating clearance of LDL-C from the plasma [22, 23].
The beneficial effect of using these drugs is well documented through five landmark trials showing reductions in cardiovascular events in a diversity of patient populations, representing the continuum of individuals at risk for CHD [24]. The Scandinavian Simvastatin Survival Study (4S) [25] demonstrated improved survival and fewer cardiovascular events in hyperlipidemic CHD patients. The Cholesterol and Recurrent Events (CARE) [26] and the Long-term Intervention with Pravastatin in Ischemic Disease (LIPID) [27] extended the benefits to CHD patients with average cholesterol levels. In patients without CHD, evidence of benefit is provided by high risk primary prevention in men without a history of myocardial infarction (MI) who were treated with pravastatin and diet in the West of Scotland Coronary Prevention Study (WOSCOPS) [28]. In addition, the beneficial effects were further demonstrated in low and moderate risk primary prevention in men and women with below average high density lipoprotein cholesterol (HDL-C) levels treated with lovastatin and diet in the Air Force Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TEXCAPS) [29] that extended these benefits to a substantial portion of the population.

Bile-acids-binding resins have been in clinical use for more than 30 years [30] and are now mainly utilized as adjuncts to statin therapy for patients for whom further lowering of cholesterol is indicated [10, 31]. They act by binding to bile acids in the intestine resulting in a compensatory increase in bile acid synthesis and an up-regulation of LDL-C receptors in hepatocytes [10, 30]. Available agents include cholestyramine and colestipol. They decrease LDL-C by 10-20% in doses of 5-10 mg twice daily [10, 32, 33].
Nicotinic acid is the oldest available LLA, used since the 1950s [30]. It acts by inhibiting mobilization of free fatty acids from peripheral tissues, thereby reducing hepatic synthesis of triglycerides (TG) and secretion of very-low-density-lipoproteins (VLDL) [10]. It is the most powerful agent for elevating HDL-C [30], and is effective in lowering TGs; thus it is helpful in management of mixed dyslipidemia [30]. Treatment with monotherapy has been shown to reduce fatal and nonfatal MI in secondary prevention [34] and the 15-year mortality rate [35]. It has been proven most effective in preventing CHD when given in combination with other drugs like bile acid binding resins [10, 36, 37] or fibrates [10, 38].

Fibrates include clofibrate, gemfibrozil, and fenofibrate [10]. They resemble, in part, a short chain of fatty acids and increase the oxidation of fatty acids in the liver, causing a decreased secretion of TG-rich lipoproteins, and in the muscles causing an increase in the lipoprotein lipase activity and uptake of fatty acids [10]. Fibrates are the most effective TG-lowering drugs [10, 30, 31], causing 25-40% reduction in TG [10]. Treatment with gemfibrozil was shown to reduce the frequency of heart disease in a 5-year placebo controlled study of patients with high VLDL and LDL-C concentrations in the primary prevention Helsinki Heart Study [39], and in a secondary prevention trial in men with low serum HDL [40]. Treatment with clofibrate produced similar results as well [41]. They are also useful in increasing HDL-C [42].

A meta-analysis by Gould et al [1] reinforced our understanding of the beneficial effects of all LLAs. It showed that the reduction of CHD and total mortality by LLAs could be explained by their lipid-lowering ability, and this reduction appears
to be directly proportional to the degree to which they lower lipids. The declines in CHD mortality this century [6-8] can be partially explained by the improvement in treatments and secondary prevention of MI [7].

In deciding the most appropriate approach to lipid-lowering therapy, prescribers are encouraged to use clinical judgment [2, 3, 31]. Therefore, the choice among LLAs is left to the prescriber. Even though patient characteristics may influence the choice of a certain agent, the prescriber’s preferences and experience can, to some extent, determine the type of drug prescribed. Furthermore, despite the availability of several studies assessing the lipid-lowering ability of various drug classes, the choice among various LLAs in a population of elderly patients has not been largely explored.

We examined the LLAs prescribed during a one-year period among a group Medicare beneficiaries with high cholesterol levels and enrolled in managed care. We compared this utilization with various patient characteristics including gender, age group, prescriber specialty, comorbidities (CHD, diabetes, hypertension), and choice of drug benefit plan option. This was carried out for both new and prevalent users during the one-year period. We hypothesized that significant differences in the prescribed LLAs mainly exist with comorbidities and age, and not with other factors including gender, type of drug benefit plan, and prescriber specialty. This was based on the risk factors of the ATP II guidelines [2] that were the standard of practice at the time of this research.
METHODS

Data Source and study population

The study population consisted of older adult members (Medicare beneficiaries) of a Health Maintenance Organization (HMO) operating in central Massachusetts, who were continuously enrolled in the plan during the period of July 1, 1993 – June 30, 1996, and were prescribed an LLA. These members were able to choose among 3 drug benefit options starting January 1, 1994: full coverage for prescription drugs, a maximum of $1000/year in coverage, or no drug coverage. Those selecting full coverage paid an additional premium of $72.50/month ($870/year). Those with a $1000 maximum coverage paid an additional $39.16/month ($469.92/year). Those without coverage paid no additional premium.

Information on demographic characteristics, drug benefit plan type, prescriptions, ambulatory visits, hospitalization, and diagnoses was available for this population cohort. The population study cohort was comprised of 2229 members. We deleted 325 (14.6%) members who switched from the original plan chosen on January 1, 1994, since we were unable to explore the effects of the type of drug benefit in these individuals. Of those, 251 (77.2%) switched from the full coverage plan, 61 (18.8%) from the $1000 maximum plan, and 13 (4.0%) from the no coverage plan. The final plans chosen by these patients were the full coverage plan in 89 patients (27.4%), the $1000 maximum plan in 186 (57.2%), and the no coverage plan in 50 (15.4%).

We then identified patients who had a prescription for an LLA during the one-year period between July 1, 1995 and June 30, 1996. Of 1904 patients, 1551 (81.5%) met the criteria, and were considered prevalent users of LLAs during the time period.
The first prescription during this one-year was considered for further evaluation in our analysis. New users were then defined as patients who did not have a prescription for the LLA during the one-year prior to the study period, between July 1, 1994 through June 30, 1995. This definition of new users has been previously used [43, 44]. Of 1551 patients, 345 (22.2%) met the criteria.

We determined the frequencies of the following regimens among both prevalent and new users: statins monotherapy, bile acid binding resins monotherapy, nicotinic acid monotherapy, fibrates monotherapy, and combination therapy of 2 or more LLAs. Combination therapy was defined as having prescriptions for 2 LLAs of 2 classes in the first or second month, and again in the third and fourth month. This definition was used to avoid misclassifying switching from one type of LLA to another as combination therapy.

For all patients we determined the gender, age, drug benefit plan type, physician prescriber specialty, and presence of comorbidities including CHD, diabetes and hypertension. Age was categorized into three groups: 65-69, 70-74, and 75 years or older, based on the frequency distribution of different age groups in this population cohort. The prescriber specialty was categorized as cardiology, internal medicine, or other. A patient was considered to have CHD if there was a CHD diagnosis (ICD-9 code= 410-414) prior to the LLA prescription or during the one year prior to the study period. Patients with a diabetes diagnosis (ICD-9 code=250) prior to the LLA prescription or during the one-year prior to the study date were labeled as diabetics. Finally, patients with a hypertension diagnosis (ICD-9 code= 401-405) prior to the
LLA prescription or during the one year prior to the study date were regarded as having hypertension.

Additional analyses

- A Chi-square test was performed separately for previous bile acid supplementation and for previous bile acid extraction.

Statistical analysis: All p-values were adjusted using the Bonferroni correction. p < 0.05 was considered statistically significant.
**Statistical analysis**

Descriptive statistics were used to determine the frequency of each regimen prescribed, overall and stratified by gender, age categories, presence of co-morbidities (diabetes, hypertension, or CHD), physician prescriber type, and the type drug benefit plan option.

Chi-square analyses were used to assess differences in frequencies of drug regimens utilized by gender, age group, type of drug benefit plan, prescriber specialty, and comorbidities categories. This was carried out separately for both prevalent and new users of various LLAs.

**Additional analyses**

A Chi-square test was conducted among diabetic and non-diabetic patients separately for prevalent and new bile acid sequestrant use by gender, as well as for prevalent bile acid sequestrant use by age group.

This test was conducted in different age groups separately for prevalent and new bile acid sequestrant use by gender.

Statistical analyses were performed using SAS for Windows version 8.01 with \( P<0.05 \) as the level of significance.
RESULTS

Descriptive statistics

A total of 1551 patients were continuously enrolled between July 1, 1993 and June 30, 1996, and prescribed an LLA during the one-year period between July 1, 1995 through June 30, 1996. The mean age of these patients was approximately 71 years of age, with 686 (44.2%) between 65 and 69 years of age, 555 (35.8%) between 70 and 74 years of age, and 310 (20.0%) 75 years or older. There were more female patients (n=946; 61.0%) than males (n=605; 39.0%) in our study population.

Most of these patients were covered by the full coverage drug benefit plan (n=1108; 71.4%), nearly a quarter of them by the partial coverage plan (n=410; 26.4%), and a small percentage by the no coverage drug benefit plan (n=33, 2.1%). Internal medicine physicians accounted for most of the prescriptions dispensed to these patients (n=1234; 79.8%), cardiologists for approximately 5% (n=77), other specialties for approximately 15% of the prescriptions (n=235), while we could not determine the specialty of 5 (0.3%) prescribers. Approximately half (52.3%) of patients had a CHD diagnosis prior to the LLA prescription (n=811), 28.4% had a diabetes diagnosis prior to the prescription (n=441), and most had a hypertension diagnosis prior to the prescription (n=1244; 80.2%). This information is presented in Table 1.

Out of 1551 prevalent users of LLAs, 345 (22.2%) were found to be newly prescribed during the one-year study period. The mean age of these patients was approximately 71 years of age, with 139 (40.3%) between 65 and 69 years of age, 133 (38.6%) between 70 and 74 years of age, and 73 (21.2%) 75 years or older. There
were slightly more female patients (n=187; 54.2%) than males (n=158; 45.8%) in this population.

Approximately 62% of the patients were covered by the full coverage drug benefit plan (n=213; 61.7%), nearly a third of them by the partial coverage plan (n=110; 31.9%), and a small percentage by the no coverage drug benefit plan (n=22, 6.4%). Internal medicine physicians accounted for most of the prescriptions given to these patients (n=260; 76.3%), cardiologists for 9.1% of the prescriptions (n=31), other specialties for approximately 15% of the prescriptions (n=50; 14.7%), while we could not determine the specialty of 4 (1.2%) prescribers. 62.0% of patients had a CHD diagnosis prior the LLA prescription (n=214), approximately a third had a diabetes diagnosis prior to the prescription (n=116, 33.6%), and most had a hypertension diagnosis prior to the prescription (n=279; 80.9%). These data are presented in Table 2.

**Drug regimens prescribed**

Statin monotherapy was the most frequently prescribed LLA in both prevalent (n=959; 61.8%) and new users (n=226; 65.5%). The next most frequently prescribed LLA was the bile acid sequestrant monotherapy in both the prevalent users (n=230; 14.8%) and new users (42; 12.2%). Among prevalent users fibrate monotherapy (n=205; 13.2%) and niacin monotherapy (n=132; 8.5%) were less common. This was also observed in new users, where niacin (n=39; 11.3%) and fibrates (n=35; 10.1%) utilization was similar. Combination therapy was the least prescribed regimen among both prevalent (n=25; 1.6%) and new users (n=3; 0.9%). These statistics are presented in Table 3.
Stratification by patient characteristics

Prevalent users

Table 4a summarizes the frequencies of various medication regimens stratified by gender, age group, drug coverage plan, LLA prescriber specialty, CHD diagnosis prior to prescription, diabetes diagnosis prior to prescription, and hypertension diagnosis prior to prescription, among prevalent users of LLA.

Among patients on statin monotherapy, those with a CHD diagnosis prior to the prescription were more frequently prescribed a statin compared to those without a CHD prior to the prescription (66.6% versus 56.6%, p<0.0001). No significant differences existed among statin users stratified by gender, age group, drug coverage plan, LLA prescriber specialty, diabetes diagnosis prior to prescription, and hypertension diagnosis prior to prescription. The probability values are summarized in Table 5a.

Cardiologists less frequently prescribed a fibrate monotherapy regimen compared to internal medicine physicians or other specialties (2.6% versus 13.3% and 16.2% respectively; p=0.0092). Patients with a diabetes diagnosis prior to the LLA prescription were more frequently prescribed a fibrate compared to those without a diabetes diagnosis prior to prescription (17.2% versus 11.6%; p=0.0032). No significant differences existed among fibrate users stratified by gender, age group, drug coverage plan, CHD diagnosis prior to prescription, and hypertension diagnosis prior to prescription. The probability values are summarized in Table 5b.

Examining patients using bile acid sequestrant monotherapy, we found that females more frequently received a bile acid sequestrant compared to males (16.5%
versus 12.2%; p=0.0213). When the analysis was conducted in different age groups separately, a significant difference still existed in age group 65-69 (p=0.0145). When the analysis was conducted in diabetic patients and non-diabetic patients separately, a significant difference between genders was not observed (p=0.4846 for diabetics; p=0.6238 for non-diabetics).

Patients in the 65-69 age group were less frequently prescribed a bile acid sequestrant compared to the 70-74 and above 75 age categories (10.9% versus 17.8% and 18.1% respectively; p=0.0006). This result was significant after conducting the analysis in non-diabetics only (p=0.0038), but was not significant in diabetics only (p=0.0710). Patients with a CHD diagnosis prior to prescription were less frequently prescribed a bile acid sequestrant compared to patients without a CHD diagnosis prior to the prescription (11.1% versus 18.9%; p<0.0001). Finally, patients with a diabetes diagnosis prior to the prescription were less frequently prescribed a bile acid sequestrant compared to patients with no diabetes diagnosis (10.0% versus 16.8%; p=0.0007). No significant differences existed among bile aid users stratified by drug coverage plan, prescriber specialty, and hypertension diagnosis prior to prescription or not. The probability values are summarized in Table 5c.

With patients prescribed niacin monotherapy, those with a diabetes diagnosis prior to the prescription were less frequently prescribed niacin compared to those without a diabetes diagnosis (6.1% versus 9.5%; p=0.0336). No significant differences existed among prevalent niacin users stratified by gender, age group, drug coverage plan, LLA prescriber specialty, CHD diagnosis prior to prescription, and hypertension diagnosis prior to prescription. The probability values are summarized in Table 5d.
As for combination therapy users, patients with a CHD diagnosis prior to the prescription were more frequently prescribed combination therapy compared to those without a CHD diagnosis (2.2% versus 1.0%; $p=0.0467$). A chi-square test for prescriber specialty would not be valid because of low cell counts, thus we did not conduct it. No significant differences existed among combination prevalent users stratified by gender, age group, drug coverage plan, diabetes diagnosis prior to prescription, and hypertension diagnosis prior to prescription. The probability values are summarized in Table 5e.

New Users

Table 4b summarizes the frequencies of various medication regimens stratified by gender, age group, drug coverage plan, LLA prescriber specialty, CHD diagnosis prior to prescription, diabetes diagnosis prior to prescription, and hypertension diagnosis prior to prescription, among new users of LLA.

Among patients prescribed statin monotherapy, those with a CHD diagnosis prior to the prescription were more frequently prescribed a statin compared to those without a CHD prior to the prescription (71.5% versus 55.7%, $p=0.0028$). No significant differences existed among statin users stratified by gender, age group, drug coverage plan, LLA prescriber specialty, diabetes diagnosis prior to prescription, and hypertension diagnosis prior to prescription. The probability values are summarized in Table 5a.

With fibrate monotherapy users, no significant differences existed when stratified by gender, age group, drug coverage plan, physician prescriber, CHD
diagnosis prior to prescription, diabetes diagnosis prior to prescription, and hypertension diagnosis prior to prescription. The probability values are summarized in Table 5b.

Examining patients on bile acid sequestrant monotherapy, females more frequently received a bile acid sequestrant compared to males (16.0% versus 7.6%; p=0.0168). When the analysis was conducted in different age groups separately, a significant difference was observed in the 70-74 age group (p=0.0298), and we could not conduct a valid chi-square in the 75+ age group because of low cell counts. When the analysis was conducted in non-diabetic patients separately, a significant difference was not observed (p=0.3687). We did not conduct a chi-square test among diabetics because of low cell counts.

Internal medicine physicians prescribed bile acids less frequently than cardiologists and other specialties (8.1% versus 22.6% and 24.00% respectively; p=0.0008).

Finally, patients with a diabetes diagnosis prior to the prescription were less frequently prescribed a bile acid sequestrant compared to patients with no diabetes diagnosis (6.9% versus 14.9%; p=0.0329). No significant differences existed among bile acid sequestrant users stratified by age group, drug coverage plan, CHD diagnosis prior to prescription, and hypertension diagnosis prior to prescription. The probability values are summarized in Table 5c.

Among patients using niacin monotherapy, no significant differences existed when stratified by gender, age group, drug coverage plan, physician prescriber, CHD diagnosis prior to prescription, diabetes diagnosis prior to prescription, and
hypertension diagnosis prior to prescription. The probability values are summarized in Table 5d.

There were only 3 new users for combination therapy, thus we were not able to conduct a valid chi-square test because of low cell counts.
DISCUSSION

Insurance claims data are increasingly being used in pharmacoepidemiologic research. Automated databases have been used to assess prescribing patterns [45-47], impact of policies [48], and drug adherence [43, 44, 49-52]. They provide a cost-effective alternative to post-marketing clinical trials in a real world setting [53, 54]. Such databases provide a good source for describing drug use in the population, and for comparing patterns of use in subpopulations. Furthermore, data from the same HMO used in this investigation has been successfully used in previous research [48, 50].

The study population of both prevalent and new users had a high prevalence of CHD (52.3% in prevalent users, 62.0% in new users), diabetes (28.4% in prevalent users, 33.6% in new users), and hypertension (80.2% in prevalent users, 80.9% in new users) compared to the reported prevalences in the general population [11, 55, 56], which is understandable considering it is a population of older adults being treated for hypercholesterolemia. The fact that most patients also chose the full coverage benefit plan (71.4% in prevalent users, 61.7% in new users) can be explained by higher drug use in this age group compared to younger patients [17, 18].

Among all specialties, internists, family and general practice physicians, and cardiologists have been reported to be the most frequent prescribers of LLAs [57]. Family care physicians and general practice physicians are included in our others category. Another important specialty included in the others category is endocrinology, because of the increased risk of cardiovascular complications among diabetics [58].
Internists are reported to have more patients on LLAs compared to cardiologists and family physicians [59, 60], and general practice physicians are more likely to initiate therapy at a higher LDL-C compared to cardiologists and internists [61]. We found that most prescriptions (79.8% in prevalent users and 76.3% in new users) were written by internists, which is consistent with previous research [59, 60].

**Frequency of drug regimens prescribed**

Statin drugs were the most prescribed regimen in this patient population among both prevalent (61.83=%) and new (65.51=%) users. Among different LLAs, statins have been shown to be the most widely prescribed [30, 31, 60, 62, 63]. They are recommended as first line agents when drugs are indicated to achieve treatment goals [3, 31, 64, 65]. They are the most effective in LDL-C lowering, and the best tolerated among LLAs [30, 64, 65]. The use of statin as a proportion of LLAs in the US retail pharmacies increased from 47% in 1991 to 78% in 1997 [66], and accounted for 70% of the LLA prescriptions in Finland in 1993. The market share of fibrate derivatives and nicotinic acid declined at the same period [60, 66]. The poor tolerability of other agents including bile acid sequestrants, nicotinic acid, and fibrates, limits adherence and explains the relative lower rates of these drugs in this patient population [31].

Combination therapy, on the other hand, was the least prescribed regimen among both prevalent (1.6%) and new (0.9%) users of LLAs, despite the fact that combination therapy is safe, effective, and well tolerated [21, 67]. This is consistent with what has been reported in previous research; surveys show that only a few
patients are receiving combination therapy [21]. Hyperlipidemia is generally under-treated, and less than 45% of patients who qualify for therapy receive it [68]. Only 38% of those who receive therapy achieve their target LDL-C goals [69]. Elderly patients fail to receive indicated lipid-lowering medications as often as 80% of the time [70, 71] and even fewer achieve their target cholesterol levels [71, 72]. The ATPII guidelines [2] recommend switching to another drug or a combination of two drugs if LDL-C targets are not achieved. The combination of 2 low dose drugs can achieve lipid reductions that exceed those observed with high dose monotherapy [21, 73], since the combination employs two different classes with complimentary mechanisms of action to give an additive effect [21] or possibly a synergistic one [67]. Some combinations may prove to be better tolerated than high-dose monotherapy with statins, because they allow the reduction of the dose and a favorable side effect profile [21]. There could also be a cost benefit as well, since the combination may cost less than the high-dose monotherapy. The low rate of combination therapy observed can partly explain why so many patients fail to achieve their target cholesterol levels [71, 72], and thus are not getting the intended benefit of their therapy.

We compared the frequency of drug regimen prescribed among various patient characteristics including gender; age group, prescriber specialty, comorbidities (CHD, diabetes, hypertension), and choice of drug benefit plan option.

The type of drug benefit plan was not associated with any of the drug classes in prevalent or new users of LLAs. Therefore, it was not among the factors affecting the choice among various agents, consistent with what we had hypothesized.
Among patients receiving statin monotherapy, those with a CHD diagnosis prior to the prescription were more frequently prescribed a statin compared to those without a CHD diagnosis prior to the prescription in both prevalent (66.6% versus 56.6%, p<0.0001) and new (71.5% versus 55.7%, p=0.0028) users. According to ATPIII guidelines that were available at the time of this study [2], and the more recent ATPIII guidelines [3], CHD places patients in the high-risk group with a lower target LDL-C of 100mg/dl. Statins are the most effective in LDL-C lowering, and the best tolerated among LLAs [30, 64], thus we would expect these drugs to be the most prescribed in this high-risk patient group.

In prevalent patients prescribed fibrate monotherapy, those with a diabetes diagnosis prior to the LLA prescription were more frequently prescribed a fibrate compared to those without a diabetes diagnosis prior to prescription (17.2% versus 11.6%; p=0.0032). Atherosclerosis accounts for more than 80% of all mortality caused by diabetes and for most hospitalizations necessitated by diabetic complications, and the cardiovascular risk of a diabetic patient is 2-3 fold higher than a non-diabetic individual [58]. Furthermore, the lipid profile of diabetics is generally different from a non-diabetic [58]. Approximately 90% of diabetic patients have type II diabetes [74], and the lipid profile in these patients is characterized by elevated plasma triglycerides [58, 74, 75] and reduced HDL-C [74, 75], although the total cholesterol and LDL-C levels are similar to a non-diabetic [58].

Several studies in lipid modifying therapy have included sufficient numbers of type II diabetics to be able to conclude that, as in non-diabetics, treatment of lipid abnormalities reduces the risk of future coronary risk [27, 76-78]. Fibrates have been
shown to be effective in diabetic patients [27, 76-78], since they are the most effective triglyceride lowering drugs [10, 30, 31], causing 25-40% reduction in triglycerides [10, 42] and are useful for increasing HDL-C [42], consistent with the lipid profile of diabetics. When triglycerides are high, the ATPII [2] guidelines also recommend that the choice of drug is preferably one that lowers triglycerides. This could explain the increased used of fibrates in diabetics compared to non-diabetics. Among patients who were newly prescribed a fibrate, the trend was the same with more frequent fibrate use among diabetics (12.1%) compared to non-diabetics (9.2%). However, this did not reach statistical significance in our study, possibly because of the lower number of patients.

Cardiologists less frequently prescribed a fibrate compared to internal medicine physicians or other specialties (2.6% versus 13.3% and 16.2% respectively; p=0.0092). A possible explanation for this could be the type of patients seen by these different specialties. Diabetics mainly visit endocrinologists, who are in the others category, or by internists, and not by cardiologists.

For patients using bile acid sequestrant monotherapy, females more frequently received a bile acid sequestrant compared to males in both prevalent (16.5% versus 12.2%; p=0.0213) and new (16.0% versus 7.6%; p=0.0168) users. We believed that this could be due to the confounding effect of other factors like diabetes, since a slightly higher prevalence of diabetes in men over 60 has been reported, even though the prevalence in men and women is similar in other age groups [56]. Bile acid sequestrants have a tendency to raise triglycerides; thus, they are useful for patients with high LDL-C and normal triglycerides [10]. The lipid profile in diabetic patient
profile is characterized by elevated plasma triglycerides [58, 74, 75]. Other possible explanations include increased body weight, since the percentage of men who are reported to be overweight (63%) is higher than the percentage women (55%) [79], and higher Body Mass Indices (BMI) have been associated with higher triglyceride levels [80], where bile acid sequestrants are avoided [58, 74, 75]; and age, since the onset of elevated cholesterol levels occurs in women and men at different ages and with different severity [63]. We explored the effects of age by restricting the analysis into 3 different age groups, but a significant difference still existed in some age groups. When we restricted the analysis to diabetics only or non-diabetics only, the gender differences no longer existed, indicating a confounding effect of diabetes. We could not investigate the effects of body weight because of the unavailability of such information in the dataset.

Patients in the 65-69 age group were less frequently prescribed a bile acid sequestrant compared to the 70-74 and above 75 age categories (10.9% versus 17.8% and 18.1% respectively; p=0.0006). We could not find an explanation for this; it could be related to the reported decreased prevalence of diabetes after the age of 75 [81], but the significant difference still existed when restricting the analysis to non-diabetics. This result could be due to other factors, such as differences in the body weights of these patients, which we could not explore. This effect was not observed among the new users of these agents.

Patients with a CHD diagnosis prior to prescription were less frequently prescribed a bile acid sequestrant compared to patients without a CHD diagnosis prior to the prescription among prevalent users (11.1% versus 18.9%; p<0.0001), possibly
related to the their poor tolerability and inconvenient dosing that make adherence
difficult [31]. Thus, more effective agents might be preferred in this high-risk group.
The same trend was observed in new users, but did not reach statistical significance.

Patients with a diabetes diagnosis prior to the prescription were less frequently
prescribed a bile acid sequestrant compared to patients with no diabetes diagnosis in
prevalent (10.0% versus 16.8%; p=0.0007) and new users (6.9% versus 14.9%;
p=0.0329). This result was expected, since bile acid sequestrants are usually avoided
in diabetics because of their tendency to raise triglycerides [10], and the ATPII
guidelines recommend that the choice of drug is preferably one that lowers
triglycerides when they are high [2].

We could not explain why internal medicine physicians prescribed bile acids
less frequently than cardiologists and other specialties in new users (8.1% versus
22.6% and 24.0% respectively; p=0.0008). Our findings could be related to the type of
patients seen by these physicians; diabetics are not usually seen by cardiologists, thus
we would observe more prescriptions by this subspecialty. This effect was not
observed in prevalent users.

In members prevalently using a niacin monotherapy regimen, patients with a
diabetes diagnosis prior to the prescription were less frequently prescribed niacin
compared to those without a diabetes diagnosis (6.1% versus 9.5%; p=0.0336). The
same trend was observed but did not reach statistical significance in the new users.
Niacin has a propensity to worsen the control of blood sugar [82, 83] and should be
used in caution with diabetic patients [83], thus the result is understandable.
As for prevalent combination therapy users, patients with a CHD diagnosis prior to the prescription were more frequently prescribed combination therapy compared to those without a CHD diagnosis (2.2% versus 1.0%; \( p=0.0467 \)). This is to be expected, considering the 100mg/dl target LDL-C set by the ATPII guidelines [2] that were the standard of practice at the time of this study, and ATPIII guidelines [3] for these high-risk patients. The ATPII guidelines [2] recommend switching to another drug or a combination of two drugs if LDL-C targets are not achieved after 3 months of therapy. They also state that most LLAs can be used in combination, but a statin plus fibrate (and possibly a statin plus nicotinic acid) carries an increased risk of myopathy. Combination therapy is generally safe, effective, well-tolerated, and can achieve lipid reductions that exceed those observed with high dose monotherapy, since the combination employs two different classes with complimentary mechanisms of action to give an additive effect [21]. The low rate of combination therapy in this patient population, however, is noted.

LIMITATIONS

Several limitations to this study can be described. Regarding the dataset used, patients may fill their prescriptions from pharmacies outside the HMO network and thus will not be captured. This, however, is unlikely, since the drugs were provided at discounted prices for patients in these pharmacies, and the assumption that patients fill most of prescriptions within the pharmacy system under study has been confirmed in one HMO and 2 Veterans Affairs (VA) Medical Centers [84]. One study that tried to assess medication use outside the central pharmacy of the VA through a questionnaire
found that 98.5% of patients reported using the central pharmacy as their only source of medication [51]. Even though the unique characteristics of the population studied may somewhat limit generalizability of results, administrative databases provide a cost-effective alternative to post marketing clinical trials in a real world setting [53, 54].

Other limitations include lack of comprehensive clinical data including lipid levels, lack of information regarding family history of CHD and smoking status (which are risk factors for CHD), in addition to weight, diet and exercise that may in turn affect lipid profiles and levels of patients. Availability of lipid levels and profiles would have confirmed some of the study conclusions. Misclassification of patients with regard to various diagnoses is also a possibility. In prevalent use, we cannot tell if the patients were switched from a previous medication due to side effects, even though assessing new users somewhat limits this problem. We also do not know how many internists versus sub-specialists are employed within the HMO. The data is relatively old, but it provides a unique opportunity to study the effect of drug benefit plan options and to compare changes in practice with the publication of recent guidelines in a 'real world' setting.
CONCLUSION

Automated data from an HMO was used to describe LLA use in a large population of Medicare beneficiaries under managed care. Several important findings are noted. First, statins remain the most widely prescribed LLA. Second, a very low rate of combination drug use was found, which may, in part, explain why so many patients on LLAs do not reach their target cholesterol levels. This finding may help to increase the use of combination therapy, shown to be safe and effective, in the near future. Third, while the type of drug benefit plan option did not affect the choice among LLAs, comorbidities -mainly CHD and diabetes- seem to be among the main factors that influence drug selection, possibly through affecting the lipid levels, in accordance with ATPIII guidelines that were the standard of practice at the time of this study. Patients with CHD were more frequently prescribed statin monotherapy and combination therapy and less frequently prescribed bile acid sequestrants. Diabetic patients used fibrates more frequently, and bile acid sequestrants and niacin less frequently compared to non-diabetics.

Other observed differences include: females were more frequently prescribed bile acid sequestrants compared to males, a difference that disappeared when controlling for diabetes. Cardiologists prescribed bile acid more frequently and prescribed fibrates less frequently than internists; and finally, patients aged 65-69 were less likely to be prescribed a bile acid sequestrant compared to other age groups.

These differences may have been in part related to the patient lipid profile as a result of comorbidities among other factors like body weight. Further research that includes lipid levels is required to investigate such findings.
Table 1 Characteristics of prevalent users of lipid-lowering agents in an elderly population enrolled in a Medicare managed care health plan (n=1551)

| Characteristic                                      | N     | %     |
|-----------------------------------------------------|-------|-------|
| **Gender**                                          |       |       |
| Females                                             | 946   | (61.0%) |
| Males                                               | 605   | (39.0%) |
| **Age groups**                                      |       |       |
| 65-69                                               | 686   | (44.2%) |
| 70-74                                               | 555   | (35.8%) |
| 75+                                                 | 310   | (20.0%) |
| **Plan type**                                       |       |       |
| No coverage                                         | 33    | (2.10%) |
| $1000 max                                           | 410   | (26.4%) |
| Full coverage                                       | 1108  | (71.4%) |
| **Presciber specialty**                             |       |       |
| Cardiology                                          | 77    | (5.00%) |
| Internal medicine                                   | 1234  | (79.8%) |
| Others                                              | 235   | (15.2%) |
| Missing                                             | 5     | (0.30%) |
| **CHD diagnosis prior to prescription**             |       |       |
| CHD diagnosis                                       | 811   | (52.3%) |
| No CHD diagnosis                                    | 740   | (47.7%) |
| **Diabetes diagnosis prior to prescription**        |       |       |
| DM diagnosis                                        | 441   | (28.4%) |
| No DM diagnosis                                     | 1110  | (71.6%) |
| **Hypertension diagnosis prior to prescription**   |       |       |
| HTN diagnosis                                       | 1244  | (80.2%) |
| No HTN diagnosis                                    | 307   | (19.8%) |

SD = Standard Deviation, CHD = Coronary Heart Disease, HTN = Hypertension, DM = Diabetes
Table 2 Characteristics of new users of lipid-lowering agents in an elderly population enrolled in a Medicare managed care health plan (n=345)

| Characteristic                          | N     | %     |
|-----------------------------------------|-------|-------|
| Gender                                  |       |       |
| Females                                 | 187   | (54.2%)|
| Males                                   | 158   | (45.8%)|
| Age groups                              |       |       |
| 65-69                                   | 139   | (40.3%)|
| Mean age= 71.1 SD=4.5                   |       |       |
| 70-74                                   | 133   | (38.5%)|
| 75+                                     | 73    | (21.2%)|
| Plan type                               |       |       |
| No coverage                             | 22    | (6.40%)|
| $1000 max                               | 110   | (31.9%)|
| Full coverage                           | 213   | (61.8%)|
| Prescriber specialty                    |       |       |
| Cardiology                              | 31    | (9.10%)|
| Internal medicine                       | 260   | (76.3%)|
| Others                                  | 50    | (14.7%)|
| Missing                                 | 4     | (1.20%)|
| CHD diagnosis prior to prescription     |       |       |
| CHD diagnosis                           | 214   | (62.0%)|
| No CHD diagnosis                        | 131   | (38.0%)|
| Diabetes diagnosis prior to prescription|       |       |
| DM diagnosis                            | 116   | (33.6%)|
| No DM diagnosis                         | 229   | (66.4%)|
| Hypertension diagnosis prior to prescription|     |       |
| HTN diagnosis                           | 279   | (80.9%)|
| No HTN diagnosis                        | 66    | (19.1%)|

SD=Standard Deviation, CHD=Coronary Heart Disease, HTN=Hypertension, DM=Diabetes
Table 3 Frequencies and percentages of different lipid-lowering agent drug groups for both prevalent and new users of lipid-lowering agents in an elderly population enrolled in a Medicare managed care health plan

| Drug group              | Prevalent users | New users |
|-------------------------|-----------------|-----------|
|                         | n               | %         | n        | %         |
| Statin                  | 959             | (61.8%)   | 226      | (65.5%)   |
| Niacin                  | 132             | (8.50%)   | 39       | (11.3%)   |
| Fibrate                 | 205             | (13.2%)   | 35       | (10.1%)   |
| Bile acid Sequestrant   | 230             | (14.8%)   | 42       | (12.2%)   |
| Combination             | 25              | (1.60%)   | 3        | (0.90%)   |
| Total                   | 1551            | (100%)    | 345      | (100%)    |
Table 4a Results of stratification of prevalent users of lipid-lowering agents in an elderly population enrolled in a Medicare managed care health plan with patient characteristics (n=1551)

|          | Statin N=959 (61.8%) | Fibrate N=205 (13.2%) | Bile N=230 (14.8%) | Niacin N=132 (8.5%) | Combin N=25 (1.6%) | Total N=1551 (100%) |
|----------|----------------------|-----------------------|---------------------|---------------------|-------------------|---------------------|
| **Gender** |                      |                       |                     |                     |                   |                     |
| Female %  | 585 (61.8%)          | 114 (12.1%)           | 156 (16.5%)         | 77 (8.1%)           | 14 (1.5%)         | 946 (100%)          |
| Male %    | 374 (61.8%)          | 91 (15.0%)            | 74 (12.2%)          | 55 (9.1%)           | 11 (1.8%)         | 605 (100%)          |
| **Age group** |                      |                       |                     |                     |                   |                     |
| 65-69 %  | 446 (65.0%)          | 89 (13.0%)            | 75 (10.9%)          | 65 (9.5%)           | 11 (1.6%)         | 686 (100%)          |
| 70-74 %  | 328 (59.1%)          | 76 (13.7%)            | 99 (17.8%)          | 40 (7.2%)           | 12 (2.2%)         | 555 (100%)          |
| 75+ %    | 185 (59.7%)          | 40 (12.9%)            | 56 (18.1%)          | 27 (8.7%)           | 2 (0.7%)          | 310 (100%)          |
| **Drug benefit plan** |              |                       |                     |                     |                   |                     |
| Full %   | 704 (63.5%)          | 134 (12.1%)           | 159 (14.4%)         | 91 (8.2%)           | 20 (1.8%)         | 1108 (100%)         |
| $1000 max % | 235 (57.3%)          | 67 (16.3%)            | 68 (16.6%)          | 35 (8.5%)           | 5 (1.2%)          | 410 (100%)          |
| No benefit % | 20 (60.6%)           | 4 (12.1%)             | 3 (9.1%)            | 6 (18.2%)           | 0 (0.0%)          | 33 (100%)           |
| Prescriber Specialty | Statin N=959 (61.8%) | Fibrate N=205 (13.2%) | Bile N=230 (14.8%) | Niacin N=132 (8.5%) | Combin N=25 (1.6%) | Total N=1551 (100%) |
|----------------------|----------------------|-----------------------|---------------------|---------------------|-------------------|--------------------|
| Cardiology %         | 54 (70.1%)           | 2 (2.6%)              | 13 (16.9%)          | 6 (7.8%)            | 2 (2.6%)          | 77 (100%)          |
| Internal medicine %  | 768 (62.2%)          | 164 (13.3%)           | 175 (14.2%)         | 105 (8.5%)          | 22 (1.8%)         | 1234 (100%)        |
| Others %             | 136 (57.9%)          | 38 (16.2%)            | 40 (17.0%)          | 20 (8.5%)           | 1 (0.4%)          | 235 (100%)         |
| CHD *** p<0.0001     |                      |                       |                     |                     |                   |                    |
| No CHD %             | 419 (56.6%)          | 107 (14.5%)           | 140 (18.9%)         | 67 (9.0%)           | 7 (1.0%)          | 740 (100%)         |
| CHD %                | 540 (66.6%)          | 98 (12.1%)            | 90 (11.1%)          | 65 (8.0%)           | 18 (2.2%)         | 811 (100%)         |
| Diabetes *** p=0.0032 |                      |                       |                     |                     |                   |                    |
| No diabetes %        | 672 (60.5%)          | 129 (11.6%)           | 186 (16.8%)         | 105 (9.5%)          | 18 (1.6%)         | 1110 (100%)        |
| diabetes %           | 287 (65.1%)          | 76 (17.2%)            | 44 (10.0%)          | 27 (6.1%)           | 7 (1.6%)          | 441 (100%)         |
| Hypertension #       |                      |                       |                     |                     |                   |                    |
| No hypertension %    | 184 (59.9%)          | 43 (14.0%)            | 51 (16.6%)          | 24 (7.8%)           | 5 (1.6%)          | 307 (100%)         |
| hypertension %       | 775 (62.3%)          | 162 (13.0%)           | 179 (14.4%)         | 108 (8.7%)          | 20 (1.6%)         | 1244 (100%)        |

CHD=Coronary Heart Disease, Bile=Bile acid sequestrant, Combin=Combination therapy  
P=probability, ***=p<0.005, significant
Table 4b Results of stratification of new users of lipid-lowering agents in an elderly population enrolled in a Medicare managed care health plan with patient characteristics (n=345)

|                | Statins N\=226 (65.5\%) | Fibrates N\=35 (10.1\%) | Bile N\=42 (12.2\%) | Niacin N\=39 (11.3\%) | Combin (N=3) (0.9\%) | Total N\=345 (100\%) |
|----------------|--------------------------|--------------------------|---------------------|-----------------------|---------------------|----------------------|
| Gender         |                          |                          |                     |                       |                     |                      |
| Female %       | 117 (62.6\%)             | 15 (8.0\%)               | 30 (16.0\%)         | 23 (12.0\%)           | 2 (1.0\%)           | 187 (100\%)          |
| Male %         | 109 (69.0\%)             | 20 (12.7\%)              | 12 (7.6\%)          | 16 (10.1\%)           | 1 (0.6\%)           | 158 (100\%)          |
|                |                          |                          |                     |                       |                     |                      |
| Age group      |                          |                          |                     |                       |                     |                      |
| Age 65-69 \%  | 92 (66.2\%)              | 14 (10.1\%)              | 13 (9.4\%)          | 20 (14.4\%)           | 0 (0.00\%)          | 139 (100\%)          |
| Age 70-74 \%  | 86 (64.7\%)              | 12 (9.0\%)               | 17 (12.8\%)         | 15 (11.3\%)           | 3 (2.3\%)           | 133 (100\%)          |
| Age 75+ \%    | 48 (65.8\%)              | 9 (12.3\%)               | 12 (16.4\%)         | 4 (5.5\%)             | 0 (0.00\%)          | 73 (100\%)           |
|                |                          |                          |                     |                       |                     |                      |
| Drug Coverage  |                          |                          |                     |                       |                     |                      |
| Full \%       | 138 (64.8\%)             | 22 (10.3\%)              | 24 (11.3\%)         | 26 (12.2\%)           | 3 (1.4\%)           | 213 (100\%)          |
| $1000 max \%  | 73 (66.4\%)              | 11 (10.0\%)              | 15 (13.6\%)         | 11 (10.0\%)           | 0 (0.0\%)           | 110 (100\%)          |
| No benefit \% | 15 (68.2\%)              | 2 (9.0\%)                | 3 (13.6\%)          | 2 (9.1\%)             | 0 (0.00\%)          | 22 (100\%)           |

p=0.0168
| Prescriber specialty | Statins N=226 (65.5%) | Fibrates N=35 (10.1%) | Bile N=42 (12.2%) | Niacin N=39 (11.3%) | Combin (N=3) (0.9%) | Total N=345 (100%) | Missing (n=4) |
|----------------------|-----------------------|-----------------------|-------------------|---------------------|---------------------|---------------------|-----------------|
| Cardiology %         | 21 (67.7%)            | 1 (3.2%)              | 7 (22.6%)         | 2 (6.5%)            | 0 (0.0%)            | 31 (0.0%)          |
| Internal %           | 175 (67.3%)           | 27 (10.4%)            | 21 (8.1%)         | 34 (13.1%)          | 3 (1.2%)            | 260 (100%)        |
| Others %             | 29 (58.0%)            | 7 (14.0%)             | 12 (24.0%)        | 2 (4.0%)            | 0 (0.0%)            | 50 (100%)          |
| CHD *** p=0.00028    |                       |                       |                   |                     |                     |                    |
| No CHD %             | 73 (55.7%)            | 18 (13.7%)            | 19 (14.5%)        | 19 (14.5%)          | 2 (1.5%)            | 131 (100%)        |
| CHD diagnosis %      | 153 (71.5%)           | 17 (7.9%)             | 23 (10.8%)        | 20 (9.4%)           | 1 (0.5%)            | 214 (100%)        |
| Diabetes *** p=0.0329|                       |                       |                   |                     |                     |                    |
| No diabetes %        | 143 (62.5%)           | 21 (9.2%)             | 34 (14.9%)        | 29 (12.7%)          | 2 (0.9%)            | 229 (100%)        |
| Diabetes %           | 83 (71.6%)            | 14 (12.1%)            | 8 (6.9%)          | 10 (8.6%)           | 1 (0.9%)            | 116 (100%)        |
| Hypertension         |                       |                       |                   |                     |                     |                    |
| No Hypertension %    | 44 (66.7%)            | 7 (10.6%)             | 9 (13.6%)         | 5 (7.6%)            | 1 (1.5%)            | 66 (100%)          |
| Hypertension %       | 182 (65.2%)           | 28 (10.0%)            | 33 (11.8%)        | 34 (12.2%)          | 2 (0.7%)            | 279 (100%)        |

CHD=Coronary Heart Disease, Bile=Bile acid sequestrant, Combin=Combination therapy
P=probability, ***=p<005, significant
Table 5a Summary of p-values for statin users in an elderly population enrolled in a Medicare managed care health plan stratified by patient characteristics (prevalent users n=959, new users n=226)

| Stratification variable | Prevalent user p-value | New user p-value |
|-------------------------|------------------------|------------------|
| Gender                  | 0.9933                 | 0.2113           |
| Age group               | 0.0703                 | 0.9644           |
| Plan type               | 0.0851                 | 0.9259           |
| Prescriber specialty    | 0.1432                 | 0.4348           |
| CHD diagnosis           | <0.0001*               | 0.0028*          |
| DM diagnosis            | 0.0970                 | 0.0928           |
| HTN diagnosis           | 0.4451                 | 0.8256           |

*p<0.05=significant, CHD=Coronary Heart Disease, DM=Diabetes, HTN=Hypertension

Table 5b Summary of p-values for fibrate users in an elderly population enrolled in a Medicare managed care health plan stratified by patient characteristics (prevalent users n=205, new users n=35)

| Stratification variable | Prevalent user p-value | New user p-value |
|-------------------------|------------------------|------------------|
| Gender                  | 0.0898                 | 0.1552           |
| Age group               | 0.9176                 | 0.7533           |
| Plan type               | 0.0934                 | 0.9816           |
| Prescriber specialty    | 0.0092*                | 0.2968           |
| CHD diagnosis           | 0.1677                 | 0.0835           |
| DM diagnosis            | 0.0032*                | 0.3995           |
| HTN diagnosis           | 0.6485                 | 0.8903           |

*p<0.05=significant, CHD=Coronary Heart Disease, DM=Diabetes, HTN=Hypertension
Table 5c Summary of p-values for bile acid binding resins users in an elderly population enrolled in a Medicare managed care health plan stratified by patient characteristics (prevalent users n=230, new users n=42)

| Stratification variable | Prevalent user p-value | New user p-value |
|-------------------------|------------------------|-----------------|
| Gender                  | 0.0213*                | 0.0168*         |
| Age group               | 0.0006*                | 0.3131          |
| Plan type               | 0.3565                 | 0.8075          |
| Prescriber specialty    | 0.4584                 | 0.0008*         |
| CHD diagnosis           | <0.0001*               | 0.3004          |
| DM diagnosis            | 0.0007*                | 0.0329*         |
| HTN diagnosis           | 0.3263                 | 0.6862          |

*p<0.05=significant, CHD=Coronary Heart Disease, DM=Diabetes, HTN=Hypertension

Table 5d Summary of p-values for niacin users in an elderly population enrolled in a Medicare managed care health plan stratified by patient characteristics (prevalent users n=132, new users n=39)

| Stratification variable | Prevalent user p-value | New user p-value |
|-------------------------|------------------------|-----------------|
| Gender                  | 0.5125                 | 0.5254          |
| Age group               | 0.3594                 | 0.1504          |
| Plan type               | 0.1293                 | 0.7917          |
| Prescriber specialty    | 0.9760                 | 0.1196          |
| CHD diagnosis           | 0.4638                 | 0.1420          |
| DM diagnosis            | 0.0336*                | 0.2625          |
| HTN diagnosis           | 0.6270                 | 0.2874          |

*p<0.05=significant, CHD=Coronary Heart Disease, DM=Diabetes, HTN=Hypertension
Table 5e Summary of p-values for combination therapy users in an elderly population enrolled in a Medicare managed care health plan stratified by patient characteristics (prevalent users n=25, new users n=3)

| Stratification variable | Prevalent user p-value | New user p-value |
|-------------------------|------------------------|------------------|
| Gender                  | 0.6059                 | NA**             |
| Age group               | 0.2361                 | NA**             |
| Plan type               | 0.5490                 | NA**             |
| Prescriber specialty    | NA**                   | NA**             |
| CHD diagnosis           | 0.0467*                | NA**             |
| DM diagnosis            | 0.9614                 | NA**             |
| HTN diagnosis           | NA**                   | NA**             |

*p<0.05=significant, CHD=Coronary Heart Disease, DM=Diabetes, HTN=Hypertension
**NA=Chi-Square test not accurate because 25% of cells or more have expected counts less than five.
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Persistence of lipid-lowering therapy: Influence of drug benefit plan options on time to discontinuation.

ABSTRACT

Background Many health maintenance organizations (HMOs) have implemented programs providing varying degrees of annual drug coverage for Medicare beneficiaries enrolled in their plans. The unintended effects of such policies are important to consider. Several studies have documented the beneficial effects of lipid-lowering agents (LLA), but long-term persistence to therapy is crucial to achieve this benefit.

Objective To determine the effect of drug plan benefit options among elderly patients enrolled in managed care on persistence to LLAs controlling for potential confounders.

Methods A retrospective cohort study using 322 older adult members in an HMO operating in Massachusetts who were prescribed an LLA between July 1, 1994 and June 30, 1996 among individuals with no dispensing during the previous one year prior to July 1, 1994, and with initial dispensing prior to January 1, 1996.

Survival analysis was used to examine differences in discontinuation of LLAs between different drug benefit plans controlling for potential confounding effects of patient sex, age (≥70), hospitalization for CHD prior to initial prescription,
hypertension or diabetes mellitus diagnoses prior to initial prescription, statin (a class of lipid-lowering agents) use, and number of other medications used (≥3). The outcome measure used was time until discontinuation, defined as greater than 180 days between refills or between the last refill and the end of the study period.

Results The overall discontinuation rate increased with time from 18.3% at 6 months, to 46.4% at 12 months, to 66.3% at 18 months.

In the bivariate models, males had lower discontinuation than females (p=0.0078), CHD patients had lower discontinuation than non-CHD patients (p=0.0424), and statin users had lower discontinuation than non-statin users (p=0.0004). In the multivariate model, a significant difference existed with statin use (HR=0.536; CI=0.375-0.766; p=0.0006), indicating that statin users were less likely to discontinue compared to nonusers. No significant differences existed with plan type, gender, age, CHD, diabetes, and number of other medications.

Conclusion Persistence to lipid-lowering therapy among elderly patients declines over time with the greatest drop during the first year. We did not find an association between drug benefit plan options and discontinuation. Our findings suggest that adequate payment mechanisms are not enough to guarantee persistence. To achieve the desired benefit of therapy, long-term commitment to patient education, monitoring and reinforcement with a multidisciplinary approach (including pharmacists, nurses, physicians and dieticians) is warranted.
BACKGROUND

During the 1990s, increasing numbers of Medicare beneficiaries were becoming enrolled in managed care plans. Between 1989 and 1994, the HMO share of Medicare almost doubled [1]. In 1997, managed care enrolled 14.9% of the Medicare population (5.6 million) [2], and in year 2000, about 16% of Medicare beneficiaries were enrolled in Medicare plans associated with HMOs [3]. These differ from traditional Medicare plans in that the enrollees receive their coverage from the HMO rather than individual providers in private practice [3].

The growth in medical care expenditure is an important issue. The cost of pharmaceuticals has been reported to be among the fastest rising components of healthcare costs, with a 17.3% increase in national expenditures for prescription drugs from 1999 to 2000 [4]. Spending on prescription drugs has increased at double-digit rates for the past decade and is now the third largest component of healthcare expenditures behind hospital care and physician services [5]. Policy responses have included limits on prescription costs, restriction on the supply of healthcare, and shifting of the financial risk to providers and beneficiaries [6-8]. Patient cost-sharing through deductibles, coinsurance, and co-payments is one technique increasingly being used to contain medical costs in general, and prescription costs in particular, to deter patients from unnecessary use [6-9]. There is, however, a concern that necessary utilization could be reduced, which may in turn increase the risk of adverse health consequences and resulting costs [4, 6-8, 10-12]. Cost-sharing does not affect everyone equally; those with lower incomes, like many elderly, are more likely to reduce medication use than those with higher incomes. Stuart et al. [13] found that the
probability of the elderly medicating a health problem decreases 2-3% for every $3000 reduction in income for annual incomes below $18,000. Low income populations appear to be sensitive to drug co-payments as low as 10-15% of average prescription expenses with declines of 5-10% observed in drug utilization [14].

When the Medicaid program in New Hampshire placed a limit of 3 reimbursable medications that a patient could receive per month, there was a 30% drop in the number of prescriptions filled per month among 10,734 enrollees, and reduced use of essential medications like insulin and antihypertensives [15]. Several other studies have reported a decrease in prescription filling due to cost-sharing [16-18]. At the same time, changes in cost-sharing for one service should not be considered separately from another service, since patients may simply shift the type of service sought to deal with the health problem [6]. The 3-drug limit placed by Medicaid in New Hampshire increased the risk of nursing home admissions and overall healthcare costs [19]. The Medicare population is demographically different from the Medicaid population, and thus its response to such policies may differ. Research has shown, however, that Medicare patients who lack coverage receive fewer prescription medications than those with coverage [11, 20] and that medication restriction is common in older adults who lack prescription drug coverage [12]. Other studies have shown the negative effect of reducing drug coverage among the poor elderly and the consequences of inadequate coverage for older adults patients receiving medications that can prevent serious adverse health consequences [4, 21]. Comparing Medicare beneficiaries with and without drug coverage shows those with poor health and no coverage fill 36% fewer prescription than those with coverage, and
that those with incomes below poverty line and without coverage fill 48% fewer annual prescriptions [11].

Starting January 1, 1994, an HMO in central Massachusetts introduced a policy in which older adult plan members were able to choose among 3 drug benefit plans. This research explored the effects of this policy on discontinuation rates of lipid-lowering agents (LLA), group of drugs of well-documented benefit for both primary [22-25] and secondary [26-30] prevention of coronary heart disease (CHD).

CHD continues to be the leading cause of death among the United States (US) population [31-33], and worldwide [32, 34], despite reported declines in mortality during this century [35]. Cardiovascular disease accounts for 950,000 deaths annually in the US, including 460,000 from CHD [31], and 85% of those who die from CHD are 65 years of age or older [31]. In 1990, there were 489,171 deaths attributed to CHD [35], and 675,000 patients were discharged from US hospitals with a primary diagnosis of myocardial infarction [36], and hospitalization for CHD continues to increase [37]. The prevalence of nonfatal CHD among US adults aged 40 and above was reported to be 11.8% [33]. It remains an important disease with significant burden. Estimated yearly costs of CHD for medical treatment and lost wages in the US range from $50 billion to $100 billion [31, 38, 39].

High cholesterol, specifically elevated low-density lipoprotein cholesterol (LDL-C), is a major cause of CHD [38, 40-42], a link that was first made by the Framingham Heart Study [43].
Currently, the American Heart Association estimates that 70 million adults in the US have total cholesterol levels >200mg/dl, and that at least 40% of these individuals have cholesterol levels in excess of 240mg/dl [31,44].

Hypercholesterolemia remains under-treated [44-46] especially in the elderly [47-49]. Elderly patients fail to receive indicated lipid-lowering medications as often as 80% of the time [47, 49] and even fewer achieve their target cholesterol [48, 49]. This may be because physicians fail to prescribe LLAs, patients fail to consume them, or both [49]. The use of statins in clinical practice were shown to lead to reductions in LDL-C that were significantly less than those projected in the pharmaceutical manufacturer guidelines, a gap that could reflect poor adherence in clinical practice settings [50].

Adherence to cholesterol lowering therapy is expected to be a problem based on previous reports showing that compliance with drug therapy for chronic diseases is frequently sub-optimal [51]. The cumulative treatment discontinuations among long term regimens of all types is about 50% of patients at the first year [51-58], and there are no reasons for discontinuation rates in LLA to be any different [51], especially when considering that hypercholesterolemia is a chronic condition that is perceived by the patient as having deleterious health consequences that are far in the future [59].

Compliance/adherence is defined as the extent to which a patient’s behavior corresponds to the physician’s therapy recommendations [60, 61]. Filling the prescription is the first step of the compliance process [51, 62]. Refill persistence is a form of compliance while failure to obtain refills or stopping the medication sooner than the physician’s recommendation are forms of noncompliance [61, 63]. Drug
Discontinuation rates are useful tools for evaluating patients' failure to adhere to therapy [39, 61, 64] and are commonly used as a measure of compliance rates [51, 54, 61]. They are useful mainly for medications intended for long-term use and population-based studies that assess drug use retrospectively [61].

Noncompliance with medication has a significant negative health impact [65-73], and is estimated to cost the US $25 billion annually when indirect costs are included [74]. In a number of chronic illnesses, it has been associated with increased hospitalization [66, 75, 76] and poor outcomes in the long run [68-73]. The stark contrast in benefit experienced between compliant and noncompliant patients was demonstrated in the West of Scotland Coronary Prevention Study (WOSCPS) [22]. By the end of the 5 year follow-up, the relative risk reduction for cardiovascular death in compliant patients (who took more than 75% of prescribed drug) was 37% compared to 32% in the less compliant group [77], and the need for revascularization procedures was reduced by 46% in the compliant group compared to 37% in the less compliant patients [78]. In the Lipid Research Clinics Coronary Primary Prevention Trial [79], a randomized placebo controlled study of 3806 patients followed for 7 years, only half of the patients took the recommended dose of six packets of cholestyramine (24gm) a day. The study documented an overall 19% lowering of cardiovascular risk. However, among patients taking the full-recommended dose, the reduction was twice as great (39.3%), and there was a dose response relationship [24, 52, 79, 80]. A significant reduction in recurrent myocardial infarction among 5595 patients in the UK was observed in patients taking statins with adherence of 80% or more compared to those not taking statins (RR 0.19; CI=0.08-0.47). For those with adherence of less than 80%,
there was no significant reduction in recurrent MI risk [81]. Such differences were not observed in a community setting when Andrade et al. [82] compared rates of hospitalizations and LDL-C levels after discontinuation of antihyperlipidemic therapy. A possible explanation for this finding is that most patients discontinued therapy before an effect could be observed, or failed to achieve desired LDL-C reduction.

The public health importance of adherence for gaining a widespread benefit from LLAs is emphasized by the dominance of atherosclerotic disease as the major cause of morbidity and mortality in the United States [33, 35, 36], and the efficacy of cholesterol drugs in obtaining benefits in both primary [22-25] and secondary [26-30] prevention of CHD. The success of an intervention requires that patients’ adherence to treatment instructions is maintained throughout. The economical and widespread achievement of benefits depends on all risk-qualified patients obtaining a high level of adherence to these regimens of proven efficacy. Adherence is the critical link between prescription and treatment success [41, 51, 83].

Little is known about persistence to lipid-lowering therapy among older patients since studies have preferentially enrolled younger patients or informed subjects they were being monitored, thus reducing generalizability of the results [49, 84, 85]. Elderly patients are of particular concern since they may exhibit an increased susceptibility to adverse events [86] because of deficits in physical dexterity, cognitive skills, and memory, as well as the large number of medications they are prescribed [87]. Elderly patients are also more likely to discontinue medications than younger patients [49, 64, 88].
Targeting persistence-enhancing interventions so that they have the most leverage and potential benefit requires knowledge of time during therapy where discontinuation is most likely, and which patient subgroups are of high risk. Furthermore, discontinuation rates are important to estimate population level cost and benefit of LLAs in actual practice, especially since discontinuation rates in HMO clinical practices were reported to be higher than those in clinical trials [56]. Our objectives were to describe trends of LLA use in actual practice, identify patient characteristics that predict poor persistence, and explore the effect of drug benefit plan option on persistence to these drugs. We hypothesized that members of the full drug benefit plan would have better persistence with LLAs compared to the $1000 maximum or no drug coverage plans.
METHODS

Data source and study population

The study is a retrospective cohort design among older adult enrollees (Medicare beneficiaries) of an HMO operating in Massachusetts, who were continuously enrolled in the plan during the period of July 1, 1993 – June 30, 1996, and were prescribed a LLA. These members were able to choose among 3 drug benefit options starting January 1, 1994: full coverage for prescription drugs, a maximum of $1000/year in coverage, or no drug coverage. Those selecting full coverage paid an additional premium of $72.50/month ($870/year). Those with a $1000 maximum coverage paid an additional $39.16/month ($469.92/year). Those without coverage paid no additional premium.

Information on demographic characteristics, drug benefit plan type, prescriptions, ambulatory visits, hospitalization, and diagnoses was available for this population cohort. The population cohort was comprised of 2229 members. We deleted 325 members who switched from the original plan chosen on January 1, 1994 since we were unable to explore the effects of the type of drug benefit as a main predictor of adherence in these individuals. Of those, 251 (77.2%) switched from the full coverage plan, 61 (18.8%) from plan the $1000 maximum plan, and 13 (4.0%) from the no coverage plan. The final plans chosen by these patients in this study period were the full coverage plan in 89 patients (27.4%), the $1000 maximum in 186 (57.2%), and the no coverage plan in 50 (15.4%).
We then identified patients with a prescription of an LLA between July 1, 1994 and June 30, 1996 among individuals with no prior dispensing during the previous one-year prior to July 1, 1994, in order to identify relatively new users of LLAs, and with initial dispensing prior to January 1, 1996. The definition of new users has been previously described [64, 89].

This study examined differences in discontinuation of LLAs between different drug benefit plans controlling for potential confounding effects of patient sex, age, comorbidities (CHD, hypertension or diabetes mellitus)-which are among the CHD risk factors in the National Cholesterol Education Program (NCEP) guidelines [38, 41]-number of medications used, and statin (a class of LLAs) use.

Members with greater than a 6-month period (180 days) between refills or between the last refill and the end of the study period were considered to have discontinued the drug. Changing the type of LLA was not considered as discontinuation. Patients who had more than one prescription refilled prior to a 6-month period with no refills were not considered to have discontinued.

In previous research, Andrade et al. [56] used a 6-month period or more (180 days) between refills to flag potential discontinuation. Jackevicius et al. [64] used having a prescription every 120 days to define adherence and used 180 days for a sensitivity analysis.

For these patients we determined the gender; age; drug benefit plan type; presence of comorbidities including CHD, diabetes, and hypertension; and number of other medications used by the patient. Drug benefit plan type was categorized as full coverage versus partial or no coverage. Age was categorized into two groups: below
70, and 70 years or older. This was based on the frequency distribution of age groups in this population cohort. A patient was considered to have CHD if there was a hospitalization for CHD or a diagnosis for CHD (ICD-9 code= 410-414) prior to the LLA prescription or during the one-year prior to the study period. Patients with a diabetes diagnosis (ICD-9 code=250) prior to the LLA prescription or during the one-year prior to the study date were labeled diabetic, and patients with a hypertension diagnosis (ICD-9 code= 401-405) prior to the LLA prescription or during the one-year prior to the study date were regarded as having hypertension. Number of other medications used at the time of the first dispensing was determined by evaluating a 45-day period prior to the initial dispensing, and transformed into two groups: 0-2 other medications, or 3 and more.

**Statistical analyses**

Descriptive statistics were used to determine various patient characteristics. Survival analysis was used to assess the effect of drug benefit options on the discontinuations of LLAs. The outcome variable considered was time until discontinuation. The main predictor variable was type of drug benefit plan option. Other covariate predictors included in the model include age, gender, CHD, diabetes, hypertension, and number of other medications used.

Kaplan-Meier (KM) curves of the main predictor variable and the covariate predictor variables were independently constructed, and the log-rank statistic was used to evaluate group differences for each variable independently.

Assessment of the proportional hazards (PH) assumption for each of the predictor variables was carried out using the graphical approach of the log-log survival
curve described by Kleinbaum [90]. This approach involves comparing the log-log plots of KM survival curves for different categories of each variable separately. The PH assumption is satisfied unless there is a strong evidence of nonparallelism [90].

Stratification was used when the assumption was violated as described by Kleinbaum [91]. Testing the no-interaction assumption was also carried out in order to determine the type of model to be used (interaction model or no-interaction model). This was accomplished by calculating the difference between the $-2L$ statistics of the full and reduced models. The full model has all the variables plus interaction terms between the stratification variable and the other variables in the model, while the reduced model has only the variables and no interaction terms. Testing for significance was carried out using the chi-square distribution with degrees of freedom equal to the number of interaction terms (difference in terms between the 2 models). A difference in the $-2L$ value that was less than the chi-square statistic indicated no significant interaction [91].

Co-linearity between various variables in the model was tested using testing by SAS proc corr. as suggested by Delwiche and Slaughter [92] to give correlation coefficients described by Johnson and Bhattacharyya [93].

Interaction assessment was performed by the chunk test described by Kleinbaum [94], which involves calculating the difference between $-2L$ statistics of the full and reduced models. The full model has interaction terms while the reduced does not. Chi-square distribution was used to test for statistical significance of this difference with degrees of freedom equal to the number of interaction terms
(difference in terms between the models). A difference that was less than the chi-square statistic indicated no statistically significant interaction.

Finally a Cox proportional hazards model that incorporated the main predictor variable and other independent variables (as potential confounders) was constructed. Confounding assessment was also carried out by removing each independent variable and assessing the effect on the parameter estimate of the main predictor variable. Statistical significance was set at $p<0.05$, and the estimates were reflected by a 95% confidence interval. All statistical analysis was carried out using SAS statistical package version 8.01.
RESULTS

Descriptive statistics

A total of 322 patients met our inclusion criteria and were selected for the study. The mean age of these patients was approximately 70 years of age. There were more female patients (n=187; 58.1%) than males (n=135; 41.9%) in our study population.

Most of these patients were covered by the full coverage drug benefit plan (n=202; 62.7%), nearly a third of them by the partial coverage plan (n=108; 33.5%), and a small percentage by the no coverage drug benefit plan (n=12; 3.7%).

As for the type of LLA in the initial prescription, statins were the most widely used (n=188; 58.4%), followed by bile acid sequestrants (n=75; 23.3%) then niacin (n=34; 10.56%). Fibrates were the least used in this patient population (n=25; 7.8%).

Approximately half of this patient population was hospitalized for CHD prior to the initial LLA prescription (n=159; 49.4%), 22.1% had a diabetes diagnosis prior to the initial prescription (n=71), and most had a hypertension diagnosis prior to the initial prescription (n=231; 71.7%). The mean number of other medications used by these patients based on NDC-codes was 2.4 medications. This information is presented in Table 1.

The coding of various variables in subsequent bivariate and multivariate analyses is summarized in Table 2. Because of the low percentage of patients in the no coverage plan benefit, drug benefit plan type was further categorized as full coverage (n=202; 62.7%) versus partial or no coverage (n=120; 37.3%). Age was converted into a dichotomous variable with age below 70 years in one group, accounting for 50% of
the patient population (n=161), and 70 years or older in the other group. Number of
other medications was also converted into a dichotomous variable with 3 or more
medications in one group (n=125; 38.8%) and 0-2 medications in the other group
(n=197; 61.2%), and type of LLA at the initial dispensing was further categorized as
statin user (n=188; 58.4%) versus non-statin user (n=134; 41.6%).

KM survival curves for the various variables are shown in Figures 1a--8a in
Appendix D. Table 3 summarizes the results of the log rank test for these curves and
the discontinuation rates at 6 months, 12 months, and 18 months overall and stratified
by the variables. 322 patients were followed for 6 months, 235 for 12 months, and 187
for 18 months.

By the end of the study period, a total of 126 (39.1%) patients had
discontinued their medication. Twenty-six of these had more than 6-months between
refills, and the remainder (n=100) had a more than 6-months between last refill and
end of the study. The discontinuation increased with time, with 59 (18.3%)
discontinuing at 6 months, 109 (46.4%) at 12 months, and 124 (66.3%) at 18 months.

A significant difference existed between genders, with males having lower
discontinuation than females (Graph 2a). The discontinuation increased from 11.9%
at 6 months, to 39.8% at 12 months, to 54.9% at 18 months in males, and from 23.0%
at 6 months, to 50.3% at 12 months, to 73.2% at 18 months in females (p=0.0078).

A significant difference also existed between those who were hospitalized for
CHD and those that were not, with CHD patients having lower discontinuation than
non-CHD patients (Figure 4a). The discontinuation increased from 15.7% at 6
months, to 40.9% at 12 months, to 59.1% at 18 months in CHD-patients, and from
20.9% at 6 months, to 51.2% at 12 months, to 72.7% at 18 months in non-CHD patients (p=0.0424).

Finally, a significant difference existed between statin users and non-statin users, with statin users having better persistence than non-statin users (Figure 8a). The discontinuation increased from 23.9% at 6 months, to 55.0% at 12 months, to 77.3% at 18 months in non-statin users, and from 14.4% at 6 months, to 38.7% at one year, to 56.6% at 18 months in statin users (p=0.0004).

The survival curves were slightly higher for members of the full coverage plan compared to members of the no or $1000 maximum plans (Figure 1a), members below 70 years of age compared to age 70 or above (Figure 3a), diabetics compared to non-diabetics (Figure 5a), non-hypertensives compared to hypertensives (Figure 6a), and those with number of other medications 0-2 compared to 3 or above (Figure 7a), but these differences did not reach statistical significance.

Figures 1b–8b in Appendix D are the log-log plots of KM survival curves for assessment of the proportional hazards (PH) assumption for each of the predictor variables. The PH assumption was satisfied in all variables except hypertension (Figure 6b), since there is a strong evidence of nonparallelism by the crossing of the two lines.

Table 4 shows the results of the testing no interaction assumption. No significant interaction terms existed between hypertension and the other variables that were to be included in the model.

The highest correlation coefficient between variables was 0.26127, indicating no co-linearity between variables.
Table 5 summarizes results of interaction assessment for the variables that were to be included in the model with the main predictor variable of plan type. No significant 3-way or 2-way interactions existed.

In the multivariate model, a significant difference in discontinuation existed with statin use (HR=0.536; CI=0.375-0.766; p=0.0006), indicating that statin users were less likely to discontinue compared to nonusers. No significant differences existed with plan type, gender, age, CHD, diabetes, and number of medications. These results are summarized in Table 6.

Table 7 shows the results of confounding assessment. None of the variables when removed caused large changes in the parameter estimate (β) for the main predictor variable plan type.

The changes in the odds ratio when only statin use is kept in the model with the main predictor are presented in Table 8. It shows only minor changes in the hazard ratio of the main predictor variable, plan type, when these 2 variables are kept in the model (HR=0.851; CI=0.594-1.221; p=0.3820) compared to the full model (HR=0.877; CI=0.610-1.260; p=0.4777) with the rest of the variables included.

Multivariate adjusted survival curves for our main predictor (drug benefit plan type) stratified by hypertension and adjusted for gender, age, CHD diagnosis, diabetes diagnosis, number of medications, and statin use are presented in Figure 1. Multivariate adjusted survival curves among hypertensives is presented in Figure 2, and among non-hypertensives in Figure 3.
DISCUSSION

Administrative databases with prescription refill records are increasingly being used in pharmacoepidemiologic research. They provide a cost-effective alternative to post-marketing clinical trials in a real world setting [95, 96]. Automated databases can be used to assess prescribing patterns and trends of drug use [97-99] as well as impact of policies [100]. They have often been successfully used in adherence research [55, 61, 64, 89, 101]. Pharmacy refill data is considered a more objective measure than self-reports, which can overestimate compliance [101, 102]. Although filling the prescription is not identical to consuming the drug, patterns of prescription filling represent the most accurate way of estimating actual medication use in large populations [55]. The effectiveness of using automated databases for studying discontinuation rates in primary care settings has been well demonstrated [62, 103].

In this research, we used data from an HMO to study persistence of LLAs in a group of elderly patients, mainly to study the effect a drug benefit plan option has on the persistence of these drugs, controlling for potential confounders including gender, age, comorbidities (CHD, diabetes, and hypertension), number of medications, and statin use.

The study population had a high prevalence of CHD (49.4%), diabetes (22.1%), and hypertension (71.7%) compared to reported prevalences in the general population [33, 104, 105], which is understandable considering it is a population of older adults being treated for hypercholesterolemia. More than half of the patients also chose the full coverage benefit plan (62.7%), a fact which can be explained by the higher drug use in this age group compared to younger patients [86, 106]. Statins were
the most widely used LLA (58.4%) consistent with other reports [83, 107-110]. They are the most effective for LDL-C reduction and the best tolerated among LLAs [50, 83, 111] and are of well-documented benefit for both primary [22, 23] and secondary [26-28] prevention of coronary heart disease (CHD).

The one-year LLA discontinuation rate of 46.4% was higher than those reported in clinical trials (ranging from 4-15%) [56] and that reported by Andrade et al. (32%) [56]. Higher discontinuation rates have also been reported. In an Australian practice setting, a 60% discontinuation rate over one year was reported, with 56-57% for statins, and 78% for gemfibrozil [112]. The one-year discontinuation rate for statins was found to be 38.7%, higher than that reported by Andrade et al. [56]- which was 15% for lovastatin- and lower than that reported by Simons et al. [112] (56-57%). O’Connor et al. [113] also reported a 52% discontinuation rate for lovastatin, and Benner et al. [49] a 61% rate. The 6-month discontinuation rate that we found for statins (14.4%) was lower than that reported by Jackevicius et al. [64] (25%).

In general, all findings suggest that the discontinuation rates for LLAs are high [49, 56, 64, 112, 113], and more than those reported in clinical trials [56]. To obtain the reported full benefit of these drugs [22-30], it is important to ascertain factors contributing to discontinuation in order to target subpopulations that are more likely to discontinue.

We found that that discontinuation increased progressively with the increasing duration of treatment, consistent with what other studies previously reported [49, 51, 64]. Overall LLA discontinuation increased from 18.3% at 6 months, to 46.4% at 12 months, and to 66.3% at 18 months, and statin discontinuation rates increased from
14.4% at 6 months, to 38.7% at 12 months, to 56.6% at 18 months. We noticed that the increase in discontinuation became relatively slower after the first year.

Other factors explored in this research include drug benefit plan option as a main predictor, gender, age (≥70), number of medications (≥3), previous hospitalization for CHD, diabetes diagnosis, and hypertension diagnosis.

Our main predictor, drug benefit plan option, was not found to be significantly associated with non-persistence (HR=0.877; CI= 0.610-1.260; p=0.4777). The KM survival curves for the full coverage were higher than the no or partial coverage and the adjusted survival curves for full plan among hypertensives was also higher than the curve for no or partial coverage, indicating a trend of better persistence with the full coverage members- but this difference did not reach statistical significance. Financial effects have previously been explored in several studies. Financial incentives have been shown to improve compliance in patients [114]. Eighty-five percent of 132 physicians surveyed in eastern Massachusetts reported that inability to afford medication was a problem for some of their patients [115]. Thirty-eight percent of patients that discontinued their medication in a follow up study one year after the conclusion of the 4S study blamed acquisition costs [116]. Cost of medications was also found to be among factors contributing to noncompliance in the elderly [66, 117]. Medicare patients who do not have prescription drug coverage are reported to face higher out of pocket expenditures and are more likely to let prescriptions go unfilled or skip doses to save money [118]. Elderly Medicare beneficiaries with CHD who lack drug coverage were shown to have significantly lower rates of statin drug use (4.1%) compared to those with drug coverage (27.4%) (p<0.001) [119].
Furthermore, Medicare beneficiaries with capped dollar amounts on prescriptions have been reported to take steps to decrease their out of pocket prescription costs, including taking samples from physicians, taking less than the prescribed dose, and discontinuing the prescribed medication [120]. In a cross sectional study of 4896 older adults aged seventy or older who regularly took prescribed medications, based on a national survey, medication restriction was reported in 8% of subjects with no coverage, 3% of those with partial coverage and, 2% with full coverage (p<0.01 for trend) [12]. Still, research on elderly patients taking LLAs specifically has shown high discontinuation rates in patients with drug coverage [49, 55, 64, 101]. Benner et al. [49] found a 43% persistence of statin therapy in 6 months and only 1 in 4 were adherent in five years. Persistence was defined as proportion of days covered by a statin of 80% or more. Cost was not an issue here since patients received their medication for free or a $5 co-payment (patients were from the New Jersey Medicaid and Pharmaceutical Assistance to the Aged and Disabled program who were 65 or older). Jackevicius et al. [64] found a two-year adherence rate (defined as having a statin prescription refill every 120 days) of 36.1% in patients with coronary artery disease and 25.4% in patients of primary prevention (without CHD) in a Canadian population in which costs are covered except for a small co-payment. Avorn et al. [55] found that patients failed to fill their LLA prescriptions about 40% of the time over one year in Medicaid (New Jersey Medicaid and Pharmaceutical Assistance to the Aged and Disabled program) and Quebec (Quebec’s provincial medical care program)- systems with comprehensive drug benefits for their patients. In addition, a study in British Columbia, where there are various levels of
coverage provided by the provincial government and patients can buy additional private insurance to cover their medication costs, found no significant difference between adherent and non-adherent patients with respect to type of provincial coverage in a $X^2$ analysis ($p=0.27$), and no difference in the proportion of patients with additional coverage (56% versus 53%; $p=0.76$) [121]. One study assessing the effects of a 3-tier pharmacy benefit in chronic diseases found discontinuation to be higher for patients who switched from a 2-tier plan to a 3-tier plan compared to those who stayed in the 2-tier or 3-tier plans, but this study did not look into switching to a generic or brand formulary alternative [122]. Our findings (no association of drug benefit plan options and discontinuation) suggest that adequate payment mechanisms are not enough to guarantee persistence, since we could not document a statistically significant difference in discontinuation between members who are fully covered for their medication, and members who are not and may, in turn, have problems with their medication costs.

Gender was noted to be significantly associated with discontinuation in bivariate analysis ($p=0.0078$), but was no longer associated when adjusting for other variables in the model. Results in previous studies have been inconsistent with regard to gender effects on compliance [117], with some reporting associations [64, 89] and others not [76, 123]. Our results indicate no association, even though a trend of better persistence with males was documented.

Statin use was significantly associated with better adherence in bivariate ($P=0.0004$) and multivariate analyses (HR=0.536; CI=0.375-0.766; $p=0.0006$). Adherence to lipid-lowering therapy has been previously associated with receiving a
statin [55, 64, 112], since they are generally more tolerable than other LLAs [83, 101, 109, 111] and side effects have been commonly cited as reasons for noncompliance [56, 124].

Previous hospitalization for CHD was significantly associated with better adherence in the bivariate analysis (p=0.0424), but was no longer associated in the multivariate analysis after controlling for the other variables. Although studies have indicated better adherence to lipid-lowering drugs in secondary prevention compared to primary prevention [51, 55, 64, 67], a number of these studies did not have an element of financial issues since patients were covered for the price of the drug except for a small co-payment in some cases [49, 55, 64, 101]. Furthermore, research has shown that targeting patients during a hospitalization for an acute event or intervention procedure can improve persistence [42, 88, 125, 126], which is why current NCEP ATP III guidelines recommend initiating lipid-lowering drug therapy at hospital discharge, not after [41, 88]. In our study, we looked for a previous hospitalization prior to the prescription date, but we could not tell if the prescription was given while the patients were in the hospital or some time after discharge. This timing of treatment initiation may in turn affect patient persistence.

Presence of other comorbidities, diabetes and hypertension, have been previously associated with discontinuation, causing better persistence [49, 55, 64]. Lower compliance with comorbidities has also been reported, possibly related to a more complex regimen with comorbidities [89]. The asymptomatic nature of hyperlipidemia may also contribute to the lower adherence to LLAs when a symptomatic comorbidity like diabetes exists [89]. We did not find such associations
in the univariate analysis for both these comorbidities, and could not find an association with diabetes in the multivariate analyses. The recent ATPIII guidelines, that were not available at the time of the study, are more aggressive in treatment of hypercholesterolemia among diabetics compared the ATPII guidelines that were available at the time of our study. The ATPIII guidelines place patients with diabetes in the highest risk group of CHD-risk equivalent with a target LDL-C of 100 mg/dl. In the prior ATPII guidelines, a patient had to have another risk factor along with diabetes to have a target LDL-C of 130 mg/dl. This could in turn cause better awareness of the cardiovascular risk among diabetics since the time of the study. Thus, we might observe better adherence of diabetic patients with this growing awareness using more recent data that coincides with the newer guidelines.

Previous studies have been inconsistent with regard to the effect of number of medications [49, 55, 61, 64, 124] and age [49, 64, 89, 121, 127] on persistence. Some have even reported lower adherence with lower number of medications [121], possibly because subjects with more medications are sicker and could be more attentive to taking their drug therapy [121]. We did not find a significant association between number of other medications ≥3 or age ≥70 on persistence to LLA.

Improving patient understanding of cardiovascular risk, medication regimens, and benefits of persistence is expected to enhance adherence to LLAs [51, 80, 109], as patient education has shown to improve compliance in other diseases like hypertension [101, 128-130]. To achieve the desired benefit of therapy and improved population health, long-term commitment to patient education, monitoring and reinforcement with a multidisciplinary approach, including pharmacists, nurses, physicians, and
dieticians is warranted [39, 42, 49, 51, 63, 101, 109]. This approach can emphasize the importance of therapy and achieve a behavioral change in the patient towards better persistence.

**LIMITATIONS**

Several limitations to this study can be described. Regarding the dataset used, patients may fill their prescriptions from pharmacies outside the HMO network and thus will not be captured. This, however, is unlikely, since the drugs were provided at discounted prices for patients in these pharmacies, and the assumption that patients fill most prescriptions within the pharmacy system under study has been confirmed in one HMO and 2 Veterans Affairs (VA) Medical Centers [61]. One study that tried to assess medication use outside the central pharmacy of the VA through a questionnaire found that 98.5% of patients reported using the central pharmacy as their only source of medication [62]. Also, filling the prescription is not identical to consuming the drug, yet patterns of prescription filling represent the most accurate way of estimating actual medication use in large populations [55]. We were unable to account for nonprescription drug use; for example, niacin could be obtained without a prescription, and we were unable to conduct medical chart reviews to validate the information attained from the computerized data. Thus, there could have been some misclassification of patients, but this would be of a non-differential type. It is not expected to be a major problem, as the data has been previously used in research. Continuous enrollment of the patients used in this study minimized selection bias as well.
Characteristics of the population included may somewhat limit generalizability of results to the elderly population, but we are in need of "real world" LLA adherence studies in this age group [49] that consumes a relatively higher percentage of medications compared to other age groups [86, 106].

Other limitations include lack of comprehensive clinical data including lipid levels, and exact reason for discontinuation. We were unable to control for some potential confounders that have been reported to affect adherence like race [49, 117], socioeconomic status [123], regimen complexity [89], and perceived health [55, 89]. We also do not have information on income levels or coinsurances for our population cohort. We could not account for use of samples or hospitalizations during a follow up period, but our definition of 6 months without a drug somewhat limits the problem. It is difficult to obtain samples that cover such a period, and it is a long period for a continuous hospitalization. We did not control for some potential influencing conditions like stroke and potential statin side effects like myalgia, hepatitis, and rhabdomyolysis. These side effects, however, are not very common, myalgia occurs in 1-5% of the statin users [131], elevation in liver enzymes occurs in approximately 1% of patients, while myopathy in approximately 1 in 1000 with monotherapy, and in very rare cases can lead to rhabdomyolysis [83].

Despite these limitations, we feel this research provides evidence that drug benefit plan options does not significantly affect discontinuation of LLAs, and that full coverage of prescription drugs does not guarantee persistence.
CONCLUSION

Persistence to lipid-lowering therapy among elderly patients declined over time with the greatest drop during the first year. We did not find a significant association of drug benefit plan options with discontinuation. We noted statin use to be significantly associated with better persistence, while gender and previous hospitalization for CHD were no longer associated with persistence when controlling for other factors in the multivariate model. We also did not find an association with number of other medications $\geq 3$ and age $\geq 70$.

Our findings suggest that adequate payment mechanisms are not enough to guarantee persistence. To achieve the desired benefit of therapy, long-term commitment to patient education, monitoring, and reinforcement with a multidisciplinary approach, including pharmacists, nurses, physicians and dieticians is warranted.
Table 1 Characteristics of new users of lipid-lowering agents in an elderly population enrolled in a Medicare managed care health plan (n=322)

| Characteristic                                      | N    | %    |
|-----------------------------------------------------|------|------|
| Gender                                              |      |      |
| Females                                             | 187  | (58.1%) |
| Males                                               | 135  | (41.9%) |
| Age                                                 | Mean 70.4 |       |
| SD                                                  | 4.5  |      |
| Plan type                                           |      |      |
| No coverage                                         | 12   | (3.70%) |
| $1000 maximum                                       | 108  | (33.5%) |
| Full coverage                                       | 202  | (62.7%) |
| Type of lipid-lowering agent prescribed              |      |      |
| Statin                                              | 188  | (58.4%) |
| Niacin                                              | 34   | (10.6%) |
| Fibrate                                             | 25   | (7.80%) |
| Bile acid sequestrant                               | 75   | (23.3%) |
| CHD diagnosis prior to prescription                 |      |      |
| CHD diagnosis                                       | 159  | (49.4%) |
| No CHD diagnosis                                    | 163  | (50.6%) |
| Diabetes diagnosis prior to prescription            |      |      |
| DM diagnosis                                        | 71   | (22.1%) |
| No DM diagnosis                                     | 251  | (78.0%) |
| Hypertension diagnosis prior to prescription        |      |      |
| HTN diagnosis                                       | 231  | (71.7%) |
| No HTN diagnosis                                    | 91   | (28.3%) |
| Number of other medication                          |      |      |
| Mean                                               | 2.4  |      |
| SD                                                 | 2.0  |      |

SD=Standard deviation, CHD=Coronary Heart Disease, DM=Diabetes Mellitus, HTN=Hypertension
Table 2 Coding and distribution of variables among new users of lipid-lowering agents in an elderly population enrolled in a Medicare managed care health plan (n=322)

| Variable                      | Yes =1* | No =0* |
|-------------------------------|---------|--------|
|                               | N       | %      | N       | %      |
| Plan type (full coverage)     | 202     | (62.7%)| 120     | (37.3%)|
| Gender (male)                 | 135     | (41.9%)| 187     | (58.1%)|
| Age≥70                        | 161     | (50.0%)| 161     | (50.0%)|
| CHD diagnosis                 | 159     | (49.4%)| 163     | (50.6%)|
| Diabetes diagnosis            | 71      | (22.0%)| 251     | (78.0%)|
| Hypertension diagnosis        | 231     | (71.7%)| 91      | (28.3%)|
| Number of other medication ≥3 | 125     | (38.8%)| 197     | (61.2%)|
| Statin user                   | 188     | (58.4%)| 134     | (41.6%)|

*Coded as 1 or 0 model. CDH = coronary heart disease
Table 3  Discontinuation rates of new users of lipid-lowering agents at 6 months, 12 months, and 18 months, stratified by patient characteristics in an elderly population enrolled in a Medicare managed care health plan (n=322)

| Variable          | Failed at 6 months | Failed at 12 months | Failed at 18 months | Log-rank Probability |
|-------------------|--------------------|---------------------|---------------------|----------------------|
|                   | 59 of 322 (18.3%) | 109 of 235 (46.4%) | 124 of 187 (66.3%) |
| **Plan type:**    |                    |                     |                     |                      |
| Full coverage     | 31 of 202 (15.4%)  | 65 of 151 (43.1%)   | 75 of 119 (63.0%)   | 0.3121               |
| Partial or no     | 28 of 120 (23.3%)  | 44 of 84 (52.4%)    | 49 of 68 (72.1%)    |                      |
| coverage          |                    |                     |                     |                      |
| **Gender:**       |                    |                     |                     | 0.0078*              |
| male              | 16 of 135 (11.9%)  | 35 of 88 (39.8%)    | 39 of 71 (54.9%)    |                      |
| female            | 43 of 187 (23.0%)  | 74 of 147 (50.3%)   | 85 of 116 (73.2%)   |                      |
| **Age**           |                    |                     |                     | 0.2938               |
| ≥70               | 36 of 161 (22.4%)  | 58 of 116 (50.0%)   | 66 of 96 (68.8%)    |                      |
| <70               | 23 of 161 (14.3%)  | 51 of 119 (42.9%)   | 58 of 91 (63.7%)    |                      |
| **CHD Diagnosis** |                    |                     |                     | 0.0424*              |
| With CHD          | 25 of 159 (15.7%)  | 45 of 110 (40.9%)   | 52 of 88 (59.1%)    |                      |
| No CHD            | 34 of 163 (20.9%)  | 64 of 125 (51.2%)   | 72 of 99 (72.7%)    |                      |
| **Diabetes**      |                    |                     |                     | 0.1011               |
| diagnosis         |                    |                     |                     |                      |
| With diabetes     | 8 of 71 (11.3%)    | 18 of 46 (39.1%)    | 20 of 34 (58.8%)    |                      |
| No diabetes       | 51 of 251 (20.3%)  | 91 of 189 (48.1%)   | 104 of 153 (68.0%)  |                      |
| **Hypertension**  |                    |                     |                     | 0.2727               |
| diagnosis         |                    |                     |                     |                      |
| With hypertension | 43 of 231 (18.6%)  | 83 of 177 (46.9%)   | 96 of 144 (66.7%)   |                      |
| No hypertension   | 16 of 91 (17.6%)   | 26 of 58 (44.8%)    | 28 of 43 (65.1%)    |                      |
Table 3 continued

| Variable          | Failed at 6 months | Failed at 12 months | Failed at 18 months | Log-rank Probability |
|-------------------|--------------------|---------------------|---------------------|----------------------|
|                   | 59 of 322 (18.3%)  | 109 of 235 (46.4%)  | 124 of 187 (66.3%)  |                      |
| Number of other medications |                    |                     |                     | 0.3694               |
| ≥3                | 27 of 125 (21.6%)  | 46 of 93 (49.5%)    | 51 of 74 (68.9%)    |                      |
| 0-2               | 32 of 197 (16.2%)  | 63 of 142 (44.3%)   | 73 of 113 (64.6%)   |                      |
| Statin use        |                    |                     |                     | 0.0004*              |
| Not user          | 32 of 134 (23.9%)  | 61 of 111 (55.0%)   | 68 of 88 (77.3%)    |                      |
| User              | 27 of 188 (14.4%)  | 48 of 124 (38.7%)   | 56 of 99 (56.6%)    |                      |

*Significant result p<0.05, CHD=Coronary Heart Disease
Table 4: Testing of the no interaction assumption for the stratification variable hypertension

| Model                              | -2L       |
|------------------------------------|-----------|
| full model (with interaction terms for hypertension) | 1196.272  |
| Reduced model                      | 1200.259  |

Difference = 1200.295 - 1196.272 = 3.987, Not significant at df = 7, chi-square = 14.07, (0.5 < p < 0.9)

Table 5: Interaction assessment for variables included in the multivariate survival analysis model by the chunk test

| Model                                      | -2L       |
|--------------------------------------------|-----------|
| 3ways, 2ways, 1s (full model)             | 1178.199  |
| 2ways and 1s (reduced + 2ways)            | 1195.211  |
| 1s (reduced model)                        | 1200.259  |

Differences: 1195.211 - 1178.199 = 17.012, Not significant at df = 15, chi-square = 25, (0.1 < p < 0.5)

1200.295 - 1195.211 = 5.084, Not significant at df = 6, chi-square = 12.59, (0.5 < p < 0.9)
Table 6 Multivariate survival analysis model for new users of lipid-lowering agents in an elderly population enrolled in a Medicare managed care health plan (n=322)

| Variable          | β       | HR = e^β | Confidence interval        | Probability |
|-------------------|---------|----------|-----------------------------|-------------|
| Plan              | -0.13143| 0.877    | 0.610-1.260                 | 0.4777      |
| Gender            | -0.38646| 0.679    | 0.458-1.007                 | 0.0542      |
| Age               | 0.07065 | 1.073    | 0.745-1.547                 | 0.7048      |
| CHD Diagnosis     | -0.22617| 0.798    | 0.549-1.160                 | 0.2363      |
| Diabetes Diagnosis| -0.35411| 0.702    | 0.434-1.135                 | 0.1490      |
| #of Other medications | 0.20606 | 1.229  | 0.833-1.812                 | 0.2983      |
| Statin use        | -0.62378| 0.536    | 0.375-0.766                 | 0.0006      |

*Significant result p<0.05, HR=Hazard ratio, CHD=Coronary Heart Disease*
Table 7 Confounding assessment for the multivariate survival analysis model of new users of lipid-lowering agents in an elderly population enrolled in a Medicare managed care health plan (n=322)

| Model                      | β     | HR=$e^\beta$ | Confidence interval | Probability |
|----------------------------|-------|--------------|---------------------|-------------|
| Full                       | -0.13143 | 0.877       | 0.610-1.260         | 0.4777      |
| Full-gender                | -0.14542 | 0.865       | 0.601-1.243         | 0.4328      |
| Full-age                   | -0.13375 | 0.875       | 0.609-1.257         | 0.4698      |
| Full-CHD diagnosis         | -0.13173 | 0.877       | 0.610-1.259         | 0.4760      |
| Full-Diabetes diagnosis    | -0.14740 | 0.863       | 0.601-1.239         | 0.4250      |
| Full-#of other medications | -0.12280 | 0.884       | 0.616-1.270         | 0.5063      |
| Full-statin use            | -0.14870 | 0.862       | 0.600-1.238         | 0.4208      |

CHD = Coronary Heart Disease

Table 8 Changes in hazards ratio with different control variables in the survival analysis model for new users of lipid-lowering agents in an elderly population enrolled in a Medicare managed care health plan (n=322)

| Model                          | β     | HR=$e^\beta$ | Confidence interval | Probability |
|--------------------------------|-------|--------------|---------------------|-------------|
| Controlled for all variables   | -0.13143 | 0.877       | 0.610-1.260         | 0.4777      |
| Controlled for statin use      | -0.16087 | 0.851       | 0.594-1.221         | 0.3820      |
Figure 1 Adjusted survival curves for members of the full drug benefit plan and members of the $1000 maximum or no drug benefit plan in an elderly population of new users of lipid-lowering agents enrolled in a Medicare managed care health plan stratified by hypertension (n=322)

Plot of $S_1 \times \text{time}$. Symbol is value of plan.

NOTE: 42 obs hidden time
Figure 2 Adjusted survival curves for members of the full drug benefit plan and members of the $1000 maximum or no drug benefit plan among hypertensive patients in an elderly population of new users of lipid-lowering agents enrolled in a Medicare managed care health plan (n=322)

Plot of S11*time. Symbol is value of plan.

NOTE: 31 obs hidden time
Figure 3 Adjusted survival curves for members of the full drug benefit plan and members of the $1000 maximum or no drug benefit plan among non-hypertensive patients in an elderly population of new users of lipid lowering agents enrolled in a Medicare managed care health plan (n=322)

Plot of $S12$*time. Symbol is value of plan.

NOTE: 6 obs hidden.
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Predictors of prescriber's choice among three statins: Influence of drug benefit plan option.

ABSTRACT

Background Many health maintenance organizations (HMOs) have implemented programs providing varying degrees of annual drug coverage for Medicare beneficiaries enrolled in their plans. The unintended effects of such policies are important to consider. The beneficial effects of the statins class of dyslipidemic agents are widely documented. Fluvastatin can reduce low-density lipoprotein cholesterol (LDL-C) by 20-30%, which is enough to achieve the National Cholesterol Education Program (NCEP) target in most patients with high cholesterol and is the most cost-effective in this range of LDL-C reduction. When a higher degree of cholesterol reduction is required other, more expensive, statins may be more appropriate.

Objective To determine the effect of drug plan benefit options among elderly patients enrolled in managed care on the type of statin prescribed based on their relative cost.

Methods A retrospective cohort study using 484 older adult members in a Massachusetts HMO who were prescribed a statin between September 1, 1994 and June 30, 1996 and who had no prior dispensing during the previous one year prior to September 1, 1994.
Logistic regression analysis was used to examine differences in type of statin prescribed between different drug benefit plans controlling for potential confounding effects of patient sex, age ≥70, hospitalization for CHD prior to initial prescription, hypertension or diabetes mellitus diagnoses prior to initial prescription, and physician prescriber specialty.

**Results** There was no significant association between the drug benefit plan option and statin type prescribed (OR=0.654; CI=0.376-1.139; p=0.1335) after controlling for potential confounders. There were no significant associations with other predictor variables as well.

**Conclusions** Among the 3 on-formulary statin drugs available for prescribing (pravastatin, lovastatin and fluvastatin), fluvastatin was the most widely prescribed. The results demonstrated that the drug benefit plan options did not affect the selection among statin drugs, based upon their relative cost. Further investigation using initial lipid levels is needed to investigate whether the more expensive drugs are being used in patients in need of further lowering of LDL-C beyond the capacity of fluvastatin, and that target cholesterol levels are being achieved among all patients to gain the potential benefit of these drugs.
BACKGROUND

High cholesterol, specifically elevated low-density lipoprotein cholesterol (LDL-C), is a major cause of Coronary Heart Disease (CHD) [1-4], a link that was first made by the Framingham Heart Study [5]. Despite marked declines in mortality during this century [6-8], CHD continues to be the leading cause of death among the US population [9-11] and worldwide [10, 12]. Cardiovascular disease accounts for 950,000 deaths annually in the US including 460,000 from CHD [9]. Eight-five percent of those who die from CHD are 65 years of age or older [9]. In 1990, there were 489,171 deaths attributed to CHD [6], and 675,000 patients were discharged from US hospitals with a primary diagnosis of myocardial infarction [13]. Hospitalization for CHD continues to increase [7]. The prevalence of nonfatal CHD among US adults aged 40 and above was reported to be 11.8% [11]. It remains an important disease with significant burden. Estimated yearly costs of CHD for medical treatment and lost wages in the US range between $50 billion and $100 billion [2, 9,14].

Currently, the American Heart Association estimates that 70 million adults in the US have total cholesterol levels>200mg/dl, and that at least 40% of these individuals have cholesterol levels in excess of 240mg/dl [9,15]. The number of adults eligible for lipid modifying therapy was recently increased in the NCEP ATPIII guidelines to more than 65 million [3, 15].

Statin drugs have assumed a major role in the treatment of LDL-C elevations. They are reversible inhibitors of HMG-CoA reductase. By inhibiting the rate-limiting step in cholesterol biosynthesis, these drugs reduce intracellular cholesterol stores.
Increased numbers of LDL receptors are then generated, thereby restoring intracellular cholesterol homeostasis and accelerating clearance of LDL-C from the plasma [16, 17].

The beneficial effects of cholesterol-lowering using these drugs are well documented through five landmark trials showing reductions in cardiovascular events in a diversity of patient populations, representing the continuum of individuals at risk for CHD [18]. The Scandinavian Simvastatin Survival Study (4S) [19] demonstrated improved survival and fewer cardiovascular events in hyperlipidemic CHD patients. The Cholesterol and Recurrent Events (CARE) [20] and the Long-term Intervention with Pravastatin in Ischemic Disease (LIPID) [21] extended the benefits to CHD patients with average cholesterol levels. In patients without CHD, evidence of benefit is provided by high risk primary prevention in men without a history of myocardial infarction (MI) who were treated with pravastatin and diet in the West of Scotland Coronary Prevention Study (WOSCOPS) [22], and with low and moderate risk primary prevention in men and women with below average high density lipoprotein cholesterol (HDL-C) levels treated with lovastatin and diet in the Air Force Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TEXCAPS) [23] that extended the benefits to a substantial portion of the population.

A meta-analysis by Gould et al. [1] reinforced the beneficial effects of these agents. It showed that the reduction of CHD and total mortality by LLAs could be explained by their lipid-lowering ability. The declines in CHD mortality this century [6-8] can in large part be explained by the improvement in treatments and secondary prevention of MI [7].
Statins are the most widely prescribed lipid-lowering agents [24-28]. They are recommended as first-line agents when drugs are indicated to achieve treatment goals [3, 27, 29, 30]. They are the most effective in reducing LDL-C, and the best tolerated among LLAs [26, 29, 30].

During the 1990s, increasing numbers of Medicare beneficiaries were becoming enrolled in managed care plans. Between 1989 and 1994, the HMO share of Medicare almost doubled [31]. In 1997, managed care enrolled 14.9% of the Medicare population (5.6 million) [32], and in 2000, about 16% of Medicare patients were enrolled in Medicare plans associated with HMOs [33]. These differ from traditional Medicare plans in that the enrollees receive their coverage from the HMO rather than individual providers in private practice [33].

The growth in medical care expenditures is an important issue. The cost of pharmaceuticals has been reported to be among the fastest-rising components of healthcare costs, with a 17.3% increase in national expenditures for prescription drugs from 1999 to 2000 [34]. Spending on prescription drugs has increased at double-digit rates for the past decade and is now the third largest component of healthcare expenditures behind hospital care and physician services [35]. Policy responses have included limits on prescription costs, restriction on the supply of healthcare, and shifting of the financial risk to providers and beneficiaries [36-38]. Patient cost-sharing through deductibles, coinsurance, and co-payments is one technique increasingly being used to contain medical costs in general, and prescription costs in particular, to deter patients from unnecessary use [36-39]. The unintended effects of such policies are important to consider. There is a concern that necessary utilization
could be reduced, which may in turn increase the risk of adverse health consequences and resulting costs [34, 36-38, 40-42]. Cost-sharing does not affect everyone equally; those with small incomes, like many older adults are more likely to reduce use than those with higher incomes [43]. Low income populations appear to be sensitive to drug co-payments as low as 10-15% of average prescription expenses, with declines of 5-10% observed in drug utilization [44]. Research has shown that Medicare patients who lack coverage receive fewer prescription medications than those with coverage [41, 45, 46]. Other studies have shown the negative effect of reducing drug coverage among the poor elderly and the consequences of inadequate coverage for older adults receiving medications that can prevent serious adverse health consequences [34, 47].

From January 1994 to December 1998, older adult members in an HMO in central Massachusetts were able to choose among 3 drug benefit plans: full drug coverage, a drug benefit plan with a maximum of $1000/year in coverage, and no drug benefit plan. Our objective was to examine the effect of this policy on the type of statin prescribed based on its price. Eighty-five percent of 132 physicians surveyed in eastern Massachusetts reported that inability to afford medication was a problem for some of their patients [48], and physicians may respond to the economic needs of their patients when prescribing drugs [49].

There are currently 5 available statins in the market: atorvastatin, fluvastatin, lovastatin, pravastatin, and simvastatin [50]. Although studies have indicated that fluvastatin on a mg to mg basis is less potent than other statins in reducing LDL-C [51-53], it has been shown to reduce LDL-C by 20-30% [50, 51, 54]- which is enough to achieve the National Cholesterol Education program (NCEP) target LDL-C in most
patients with high cholesterol [2, 3]. Priced at 40% lower than other statins, based on
the annual wholesale cost of therapy per 1% reduction of LDL-C [54, 55], it is the
most cost-effective in this range of LDL-C reduction [17, 53-56]. In high-risk patients,
not the majority, when a higher degree of cholesterol reduction is required [2, 3],
higher potency statins—simvastatin [17, 56] and atorvastatin [56]—appear to be more
appropriate.

In a study assessing the impact of switching from simvastatin to fluvastatin in
an attempt to curb rising pharmaceutical cost after reference pricing was introduced in
New Zealand [57], there was a significant increase in cholesterol, LDL-C and
triglycerides (p<0.01). The elevation was less pronounced when higher incremental
doses of fluvastatin were used, so the lipid elevation relates to both lesser potency of
fluvastatin and under-dosing. This was in a patient population requiring more than
30% reduction in LDL-C to reach therapeutic goals (eligible for subsidized statin
therapy). In such high-risk populations, significant lipid elevations may conceivably
produce excess vascular events. Sub-therapeutic treatment may prove more costly than
savings from reference pricing [57].

Prescribing of more expensive drugs in the more comprehensive drug benefit
plans with small or no increase in therapeutic benefit may cause an unnecessary rise in
cost. At the same time, optimal LDL-C reduction may not be achieved in high-risk
patients if cheaper drugs are prescribed because of the drug benefit option, and
prescribing less expensive but lower potency agents may be more costly than savings
in the price of the drug in the long run. This study examined the implications of drug
benefit plan options among Medicare beneficiaries enrolled in managed care on the
type of statin drug prescribed. We hypothesized that members of full coverage drug
benefit plan were prescribed the higher priced statins more often than members of the
$1000 maximum or no coverage plan members.
METHODS

Data source and study population

This research is a retrospective cohort study among older adult enrollees (Medicare beneficiaries) of an HMO operating in central Massachusetts, who were continuously enrolled in the plan during the period of July 1, 1993 – June 30, 1996, and were prescribed an LLA. These members were able to choose among 3 drug benefit options starting January 1, 1994: full coverage for prescription drugs, a maximum of $1000/year in coverage, or no drug coverage. Those selecting full coverage paid an additional premium of $72.50/month ($870/year). Those with a $1000 maximum coverage paid an additional $39.16/month ($469.92/year). Those without coverage paid no additional premium.

Information on demographic characteristics, drug benefit plan type, prescriptions, ambulatory visits, hospitalization, and diagnoses was available for this population cohort. The population cohort was comprised of 2229 members. We deleted 325 members who switched from the original plan chosen on January 1, 1994, since we were unable to explore the effects of the type of drug benefit as a main predictor of the type of statin in these individuals. Of those, 251 (77.2%) switched from the full coverage plan, 61 (18.8%) from the $1000 maximum plan, and 13 (4.0%) from the no coverage plan. The final plans chosen by these patients were the full coverage plan in 89 patients (27.4%), the $1000 maximum plan in 186 (57.2%), and the no coverage plan in 50 (15.4%).
We then identified patients with a statin prescription between September 1, 1994 and June 30, 1996 among individuals with no prior dispensing of statin drugs in the one-year period before September 1, 1994, in order to identify relatively new users of statins. The definition of new users has been used in previous research [58, 59]. September 1, 1994 was chosen as a starting date because it is the date that fluvastatin was added to the HMO formulary.

The dependent variable in the analysis was the type of statin drug received categorized into 2 groups based upon expense, pravastatin and lovastatin in one group as the more expensive drugs, and fluvastatin in the other group as the less expensive type. These 3 statins were the only ones available in the HMO formulary at the time of the study. Pravastatin and fluvastatin were preferred drugs in the formulary during that time period. Our main predictor of statin-prescribing patterns was type of drug benefit plan option. Other covariate predictors included age, gender, prescriber specialty, previous hospitalization for CHD, diabetes, and hypertension. These comorbidities were included since they are among the risk factors for CHD in the NCEP ATPII guidelines [2]. Age was categorized into two groups (below 70 years and 70 years or older).

A patient was considered to have CHD if there was a hospitalization for CHD or a diagnosis for CHD (ICD-9 code= 410-414) prior to the statin prescription or during the one year prior to the study period. Patients with a diabetes diagnosis (ICD-9 code=250) prior to the statin prescription or during the one year prior to the study date were labeled diabetic, and patients with a hypertension diagnosis (ICD-9 code= 401-405) prior to the statin prescription or during the one year prior to the study date were
regarded as having hypertension. Finally, physician prescriber specialty was
categorized into cardiologists and noncardiologists.

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**Statistical analyses**

Descriptive statistics were used to determine various patient characteristics. Parametric assessment of age was carried out to examine the linearity of the association of age with the dependent variable.

Bivariate analyses were used to assess the relationship between different independent variables and the dependent variable through chi-square analyses. Then, logistic regression was carried out to examine the association of each independent variable with the dependent variable separately. Results were presented as odds ratios with 95% confidence intervals.

Co-linearity between various variables in the model was tested utilizing SAS proc corr. as suggested by Delwiche and Slaughter [60], to give correlation coefficients described by Johnson and Bhattacharyya [61].

Interaction assessment using the chunk test as described by Kleinbaum [62] calculated the difference between \(-2L\) statistics of the full and reduced models. The full model has interaction terms while the reduced does not. Testing for significance was carried out using chi-square distribution with degrees of freedom equal to the number of interaction terms (difference in terms between the 2 models). A difference in \(-2L\) value that was less than the chi-square statistic indicated no significant interaction. In case of significance (\(p<0.05\)), further evaluation of each of the interaction terms was carried out, and interaction terms with probabilities of more than 1% were dropped from the subsequent multivariate model.

A multivariate logistic model with all independent variables and the outcome variable was then formulated. Potential confounding was addressed by removing each
variable alone from the model and assessing the effect on the parameter estimate of the main predictor variable. Statistical significance was set at $p<0.05$, and the estimates were reflected by a 95% confidence interval. All statistical analysis was carried out using SAS statistical package version 8.1.
RESULTS

Descriptive statistics

A total of 484 patients met our inclusion criteria and were selected for the study. The mean age of these patients was 70.7 years of age. There were more female patients (n=287; 59.3%) than males (n=197; 40.7%) in our study population.

More than half of the patients were covered by the full coverage drug benefit plan (n=320; 66.1%), 30.4% by the partial coverage plan (n=147), and a small percentage by the no coverage drug benefit plan (n=17; 3.5%). Most of the prescriptions were written by internal medicine physicians (n=380; 78.5%). Cardiologists accounted for 7.9% (n=38) of the prescriptions, other specialties for 12.8% (n=62), and we could not determine the specialty of the prescriber for four (0.8%) of our patient population.

Approximately half of this patient population was hospitalized for CHD prior to the initial LLA prescription (n=243; 50.2%), 24.2% had a diabetes diagnosis prior to the initial prescription (n=117), and most had a hypertension diagnosis prior to the initial prescription (n=340; 70.3%). Fluvastatin was the most prescribed statin accounting for 87.4% (n=423) of the prescriptions. Pravastatin accounted for 9.3% (n=45) of the prescriptions, while lovastatin for 3.3% (n=16). This information is summarized in Table 1.

The coding of various variables in subsequent bivariate and multivariate analyses is presented in Table 2. Because of the low percentage of patients in the no coverage plan benefit, drug benefit plan type was further categorized as full coverage (n=320; 66.1%) versus partial or no coverage (n=164; 33.9%). Physician prescriber
specialty was categorized further into cardiologists (n=38; 7.9%) and noncardiologists (n=446; 92.2%). Age was converted into a dichotomous variable with age below 70 years in one group (n=221; 45.7%), and 70 years or older in the other group (n=263; 54.3%), based on a parametric assessment. Statin use, the outcome variable, was categorized into higher-priced statin (lovastatin and pravastatin) in one group (n=61; 12.6%) and lower-priced statin (fluvastatin) in the other (n=423; 87.4%).

Results of the bivariate chi-square analyses are presented in Table 3. Our main predictor variable, plan type, was not found to be significantly associated with the outcome variable of statin type prescribed (p=0.1230). The more expensive statins were prescribed in 10.9% of those with full coverage and 15.9% of partial or no coverage members. There were no significant associations between the other independent variables and the outcome variable as well.

In the univariate logistic regression model, the drug benefit plan type was also not significantly associated with the type of statin prescribed (OR=0.65; CI=0.377-1.126; p=0.1247). No significant associations were found between other independent variables and the outcome variable. These results are shown in Table 4.

Table 5 summarizes results of interaction assessment for the variables that were to be included in the model with the main predictor variable of plan type. No significant 3-way or 2-way interactions existed.

The multivariate logistic regression model showed no significant association between the drug benefit plan type and the outcome variable of statin drug type prescribed (OR=0.65; CI=0.376-1.139; p=0.1335). Other covariates- gender, age, prescriber specialty, CHD hospitalization prior to prescription, diabetes diagnosis prior
to prescription, and hypertension diagnosis prior to prescription—were also not significantly associated with the outcome variable. These results are presented in Table 6.

Results of confounding assessment are presented in Table 7. None of the variables removed caused major changes in the parameter estimate of the main predictor variable.
**DISCUSSION**

Administrative databases provide a cost-effective alternative to post-marketing clinical trials in a real world setting [63, 64], and provide a useful source of pharmacoepidemiologic assessments of drug utilization. Automated databases can be used to assess prescribing patterns and trends of drug use [65-67], impact of policies [68], and drug adherence [58, 59, 69-72].

In this study, we used data from an HMO operating in Massachusetts to study the effect of drug benefit plan options on the type of statin drug prescribed among new older adult users.

The study population had a high prevalence of CHD (50.2%), diabetes (24.2%), and hypertension (70.3%) compared to the reported prevalences in the general population [11, 73, 74], which is understandable considering it is a population of older adults being treated for hypercholesterolemia. Most patients also chose the full coverage benefit plan (66.1%), which can be explained by the higher drug use in this age group compared to younger patients [75, 76].

Most prescriptions were written by internists (78.5%), which is consistent with previous reports of internists having more patients on LLAs compared to cardiologists and family physicians [25, 77].

The majority of our patients (87.4%) were on fluvastatin. Fluvastatin has been shown to reduce LDL-C by 20-30% in doses 20-80mg [50, 51, 54], which is enough to achieve the NCEP target LDL-C in most patients with high cholesterol [2, 3]. Furthermore, Jacocot et al. demonstrated that fluvastatin 40mg provided more LDL-C reduction (with 30.4% reduction) than pravastatin 20mg (with 26.4% reduction) after
16 weeks of treatment. Priced at 40% lower than other statins, based on the annual wholesale cost of therapy per 1% reduction of LDL-C [54, 55], it is the most cost-effective in this range of LDL-C reduction [17, 53-56]. The HMO also had a negotiated price that was even lower for fluvastatin, making the price difference with other statins even higher.

Furthermore, the majority of prescriptions for statin drugs are written for low doses that produce moderate levels of LDL-C reductions. A 1993 audit [78] of usage of HMG-CoA reductase inhibitors showed that in 72% of instances, lovastatin was written in doses not exceeding 20mg daily (expected LDL reduction <24%), simvastatin in 64% of the cases was used in doses not exceeding 10mg/day (expected LDL-C reduction <28%), and pravastatin in 88% of the cases was used in doses not exceeding 20mg daily (expected LDL-C reduction <25%) [56]. Another study in South Africa reported patients on pravastatin to be using a relatively low dose (average =12.5mg; SD= 5.1) [28]. These drugs are most commonly used in doses that reduce LDL-C by 20-30%, the range where fluvastatin is the most cost effective [17, 53-56, 79].

An association between insurance type and cost of drugs prescribed has been previously reported [49, 80], and patients who pay out of pocket have also been reported to receive lower cost drugs [46, 49, 80, 81]. Mott et al. reported that indemnity patients and uninsured were found to be dispensed brand names and generic drugs of lower cost compared to private third party and Medicaid patients, suggesting that physicians may respond to the economic needs of their patients when prescribing drugs [49], as persistence with these medications [58, 72, 82, 83]- as well as inability
to afford them-[48, 84-86] is a concern. These studies, however, did not control for factors that may affect the price of product chosen, including demographic variables and patient comorbidities [46, 49], and were not specific to statins [46, 49, 80]. The final choice among different agents is left to the clinical judgment of physicians [2, 3, 27].

In this study, the drug benefit plan type was not found to be significantly associated with the outcome variable of statin type prescribed in the chi-square (p=0.1230), bivariate logistic regression model, (OR=0.65; CI=0.377-1.126; p=0.1247), or multivariate logistic regression model (OR=0.65; CI=0.376-1.139; p=0.1335). Although we did not have information on the initial LDL-C levels of our patients prior to the prescription or their exact target LDL-C level, we have controlled for risk factors that affect the target level LDL-C when possible in the multivariate model, which may to some extent be indicative of the amount of lowering needed. At the time of the study, NCEP ATPII [2] guidelines were available. Risk factors for CHD included age (≥45 for men ≥55 or premature menopause for women), family history of premature heart disease, current smoking, hypertension, low high-density lipoprotein cholesterol (<35mg/dl), and diabetes mellitus. Having 2 or more risk factors placed the patient in an intermediate risk group with target LDL-C of 130mg/dl, while having CHD placed the patient in the highest risk group with target LDL-C of 100mg/dl. The target levels and risk factors are presented in Table 8. We controlled for diabetes, hypertension, and CHD, prior to the prescription, as well as for age, gender, and physician prescriber specialty. None of these factors were found to be associated with the type of statin drugs prescribed in bivariate or multivariate analyses.
This is understandable with regard to diabetes and hypertension, since having either of these diseases does not place the patient in the highest risk group, even though diabetes in the more recent guidelines (NECP ATPIII) is considered a coronary heart disease risk-equivalent that lowers the target LDL-C to 100mg/dl [3]. At the time of the study, that was not the case. As for CHD, we would expect that patients with CHD may need a higher percentage of lowering considering the lower target LDL-C of 100mg/dl, but we cannot be sure of this, since information on the initial LDL-C must be known to determine the exact percentage of lowering needed. It could be that most of the CHD patients in this cohort did not need more than 30% lowering. Furthermore, fluvastatin dose can be increased further to 80 mg, providing better LDL-C reduction [53]. CHD patients on fluvastatin might have been receiving higher doses or they might have been receiving combination therapy for further lowering. Combination therapy is safe, effective, well-tolerated, and can achieve lipid reductions that exceed those observed with high dose monotherapy, since the combination employs two different classes with complimentary mechanisms of action to give an additive effect [87, 88].

Our results demonstrated that the drug benefit plan options selected by the patient did not affect the type of statin drug prescribed, whether it is the more expensive or less expensive type, after controlling for potential confounders. While it is desirable for physicians to take into consideration the financial abilities of their patients to improve persistence, it would not be advantageous to compromise the potential benefit of therapy. This is especially true because many patients are not achieving their target LDL-C levels, a problem which is more prominent among the
older adults [89, 90]. Further investigation with documented initial cholesterol levels would give a clearer understanding of whether the more expensive drugs are being used in patients in need of further lowering of LDL-C beyond the capacity of fluvastatin, and that target cholesterol levels are being achieved among all patients.

LIMITATIONS

Several limitations to this study can be described. Regarding the dataset used, patients may fill their prescriptions from pharmacies outside the HMO network and thus will not be captured as users of statin drugs. This, however, is unlikely, since the drugs were provided at discounted prices for patients in these pharmacies, and the assumption that patients fill most of prescriptions within the pharmacy system under study has been confirmed in one HMO and 2 Veterans Affairs (VA) Medical Centers [91]. One study that tried to assess medication use outside the central pharmacy of the VA through a questionnaire found that 98.5% of patients reported using the central pharmacy as their only source of medication [71]. Characteristics of the population included may somewhat limit generalizability of results to the general population. The drug dispensed may sometimes be different from that prescribed by the physician and we can only capture that dispensed. Using new users of drugs may somewhat limit this problem.

We also have no information regarding incentives to physicians at the HMO for prescribing fluvastatin, the lowest priced drug and the most prescribed in this patient population, although we know that both fluvastatin and pravastatin were preferred drugs on the formulary. As with automated data, misclassification of patients
may have occurred, since we could not validate the information with medical charts, but would be of the nondifferential type. The data is relatively old, but it provides a unique opportunity to study the effect of drug benefit plan options and to compare changes in practice with the publication of recent guidelines, and with newer agents that were not on the formulary at the time of the study in a 'real world' setting.

Other limitations include lack of comprehensive clinical data including initial lipid levels. Such information would have allowed us to control for the exact amount of LDL-C lowering needed for the patients. Information on some potential confounders like family history of CHD and smoking status is also lacking. We also do not have information on income levels or coinsurances for our population cohort, and did not control for some potential influencing conditions like stroke.

Despite these limitations we believe our study provided evidence showing the absence of a significant association between the drug benefit plan option selected by the patients and type of statin prescribed.
CONCLUSION

Among the 3 on-formulary statin drugs available for prescribing (pravastatin, lovastatin and fluvastatin), fluvastatin was the most widely prescribed in this patient population. The results demonstrated that the drug benefit plan option did not affect choice among statins, whether it was the more expensive or less expensive type, after controlling for potential confounders including gender, age, physician prescriber specialty, CHD, diabetes, and hypertension diagnoses prior to the prescription. Further investigation with initial lipid levels is needed to determine whether more expensive drugs are being used in patients in need of further lowering of LDL-C beyond the capacity of fluvastatin, and whether target cholesterol levels are being achieved among all patients to gain the potential benefit of these drugs.
Table 1 Characteristics of new users of statin drugs in an elderly population enrolled in a Medicare managed care health plan (n=484)

| Characteristic                              | N     | %    |
|---------------------------------------------|-------|------|
| Gender                                      |       |      |
| Females                                    | 287   | (59.3%) |
| Males                                       | 197   | (40.7%) |
| Age                                         |       |      |
| Mean                                        | 70.7  |      |
| SD                                          | 4.5   |      |
| Plan type                                   |       |      |
| No coverage                                 | 17    | (3.50%) |
| $1000 max                                   | 147   | (30.4%) |
| Full coverage                               | 320   | (66.1%) |
| Prescriber specialty                        |       |      |
| Cardiology                                  | 38    | (7.90%) |
| Internal medicine                           | 380   | (78.5%) |
| Others                                      | 62    | (12.8%) |
| Missing                                     | 4     | (0.80%) |
| CHD diagnosis prior to prescription         |       |      |
| CHD diagnosis                               | 243   | (50.2%) |
| No CHD diagnosis                            | 241   | (49.8%) |
| Diabetes diagnosis prior to prescription    |       |      |
| DM diagnosis                                | 117   | (24.2%) |
| No DM diagnosis                             | 367   | (75.8%) |
| Hypertension diagnosis prior to prescription|       |      |
| HTN diagnosis                               | 340   | (70.3%) |
| No HTN diagnosis                            | 144   | (29.8%) |
| Statin drug prescribed                      |       |      |
| Fluvastatin                                 | 423   | (87.4%) |
| Pravastain                                  | 45    | (9.30%) |
| Lovastatin                                  | 16    | (3.30%) |

SD=Standard deviation, CHD= Coronary Heart Disease, DM=Diabetes Mellitus, HTN=Hypertension
Table 2 Coding and distribution of variables among new users of statin drugs in an elderly population enrolled in a Medicare managed care health plan (n=484)

| Variable                        | Yes =1*  | No =0*  |
|---------------------------------|----------|---------|
| Plan type (full coverage)       | 320 (66.1%) | 164 (33.9%) |
| Gender (male)                   | 197 (40.7%) | 287 (59.3%) |
| Age ≥70                         | 263 (54.3%) | 221 (45.7%) |
| Prescriber specialty (cardiologist) | 38 (7.9%) | 446 (92.1%) |
| CHD diagnosis                   | 243 (50.2%) | 241 (49.8%) |
| Diabetes diagnosis              | 117 (24.2%) | 367 (75.8%) |
| Hypertension diagnosis          | 340 (70.3%) | 144 (29.8%) |
| Higher priced statin (pravastatin or lovastatin) | 61 (12.6%) | 423 (87.4%) |

*Coded as 1 or 0 in the logistic regression model. CDH= coronary heart disease
Table 3 Distribution of patients with regard to different variables and the outcome variable of statin drug type among new users of statin drugs in an elderly population enrolled in a Medicare managed care health plan (n=484)

| Plan type                  | Lower priced statin N=423 (87.40%) | Higher priced statin N=61 (12.60%) | Total N=484 (100%) | probability |
|----------------------------|------------------------------------|------------------------------------|--------------------|-------------|
| Full coverage %            | 285 (89.0%)                        | 35 (10.9%)                         | 320 (100%)         | 0.1230      |
| Partial / no coverage %    | 138 (84.2%)                        | 26 (15.9%)                         | 164 (100%)         |             |
| Gender                     |                                     |                                    |                    | 0.8173      |
| Male %                     | 173 (87.8%)                        | 24 (12.2%)                         | 197 (100%)         |             |
| Female %                   | 250 (87.1%)                        | 37 (12.9%)                         | 287 (100%)         |             |
| Age %                      |                                     |                                    |                    | 0.2894      |
| ≥70 %                      | 226 (85.9%)                        | 37 (14.1%)                         | 263 (100%)         |             |
| <70 %                      | 197 (89.1%)                        | 24 (10.9%)                         | 221 (100%)         |             |
| Prescriber specialty       |                                     |                                    |                    | 0.5376      |
| Cardiologist %             | 32 (84.2%)                         | 6 (15.8%)                          | 38 (100%)          |             |
| Non-cardiologist %         | 391 (87.7%)                        | 55 (12.3%)                         | 446 (100%)         |             |
| Diagnosis               | Lower priced statin (N=423) | Higher priced statin (N=61) | Total (N=484) | Probability |
|------------------------|-----------------------------|-----------------------------|---------------|-------------|
|                       | %                           | N                           |               |             |
| CHD diagnosis          |                             |                             |               |             |
| With CHD %             | 207                         | 36                          | 243           | 0.1410      |
|                        | (85.2%)                     | (14.8%)                     | (100%)        |             |
| No CHD %               | 216                         | 25                          | 241           |             |
|                        | (89.6%)                     | (10.4%)                     | (100%)        |             |
| Diabetes diagnosis:    |                             |                             |               |             |
| With diabetes %        | 103                         | 14                          | 117           | 0.8114      |
|                        | (88.0%)                     | (12.0%)                     | (100%)        |             |
| No diabetes %          | 320                         | 47                          | 367           |             |
|                        | (87.2%)                     | (12.8%)                     | (100%)        |             |
| Hypertension diagnosis |                             |                             |               |             |
| With hypertension %    | 301                         | 39                          | 340           | 0.2486      |
|                        | (88.5%)                     | (11.5%)                     | (100%)        |             |
| No hypertension %      | 122                         | 22                          | 144           |             |
|                        | (84.7%)                     | (15.3%)                     | (100%)        |             |

CHD = Coronary Heart Disease
Table 4 Univariate logistic regression for new users of statin drugs in an elderly population enrolled in a Medicare managed care health plan (n=484)

| IV                  | OR = $e^B$ | Confidence interval | Probability |
|---------------------|------------|---------------------|-------------|
| Plan type           | 0.652      | 0.377-1.126         | 0.1247      |
| 0 = partial / no coverage |           |                     |             |
| 1 = full coverage   |            |                     |             |
| Gender              | 0.973      | 0.541-1.623         | 0.8174      |
| 0 = female          |            |                     |             |
| 1 = male            |            |                     |             |
| Age                 | 1.344      | 0.777-2.325         | 0.2906      |
| 0 = age <75         |            |                     |             |
| 1 = Age ≥75         |            |                     |             |
| Prescriber specialty| 1.333      | 0.533-3.334         | 0.5384      |
| 0 = noncardiologist |            |                     |             |
| 1 = cardiologist    |            |                     |             |
| CHD diagnosis       | 1.503      | 0.871-2.590         | 0.1429      |
| 0 = no CHD          |            |                     |             |
| 1 = with CHD        |            |                     |             |
| Diabetes diagnosis  | 0.952      | 0.490-1.749         | 0.8115      |
| 0 = no diabetes     |            |                     |             |
| 1 = with diabetes   |            |                     |             |
| Hypertension Diagnosis | 0.718    | 0.409-1.262         | 0.2499      |
| 0 = no hypertension |            |                     |             |
| 1 = with hypertension|           |                     |             |

OR=odds ratio. CHD=Coronary Heart Disease
Table 5 Interaction assessment for variables included in the multivariate logistic regression model by the chunk test

| Model                                    | -2L    |
|------------------------------------------|--------|
| 3ways, 2ways, 1s (full model)            | 333.231|
| 2ways and 1s (reduced + 2ways)           | 346.042|
| 1s (reduced model)                       | 359.241|

Differences: 346.042-333.231=12.811, NS at df=15,  
chi-square=25, (0.1<p<0.5)

359.241-346.042=13.199, at df=6,  
chi-square=12.59 (0.025<p<0.5)

Lowest probability for interaction term=0.0149>0.01
Table 6 Multivariate logistic regression model for new users of statin drugs in an elderly population enrolled in a Medicare managed care health plan (n=484)

| Variable | β     | OR = e^β | CI      | Probability |
|----------|-------|----------|---------|-------------|
| Plan     | -0.4245 | 0.654 | 0.376-1.139 | 0.1335 |
| Gender   | -0.2069 | 0.813 | 0.457-1.446 | 0.4810 |
| Age      | 0.2929  | 1.340 | 0.765-2.349 | 0.3064 |
| Prescriber Specialty | 0.1767 | 1.193 | 0.462-3.080 | 0.7150 |
| CHD      | 0.4271  | 1.533 | 0.861-2.729 | 0.1468 |
| Diabetes Diagnosis | -0.0787 | 0.924 | 0.483-1.768 | 0.8120 |

OR=odds ratio, CI=Confidence Interval, CHD=Coronary Heart Disease
Table 7 Confounding assessment for the Multivariate logistic regression model of new users of statin drugs in an elderly population enrolled in a Medicare managed care health plan (n=484)

| Model                          | β     | OR=$e^\beta$ | CI      | Probability |
|--------------------------------|-------|---------------|---------|-------------|
| Full                           | -0.4245 | 0.654        | 0.376-1.139 | 0.1335      |
| Full-gender                    | -0.4295 | 0.653        | 0.375-1.137 | 0.1321      |
| Full-age                       | -0.4239 | 0.654        | 0.376-1.139 | 0.1337      |
| Full-Prescriber Specialty      | -0.4219 | 0.656        | 0.377-1.141 | 0.1357      |
| Full-CHD Diagnosis             | -0.4030 | 0.668        | 0.385-1.161 | 0.1526      |
| Full-Diabetes Diagnosis        | -0.4246 | 0.654        | 0.376-1.139 | 0.1334      |
| Full-hypertension Diagnosis    | -0.4588 | 0.632        | 0.364-1.096 | 0.1024      |

OR=odds ratio, CI=confidence Interval, CHD=Coronary Heart Disease
Table 8 Coronary heart disease risk groups based on Adult Treatment Panel II treatment recommendations.

| Coronary Heart Disease Risk Group | LDL-cholesterol to initiate diet mg/dl | LDL-cholesterol to initiate drug mg/dl | LDL-cholesterol goal mg/dl |
|----------------------------------|----------------------------------------|----------------------------------------|---------------------------|
| Without CHD* and <2 risk factors* | ≥160mg/dl                              | ≥190mg/dl                              | <160mg/dl                 |
| Without CHD* and with ≥2 risk factors* | ≥130mg/dl                              | ≥160mg/dl                              | <130mg/dl                 |
| With CHD*                         | >100mg/dl                               | ≥130mg/dl                              | ≤100mg/dl                 |

*CHD=Coronary heart disease.

* Positive risk factors for CHD include age (≥45 for men ≥55 or premature menopause for women), family history of premature heart disease, current smoking, hypertension, low high-density lipoprotein cholesterol (<35mg/dl), and diabetes mellitus. High-density lipoprotein (≥60mg/dl) is a negative risk factor.

Source: Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults: Summary of the second report of National Cholesterol Education Program (NCEP) expert panel on detection evaluation and treatment of high blood cholesterol in adults (Adult Treatment Panel II). JAMA 1993; 269:3015-3023.
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PART 2

Part 2 includes the following appendices:

Appendix A. Background and significance

Appendix B. Details of the methods

Appendix C. Overview of major findings

Appendix D. Kaplan Meier survival curves and log-log Kaplan Meier survival curves
APPENDIX A.  BACKGROUND AND REVIEW OF THE PROBLEM

The growth in medical care expenditures is an important issue. The cost of pharmaceuticals has been reported to be among the fastest-rising components of healthcare costs, with a 17.3% increase in national expenditures for prescription drugs from 1999 to 2000 [1]. Spending on prescription drugs has increased at double-digit rates for the past decade and is now the third largest component of healthcare expenditures behind hospital care and physician services [2]. Policy responses have included limits on prescription costs, restriction on the supply of healthcare, and shifting of the financial risk to providers and beneficiaries [3-5]. Patient cost-sharing through deductibles, coinsurance, and co-payments is one technique increasingly being used to contain medical costs in general, and prescription costs in particular, to deter patients from unnecessary use [3-6]. There is, however, a concern that necessary utilization could also be reduced, which may increase the risk of adverse health consequences and resulting costs [1, 3-5, 7-9]. When the Medicaid program in New Hampshire placed a limit of 3 reimbursable medications that a patient could receive per month, there was a 30% drop in the number of prescriptions filled per month among 10,734 enrollees, and a reduction in the use of essential medications like insulin and antihypertensives [10]. This, in turn, increased the risk of nursing home admissions and overall healthcare costs [11], since patients may simply shift the type of service sought to deal with the health problem [3]. Several other studies have reported a decrease in prescription filling due to cost-sharing [12-14]. Older adult patients are of particular concern since cost-sharing does not affect everyone equally;
those with small incomes, like many older adults, are more likely to reduce use than those with higher incomes [15].

The Medicare population is demographically different from the Medicaid population, and thus its response to such policies may differ. Research has shown, however, that Medicare patients who lack coverage receive fewer prescription medications than those with coverage [8, 16] and that medication restriction is common in older adults who lack prescription drug coverage [9]. Other studies have demonstrated the negative effect of reducing drug coverage among poor older adults and the consequences of inadequate coverage for the older adult patients receiving medications that can prevent serious adverse health consequences [1, 17].

Many health maintenance organizations (HMOs) have implemented programs providing varying degrees of annual drug coverage for Medicare beneficiaries enrolled in their plans. Older adult plan members in an HMO operating in Massachusetts were able to choose among 3 drug benefit options starting January 1, 1994: full coverage for prescription drugs, a maximum of $1000/year in coverage, or no drug coverage. This research looks into the effects of this policy on lipid-lowering agents (LLAs), a group of drugs of well-documented benefit for both primary [18-21] and secondary [22-26] prevention of coronary heart disease (CHD).

Despite marked declines in mortality during this century [27-29], CHD continues to be the leading cause of death among the US population [30-32] and worldwide [31, 33]. Cardiovascular disease accounts for 950,000 deaths annually in the US, including 460,000 from CHD [30]. Eighty-five percent of those who die from CHD are 65 years of age or older [30]. In 1990, there were 489,171 deaths attributed
to CHD [27], and 675,000 patients were discharged from US hospitals with a primary diagnosis as myocardial infarction [34]. Hospitalization for CHD continues to increase [28]. The prevalence of nonfatal CHD among US adults aged 40 and above was reported to be 11.8% [32]. It remains an important disease with significant burden. Estimated yearly costs of CHD for medical treatment and lost wages in the US range between $50 billion and $100 billion [30, 35, 36]. The aging population, increased prevalence of diabetes and hypertension, and growing number of overweight Americans can explain the persistence of CHD as the leading cause of death [37]. The declines from previous years can, in part, be explained by the improvement in treatments and secondary prevention of MI [28].

High cholesterol, specifically elevated low-density lipoprotein cholesterol (LDL-C), is a major cause of CHD [35, 37, 38, 39], a link that was first made by the Framingham Heart Study [40].

Twenty-eight percent of US adults over age 20 have hyperlipidemia that warrants treatment [41], based on the National Health and Nutrition Examination Survey (NHANES) III phase 2 data (collected from 1991-1994) and the 1993 National Cholesterol Education Program (NCEP) recommendations that were the standard of practice at the time of the study [35].

Currently the American Heart Association estimates that 70 million adults in the US have total cholesterol levels>200mg/dl, and that at least 40% of these individuals have cholesterol levels in excess of 240mg/dl [30,42]. The number of adults eligible for lipid-modifying therapy was recently increased in the NCEP ATP III guidelines to more than 65 million [39, 42]. Furthermore, guidelines recognize that
the majority of these patients will require drug therapy to achieve target cholesterol levels goals [39, 43].

Currently, there are 4 major classes of LLAs in use: statins, bile-acid-binding resins, nicotinic acid, and fibrates [31]. The first objective of this research project was to describe LLA use among a group of Medicare beneficiaries enrolled in managed care with high cholesterol levels. We examined the LLAs prescribed during a one-year period and compared this utilization with various patient characteristics including gender, age group, prescriber specialty, comorbidities (CHD, diabetes, hypertension), and choice of drug benefit plan option. This was carried out for both new and prevalent users during the one-year period. The study provides insight into ‘real world’ patterns of LLA drug use and variation among sub-populations.

The second objective of this research was to investigate the effects of the drug benefit plan options on the persistence of lipid-lowering therapy.

Persistence of cholesterol-therapy is expected to be a problem, based on previous reports showing that compliance with drug therapy for chronic diseases is frequently sub-optimal [44]. The cumulative treatment discontinuation among long-term regimens of all types is about 50% of patients at the first year [44-51], and there are no reasons for persistence in LLAs to be any different [44]- especially that hypercholesterolemia is a chronic condition that is perceived by the patient as having deleterious health consequences that are far in the future [52].

The public health importance of persistence for gaining a widespread benefit from LLA is emphasized by the dominance of atherosclerotic disease as the major cause of morbidity and mortality in the United States [27, 32, 34], and the efficacy of
cholesterol drugs in obtaining benefits in both primary [18-21] and secondary [22-26] prevention of CHD. The economical and widespread achievement of benefits depends on all risk-qualified patients obtaining a high level of persistence to these regimens of proven efficacy. Little is known about persistence to lipid-lowering therapy among older patients, since studies have preferentially enrolled younger patients or informed subjects they were being monitored, thus reducing generalizability of the results [53-55].

Financial incentives have been shown to improve compliance in patients [56]. Eighty-five percent of 132 physicians surveyed in eastern Massachusetts reported that inability to afford medication was a problem for some of their patients [57]. Thirty-eight of patients who discontinued their medication in a follow-up study one year after the conclusion of the 4S study, blamed acquisition costs [58]. Cost of medications was also found to be among factors contributing to noncompliance in the older adults [59]. Medicare patients who do not have prescription drug coverage face higher out of pocket expenditures and may not comply with their medications to save money [60].

Furthermore, Medicare beneficiaries with capped prescriptions have been shown to take steps to decrease their out of pocket prescription costs, including taking samples from physicians, taking less than the prescribed dose, and discontinuing the prescribed medication [61]. Still, research in older adult patients taking specifically LLAs has shown high discontinuation rates in patients with drug coverage [48, 55, 62, 63]. A study in British Columbia, where there are various levels of coverage provided by the provincial government, found no significant difference between adherent and non-adherent patients with respect to type of provincial coverage [64]. This research
explored the effects of drug benefit plans chosen among Medicare beneficiaries enrolled in managed care on persistence of LLAs. We hypothesized that patients with full coverage have lower discontinuation rates compared to those with partial or no coverage.

The third objective of this research was to explore the effects of the drug benefit plan options on the type of statin drug prescribed.

There are currently 5 available statins in the market: atorvastatin, fluvastatin, lovastatin, pravastatin, and simvastatin [65]. Although studies have indicated that fluvastatin on a mg to mg basis is less potent than other statins in reducing LDL-C [66-68], it has been shown to reduce LDL-C by 20-30% in doses 20-80mg [65, 66, 69] which is enough to achieve the NCEP target LDL-C in most patients with high cholesterol [35, 39]. Jacocot et al. demonstrated that fluvastatin 40 mg provided more LDL-C reduction (with 30.4% reduction) than pravastatin 20mg (with 26.4% reduction) after 16 weeks of treatment. The fluvastatin dose can be increased further to 80mg, providing better LDLC reduction [68]. Priced at 40% lower than other statins, based on the annual wholesale cost of therapy per 1% reduction of LDL-C [69, 70], it is the most cost-effective in this range of LDL-C reduction [68-72]. For higher degrees of LDL reduction, simvastatin [71, 72] and atorvastatin are more effective [72].

Furthermore, the majority of prescriptions for statin drugs are written for low doses that produce moderate levels of LDL-C reductions. A 1993 audit [73] of usage of HMG-Co-A reductase inhibitors showed that in 72% of instances, lovastatin was written in doses not exceeding 20mg daily (expected LDL reduction<24%), simvastatin in 64% of the cases was used in doses not exceeding 10mg/day (expected
LDL-C reduction <28%), and pravastatin in 88% of the cases was used in doses not exceeding 20mg daily (expected LDL-C reduction <25%) [72]. Thus, these drugs are most commonly used in doses that reduce LDL-C by 20-30%, the range where fluvastatin is the most cost effective [68-72, 74].

Still, in high-risk patients, not the majority, when a higher degree of cholesterol reduction is required, higher potency statins appear to be more appropriate [71, 72]. In a study assessing the impact of switching from simvastatin to fluvastatin in an attempt to curb rising pharmaceutical costs after reference pricing was introduced in New Zealand [75], there was a significant increase in cholesterol, LDL-C and TGs (p<0.01). The elevation was less pronounced when higher incremental doses of fluvastatin were used, so the lipid elevation relates to both lesser potency of fluvastatin and under-dosing. In high-risk populations, significant lipid elevations may conceivably produce excess vascular events. Sub-therapeutic treatment may prove more costly than savings from reference pricing [75].

An association between insurance type and costs of drugs prescribed has been previously reported by Mott et al. [76]. Private third party and indemnity prescriptions were more likely to be dispensed with brand name drugs compared to Medicaid and the uninsured. Also, indemnity patients and uninsured were found to be dispensed brand names and generic drugs of lower cost, suggesting that physicians may respond to the economic needs of their patients when prescribing drugs [76].

Patients who pay out of pocket have also been reported to receive lower cost drugs [77]. We examined the effects of drug benefit plan options on type of statin drug
prescribed and hypothesized that more expensive statins are more prescribed in the full coverage plan compared to the other two plans.

In sum, this research explored the effects of various degrees of annual drug coverage on prescribing and persistence of LLAs in a group of Medicare beneficiaries under managed care in a real world setting. It provides insight into the effects of such policies in this fastest growing age group [78], why target cholesterol levels are not always met, and factors affecting persistence as well as choice of LLA. It also gives rise to more questions in need of further investigations, like the effects in specific sub-populations such as those with higher risk and in need of relatively higher degrees of cholesterol lowering.
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APPENDIX B  
DETAILS OF THE METHODS

Data source and patient population

Data for research were provided by an HMO in central Massachusetts to the 
Department of Applied Pharmaceutical Sciences at the University of Rhode Island. 
Data consisted of several SAS datasets including demographic data, enrollment data, diagnosis data, referral data, and pharmacy data, with a unique patient identifier for linkage. In addition, one excel sheet for the physician specialties, and a drug dictionary that gave NDC codes of different drugs were provided. The data had information for 2229 patients who were continuously enrolled between July 1, 1993 and June 30, 1996, and had a prescription for an LLA.

The demographic data had the following variables:

ID: Unique patient identifier.

DOB: Patient date of birth; in mm/dd/yy format.

SEX: Male or female, (included as ‘M’ or ‘F’).

The enrollment data had 4956 lines for the 2229 patients and the following variables:

ID: Unique patient identifier.

EFFDATE: The effective date of starting enrollment in mm/dd/yy format

PLANTYPE: Drug coverage type with ‘X’ for full coverage, ‘N’ for no coverage, 
and ‘P’ for the $1000 maximum coverage.
**SPEC**: Number for the physician specialty.

**TERMDATE**: Termination date in *mm/dd/yy* format.

**TERMDESC**: Termination description which describes the reason for enrollment termination. Examples include ‘DOCTOR NUMBER CHANGE’, ‘DECEASED’, or ‘GROUP CONSOLIDATION-DIFFERENT BENEFITS’.

Thus, there were several observations per patient with a new observation for every termination reason.

The **diagnosis data** had 544132 diagnoses for the 2229 patients and the following variables:

**ID**: Unique patient identifier.

**DXDATE**: date of diagnosis in *mm/dd/yy* format.

**ICD1**: The ICD-9 code for diagnosis.

**SPEC**: Number for the physician specialty.

For each patient, diagnoses were in many cases repeated with multiple entries at different dates.

The **referral data** had 55988 referrals for the 2229 patients and the following variables:

**ID**: Unique patient identifier.

**ADMDATE**: Admission date in *mm/dd/yy* format.

**DCDATE**: Discharge date in *mm/dd/yy* format.
**ADMTYPE:** Admission type with 'I' for inpatient, 'O' for outpatient, and 'P' for professional visits.

**ICD1, ICD2, and ICD3:** Diagnoses codes (ICD-9 diagnoses codes).

**CPT1-CPT18:** Procedure codes.

For each patient, diagnoses were in many cases repeated with multiple entries at different dates.

The pharmacy data **(Rxs data)** had 435392 dispensings for the 2229 patients and the following variables:

- **ID:** Unique patient identifier.
- **DRGDATE:** Drug date.
- **NDCCODE:** NDC drug code
- **GENERIC:** Generic product identifier.
- **DRGNAME:** Drug name.
- **REFILL:** with 'F' for fill and 'R' for refill.
- **QUANT:** Quantity.
- **RXMD:** Prescribing physician number.
- **NOSCRIPT:** Number of scripts.

There was an observation for each dispensing.

An excel sheet provided 2 variables:

- **RXMD:** Prescribing physician number.
- **Specialty:** Stated the specialty of the physician.
Data cleaning and preparation:

Screening for missing data was carried out using SAS procedures such as PROC FREQ and PROC UNIVARIATE. A series of checks were conducted to check for duplicates and ensure the data was plausible. For example, records in enrollment data that had the termination date prior to the effective date were removed. A few patients had plantype in the enrollment data as ‘P’ or ‘N’ and a termination date prior to January 1, 1994, which is the starting date for the drug benefit plan type options. These were changed to ’U’ for unknown. All datasets were also separately merged with the demographic data by the ID to ensure the availability of all patient IDs.

The next step was to identify patients that had switched from the original drug benefit plan option chosen on January 1, 1994. This was carried out using the enrollment data, with ‘GROUP CONSOLIDATION-DIFFERENT BENEFITS’ for the termination description, and a termination date after January 1, 1994. A (0,1) variable was created to indicate switching with 1 as switching. A dataset was then created with switchers only and duplicates by ID were removed using the NODUPKEY option. This was then merged with all other datasets by ID, and switchers were then deleted. Among the 325 switchers identified, 251 (77.2%) switched from the full coverage plan, with 31 of 251 (12.4%) to the no coverage plan, 173 of 251 (68.9%) to the partial coverage, and 47 of 251 (18.7%) going back to the full coverage plan later in the study. Also, 61 (18.8%) of these 325 patients switched from the $1000 maximum plan, with 18 of 61 (29.5%) to the no coverage, 38 of 61 (62.3%) to the full coverage, and 5 of 61 (8.2%) going back to the $1000 maximum coverage later in the study. Finally, 13 (4.0%) of the 325 patients switched from the no coverage plan, 8 of 13
(61.5%) to the partial coverage, 4 of 13 (30.8%) to the full coverage, and 1 of 13 (7.7%) going back to the no coverage later in the study. The final plans chosen by these 325 patients were the full coverage plan in 89 patients (27.4%), the $1000 maximum coverage plan in 186 (57.2%), and the no coverage plan in 50 (15.4%).

By that, the resulting datasets were for 1904 patients who did not change the original plan chosen on January 1, 1994. These datasets were used in all other analyses for the 3 manuscripts.

**Manuscript 1 coding and analyses:**

For the first manuscript, the pharmacy data were then used to identify LLA prescriptions between July 1, 1995 and June 30, 1996. The first prescription was identified. NDC-codes provided by the drug dictionary were used to identify LLAs. Separate (0,1) variables were created to indicate statin, niacin, fibrates, and bile acid sequestrant drug use based on NDC codes.

The pharmacy data were also used to identify LLA prescriptions in the previous one year July 1, 1994 - June 30, 1995, and a (0,1) variable was created to indicate new or prevalent use of the different LLA classes based on availability of an old prescription or not. Thus, (0,1) variables indicating new statin (snew), new niacin (nnew), new fibrate (fnew), and new bile (bnew) were formed.

Combination therapy was also determined using the pharmacy data. A (0,1) combination variable (combin) was created, which was 1 if a patient had prescriptions for 2 drugs from 2 classes in month1 and month 2 (between June 1, 1995 and July 30, 1995) and again in month 3 and 4 (between August 1, 1995 and September 30, 1995). A patient was a new user if either of the 2 drugs were new. Combination users were no
longer considered monotherpay users (separate datasets for each monotherpay class were formed and patients who were combination users were removed and then the datasets were stacked again by the SET statement).

By that, we obtained a dataset with variables, ID, statin, niacin, fibrate, bile and combin, and snew, fnew, nnew, and bnew. Variables drgdate and RXMD was also kept.

Demographic data were used to determine the sex and age of these patients through merging by ID. Age, calculated from the DOB variable, was converted into three age groups: 65-69, 70-74, and above 75.

Enrollment data were used to obtain plan type chosen for the patients through merging by ID.

To obtain the physician prescriber specialty, the data on the excel sheet was imported into SAS and merged by RXMD. Prescriber specialty was categorized into internal medicine, cardiologists and others.

Comorbidities were determined by using both referral and diagnosis data and merging by ID. A patient was considered to have CHD if there was a diagnosis (ICD-9 codes 410-414) in the referral data with ADMDATE prior to DRGDATE, or a diagnosis in the diagnosis data with DXDATE prior to DRGDATE. A patient was considered to have diabetes if there was a diagnosis (ICD-9 codes 250) in the referral data with ADMDATE prior to DRGDATE, or a diagnosis in the diagnosis data with DXDATE prior to DRGDATE. A patient was considered to have hypertension if there was a diagnosis (ICD-9 codes 401-405) in the referral data with ADMDATE prior to DRGDATE, or a diagnosis in the diagnosis data with DXDATE prior to DRGDATE.
DRGDATE, or a diagnosis in the diagnosis data with DXDATE prior to DRGDATE. Thus, three (0,1) variables were obtained.

Each drug class was then stratified by the patient characteristics (sex, age group, plan type, physician prescriber specialty, CHD, diabetes, and hypertension) by PROC FREQ, and cross tabulation. CHISQ was also carried out. This was carried out for prevalent and then new users in each of the five classes of drugs.

**Manuscript 2 coding and analyses:**

For the second manuscript, we identified patients with prescriptions of LLAs using NDC-codes between July 1, 1994 and June 30, 1996. We deleted from them patients who had an LLA prescription between July 1, 1993 and June 30, 1996. The data was then transposed to create a dataset with one record per patient using the PROC TRANSPOSE procedure. Patients with first DRGDATE after January 1, 1996 were deleted. The type of LLA in the first prescription was identified as statin, fibrate, bile acid sequestrant, niacin, based on NDC-codes. It was later further categorized into a (0,1) variable indicating statin versus other LLAs.

Demographic data were used to determine the sex and age of these patients through merging by ID. Age, calculated from the DOB variable, was converted into two age groups: 70 and above, and below 70.

Enrollment data were used to obtain plan type chosen for the patients through merging by ID. Plan type was further categorized into a (0,1) variable with full coverage as 1 (PLANTYP ‘X’).

Comorbidities were determined by using both referral and diagnosis data through merging by ID. A patient was considered to have been hospitalized for CHD
if there was a diagnosis (ICD-9 codes 410-414) in the referral data with ADMDATE prior to DRGDATE of the first prescription and ADMTYPE = 'I', or a diagnosis in the diagnosis data with DXDATE prior to DRGDATE of the first prescription. A patient was considered to have diabetes if there was a diagnosis (ICD-9 codes 250) in the referral data with ADMDATE prior to DRGDATE of the first prescription, or a diagnosis in the diagnosis data with DXDATE prior to DRGDATE of the first prescription. A patient was considered to have hypertension if there was a diagnosis (ICD-9 codes 401-405) in the referral data with ADMDATE prior to DRGDATE of the first prescription, or a diagnosis in the diagnosis data with DXDATE prior to DRGDATE of the first prescription. Thus, three (0,1) variables were obtained for CHD, diabetes, and hypertension.

To determine the number of other medications prescribed to the patient within 45 days of the first LLA prescription, pharmacy data were used to determine the other medications by removing the prescriptions with NDC-codes of LLAs. This was then merged with the previous dataset and a (0,1) variable was created to indicate a 45 day period between the first LLA prescription and the other medications prescription. Prescriptions not satisfying the 45-day period were deleted. The remainder were then transposed by the PROC TRANSPOSE procedure. An array was formed to determine repeated medications based on their NDC-codes. The final number of medications was obtained by adding up the columns after converting the NDC-codes to ones. The variable was further categorized into 2 categories of three and above or less than three.
To determine discontinuation, a (0,1) variable was formed to indicate discontinuation if a patient had 180 or more days between any two LLA prescriptions, or 180 days or more between the last prescription and end of study period. The latter was found by using the PROC SORT procedure to sort the pharmacy data (with new LLAs between July 1, 1994 and June 30, 1996) by DESCENDING DRGDATE with NODUPKEY option by ID to identify the last LLA prescription and then merging by ID. A variable to indicate discontinuation date was formed which was the date of the last prescription prior to the 6-months without a prescription +180 days. A variable indicating time till discontinuation was also created which was the difference between the discontinuation date and the date of the first prescription. A (0,1) censorship variable was created as well, which was zero for patients that did not discontinue. The end of follow up for patients was considered to be the discontinuation date for patients that discontinued, or the end of study date for patients that did not discontinue.

Frequencies obtained by the SAS procedure PROC FREQ. The SAS procedure PROC LIFETEST was used to obtain KM plots, log-log KM plots, and the log rank statistics. The log-log KM plots were used to test the PH assumption by the graphical approach, where the assumption is satisfied unless there is a strong evidence of nonparallelism. PROC PHREG was used to fit the stratified Cox PH model with the STRATA statement for stratification, and PROC PLOT to obtain adjusted survival plots.

Manuscript 3 coding and analyses:

For the third manuscript, pharmacy data were used to determine patients with a statin prescription between September 1, 1994 and June 30, 1995. Patients with
a prescription in the previous year were deleted. The first prescription was used, and type of statin in each prescription was determined based on NDC-codes. The statin type was further categorized into a (0,1) variable, with one indicating the more expensive statins (pravastatin and lovastatin).

Demographic data were used to determine the sex and age of these patients through merging by ID. Age was calculated from the DOB variable. The linearity of the association of age with the dependent variable was examined and age was converted into two age groups: 70 and above, and below 70 based on this linearity check.

Enrollment data were used to obtain plan type chosen for the patients through merging by ID. Plan type was further categorized into a (0,1) variable with full coverage as 1 (PLANTYP ‘X’).

Comorbidities were determined by using both referral and diagnosis data through merging by ID. A patient was considered to have been hospitalized for CHD if there was a diagnosis (ICD-9 codes 410-414) in the referral data with ADMDATE prior to DRGDATE and ADMTYPE = ‘1’, or a diagnosis in the diagnosis data with DXDATE prior to DRGDATE. A patient was considered to have diabetes if there was a diagnosis (ICD-9 codes 250) in the referral data with ADMDATE prior to DRGDATE, or a diagnosis in the diagnosis data with DXDATE prior to DRGDATE. A patient was considered to have hypertension if there was a diagnosis (ICD-9 codes 401-405) in the referral data with ADMDATE prior to DRGDATE, or a diagnosis in the diagnosis data with DXDATE prior to DRGDATE. Thus, three (0,1) variables were obtained for CHD, diabetes, and hypertension.
To obtain the physician prescriber specialty, we imported the data on the excel sheet into SAS and merged by RXMD. Prescriber specialty was categorized into a (0,1) variable with cardiologists coded as 1.

The SAS procedure PROC FREQ was used to determine various frequencies. The SAS procedure PROC LOGISTIC was used for the logistic regression analyses.

All analyses were performed using SAS for microcomputers version 8.01. Writing the SAS programs and interpreting the results were based on fundamentals of SAS learned using SAS Programming by Example by Cody and Pass [1], and The little SAS Book: A Primer by Delwiche and Slaughter [2], and by studying examples presented in Klienbaum’s [3] Survival Analysis: A Self Learning Text, and Allison’s [4] Logistic Regression Using the SAS System.
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APPENDIX C. OVERVIEW OF MAJOR FINDINGS

The objective of the analyses described in manuscript 1 was to assess utilization the LLAs during a one-year period among a group Medicare beneficiaries enrolled in managed care and with high cholesterol levels. We compared this utilization with various patient characteristics including gender, age group, prescriber specialty, comorbidities (CHD, diabetes, hypertension), and choice of drug benefit plan option. This was carried out for both new and prevalent users during the one-year period.

Statin monotherapy was the most frequently prescribed LLA in both prevalent (61.8%) and new users (65.5%). Combination therapy was the least prescribed regimen among both prevalent (1.6%) and new users (0.9%).

In prevalent LLA use, patients with CHD were more frequently prescribed statin monotherapy (p<0.0001) and combination therapy (p=0.0467), but less frequently prescribed bile acid sequestrants (p<0.0001) compared to patients without CHD. Diabetic patients more frequently used fibrates (p=0.0032), less frequently used bile acid sequestrants (p=0.0007) and niacin (p=0.0336), compared to non-diabetics. Females were more frequently prescribed bile acid sequestrants compared to males (p=0.0213), but this difference no longer existed when the analysis was restricted to diabetics or non-diabetics only, indicating a confounding effect of diabetes. Cardiologists prescribed fibrates less frequently than internists and other specialties (p=0.0092), and patients aged 65-69 were less frequently prescribed a bile acid sequestrant compared to other age groups (p=0.0006).
In new LLA use, patients with CHD were more frequently prescribed statin monotherapy (p=0.0028). Diabetic patients less frequently used bile acid sequestrants (p=0.0329) compared to non-diabetics. Females were more frequently prescribed bile acid sequestrants compared to males (p=0.0168), a result that could be confounded by diabetes since the result no longer existed when we restricted the analysis to non-diabetics. The low number of new bile sequestrant users with diabetes prevented us from conducting a valid chi-square among diabetics. Finally, internal medicine physicians prescribed bile acid sequestrants less frequently than cardiologists and other specialties (p=0.0008).

The type of drug benefit plan chosen was not associated with any of the drug regimens prescribed.

Our results indicate that statins remain the mainstay of hyperlipidemic therapy. The very low rate of combination drug use found may, in part, explain why many patients on LLAs do not reach their target cholesterol levels, and perhaps help increase the use of combination therapy, shown to be safe and effective, in the near future. Observed differences in LLA selection in various characteristics could be reflective of different lipid levels resulting from comorbidities, mainly CHD and diabetes. Further follow-up with lipid levels of patients would give a more definitive explanation to these differences.

The analyses described in manuscript 2 gave insight into the relationship between drug benefit plan options for older adults under managed care and persistence to lipid-lowering therapy, controlling for potential confounding effects of patient sex,
age, co-morbidities (CHD, hypertension or diabetes mellitus), number of medications used, and statin use.

By the end of the study period, 39.1% of patients had discontinued their medication. The discontinuation increased with time, from 18.3% discontinuing at 6 months days, to 46.4% at 12 months, and 66.3% at 18 months, with the greatest drop occurring in the second half of the first year.

In the bivariate analysis, a significant difference existed between genders, with males having lower discontinuation than females. The discontinuation increased from 11.9% at 6 months, to 39.8% at 12 months, to 52.9% at 18 months in males, and from 23% at 6 months, to 50.3% at 12 months, to 73.2% at two years in females (p=0.0078).

A significant difference also existed between those who were hospitalized for CHD and those who were not, with CHD patients having lower discontinuation than non-CHD patients. The discontinuation increased from 15.7% at 6 months, to 40.9% at 12 months, to 59.1% at 18 months in CHD-patients, and from 20.9% at 6 months, to 51.2% at 12 months, to 72.7% at 18 months in non-CHD patients (p=0.0424).

Finally, a significant difference existed between statin users and non-statins users, with statin users having lower discontinuation than non-statin users. The discontinuation increased from 23.9% at 6 months, to 55.0% at 12 months, to 77.3% at 18 months in non-statin users, and from 14.4% at 6 months, to 38.7% at 12 months, to 56.6% at 18 months in statin users (p=0.0004).

In the multivariate model, a significant difference in discontinuation existed with statin use (HR=0.536; CI=0.375-0.766; p=0.0006), indicating that statin users
were less likely to discontinue compared to nonusers. CHD and gender were no longer significantly associated with discontinuation.

The type of drug benefit plan chosen was not significantly associated with the discontinuation in the bivariate (p=0.3121) or multivariate model that controls for potential confounders (HR=0.877; CI=0.610-1.260; p=0.477). Our findings suggest that adequate payment mechanisms are not enough to guarantee persistence of lipid-lowering therapy.

The aim of the analysis presented in manuscript 3 was to investigate the association between the drug benefit plan type and the type of statin drug prescribed (based on relative price) for a group of older adults under managed care, while controlling for the potential confounding effects of gender, age, prescriber specialty, CHD hospitalization prior to prescription, diabetes diagnosis prior to prescription, and hypertension diagnosis prior to prescription.

Results showed fluvastatin to be the most prescribed statin accounting for 87.4% of the prescriptions in this patient population.

The drug benefit plan type was not significantly associated with the type of statin prescribed in the bivariate (OR=0.652; CI=0.377-1.126; p=0.1247) or multivariate logistic regression model (OR=0.654; CI=0.376-1.139; p=0.1335). Other covariates- gender, age, prescriber specialty, CHD hospitalization prior to prescription, diabetes diagnosis prior to prescription, and hypertension diagnosis prior to prescription- were also not significantly associated with the type of statin prescribed.
Our results suggest that the drug benefit plan chosen did not affect the choice among different statins. Further investigation with initial lipid levels is needed to investigate whether the more expensive drugs are being used in patients in need of further lowering of LDL-C beyond the capacity of fluvastatin, and whether target cholesterol levels are being achieved among all patients to gain the potential benefit of these drugs.

In sum, our results generally indicate that the policy of drug benefit plan option initiated at the HMO among older adult members did not significantly influence the choice among or persistence of LLAs.
Figure 1a Kaplan-Meier survival curves for members of the full drug benefit plan and members of the $1000 maximum or no drug benefit plan in an elderly population of new users of lipid-lowering agents enrolled in a Medicare managed care health plan (n=322)

plan 0 = $1000 maximum or no coverage plans
plan 1 = full coverage plan
Figure 1b Log-log Kaplan-Meier survival curves for members of the full drug benefit plan and members of the $1000 maximum or no drug benefit plan in an elderly population of new users of lipid-lowering agents enrolled in a Medicare managed care health plan (n=322)

plan 0= $1000 maximum or no coverage plans
plan 1= full coverage plan
Figure 2a Kaplan-Meier survival curves for males and females in an elderly population of new users of lipid-lowering agents enrolled in a Medicare managed care health plan (n=322)

Gender 0 = females
Gender 1 = males
Figure 2b Log-log Kaplan-Meier survival curves for males and females in an elderly population of new users of lipid-lowering agents enrolled in a Medicare managed care health plan (n=322)

Gender 0 = females
Gender 1 = males
Figure 3a Kaplan-Meier survival curves for ages ≥70 and ages < 70 in an elderly population of new users of lipid-lowering agents enrolled in a Medicare managed care health plan (n=322)

STRATA:  
- Agegp=0
- Agegp=1

Censored Agegp=0
Censored Agegp=1

Age 0 = below 70
Age 1 = 70 or more
Figure 3b Log–log Kaplan-Meier survival curves for ages ≥70 and ages < 70 in an elderly population of new users of lipid-lowering agents enrolled in a Medicare managed care health plan (n=322)

Age 0 = below 70
Age 1 = 70 or more
Figure 4a Kaplan-Meier survival curves for patients with CHD and patients without CHD in an elderly population of new users of lipid-lowering agents enrolled in a Medicare managed care health plan (n=322)

fchd 0 = patients without coronary heart disease
fchd 1 = patients with coronary heart disease
Figure 4b Log-log Kaplan-Meier survival curves for patients with CHD and patients without CHD in an elderly population of new users of lipid-lowering agents enrolled in a Medicare managed care health plan (n=322)

Neglecting the log-log transformation, we display the survival function by

\[ S(t) = \exp\left(\frac{-t}{\theta}\right) \]

where \( S(t) \) is the survival function and \( \theta \) is the scale parameter. The log-log plot yields a straight line if the hazards are proportional with

\[ \log(-\log(S(t))) = \log(\frac{1}{\theta}) + \log(t) \]

The log-log survival curves for the patients with CHD (fchd=1) and the patients without CHD (fchd=0) are shown in the figure. The log-log survival curves differ significantly for the two groups, indicating that the hazard rates are not proportional. The log-log survival curves for the patients with CHD are steeper than the curves for the patients without CHD, indicating a higher hazard rate for patients with CHD.

fchd 0 = patients without coronary heart disease
fchd 1 = patients with coronary heart disease
Figure 5a Kaplan-Meier survival curves for patients with diabetes and patients without diabetes in an elderly population of new users of lipid-lowering agents enrolled in a Medicare managed care health plan (n=322)

\[\text{Survival Distribution Function}\]

\[\text{STRATA: } f_{dm}=0 \quad f_{dm}=1\]

\[f_{dm} \, 0= \text{ patients without diabetes}\]

\[f_{dm} \, 1= \text{ patients with diabetes}\]
Figure 5b Log-log Kaplan-Meier survival curves for patients with diabetes and patients without diabetes in an elderly population of new users of lipid-lowering agents enrolled in a Medicare managed care health plan (n=322)

fdm 0 = patients without diabetes
fdm 1 = patients with diabetes
Figure 6a Kaplan-Meier survival curves for patients with hypertension and patients without in an elderly population of new users of lipid-lowering agents enrolled in a Medicare managed care health plan (n=322)

\[ \text{STRATA: } \begin{align*} \text{fhtn=0} & : \text{patients without hypertension} \\ \text{fhtn=1} & : \text{patients with hypertension} \end{align*} \]
Figure 6b Log-log Kaplan-Meier survival curves for patients with hypertension and patients without hypertension in an elderly population of new users of lipid-lowering agents enrolled in a Medicare managed care health plan (n=322)

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fhtn 0 = patients without hypertension
fhtn 1 = patients with hypertension
Figure 7a Kaplan-Meier survival curves for patients with number of other medications ≥3 and patients with number of other medications 0-2 in an elderly population of new users of lipid-lowering agents enrolled in a Medicare managed care health plan (n=322)

medsgp 0= number of other medications 0-2
medsgp 1= number of other medications 3 or more
Figure 7b Log-log Kaplan-Meier survival curves for patients with number of other medications $\geq 3$ and patients with number of other medications 0-2 in an elderly population of new users of lipid-lowering agents enrolled in a Medicare managed care health plan (n=322)

Log of time

STRATA: +--- medsgp=0 +--- medsgp=1

medsgp 0= number of other medications 0-2
medsgp 1= number of other medications 3 or more
Figure 8a Kaplan-Meier survival curves for statin users and nonstatin users in an elderly population of new users of lipid-lowering agents enrolled in a Medicare managed care health plan (n=322)

statin 0 = not a statin user (using other class of lipid-lowering agents)
statin 1 = statin user
Figure 8b Log-log Kaplan-Meier survival curves for statin users and non-statin users in an elderly population of new users of lipid-lowering agents enrolled in a Medicare managed care health plan (n=322)

statin 0 = not a statin user (using other class of lipid-lowering agents)
statin 1 = statin user
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