

Effect of Medication Burden on Persistent Use of Lipid-Lowering Drugs Among Patients With Hypertension

Teisha A. Robertson, PharmD, MBA; Catherine E. Cooke, PharmD, BCPS; Jingshu Wang, PhD; Fadia T. Shaya, PhD, MPH; and Helen Y. Lee, PharmD, MBA

Objective: To determine the effect of medication burden on persistent use of newly added lipid-lowering (LL) drugs among patients with hypertension.

Study Design: This retrospective database study used medical and pharmacy claims from a mid-Atlantic managed care organization. The cohort was obtained from continuous member enrollment in pharmacy and medical benefits from January 1, 2003, to December 31, 2005.

Methods: Prescription claims were obtained for 18 months following the date of the first filled LL prescription (ie, index date). Patients were stratified into patients who changed LL drug or strength (group 1) and patients who did not change LL drug or strength (group 2). The primary outcome measure was persistence to newly added LL therapy. Persistence was defined by the length of time a member remained on therapy following the index date. The secondary outcome measure was the medication possession ratio (MPR). The MPR was calculated as the ratio of the sum of the days' supply of prescription filled divided by the number of days filled, plus the days' supply for the final prescription fill. Associations between the daily medication burden, defined as the number of unique drug products, and the outcome measures were analyzed.

Results: In the cohort of 3058 patients, the mean medication burden was 2.9 medications. Medication burden was positively associated with persistence and MPR through 18 months. Patients who had greater medication burden had longer persistence ($P < .001$). Likewise, patients who had greater medication burden had higher MPRs and were more likely to be considered adherent (MPR, $\geq 80\%$) ($P < .001$ for both).

Conclusions: Patients with higher medication burden had greater adherence to newly added LL therapy. Medication burden should not deter clinicians from adding LL therapy. Among patients with added LL therapy, more attention should focus on patients who have changes to their LL regimen compared with patients who continue on the same LL prescription.

(*Am J Manag Care.* 2008;14(11):710-716)

For author information and disclosures, see end of text.

Cardiovascular disease (CVD) continues to be the leading cause of morbidity and mortality in the United States.^{1,2} In 2002, CVD in the United States accounted for 1.4 million deaths.^{1,2} Annual direct and indirect costs of CVD in 2007 were estimated to be approximately \$431.8 billion.^{1,2} Several factors increase the risk of CVD such as hypertension, age (>55 years for men and >65 years for women), dyslipidemia, diabetes mellitus or glucose intolerance, renal dysfunction, family history of premature CVD (relative's age <55 years in men and <65 years in women), obesity, physical inactivity, and smoking.³ Studies have shown that CVD risk factors coexist. Patients with hypertension often have 1 or more concomitant risk factors, including diabetes mellitus or glucose intolerance, obesity, and dyslipidemia, all components of the metabolic syndrome.^{4,5} Less than 20% of patients with hypertension have no other CVD risk factors.⁴ Two of the most prevalent and asymptomatic risk factors for CVD, hypertension and dyslipidemia, commonly coexist, and the risk of CVD associated with having both is greater than the risk associated with having hypertension or dyslipidemia alone.^{4,6} The US Third National Health and Nutrition Examination Survey provides an estimated prevalence of concomitant hypertension and dyslipidemia of about 15% among adults, which equates to approximately 30 million adults in the United States.⁷

The National Cholesterol Education Program Adult Treatment Panel III guideline recommends aggressive management of patients with concomitant hypertension and dyslipidemia.⁸ Meta-analyses and clinical trials have found that antihypertensive and lipid-lowering (LL) medications significantly reduce the risk of CVD and all-cause mortality among patients with CVD risk factors.⁹⁻¹²

Medication therapy for the treatment of hypertension and dyslipidemia is becoming more challenging, as more than two-thirds of patients require 2 or more antihypertensive drugs and an LL drug, with high-risk patients requiring 2 or more LL drugs to achieve optimal blood pressure and cholesterol levels.^{3,8,13} Adequate adherence to medication regimens is essential to decrease the risk for hospitalization and healthcare expenditures.¹⁴ Poor adherence to antihypertensive and LL regimens can accelerate the development of CVD, which can lead to a decreased quality of life and premature death.³ The medication burden of patients with

In this issue

Take-away Points / p716

www.ajmc.com

Full text and PDF

Web exclusive

eAppendix Table

Burden of Lipid-Lowering Drugs Among Patients With Hypertension

CVD risk factors can be high and may affect medication adherence; however, conflicting assessments have been reported. Some investigators have reported an increase in adherence among patients with higher medication burden, while others have reported the opposite result.¹⁵⁻²⁰ Given the need to manage patients at high risk for CVD with multiple medications, it is important to elucidate the true effect of the number of medications on adherence.

A retrospective study of medical and pharmacy claims was performed to evaluate this. The objective was to assess the effect of medication burden on persistence of newly added LL drugs among patients with hypertension.

METHODS

Data Sources and Patients

This retrospective database analysis used medical and pharmacy claims from a mid-Atlantic managed care organization serving more than 1.2 million members with medical and pharmacy benefits. The cohort included members with continuous enrollment of pharmacy and medical benefits from January 1, 2003, to December 31, 2005. Members were included in the analysis if they had at least 1 *International Classification of Diseases, Ninth Revision, Clinical Modification* (ICD-9-CM) code for hypertension (401.xx) from January 1, 2003, to June 30, 2004, and at least 1 prescription for an LL drug dispensed between July 1, 2003, and June 30, 2004. Members were excluded from analysis if they had any of the following: prescriptions for LL therapy before the first ICD-9-CM code for hypertension in the study period; LL prescriptions dispensed from January 1, 2003, to June 30, 2003; age younger than 18 years on the index date (ie, the date of the first filled LL prescription); more than 1 prescription for an LL drug filled on the index date; an LL prescription with negative days' supply (a void in the prescription and the patient did not receive the drug); only 1 filled LL prescription during the study period; or ICD-9-CM diagnosis codes from January 1, 2003, to December 31, 2005, for comorbid diseases, including HIV, cancer, dementia, Alzheimer's disease, mental retardation or Down syndrome, schizophrenia, bipolar disorder, or depression, that could affect adherence (Figure).

The first filled LL drug during the study interval was considered the index prescription. Patients included in the study had the same observation period of 18 months following the index date. Prescription claims were obtained for patients included in the cohort for 18 months following the index date. To assess for differences among patients who change or switch from 1 drug to another or change the dosage of their medication versus patients who remained on the same medication and dosage, patients were stratified into 2 groups. Group 1 included pa-

tients who changed LL drug (including patients who switched to a different strength of the same drug or to a different class of the drug, as well as patients who added an LL drug). Group 2 included patients who did not change LL drug or strength (ie, had the same prescription throughout the study).

Lipid-lowering drugs included all those on the US market during the study period, including bile acid sequestrants, statins, fibric acid derivatives (fibrates), cholesterol absorption blockers, combination therapy of 2 medications in 1 formulation, and others (eg, niacin). Data from medical and pharmacy claims included unique deidentified patient number, patient's age on the index date, sex, disease diagnoses as defined by ICD-9-CM codes, prescription information for all filled LL drugs (drug name, prescription fill date, days' supply, and copayment), and a list of concurrently filled prescription medicines 6 months before and within 6 months after the index date.

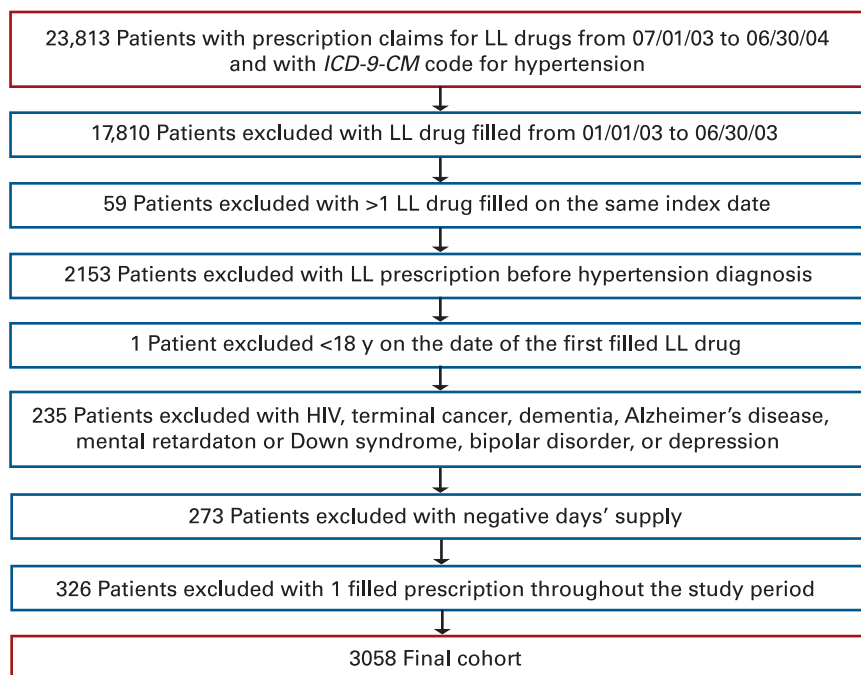
Outcome Measures

Medication adherence was evaluated based on persistence and the medication possession ratio (MPR). The primary outcome measure, persistent use of an LL drug, was specified as the length of time in days that patients remained on an LL drug following the index date. A patient was deemed persistent if he or she filled a prescription within a grace period of 30 days from the end of the days' supply of the prior prescription.²¹⁻²³ For patients who had changes to their index LL regimen (group 1), persistent use of the index LL prescription and persistent use of the switched LL prescriptions were combined. Persistence was truncated to 548 days (18 months) for patients with LL prescriptions that extended beyond the 18-month study period. The secondary outcome measure, MPR, was calculated as the ratio of the sum of the days' supply of prescription filled by the patient divided by the number of days from the fill date of the index prescription to the last fill date, plus the days' supply for the final prescription fill.²⁴ For patients who had changes to their index LL regimen, the sum of the days' supply of the index LL drug was added to the sum of the days' supply of the changed LL drugs, divided by the number of days from the fill date of the index prescription to the last fill date of the changed LL drugs, plus the days' supply for the final prescription fill. The MPR was truncated to a ratio of 1 for patients with a sum of days' supply of filled LL prescriptions exceeding 548 days. Patients were deemed to be adherent if the MPR was at least 80%, a cutoff percentage that is frequently cited in the literature.²⁵

Operational Definition of Medication Burden

The medication burden was defined as the number of unique drug products. The number of unique drug products was determined by averaging the covered medications taken

■ **Figure.** Timeline of Events.



HIV indicates human immunodeficiency virus; ICD-9-CM, *International Classification of Diseases, Ninth Revision, Clinical Modification*; LL, lipid lowering.

chronically (>90 days) for which the days' supply of the medication overlapped or was within 30 days after the end of the days' supply of the index prescription. This definition excludes medications prescribed for acute treatment (eg, anti-infective drugs and cough and cold drugs) during the study period (eAppendix available at www.ajmc.com). As an example, for a patient who filled a prescription for simvastatin on March 20, 2004 (index date), the patient's medication burden would be assessed as follows: lisinopril (20 mg) filled with a 30-day supply on March 1, 2004, would count as a unique drug product; alendronate sodium (70 mg) filled with a 90-day supply on April 15, 2004, would count as a unique drug product; metformin (1000 mg) filled with a 30-day supply on March 20, 2004, would count as a unique drug product; and amoxicillin (500 mg) with a 10-day supply on March 15, 2004, would not count as a unique drug product. The medication burden for the patient would be 3 medications.

Statistical Analysis

Descriptive statistical analyses were performed for socio-demographic and clinical characteristics of the entire cohort and of the 2 subgroups. Multivariate regression models were used to examine the unique associations between clinical or demographic characteristics and adherence measures. Cox proportional hazards model was used to assess persistence, lin-

ear regression analysis was used for MPR, and logistic regression analysis was used for adherence as an indicator variable for an MPR of at least 80%. Statistical significance was set at $P < .05$.

This study was approved by the University of Maryland Institutional Review Board. The board assigned an exempt status to the research protocol.

RESULTS

Demographics and LL Drug Therapy

The query of medical and pharmacy claims found 23,813 patients with at least 1 ICD-9-CM code for hypertension and prescription claim for an LL drug (Figure). Three hundred twenty-six patients with 1 filled LL drug throughout the study period were excluded. A total

of 3058 patients (12.8%) with hypertension who had newly started an LL drug met the inclusion and exclusion criteria.

Among the entire cohort on the index date, 2594 patients (84.8%) filled a statin prescription, 190 patients (6.2%) filled a fibrate prescription, and 175 patients (5.7%) filled a cholesterol absorption blocker prescription, while the remainder (3.3% of patients) filled a niacin prescription, a bile acid sequestrant prescription, or a combination prescription. The mean (SD) copayment was \$26.07 (\$22.64) (range, \$0.00-\$299.64).

There were 1288 patients (42.1%) in group 1 and 1770 patients (57.9%) in group 2. Both groups had a mean age of about 55 years, with most patients aged 45 to 64 years, and approximately 51% were male (Table 1). The medication burden for patients in both groups was 2.9 medications, excluding the newly prescribed LL drug.

Effect of Medication Burden on Adherence

In multivariate analysis (Table 2), medication burden was positively associated with persistence. Patients who had greater medication burden had longer persistence (hazard ratio for discontinuation, 0.96; 95% confidence interval, 0.94-0.98; $P < .001$). Likewise, patients who had greater medication burden had higher MPR: an increase of 1 medication will increase the MPR by 1.3 percentage points ($P < .001$). Moreover, using the binary variable of an MPR of at least 80% as a threshold

■ **Table 1.** Study Cohort Demographics

Variable	Entire Cohort (N = 3058)	Group 1 (n = 1288)	Group 2 (n = 1770)	P
Age, y				
Mean (SD)	55.2 (10.6)	55.1 (10.6)	55.3 (10.7)	.52
Range, %				
18-34	2.6	2.8	2.4	—
35-44	12.4	12.1	12.6	—
45-54	31.8	32.6	31.2	—
55-64	36.7	36.7	36.8	—
65-74	11.7	11.2	12.1	—
≥75	4.8	4.6	4.9	—
Male sex, %	51.3	51.4	51.2	—
LL therapy				
Statin, %	84.8	80.4	88.0	<.001
Adherence measure, mean (SD)				
Persistence, d	288.9 (210.1)	263.1 (207.0)	307.7 (210.4)	<.001
MPR, %	76.9 (25.5)	72.1 (25.3)	80.3 (21.5)	<.001
Adherence (MPR, ≥80%), %	56.9 (49.5)	47.8 (50.0)	63.5 (48.1)	<.001
Medication burden				
Non-LL therapy, mean (SD), No.	2.9 (2.5)	2.9 (2.5)	2.9 (2.4)	.77

LL indicates lipid lowering; MPR, medication possession ratio.

for adherence, we found that having more concurrently prescribed medicines leads to a higher probability of being adherent: each increase in medication number raised the odds by 0.10 (odds ratio for an MPR ≥80%, 1.10; 95% confidence interval, 1.06-1.14; *P* <.001) (data not shown).

Other Predictors of Adherence

The mean (SD) duration of persistence was 288.9 (210.1) days (range, 6-548 days), with a mean (SD) MPR of 76.9% (25.5%) (range, 5.8%-100.0%) (Table 1). Among the study cohort, 56.9% were deemed adherent based on an MPR of at least 80%.

The mean duration of persistence for group 1 was 263.1 days compared with 307.7 days for group 2 (Table 1). The mean MPR was 72.1% for group 1 compared with 80.3% for group 2. A total of 47.8% of patients in group 1 had an MPR of at least 80% compared with 63.5% of patients in group 2.

Men had longer persistence than women (hazard ratio for discontinuation, 0.85; *P* <.001), as summarized in Table 2. Group 1 had shorter persistence than group 2 (hazard ratio for discontinuation, 1.27; *P* <.001). There were no significant effects of age on persistence. Patients taking statin drugs did not have improved persistence compared with patients taking other LL classes of drugs. Similarly, men had higher MPRs and

were more adherent (MPR, ≥80%) than women (*P* = .003 and *P* = .002, respectively) (data not shown). Group 1 had lower MPRs and were less likely to be adherent (MPR, ≥80%) than group 2 (*P* <.001 for both).

DISCUSSION

Our study evaluated the effect of medication burden on persistence of newly added LL drugs among patients with hypertension in a managed care population. In this cohort of patients, the mean persistence of 9.63 months seems poor, as this was only 53.5% of the study period. We found that patients with longer medication lists did not have lower medication persistence or adherence to newly started chronic therapy. In fact, patients taking more medicines had longer persistence with LL therapy and tended to have higher MPRs. In addition, patients who did not change LL drug or dosage (ie, they remained on their original LL regimen) had longer persistence and were more adherent (MPR, ≥80%) compared with those who changed or added an LL drug.

Previous studies have shown conflicting results about the relationship between medication burden and adherence. The literature seems almost equally divided on the point. Three

■ **Table 2.** Multivariate Regression Analysis of Predictors of Discontinuation of Lipid-Lowering Therapy

Variable	Hazard Ratio (95% Confidence Interval)	P
Age, y		
18-34	1 [Reference]	
35-44	0.91 (0.69-1.19)	.48
45-54	0.83 (0.64-1.08)	.16
55-64	0.79 (0.61-1.03)	.07
65-74	0.78 (0.59-1.03)	.08
≥75	0.98 (0.72-1.35)	.91
Sex		
Male	0.85 (0.78-0.92)	<.001
Female	1 [Reference]	
LL therapy		
Statin	1.00 (0.89-1.12)	.98
Nonstatin	1 [Reference]	—
Medication burden	0.96 (0.94-0.98)	<.001
Group		
1	1.27 (1.16-1.38)	<.001
2	1 [Reference]	—

studies¹⁵⁻¹⁷ support a positive relationship, while 3 other studies¹⁸⁻²⁰ support a negative relationship. Our study supports the finding that adherence tends to increase among patients taking multiple medications. Grant et al,¹⁵ who studied a similar patient population, found that patients with more concurrently prescribed medications (at the time of initiation of statin therapy and at the time of their last recorded statin refill) had longer persistence with statin therapy over time. In a retrospective study of adherence (calculated as 1 minus the number of days without drug, divided by the total number of days in the study) among a high-risk Veterans Affairs population of 1054 patients, Billups et al¹⁶ reported better adherence among patients taking more concurrent medications. Another study¹⁷ that used self-reported survey questions to assess adherence (calculated based on prescription fill dates and number of days supplied) among 367 patients from an acute care ward and an on-site lipid clinic at a hospital in Canada found that nonadherent patients (<80%) took fewer prescription medications compared with adherent subjects (4.1 vs 5.9 medications).

In contrast to our results, 3 other large retrospective cohort studies¹⁸⁻²⁰ of patients receiving concomitant LL therapies found that increasing medication burden was associated with a decrease in LL drug adherence. Chapman et al¹⁸ measured the proportion of days covered by a given drug among 8406

patients enrolled in a managed care organization. The authors found that, as the number of other prescribed medications decreased, the likelihood of adherence to concomitant LL therapy increased.¹⁸ Two studies conducted by Benner et al¹⁹ and by Avorn et al²⁰ have overlapping populations with similar findings. Benner et al¹⁹ measured the proportion of days covered among an older New Jersey Medicaid population of 34,501 patients ≥65 years. These patients were prescribed a mean of 9.2 medications in the prior year. Significant suboptimal adherence over time was observed only in patients prescribed 11 or more medicines in the prior year. Avorn et al²⁰ focused on persistence (proportion of days) as the measure of LL drug adherence among a cohort of New Jersey and Quebec Medicaid patients 65 years and older. Patients in this cohort were prescribed 1 to 16 medications or more than 16 medications in the prior year. The authors found that patients with

prescriptions for more than 16 drug products per year were less likely to continue to fill prescriptions for LL drugs.

According to the health belief model,²⁶ patients who believe that they are in poor health (which could be the case for patients taking multiple medications) are more likely to take the necessary steps to monitor their health and to take medications as prescribed. Therefore, patients who are prescribed multiple medications believe that they are more responsible for their disease state and are more adherent to their prescribed medications compared with healthier patients.¹⁶ A possible explanation for the difference between our study results versus other studies that found conflicting results could be that LL drug adherence was better with higher medication burden up to a certain limit, beyond which adherence tends to be poorer. In the study by Benner et al,¹⁹ the authors found that patients who were prescribed 11 or more medicines had suboptimal adherence compared with those who were prescribed fewer than 11 medicines. The patients in the study by Benner et al¹⁹ had a mean of 9.2 medications compared with a mean of 2.9 medications among the patients in our study. Patients with the highest medication burden may be considerably sicker, and the burden of the illness may be too much for them, further decreasing medication adherence.¹⁵

According to a study²⁷ of 4068 older outpatients newly starting antihypertensive therapy, older age was associated

with good adherence ($\geq 80\%$). In our study, age was not a significant predictor of persistence, similar to findings reported by other researchers.^{15,16} Some studies^{15,16,27} have found no relationship between adherence to antihypertensive therapy and sex. However, our study found that women were less persistent than men, similar to findings reported by Chapman et al.¹⁸ The associations of age and sex with adherence to statin therapy were evaluated in a retrospective study.²⁸ The study used claims data from a large national employment-based independent practice association database. Subjects ($n = 21,239$) were at high risk of coronary heart disease and had filled a prescription for statin therapy. Patient data were captured for 12 months before and 12 months after the index date (first statin prescription fill). Adherence was defined as an adherence ratio of at least 80% or a daily dose of medication available for at least 80% of the days in the study period. According to this study, older subjects were 1.03 times as likely to be adherent compared with younger subjects, and men were 1.42 times as likely to be adherent to statin therapy compared with women. Differences in adherence rates between respective cohorts were statistically significant. The authors noted that there were limited published data that evaluated the effect of medication adherence to an index drug when the index drug is changed or another drug is added. Our study found that there was significantly higher persistence and adherence among patients who did not change their LL drug compared with those who changed or added an LL drug.

Several limitations of our study should be noted. An inherent limitation of this study is that our methods relied on ICD-9-CM coding first in identifying patients with hypertension and then in identifying patients with certain comorbid illnesses to be excluded (eg, depression and HIV). This point has the following implications: (1) we did not require members to have multiple medical claims for any of the medical diagnoses, so false-positive classification is possible; and (2) as with all medical claims, we had no way to evaluate the accuracy of the coding, which may be incomplete. Our results may not be comparable to those of other studies because we excluded patients with certain medical conditions (eg, schizophrenia, depression, bipolar disorder, mental retardation) that may affect adherence rates. Another limitation is that physician prescribing of LL therapy was determined from prescription refill claims. Although the use of prescription refill claims has been validated as effective, it has some disadvantages. We are unable to ascertain if a patient had a

Take-away Points

Cardiovascular risk factors such as hypertension and dyslipidemia commonly coexist, requiring the patient to use multiple drug therapies to achieve optimal control according to guidelines.

- Clinicians managing patients often struggle with adding more drugs to regimens of patients who already have complicated medication regimens.
- This study describes the effect of medication burden on persistent use of newly added lipid-lowering drugs among patients with hypertension.
- Patients with higher medication burden had greater adherence to newly added lipid-lowering therapy; therefore, medication burden should not deter clinicians from adding lipid-lowering therapy.

change in dosage and did not have a new prescription for that strength (eg, took half a tablet). Therefore, adherence would be underestimated or overestimated in those patients. In addition, evaluating refill records for medication burden measures the timeliness of refills and does not indicate if the dispensed drug was actually taken by the patient. As a result, overestimation of adherence occurs in patients who fill their prescriptions on time but who are not taking the drugs as prescribed or as often as would be expected based on the refill pattern. In addition, the adherence parameters could have been affected by the use of drug samples obtained from physician offices, which would result in underestimates of adherence. In addition, some variables (eg, visit frequency, hospitalizations, use of multiple providers) were not captured in our analysis that could have affected adherence. Another limitation is that nonprescription medications that could be taken chronically are not accounted for in the claims analysis. Also, the prescription refills do not provide information pertaining to the directions or indications for the drug. Therefore, a patient who fills a 30-day supply of a particular drug with directions to take 1 tablet every other day could be mistaken as nonadherent if the prescription was not refilled within 30 days. Similarly, some patients may have been told by the physician to discontinue drug therapy because they developed an adverse effect or because of ineffective drug therapy, and they too may have mistakenly been considered nonadherent.

CONCLUSIONS

Clinicians managing patients with CVD often struggle with the effect of adding additional therapies to regimens of patients who already have complicated medication regimens. This study demonstrates that medication burden does not reduce adherence or persistence. Clinicians need not be as concerned regarding patients with a mean medication burden of 2.9 medications, as the effect of increased medication burden on adherence was positive. Once LL therapy has been added, more attention should focus on patients who have

changes to their LL regimen, as they were less persistent and adherent compared with patients maintaining the same LL prescription. Given the continued trend of more aggressive management of chronic medical conditions, further research should be conducted to assess the full range of the relationship between medication burden and adherence among patients with chronic disease states.

Acknowledgment

We thank Anne G. Wood, MBA, for her assistance with obtaining medical and pharmacy claims data.

Author Affiliations: From the School of Pharmacy (TAR, CEC, JW, FTS), University of Maryland, Baltimore; PosiHealth (CEC), Baltimore, MD; and CareFirst BlueCross BlueShield (HYL), Baltimore, MD. Dr Robertson is now with Express Scripts, Bloomington, MN.

Funding Source: None reported.

Author Disclosure: The authors (TAR, JW, FTS, HYL) report no relationship or financial interest with any entity that would pose a conflict of interest with the subject matter of this article. Dr Cooke is a former employee of Pfizer, Inc, and reports owning stock in that company.

Authorship Information: Concept and design (TAR, CEC, FTS, HYL); acquisition of data (HYL); analysis and interpretation of data (TAR, CEC, JW, FTS); drafting of the manuscript (TAR); critical revision of the manuscript for important intellectual content (CEC, JW, FTS, HYL); statistical analysis (TAR, JW, FTS); administrative, technical, or logistic support (TAR, HYL); and supervision (TAR, CEC, FTS).

Address correspondence to: Teisha A. Robertson, PharmD, MBA, PO Box 6893, Largo, MD 20774. E-mail: ttay1002@umaryland.edu.

REFERENCES

- American Heart Association.** *Heart Disease and Stroke Statistics: 2007 Update.* Dallas, TX: American Heart Association; 2007.
- National Center for Health Statistics, Centers for Disease Control and Prevention.** Deaths: final data for 2003. <http://www.cdc.gov/nchs/products/pubs/pubd/hestat/finaldeaths03/finaldeaths03.htm>. Accessed October 1, 2007.
- Chobanian AV, Bakris GL, Black HR, et al; Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. National Heart, Lung, and Blood Institute; National High Blood Pressure Education Program Coordinating Committee.** Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. *Hypertension.* 2003;42(6):1206-1252.
- Kannel WB.** Risk stratification in hypertension: new insights from the Framingham Study. *Am J Hypertens.* 2000;13(pt 1 of 2):3S-10S.
- Poulter N.** Coronary heart disease is a multifactorial disease. *Am J Hypertens.* 1999;12(10 pt 2):92S-95S.
- Johnson ML, Pietz K, Battleman DS, et al.** Prevalence of comorbid hypertension and dyslipidemia and associated cardiovascular disease. *Am J Manag Care.* 2004;10(12):926-932.
- Battleman DS, Peterson ED.** Estimated prevalence of comorbid hypertension and dyslipidemia and therapeutic goal attainment among US adults in 2000, utilizing data from the National Health and Nutrition Examination Survey (NHANES III). *J Manag Care Pharm.* 2004;10:186 [Poster].
- Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults.** Executive Summary of the Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). *JAMA.* 2001;285(19):2486-2497.
- LaRosa JC, He J, Vupputuri S.** Effect of statins on risk of coronary disease: a meta-analysis of randomized controlled trials. *JAMA.* 1999;282(24):2340-2346.
- Law MR, Wald NJ, Morris JK, et al.** Value of low dose combination treatment with blood pressure lowering drugs: analysis of 354 randomized trials. *BMJ.* 2003;326(7404):e1427.
- Pignone M, Phillips C, Mulrow C.** Use of lipid lowering drugs for primary prevention of coronary heart disease: meta-analysis of randomized trials. *BMJ.* 2000;321(7267):983-986.
- Ross SD, Allen IE, Connelly JE, et al.** Clinical outcomes in statin treatment trials: a meta-analysis. *Arch Intern Med.* 1999;159(15):1793-1802.
- Kennedy AG, MacLean CD, Littenberg B, Ades PA, Pinckney RG.** The challenges of achieving national cholesterol goals in patients with diabetes. *Diabetes Care.* 2005;28(5):1029-1034.
- Col N, Fanale JE, Kronholm P.** The role of medication nonadherence and adverse drug reactions in hospitalizations of the elderly. *Arch Intern Med.* 1990;150(4):841-845.
- Grant RW, O'Leary KM, Weilburg JB, et al.** Impact of concurrent medication use on statin adherence and refill persistence. *Arch Intern Med.* 2004;164(21):2343-2348.
- Billups SJ, Malone DC, Carter BL.** The relationship between drug therapy nonadherence and patient characteristics, health-related quality of life, and health care costs. *Pharmacotherapy.* 2000;20(8):941-949.
- Shalansky S, Levy A.** Effect of number of medications on cardiovascular therapy adherence. *Ann Pharmacother.* 2002;36(10):1532-1539.
- Chapman RH, Benner JS, Petrilla AA, et al.** Predictors of adherence with antihypertensive and lipid-lowering therapy. *Arch Intern Med.* 2005;165(10):1147-1152.
- Benner JS, Glynn RJ, Mogun H, Neumann PJ, Weinstein MC, Avorn J.** Long-term persistence in use of statin therapy in elderly patients. *JAMA.* 2002;288(4):455-461.
- Avorn J, Monette J, Lacour A, et al.** Persistence of use of lipid-lowering medications: a cross-national study. *JAMA.* 1998;279(18):1458-1462.
- Thiebaud P, Patel BV, Nichol MB, Berenbeim DM.** The effect of switching on adherence and persistence: the case of statin treatment. *Am J Manag Care.* 2005;11(11):670-674.
- Larsen J, Andersen M, Kragstrup J, Gram LF.** High persistence of statin use in a Danish population: adherence study 1993-1998. *Br J Clin Pharmacol.* 2002;53(4):375-378.
- Abraha I, Montedori A, Stracci F, Rossi M, Romagnoli C.** Statin adherence in the Umbrian population. *Eur J Clin Pharmacol.* 2003;59(8-9):659-661.
- White TJ, Chang E, Leslie S, et al.** Patient adherence with HMG reductase inhibitor therapy among users of two types of prescription services. *J Manag Care Pharm.* 2002;8(3):186-191.
- Johnson ES, Mozaffari E.** Measuring patient persistency with drug therapy using methods for design and analysis of natural history studies. *Am J Manag Care.* 2002;8(10 suppl):S249-S254.
- Rosenstock IM, Strecher VJ, Becker MH.** Social learning theory and the Health Belief Model. *Health Educ Q.* 1988;15(2):175-183.
- Monane M, Bohn R, Gurwitz JH, Glynn RJ, Levin R, Avorn J.** Adherence with antihypertensive therapy among elderly Medicaid enrollees: the role of age, gender, and race. *Am J Public Health.* 1996;86(12):1805-1808.
- Schultz JS, O'Donnell JC, McDonough KL, Sasane R, Meyer J.** Determinants of adherence with statin therapy and low-density lipoprotein cholesterol goal attainment in a managed care population. *Am J Manag Care.* 2005;11(5):306-312. ■