

Predictors of Adherence With Antihypertensive and Lipid-Lowering Therapy

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Background: Patients with comorbid hypertension and dyslipidemia are at high risk for cardiovascular disease, which can be considerably mitigated by treatment. Adherence with prescribed drug therapy is, therefore, especially important in these patients. This study was undertaken to describe the patterns and predictors of adherence with concomitant antihypertensive (AH) and lipid-lowering (LL) therapy.

Methods: This retrospective cohort study examined 8406 enrollees in a US managed care plan who initiated treatment with AH and LL therapy within a 90-day period. Adherence was measured as the proportion of days covered in each 3-month interval following initiation of concomitant therapy (mean follow-up, 12.9 months). Patients were considered adherent if they had filled prescriptions sufficient to cover at least 80% of days with both classes of medications. A multivariate regression model evaluated potential predictors of adherence.

Results: The percentage of patients adherent with both AH and LL therapy declined sharply following treatment initiation, with 44.7%, 35.9%, and 35.8% of patients adherent at 3, 6, and 12 months, respectively. After adjustment for age, sex, and other potential predictors, patients were more likely to be adherent if they initiated AH and LL therapy together, had a history of coronary heart disease or congestive heart failure, or took fewer other medications.

Conclusions: Adherence with concomitant AH and LL therapy is poor, with only 1 in 3 patients adherent with both medications at 6 months. Physicians may be able to significantly improve adherence by initiating AH and LL therapy concomitantly and by reducing pill burden.

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CARDIOVASCULAR DISEASE (CVD) accounts for in excess of 930 000 deaths and \$350 billion in direct medical costs and lost productivity in the United States each year.¹ Numerous clinical trials and meta-analyses have concluded that antihypertensive (AH) and lipid-lowering (LL) medications substantially reduce the risk of coronary heart disease (CHD), stroke, and death in patients with CVD risk factors,²⁻⁶ with long-term therapy yielding the greatest benefit.^{2,3,7,8}

In actual practice, however, long-term adherence and persistence with prescribed drug therapy are poor. Of all written prescriptions, 14% are never filled and another 13% are filled but never taken.⁹ Among patients who actually initiate therapy with 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors (statins), observational studies¹⁰⁻¹² have reported 1-year discontinuation rates of 15% to 60%, depending on the patient popu-

lation, practice setting, and year of study. Among low-income elderly patients, only 26% were still taking statins regularly 5 years after initiating therapy.¹³ Similar trends have been observed with AH medications. During the first year of AH treatment, the average elderly patient had filled AH prescriptions less than 50% of the time¹⁴ and only 1 patient in 5 exhibited compliance sufficient to obtain the therapeutic benefits observed in clinical trials.¹⁴

Many patients have both hypertension and dyslipidemia.¹⁵ The presence of both of these cardiovascular risk factors places patients at substantially greater risk of CHD events than either condition alone.¹⁶ In these patients, adherence with concomitant AH and LL therapy is especially important. However, adherence with concomitant therapy is not well understood, because previous studies have examined persistence with single-drug classes.

The objectives of this study were to (1) study the pattern of adherence with con-

comitant AH and LL therapy in a US managed care population and (2) identify patient and regimen characteristics that predicted optimal adherence with concomitant therapy.

METHODS

PATIENTS

This retrospective cohort study examined enrollees in a US managed care organization from January 1, 1996, until April 30, 2001. Data were retrieved from a computerized database (the Protocare Sciences Managed Care Database) of filled prescription records and paid claims for medical services and procedures. All patient identifiers were removed before analysis to maintain patient confidentiality and to adhere to Health Information Portability and Accountability Act of 1996 standards and requirements.

All enrollees who initiated AH or LL prescription drug therapy between January 1, 1997, and January 30, 2001, and were continuously eligible for pharmacy benefits throughout enrollment were identified. The analysis was restricted to new users by requiring that patients had no filled prescriptions for the relevant drug class during the prior 12 months. New users of AH medications were also required to be diagnosed as having hypertension before initiation of therapy, because many AH medications are used for other indications.

To identify new starters of concomitant therapy, only those patients who initiated treatment with both AH and LL therapy within a 90-day window were analyzed. A 90-day window was selected to minimize the possibility that patients would have become nonadherent with the AH treatment before initiating LL therapy, and vice versa. Patients were retained in the analysis from the first date of concomitant therapy (the index date) until death, disenrollment from the health plan, or April 30, 2001, whichever occurred first.

OUTCOME MEASURES

Adherence with AH alone, LL alone, and both AH and LL was measured in 91-day intervals from the index date. Adherence was defined as the proportion of days covered by a given drug class in each time interval, based on number of days supplied and quantity of medication dispensed for each filled prescription.¹²⁻¹⁴ An imputed value for days supplied was used if missing or if the quantity dispensed divided by the days supplied yielded an implausible daily dosing frequency (0.5-2 for statins, 0.5-6 for other LL drugs, or 0.5-4 for AH medications). The imputed value was based on the modal daily dosing frequency for each drug. This imputation algorithm affected less than 1% of the patient intervals in our files. A day was assumed to be covered if any AH or LL drug was available. Thus, estimates of adherence represented an upper bound on actual adherence with prescribed therapy. Patients were classified as adherent if they had an indication-specific proportion of days covered of 80% or more in a given 91-day interval, consistent with other studies¹²⁻¹⁴ of drug adherence. Patients were considered adherent with concomitant therapy if at least 80% of days were covered by both AH and LL drugs.

POTENTIAL PREDICTORS OF ADHERENCE WITH CONCOMITANT THERAPY

To identify potential predictors of adherence with concomitant AH and LL therapy, we examined a set of demographic (eg, age and sex) and clinical (eg, outpatient diagnoses, medical pro-

cedures, and prescriptions filled during the 365 days before the index date) characteristics that have been observed previously to affect adherence with prescribed medication use for chronic conditions.^{11-14,17} Patients who had evidence of pretreatment CHD were categorized into 3 groups: (1) angina or coronary angiography; (2) coronary artery bypass graft, percutaneous transluminal coronary angioplasty, or history of CHD; and (3) acute or prior myocardial infarction.¹³ Patients who met the criteria for more than one group were assigned to the highest category whose criteria they met. Other comorbid conditions assessed included history of stroke, congestive heart failure, diabetes mellitus, depression, and dementia.

Health services use was also assessed based on the year before initiating concomitant therapy, and included frequency of hospitalizations, frequency of outpatient physician visits, and number of medications prescribed. After examining the distributions of these measures, it was determined that hospitalization would be analyzed as a binary covariate, while the number of physician visits would be analyzed in quartiles.

STATISTICAL ANALYSIS

The mean, median, and interquartile ranges for proportion of days covered were calculated for each drug indication (AH or LL) and for concomitant therapy (AH and LL). The proportion of patients classified as adherent in each 91-day interval was determined for concomitant therapy and for AH and LL drugs separately. Significant predictors of adherence with concomitant therapy were identified using generalized linear models for repeated measures¹⁸ to estimate the probability that a subject had at least 80% of days covered by both AH and LL therapy in each interval. The decline in persistence over time (in months) was assumed to be linear on the log_e scale.

Potential predictors of adherence were considered statistically significant at $P < .05$. The final multivariate model was adjusted for time since the index date and for all the characteristics previously listed. All summary statistics were performed using a commercially available software program (SPSS 11.5; SPSS Inc, Chicago, Ill), and the multivariate model was fitted using SAS statistical software, version 8.02 (SAS Institute Inc, Cary, NC).

RESULTS

POPULATION CHARACTERISTICS

A total of 8406 concomitant AH and LL therapy users met study inclusion criteria. Patients were followed up for an average of 12.9 months (range, 3-36 months). Of the patients, 33.6% initiated concomitant therapy on the same date, while 36.7%, 16.9%, and 12.7% initiated AH and LL therapy within 1 to 30, 31 to 60, and 61 to 90 days, respectively.

Approximately half of patients were younger than 65 on the date that they initiated concomitant therapy, and half were women (**Table 1**). In the year before their index date, 2.5% of patients had evidence of angina or coronary angiography, 18.2% underwent prior percutaneous transluminal coronary angioplasty, prior coronary artery bypass grafting, or treatment for chronic CHD, and 11.0% experienced or had a history of an acute myocardial infarction. Most patients (68.3%) had none of these CHD-related diagnoses or procedures. Diabetes mellitus was the most prevalent comorbid condition, followed by stroke (Table 1).

PATTERNS OF USE OVER TIME

The percentage of patients adherent with both AH and LL therapy (**Figure**) declined sharply following treatment initiation, with 44.7%, 35.9%, and 35.8% of the population adherent at 3, 6, and 12 months, respectively, after which adherence generally stabilized. In each time interval examined, an additional 25.3% to 29.6% of patients were adherent with either AH or LL therapy, but not both. Relatively few patients were adherent with LL therapy and nonadherent with AH therapy (**Figure**). The proportion of patients who were nonadherent with both AH and LL medications increased from 27.4% at 3 months to 35.0% at 6 months, and reached its maximum of 39.0% after 27 months.

PREDICTORS OF ADHERENCE WITH CONCOMITANT AH AND LL MEDICATIONS

After adjusting for age, sex, and other measured variables, the strongest predictor of adherence with concomitant therapy was the number of other prescription medications taken in the year before initiating concomitant therapy (**Table 2**). As the number of other prescribed medications decreased, the likelihood of adherence with concomitant AH and LL therapy increased. For example, patients taking no other medications were approximately twice as likely to be adherent with concomitant therapy as those taking 6 or more other medications.

The second strongest predictor of adherence with concomitant AH and LL therapy was age. Adherence was greatest among patients aged 55 to 64 years, followed by those aged 65 to 74 and 45 to 54 years. Sex also was a significant predictor of adherence, with women less likely to be adherent than men.

Time between initiation of AH and LL therapy was the third strongest predictor of adherence. Patients who started these regimens on the same day or within 1 month of each other were 34% (95% confidence interval, 18%-52%) more likely to be adherent with both medications during the 3-year study period, compared with patients who initiated therapy 2 to 3 months apart. Time since initiation of concomitant therapy also was a strong predictor of nonadherence. The adjusted odds of being adherent with concomitant therapy declined by 14% for every unit increase in months (on a natural log scale) following treatment initiation. For example, 14.3% fewer patients were adherent at 2.75 months than at 1 month ($\log_e[2.75] = 1$).

Patients with a higher CVD risk at baseline were generally more adherent than those without CVD risk factors (**Table 2**). For example, patients with a history of acute or prior myocardial infarction in the year preceding treatment initiation had 28% greater odds of adherence than those without any evidence of CHD. However, a history of diabetes mellitus, a diagnosis of angina, or a history of coronary angiography without revascularization or myocardial infarction was not associated with significantly improved adherence. Patients who had been hospitalized at least once for any cause in the pretreatment year were slightly less likely to be adherent over time.

Table 1. Characteristics of 8406 Patients Who Initiated Both Lipid-Lowering and Antihypertensive Drug Therapy Within 90 Days of Each Other

Characteristic	Value*
Demographics	
Age, y	
18-24	0.7
25-34	0.9
35-44	6.5
45-54	19.9
55-64	23.8
65-74	30.5
75-84	15.9
≥85	1.8
Female sex	46.9
Clinical history for the year before the index date	
Coronary artery disease	
Level 1 (angina or coronary angiography)	2.5
Level 2 (CHD, CABG, or PTCA)	18.2
Level 3 (acute MI)	11.0
Stroke	9.5
Congestive heart failure	7.5
Depression	5.0
Dementia	1.2
Diabetes mellitus	20.8
Charlson comorbidity index†	0.90 (1.26)
Health services in the year before the index date	
No. of prescription medications†	3.96 (3.91)
No. of outpatient physician visits†	3.89 (4.17)
Hospitalized	24.8

Abbreviations: CABG, coronary artery bypass graft; CHD, coronary heart disease; MI, myocardial infarction; PTCA, percutaneous transluminal coronary angioplasty.

*Data are given as percentage of patients unless otherwise indicated.

†Data are given as mean (SD).

COMMENT

This study, one of the first to empirically estimate patterns and predictors of joint long-term adherence with AH and LL medications, demonstrated that less than half of patients (44.7%) were adherent with both AH and LL therapies 3 months after medication initiation, a figure that decreased to 35.8% at 12 months. However, at each time point, an additional 25.3% to 29.6% of patients were adherent with either AH or LL therapy. Adherence with AH therapies was, on average, approximately 10% to 15% greater than with LL medications over time.

Age was a strong predictor of adherence with concomitant AH and LL therapy. Women were less adherent than men. After adjusting for age, sex, and other measured variables, the initiation of AH and LL therapy together, a history of CHD or congestive heart failure, and taking few other medications also were demonstrated to predict adherence with concomitant AH and LL therapy.

Of the patients in this concomitant therapy cohort, 7574 (90.1%) were between the ages of 45 and 84 years. All descriptive analyses and the multivariate model were, therefore, repeated within this subset of patients. The results of the descriptive analyses and the patterns of adherence mirrored those found in the entire cohort. These

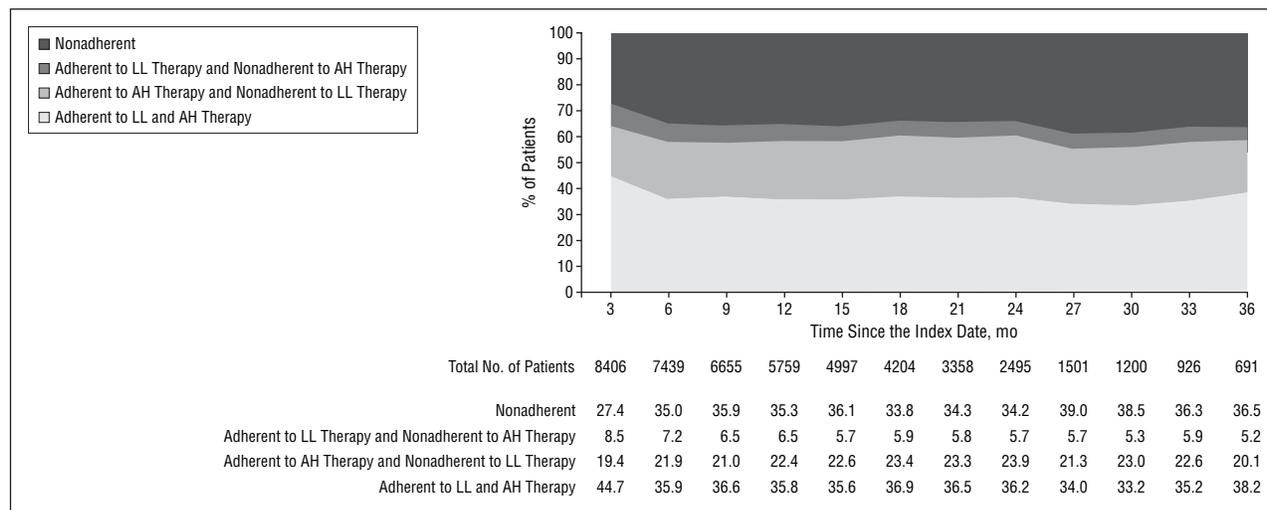


Figure. Patterns of patient adherence to concomitant therapy over 3 years. The index date was defined as the date concomitant therapy (ie, second drug) was initiated. Percentages at each date may not total 100 because of rounding. AH indicates antihypertensive; LL, lipid-lowering.

analyses also were repeated within the same subset of patients aged 45 to 84 years, with results stratified by whether patients were younger than 65 years or 65 years and older. While patients 65 years and older tended to have higher rates of comorbidity and health services use, no striking differences in patterns of compliance with AH or LL medications were observed between subjects younger than 65 years and those 65 years and older.

The pattern of adherence observed in this study—a sharp decline in the first 6 months, followed by a more gradual decline over time—is consistent with previous longitudinal studies^{13,19,20} of adherence with AH or LL therapies. However, the rates of adherence observed in this study with concomitant AH and LL therapies, and with AH or LL therapy alone, were higher than those reported in previous studies¹²⁻¹⁴ that assessed adherence to either AH or LL medications. This difference may indicate the greater motivation to be adherent with therapy among patients who had multiple cardiovascular risk factors, a finding reported in previous studies¹²⁻¹⁴ of drug adherence in patients with hypertension and dyslipidemia. The higher adherence in our study may also be related to the nature of the population studied, namely, a commercially insured cohort with pharmaceutical insurance. Higher rates of adherence have been observed previously in commercially insured populations.¹⁰

The sharp decline in adherence observed in the first 6 months after initiation of therapy for AH and/or LL and the low overall rate of adherence to concomitant therapy are major concerns. Recent studies²¹⁻²³ using meta-analysis and treatment algorithms have suggested that substantial reductions in the risk of cardiovascular events may be obtained by simultaneously targeting hypertension and dyslipidemia. Intensive treatment of modifiable cardiovascular risk factors reduced the risk of cardiovascular and microvascular events by about 50% in patients at high risk of CVD, such as those with type 2 diabetes mellitus and microalbuminuria.²⁴ Thus, improving adherence with concomitant AH and LL therapy will result in substantial health care benefits.

The data obtained concerning predictors of adherence have potential to guide efforts and interventions for improving patient adherence with prescribed AH and LL medication. For example, the observation that approximately one-fourth of the study population was adherent with one medication (usually AH therapy) but not the other demonstrates receptivity to, and partial adherence with, drug therapy to prevent CVD. Therefore, the potential exists for improved adherence with concurrent AH and LL therapies. Any effective intervention among these partially adherent patients may potentially double the percentage of adherent concomitant AH and LL therapy users.

Adherence declined most rapidly during the first 6 months of concomitant AH and LL therapy, suggesting the importance of early interventions to maintain or improve adherence. Similarly, adherence was best when AH and LL therapies were initiated on or about the same date, suggesting benefit from concomitant initiation of therapy to treat these 2 cardiovascular risk factors.

The number of other medications a patient was taking in the pretreatment year was strongly and inversely associated with adherence with concomitant therapy, consistent with previous studies¹²⁻¹⁴ of the association between the total number of medications administered and adherence with prescribed cardiovascular medications. Studies^{25,26} have suggested that simplifying a drug regimen by eliminating even one pill (by using a fixed-dose combination AH product instead of 2-pill combination therapy) could improve adherence. Randomized clinical trials²⁷ assessing the utility of combined AH and LL therapy in the treatment of concomitant hypertension and dyslipidemia have been completed and will provide further guidance on this issue.

Our results should be interpreted in light of study limitations. First, the use of proportion of days covered may overestimate adherence, because it assumes that patients take all of the medications for prescriptions that are filled. This method may also have overestimated adherence in patients prescribed AH regimens consisting

Table 2. Predictors of Adherence With Concomitant AH and LL Medications

Variable	Unadjusted Results		Adjusted Results*	
	Odds Ratio (95% CI)	P Value	Odds Ratio (95% CI)	P Value
Time between start of AH and LL therapy, d				
0-30	1.52 (1.39-1.66)	<.001	1.34 (1.18-1.52)	<.001
31-60	0.74 (0.66-0.82)	<.001	1.09 (0.94-1.27)	.25
61-90	0.66 (0.58-0.75)	<.001	1.00†	NA
Time since the initiation of concomitant therapy, log _e (mo)	0.87 (0.84-0.90)	<.001	0.86 (0.83-0.89)	<.001
Demographics				
Age, y				
18-44	0.73 (0.63-0.85)	<.001	1.00†	NA
45-54	0.95 (0.86-1.05)	.27	1.24 (1.05-1.47)	.01
55-64	1.33 (1.21-1.45)	<.001	1.56 (1.32-1.84)	<.001
65-74	1.00 (0.92-1.08)	.94	1.27 (1.08-1.49)	.004
≥75	0.87 (0.79-0.96)	.006	1.14 (0.96-1.36)	.14
Female sex	0.85 (0.79-0.92)	<.001	0.91 (0.84-0.98)	.02
Clinical history in the baseline year				
Coronary artery disease				
None	0.87 (0.80-0.94)	<.001	1.00†	NA
Level 1 (angina or coronary angiography)	0.83 (0.64-1.08)	.16	0.96 (0.74-1.24)	.73
Level 2 (PTCA, CABG, or chronic CHD)	1.15 (1.05-1.27)	.004	1.20 (1.07-1.34)	.001
Level 3 (acute MI)	1.15 (1.02-1.30)	.03	1.28 (1.09-1.50)	.003
Stroke	1.10 (0.97-1.26)	.14	1.20 (1.04-1.39)	.02
Congestive heart failure	1.22 (1.06-1.40)	.006	1.24 (1.06-1.45)	.008
Depression	0.83 (0.69-1.00)	.05	0.94 (0.78-1.13)	.51
Dementia	0.89 (0.61-1.32)	.57	0.89 (0.61-1.30)	.55
Diabetes mellitus	0.99 (0.90-1.08)	.77	1.06 (0.96-1.17)	.23
Health services used in the baseline year				
No. of other prescription medications				
0	1.73 (1.56-1.90)	<.001	1.96 (1.72-2.25)	<.001
1	1.25 (1.13-1.39)	<.001	1.61 (1.40-1.84)	<.001
2	0.96 (0.86-1.07)	.41	1.30 (1.14-1.49)	<.001
3-5	0.87 (0.79-0.94)	.001	1.23 (1.10-1.38)	<.001
≥6	0.65 (0.59-0.71)	<.001	1.00†	NA
Outpatient physician encounters (all cause)				
0-1	1.16 (1.07-1.26)	<.001	1.00†	NA
2	0.95 (0.85-1.06)	.39	0.93 (0.82-1.05)	.22
3-5	1.02 (0.94-1.11)	.59	1.03 (0.93-1.14)	.60
≥6	0.84 (0.77-0.92)	<.001	0.97 (0.87-1.09)	.61
Hospitalized	0.95 (0.87-1.04)	.24	0.83 (0.73-0.94)	.003

Abbreviations: AH, antihypertensive; CABG, coronary artery bypass graft; CHD, coronary heart disease; CI, confidence interval; LL, lipid-lowering; MI, myocardial infarction; NA, not applicable; PTCA, percutaneous transluminal coronary angioplasty.

*Each odds ratio was adjusted for all other factors in the table.

†Reference group.

of 2 or more AH medications. A given day was assumed to be covered if any drug for the indication of interest was available. Such an approach is likely to be accurate for LL therapy, which in most patients consists of statins alone. In contrast, multidrug therapy is common in the treatment of hypertension. The observed greater adherence with AH relative to LL medications may, thus, be partly a function of the measurement technique used. Second, this analysis assumes that all patients received prescription medications only through their primary health insurance plan. There are several possible scenarios under which medication use might not be captured by the plan (eg, physician-provided samples or claims submitted through other coverage), but these are unlikely to occur frequently among commercially insured patients with a pharmaceutical benefit. Third, a limitation of this study is that patient-level benefit structures and changes were not available in the data. Health

plans may have altered pharmacy benefits during the study, and increased co-payments or coverage caps could lead to decreased persistence or adherence in the affected patients.

Nevertheless, the results of this analysis have important implications for clinicians and other decision makers responsible for treating patients with comorbid hypertension and dyslipidemia. Long-term adherence with concomitant AH and LL therapy in managed care patients was poor. This is extremely concerning given the high risk of cardiovascular events in patients with concomitant hypertension and dyslipidemia¹⁶ and the benefits of treating these 2 risk factors optimally. The factors observed to predict adherence in this study, all of which are available to the physician at initiation of therapy, provide useful information about which patients are likely to be poorly adherent with prescribed therapy and the potential means to improve the management of concomi-

tant hypertension and dyslipidemia. Clinicians should be aware of the factors likely to be associated with poor adherence, such as time taking therapy, young age, female sex, and the absence of cardiovascular events, and should target interventions to increase compliance accordingly. For example, because of the sharp decline in adherence in the first 6 months of concomitant therapy, interventions to promote adherence are more likely to have significant impact if initiated soon after treatment begins. In addition, physicians may be able to improve medication adherence substantially by reducing the number of concomitant medications and by initiating AH and LL medications together or close in time. Any improvement in adherence with concomitant AH and LL medications is likely to be associated with substantial public health care benefits.

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