Impact of Concurrent Medication Use on Statin Adherence and Refill Persistence

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Background: Effective therapy for chronic illness requires daily medication adherence (DMA) for prolonged periods. Overall medical regimen complexity may represent one barrier to successful adherence.

Methods: To assess the relationship between the number of concurrently prescribed medicines and adherence to 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors (statins), we analyzed a cohort of 5488 patients in a single health insurance plan who began statin therapy between July 1, 1999, and June 30, 2002. We assessed 2 parameters of statin adherence: (1) DMA ([total number of pills dispensed/total number of days between first and last prescription] × 100) and (2) refill persistence (RP) (consecutive months of refills after initial prescription).

Results: The cohort was 61.6% male, with a mean±SD age of 52.7±9.3 years. Patients were prescribed a mean±SD of 2.9±2 total medicines (range, 1-13), with a mean±SD statin DMA of 82.1%±26.5%. By 12 months, only 68% of patients continued filling statin prescriptions. After controlling for age, income level, and treatment for hypertension or ischemic heart disease, a greater number of concurrently prescribed medicines was significantly associated with better DMA (P = .005) and longer RP (P = .03).

Conclusions: In this cohort, statin DMA was generally adequate, but RP was suboptimal. Patients with more concurrently prescribed medicines had higher DMA and better RP, even after adjusting for demographic factors and cardiovascular comorbidity. Physicians should not be deterred from initiating statin therapy by a patient’s medical regimen complexity but should be alert for lack of therapy persistence, particularly in younger and healthier patients.

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As our population ages and the prevalence of such chronic diseases as hypertension, diabetes, and congestive heart failure increases, more patients will be prescribed multiple drug regimens. Many patients with diabetes, for example, require hypoglycemic agents, antihypertensive and lipid-lowering medicines, angiotensin-converting enzyme inhibitors, and daily aspirin. Evidence-based treatment of heart failure requires similarly complex regimens.

The 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors (statins) have been demonstrated to reduce cardiovascular events in both primary and secondary prevention trials. Medicines in this drug class are taken once daily, and patients typically continue statin therapy indefinitely. Data from several sources have shown, however, that outside the clinical trial environment, many patients have suboptimal daily adherence and low rates of long-term persistence. The medication burden of other concurrently prescribed medicines has been suggested as one contributor to suboptimal adherence and persistence with statin therapy.

Prior studies have demonstrated that for an individual medicine, adherence and long-term persistence decline with an increasing number of prescribed daily doses. It is less clear whether adherence declines in patients taking multiple different medicines. Using various methods and different patient populations, some prior studies have found increased overall adherence in patients prescribed more total medicines. In contrast, 2 recent studies that focused specifically on statin adherence in elderly populations found that an increased number of total prescriptions for other medicines in the prior year was associated with decreased statin adherence.

It is important to determine the impact of polypharmacy on medication adherence. Reluctance to increase a patient’s current medication burden has been implicated as one factor that prevents phy-
sicians from adding indicated medicines (such as statins) to already complex regimens. We used a pharmacy database of 2.3 million prescriptions filled during a 3-year period by members of a single health insurance plan to test the assumption that adherence is reduced in patients who take multiple different medicines.

**METHODS**

**DATA SOURCE**

We conducted a 3-year cohort study among members of a single health insurance plan whose primary care physicians were affiliated with Partners Community Healthcare Inc, Boston, Mass (PCHI). To be eligible for plan membership, participants had to be employed or have a spouse employed by a company that offered this insurance plan. Physicians in the PCHI system provided care in private office settings, hospital outpatient departments, and affiliated community health centers. The study was approved by the Massachusetts General Hospital/Partners Health Care System institutional review board.

We obtained computerized outpatient pharmacy prescription records for all participants enrolled for at least 3 consecutive months from July 1, 1999, to June 30, 2002. A pharmacy prescription record was generated when a patient used his or her insurance plan to fill a prescription at any pharmacy. Members could fill prescriptions at any pharmacy within the state (99% of which were part of the health care plan network) and at most pharmacies out of state. Members were responsible for a small copayment that varied by medicine but was generally $10 or less per prescription per month. Pharmacy claims included the patient’s name, age, and insurance identification number; the names of the patient’s primary care physician and the prescribing physician; and the date the prescription was filled; and the drug name and dose, and number of pills supplied. Patient sex and home ZIP codes were taken from the health plan enrollment records. We obtained data on 2,293,419 pharmacy prescription records for 1,520,611 patients. To protect patient confidentiality, all personal identifiers were removed before data analysis.

**PATIENTS**

Our study cohort was restricted to members with at least 90 days of continuous enrollment between July 1, 1999, and June 30, 2003. From this group, we identified all patients who received a new prescription for a statin. New statin prescription was defined as a first prescription during an individual patient’s enrollment period that was greater than 90 days after the date of first enrollment. Statins included atorvastatin calcium, fluvastatin sodium, lovastatin, pravastatin sodium, and simvastatin and excluded the small number of cerivastatin sodium prescriptions (0.08% of total prescriptions).

During the 36 months of pharmacy record data collection, individual patient observation periods varied, depending on their specific enrollment and de-enrollment dates. Nearly half the patients (44.4%) in the analysis cohort were continuously enrolled from July 1, 1999, to June 30, 2002, with a median observed enrollment period of 27.2 months (interquartile range [IQR], 18.3–36.5 months).

**OUTCOME MEASURES**

We defined 2 parameters of medication adherence. Daily medication adherence (DMA) represents the percentage of days that the patient has pills available. This proportion is calculated by dividing the total number of prescribed pills by the total number of elapsed days. Total number of prescribed pills is the sum of pills from the first new prescription up to but not including the last recorded prescription in the observation period. The total number of elapsed days is measured from the day the first prescription was filled up to the day that the last prescription in the observation period was filled. Thus, patients who filled 3 statin prescriptions for 30 pills each who filled their last prescription 90 days after filling their first prescription would have a DMA of 67% (120/180 × 100), because they had 60 pills available for the 90 days between the first and last prescriptions. (Pills from the last prescription are not included, because the number of days taken to consume these pills is not known.) Patients who filled only 1 prescription for a statin during the entire observation period are excluded from the analysis of DMA.

We defined refill persistence (RP) as the duration that a patient continued to fill prescriptions after his or her first prescription. Persistence was assessed as both a dichotomous variable and a continuous variable. We first determined what proportion of patients initiating statin therapy during the observation period continued refilling their prescriptions at 1, 6, 9, and 12 months after the initial prescription. Patients were considered to be nonpersistent if they remained enrolled in the health plan beyond the interval of interest (1, 3, 6, or 12 months), but their duration of statin use was less than the interval. Patients were censored if they continued to take statins but their observation period was less than the prescription interval of interest.

We also calculated the total number of months that patients continued refilling prescriptions and the likelihood of persisting with medication refills. Patients were censored if the last prescription in the observation period would have lasted beyond the end of the observation period. This period was calculated by adding 30 days to the total number of pills prescribed at the final prescription.

**POTENTIAL PREDICTORS OF ADHERENCE**

All patients were members of the same health insurance plan. We collected data on sex, age, and home ZIP code at time of enrollment. We used adjusted gross income (AGI) reported for 2000 federal income tax returns for each home ZIP code area as a proxy for socioeconomic status. We also characterized the practice setting for the physician who ordered the initial statin prescription as an urban academic center or a suburban office-based practice and determined the total number of different physicians who prescribed medicines for each patient.

The total number of medicines represents the number of concurrently prescribed medicines (including the statin) at the time the statin was prescribed. This total was calculated from the sum of all unique prescriptions filled before the statin prescription date for which enough pills were dispensed to overlap with that statin prescription date. We excluded prescriptions for medical supplies and devices but included insulin, topical nitrates, and orally inhaled medicines. For each patient, we determined the total number of medicines taken both at the time of the first statin prescription and at the time of the final recorded statin prescription.

Using pharmacy claims for the overall study period, we defined 3 comorbid conditions related to cardiovascular disease based on prescription of condition-specific medications. Patients were categorized as having hypertension if prescribed any blood pressure–lowering medicines; diabetes if prescribed insulin or oral hypoglycemic agents (including sulfonylureas, metformin, thiazolidinediones, and α-glycosidase inhibitors); or ischemic heart disease (IHD) if prescribed any nitrate-containing antianginal agents. In addition, we defined a subset of patients prescribed agents commonly used to treat de-
pression or anxiety, including selective serotonin receptor inhibitors and tricyclic and tetracyclic antidepressants. This method of categorization does not include patients who may be diagnosed as having 1 of these conditions but are not medically treated or, in the case of IHD, treated with other agents.

STATISTICAL ANALYSIS

Univariate analysis of adherence predictors was performed using t tests or the Wilcoxon rank sum test for continuous variables and χ² tests for dichotomous variables. For the continuous outcome of DMA, linear regression models were constructed to assess the impact of polypharmacy after controlling for significant covariates such as age and sex. Logistic regression equations were used to model predictors of the dichotomous outcomes of 6-month and 12-month RP. We also analyzed RP as a continuous variable, with time to discontinuation based on Kaplan-Meier survival curves stratified by number of concurrently prescribed medicines.23 Strata were compared using the log-rank test. We used Cox regression models to calculate the hazard ratio for discontinuation after adjusting for patient demographic factors and comorbidities.23 SAS statistical software was used for all analyses (version 8.2; SAS Institute Inc, Cary, NC), and P < .05 was taken to indicate statistical significance. Data are presented as mean±SD.

RESULTS

PATIENTS

A total of 10640 patients (7.0%) in the pharmacy database were prescribed statins during the observation period, including 5488 patients with new statin prescriptions. Among patients with new statin prescriptions, the mean age was 52.7±9.3 years, 61.6% were men, and patients were taking a mean of 2.9±2 total medicines, including the newly prescribed statin (Table 1).

PREDICTORS OF DMA

Demographics and Comorbidity

From the total cohort of new statin users (n=5488), we excluded 970 patients (17.7%) who did not fill a second prescription during the observation period (and thus did not have a measurable DMA value). These excluded patients included 536 patients with insufficient follow-up observation time (censored) and 434 patients (8% of the total cohort of new statin initiators) who remained in the health plan but never filled a second prescription. The overall statin DMA for the remaining 4518 patients in the cohort who filled more than 1 prescription was 82.1±26.5%. Thus, the average patient had enough available pills to cover 82.1% of days between the first and last recorded prescription.

Statin DMA increased with increasing patient age and increasing AGI (Table 2). Patients treated for hypertension (86% vs 81%, P < .001) or IHD (88% vs 83%, P = .005) had higher DMA, whereas patients receiving antidepressant or anxiety therapy had lower DMA (81% vs 84%, P = .01). Sex, number of prescribing physicians, and treatment for diabetes were not significantly associated with DMA levels.

Table 1. Baseline Characteristics of Patients Beginning Treatment With 3-Hydroxy-3-Methylglutaryl Coenzyme A Reductase Inhibitors

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>No. (%) of Patients (N = 5488)*</th>
</tr>
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<tbody>
<tr>
<td>Age, mean (SD), y</td>
<td>52.7 (9.3)</td>
</tr>
<tr>
<td>Women</td>
<td>2106 (38.4)</td>
</tr>
<tr>
<td>Adjusted gross income, $ in thousands (IQR)</td>
<td>61.8 (47.0-99.9)</td>
</tr>
<tr>
<td>Urban academic practice</td>
<td>1522 (27.7)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>2715 (49.5)</td>
</tr>
<tr>
<td>Depression</td>
<td>1344 (24.5)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>664 (12.1)</td>
</tr>
<tr>
<td>Antianginal therapy</td>
<td>428 (7.8)</td>
</tr>
<tr>
<td>Observation period, mo (IQR)</td>
<td>27.2 (18.0-36.5)</td>
</tr>
<tr>
<td>Total (SD) No. of prescribed medicines when statin initiated</td>
<td>2.9 (2.0)</td>
</tr>
<tr>
<td>Total (SD) No. of prescribing physicians when statin initiated</td>
<td>1.5 (0.8)</td>
</tr>
<tr>
<td>Patients with &gt;1 prescribing physician</td>
<td>1990 (36)</td>
</tr>
</tbody>
</table>

Abbreviation: IQR, interquartile range.
*Data are given as number (percentage) of patients unless otherwise indicated. Adjusted gross income is based on federal income tax returns for patient’s home ZIP code area; comorbid conditions are defined by prescription of condition-specific medicines; observation period corresponds to the number of months the patient was enrolled in the health plan between July 1, 1999, and June 30, 2002.

Table 2. Univariate Predictors of Statin DMA*

<table>
<thead>
<tr>
<th>Predictor</th>
<th>DMA Measure of Effect, %</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td>No effect</td>
<td>NA</td>
</tr>
<tr>
<td>Concurrent treatment with:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antihypertensives</td>
<td>Increased</td>
<td>86 vs 81</td>
</tr>
<tr>
<td>Nitrates</td>
<td>Increased</td>
<td>88 vs 83</td>
</tr>
<tr>
<td>Antidepressor or anxiety therapy</td>
<td>Decreased</td>
<td>81 vs 84</td>
</tr>
<tr>
<td>Antiglycemic agents</td>
<td>No effect</td>
<td>NA</td>
</tr>
<tr>
<td>Increase in Age</td>
<td>Increased</td>
<td>4.1 Per decade</td>
</tr>
<tr>
<td>AGI</td>
<td>Increased</td>
<td>79.2 vs 86.4 (Lowest vs highest quartile)</td>
</tr>
<tr>
<td>No. of medicines</td>
<td>Increased</td>
<td>1.3 Per medicine</td>
</tr>
</tbody>
</table>

Abbreviations: AGI, adjusted gross income; DMA, daily medication adherence; NA, not applicable.
*DMA is the percentage of total days with available pills ([number of dispensed pills, excluding final prescription/days between first and final prescription]×100); AGI is the income in 2000 reported on the federal income tax forms for the patient’s home ZIP code area.

Concurrent Medications

Including the newly prescribed statin, patients were taking 2.9±2.0 different medicines at the initiation of statin therapy (median, 2; IQR, 1-4; range, 1-15) and 3.2±2.2 medicines at the time of their last recorded statin prescription (median, 3; IQR, 2-4; range, 1-19). In univariate analyses, higher statin DMA was significantly associated with an increasing number of total prescribed medicines, whether measured at initiation of therapy or...
herence,24,25 patients with adequate adherence were tak-
DMA of more than 80% as a threshold for adequate ad-
treatment for diabetes or use of antidepressants in
were each significantly associated with greater persis-
tin therapy. Statin RP was not associated
Figure 2. Percentage of patients persisting with statin therapy.
Figure 1. Daily medication adherence (DMA) by number of concurrently prescribed medicines. P<.001 for trend, adjusting for age, adjusted gross income, and comorbid conditions.

at last recorded statin prescription (Figure 1). Using DMA of more than 80% as a threshold for adequate adherence,24,25 patients with adequate adherence were taking a significantly higher number of concurrently prescribed medicines (3.0 vs 2.8 medicines at initiation of statin therapy [P<.001] and 3.5 vs 3.0 medicines at last recorded statin prescription [P<.001]).

In multivariate linear models controlling for age, AGI, and comorbid conditions, a greater number of concurrent medicines either at initiation of statin therapy (P=.005) or at the time of last recorded statin prescription (P<.001) remained significantly associated with better overall statin DMA.

PREDICTORS OF PERSISTENCE

Demographic and Comorbidity Factors

Patients who newly began statin therapy were observed for a median of 7.8 months of therapy (IQR, 2.1-16.2). Almost one quarter of patients (1284, 23.4%) discontinued therapy during their observation period. After excluding patients with censored data for each time interval, persistence with statin therapy declined in a stepwise fashion over time (Figure 2). In univariate analyses using Cox proportional hazard models, older age, higher AGI, and treatment for hypertension or IHD were each significantly associated with greater persistence with statin therapy. Statin RP was not associated with patient sex, number of prescribing physicians, or treatment for diabetes or use of antidepressants in unadjusted analyses.

Concurrent Medications

A greater number of concurrently prescribed medicines, either at initiation of statin therapy or at last recorded statin refill, was associated with greater persistence with statin therapy over time (Figure 3). In multivariate Cox models, each additional prescribed medicine at the time of the last statin prescription refill was associated with 4% increased chance of greater RP after adjusting for age, AGI, sex, and treatment for hypertension or IHD (P=.01).

In this large cohort of older patients with few financial barriers to care, average daily adherence appeared adequate, but there was a marked decline in RP over time and at least 8% of our cohort never filled a second prescription. More complex medical regimens were not associated with poorer medication adherence, even after adjusting for increasing age and treatment for cardiovascular comorbidity. In fact, patients taking more medicines tended to have higher daily adherence and were more likely to persist with therapy. This finding was consistent whether considering number of concurrent medications either at the initiation of statin therapy or during treatment. These results confirm that when isolated from significant cost and access to care barriers, polypharmacy alone is not an impediment to medication adherence, measured either as daily pill taking or in continuity of therapy over time.

Previous studies have shown differing relationships between regimen complexity and adherence. In prior work using self-reported adherence, we found that patients with diabetes reported high overall 7-day adherence rates regardless of number of prescribed medicines.17 In a study of medication RP in a rural indigent population, Schectman et al16 found that increasing number of prescribed medicines was associated with greater RP.

In contrast, 2 recent, large, pharmacy claims–based analyses of statin use found that increasing regimen complexity was modestly associated with decreased statin adherence. Benner et al18 measured proportion of days covered (analogous to DMA) in an older population of New Jersey Medicaid patients who were prescribed a mean of 9.2 medicines in the preceding 12-month period. Significant suboptimal adherence over time was observed only in patients prescribed 11 or more medicines in the prior year. Jackevicius et al19 focused on RP as the measure of statin adherence in a cohort of patients 66 years or older in Ontario, Canada. Patients in the Ontario cohorts were prescribed between 7.9 and 12.8 medicines in the preceding 12-month period. There was a small but significant trend of less persistence with more concurrent medicines. Patients in both these studies were reported to be taking a higher number of concurrent medicines compared with our cohort. The greater number of total medicines in those 2 studies may reflect either more severe comorbidity in their generally elderly patient cohorts or their method of summing all prescriptions in the

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prior year rather than only the number of concurrently prescribed medicines during statin therapy.

Patients prescribed multiple concurrent medicines likely feel more personally vulnerable to the consequences of disease and therefore may be more adherent to prescribed medicines compared with younger, healthier patients. One explanation for the disparate findings between our study and the recent statin studies described herein may be that statin adherence improves with increasing medication burden up to a certain threshold, beyond which adherence declines. Patients prescribed the highest number of total medicines may be significantly sicker, and for these patients the burden of illness itself may reduce medication adherence. Given the continuing trend of more aggressive pharmaceutical management of chronic medical illnesses, further research is needed to clarify the consequences of polypharmacy on adherence in patients with different levels of symptomatic comorbidity.

There are several strengths to our study. Use of pharmacy claims allows assessment of 2 very different parameters of medication adherence: daily pill taking and long-term RP. In addition, our method of counting only those prescriptions that overlapped with specific statin prescription dates allowed for an accurate assessment of concurrently prescribed medicines. Patients in our cohort were unaware that adherence would be assessed and thus adherence behavior was not altered by adherence measurement, a common flaw of studies based on self-report, electronic monitoring, or pill counts.

One limitation of pharmacy claims is the lack of clinical correlation. In a few cases, the prescriber may have discontinued therapy for clinically appropriate reasons such as adverse drug events, lack of efficacy, or conversion to other therapies. However, lipid-lowering therapy is generally long term, adverse drug events are rare, and other studies have shown that for lipid lowering, conversion from statins to nonstatin agents is rare. In addition, our method accounted for regimen changes related to adjustments in dose strength or change from one statin to another.

Prior studies have clearly demonstrated the importance of access to care and of medication affordability among poorer and underinsured patients. Because patients in our cohort had good access to care and few financial barriers to medication use, we were able to more directly assess the impact of regimen complexity on medication adherence independent of these barriers. When isolated from financial barriers related to purchasing prescription medicines or receiving regular access to primary care, multiple drug regimens to treat chronic diseases are not of themselves a barrier to daily adherence or long-term persistence with therapy. As a society, we must continue to find ways to provide affordable and accessible health care. As physicians, we should not underestimate patients’ capacity to adhere to multiple concurrent medication regimens.

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Figure 3. Kaplan-Meier curve of persistence with therapy, stratified by number of concurrently prescribed medicines.