

# EMR-Based Medication Adherence Metric Markedly Enhances Identification of Nonadherent Patients

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**Objectives:** To determine whether addition of written-prescription data to existing adherence measures improves identification of nonadherent patients and prediction of changes in low-density lipoprotein (LDL) cholesterol.

**Study Design:** Retrospective database analysis of all health plan members prescribed a statin in 2008 and followed through 2010.

**Methods:** We examined statin use in a 4-million-member health plan with 100% electronic medical record coverage. A novel type of medication possession ratio (MPR), integrating prescribed with dispensed medication data, was developed. This measure, MPR<sub>p</sub>, was compared with a standard dispensed-only adherence measure, MPR<sub>d</sub>. Adherence below 20% was considered nonadherence. The 2 adherence measures were compared regarding (1) the number of patients identified as nonadherent, (2) percent changes in LDL from study enrollment to study termination, and (3) receiver-operator curves assessing the association between adherence and a 24% decrease in LDL.

**Results:** A total of 67,517 patients received 1,386,270 written prescriptions over the 3-year period. MPR<sub>p</sub> identified 93% more patients as nonadherent than did MPR<sub>d</sub> ( $P < .001$ ). These newly identified patients exhibited minimal LDL decreases over the course of the study. Adherence by MPR<sub>p</sub> was more strongly associated with decreases in LDL than was adherence by MPR<sub>d</sub> (area under the curve 0.815 vs 0.770;  $P < .001$ ). During the study period, 18.2% of patients did not fill any prescriptions and were thus unidentifiable by dispensed-only measures.

**Conclusions:** Addition of written-prescription data to adherence measures identified nearly twice the number of nonadherent patients and markedly improved prediction of changes in LDL.

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For author information and disclosures, see end of text.

Nonadherence to prescribed medication is a pervasive phenomenon, more common in chronic than in acute conditions.<sup>1</sup> Poor adherence to medication regimens has been associated with poor medical outcomes over a range of diagnoses,<sup>2-6</sup> and poor adherence to statins has been found to be associated with higher healthcare costs and cardiovascular hospitalizations.<sup>7-9</sup> Clinicians and healthcare managers thus have a strong interest in accurately identifying poorly adherent patients. In the past 2 decades, estimating adherence in healthcare systems using administrative databases has become commonplace. Medication possession ratio (MPR) and related measures of medication availability are the most frequently used measures<sup>10</sup>; however, they are based almost exclusively upon dispensed-medication data. Patients never filling a prescription will be missed, and censoring follow-up at the time of the last refill may overlook periods during which physicians continued to prescribe but patients ceased to adhere. For a comprehensive overview of dispensary-based medication adherence measures, see Steiner and Prochazka.<sup>11</sup>

In recent years, several studies have attempted to integrate written-prescription data into adherence measures. However, these have focused almost entirely upon primary nonadherence (failure to fill a first prescription for a new medication).<sup>12-15</sup> Only a single study using written-prescription data looked past the initial dispensary event to calculate adherence over an extended period.<sup>16</sup> Thus, the value of integrating written prescription-based data into medication adherence measures remains unclear.

Healthcare in Israel is delivered primarily through 4 nationwide health plans, which act both as providers and insurers to essentially the entire population and through which patients are guaranteed a legally mandated minimum package of medical services.<sup>17</sup> Clalit Health Services (CHS), the largest of these plans, insures approximately 4 million people (53% of the Israeli population) and has comprehensive clinical and administrative electronic medical record coverage. Patients in CHS have a strong incentive to access primary care and obtain prescription medications within the Clalit system because primary care visits are free of charge to members, and medications included in the benefit package are subject to small copayments (approximately US \$4-\$7). Out-of-pocket quarterly outlays for chronic medications are capped at US \$110 to \$220, depending on the patient's eligibility.

Our aim was to ascertain the utility of a novel medication adherence measure incorporating

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Take-Away Points / e373  
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written-prescription data in identifying nonadherent patients and predicting clinically meaningful health outcomes in a large health plan database.

## METHODS

### Setting

We performed a retrospective database analysis, including all patients 18 years and older enrolled in CHS who had not previously been dispensed a statin, had been prescribed a statin at least once in 2008, had not since had chronic (mental, rehabilitation, or nursing home) hospitalization, and were alive on December 31, 2010. Patients were monitored for medication adherence between January 1, 2008, and December 31, 2010 (the study period), and were considered enrolled in the study from the date of the first statin prescribed in that period. CHS maintains an electronic medical record with demographic information, clinical information, and records of all medications dispensed since 1998 and of all medications prescribed by any community physician in the system since 2008.

We collected data on age, sex, socioeconomic status, concomitant medications in the month up to and including the day of study enrollment, the occurrence of an acute ischemic event in the year preceding study inclusion, statins prescribed, statins dispensed, the last low-density lipoprotein (LDL) cholesterol level available in the year before study inclusion (prestudy LDL), and the last LDL cholesterol level available at least 90 days after study inclusion but not more than 30 days after the final statin prescription (end-study LDL). All residents of Israel receive a universal identification number at birth or immigration. Each patient interaction with CHS is indexed by this number. Patient data for our study was linked by the universal identification number, but additional personal identifying information was not collected. In-hospital prescribing and dispensing data were not available for this study; however, days of acute hospitalization over the course of the study were tallied. The study was approved by the CHS institutional review board.

### Measures of Medication Adherence

Adherence measures used in this study were modeled after the concept of MPR, although with the addition of written-prescription data.<sup>10</sup> We created an MPR-type measure integrating written-prescription data with dispensed data ( $MPR_p$ ) and compared it with a commonly used version of dispensed-only MPR ( $MPR_d$ ).  $MPR_d$  was defined as the number of days of supply divided by the number of days between the day the

### Take-Away Points

Commonly used measures of medication adherence use only dispensed medication data. Attempts to integrate written-prescription data into these measures have been limited to “primary adherence” and have not been validated with respect to clinically important outcomes.

- Addition of written-prescription data to measures of adherence identified nearly twice as many nonadherent patients and markedly improved prediction of changes in low-density lipoprotein cholesterol.
- Adding such measures to existing health records would identify a large proportion of patients prescribed but not procuring any medication, allowing for improved targeting of nonadherent populations.

first medication was *dispensed* and the day before the last medication was dispensed in the study period.  $MPR_p$  was defined as the number of days of supply divided by the number of days between the day the first medication was *prescribed* and the day before the last medication was prescribed in the study period.  $MPR_p$  thus reflects adherence over the period for which statins were known to be prescribed.

Study participation was calculated as the time between the first and the last prescribed statin in the study period. Any statin prescribed or dispensed was counted; thus, a change in type of statin was considered ongoing adherence, but a change to another lipid-lowering medication group terminated study participation. Patients with a single written prescription or single dispensed medication were assigned a 29-day study duration. Patients filling more medication than necessary to cover their entire study participation period were considered 100% adherent. MPR is reported as a percent score for each patient. In this study, patients with adherence below 20% were considered nonadherent, following the methodology of Insull et al.<sup>18</sup>

To ascertain whether patients identified as nonadherent by  $MPR_p$  but not by  $MPR_d$  indeed had undertreated hyperlipidemia, we calculated the fractional decrease in LDL (the percent change in LDL cholesterol from before study enrollment until the end of study participation) in those identified as nonadherent by  $MPR_d$  and separately in those identified as nonadherent by  $MPR_p$  but not by  $MPR_d$ .

Given the known efficacy of statins in reducing LDL,<sup>19</sup> a successful measure of statin adherence should demonstrate a strong association with patient LDL reductions. In order to compare the utility of  $MPR_d$  with that of  $MPR_p$  in predicting changes in LDL, we generated receiver operator characteristic (ROC) curves. We considered a 24% or greater fractional drop in LDL as a clinically important decrease in LDL. This decrease is slightly smaller than that anticipated from full adherence to a variety of statins at low dosages (27%)<sup>19</sup> and is double the National Cholesterol Education Program Working Group on Lipoprotein Measurement allowable total error of 12%<sup>20</sup>; thus, it is unlikely to be due to chance.

■ **Table.** Characteristics of Study Population

Characteristic	Value
Patients, n	67,517
Age, mean ± SD, y	55.3 ± 12.9
Male, %	47.2
Low socioeconomic status, %	47.6%
Concomitant medications, mean ± SD	3.3 ± 2.9
Acute ischemic event, %	3.7%
Acute hospitalization days, mean	1.5
Days of study participation, mean ± SD	692.8 ± 332.0

SD indicates standard deviation.

Sensitivity analysis was performed in several ways. First, we repeated the ROC analysis using cutoffs of 20% and 30% drops in LDL. To rule out a dominant effect of patients prescribed a statin only once or patients with short durations between the first and last statin prescribed, we repeated our analysis excluding patients whose study participation was 90 days or less, which also excluded those receiving a single written prescription. Additionally, we repeated ROC analysis excluding patients who were not dispensed any statin during the study period. Finally, ROC analysis was repeated including only patients with a prestudy LDL of 100 mg/dL or greater.

Statistical analysis was conducted using SPSS version 18.0.3 (IBM Corporation, Armonk, New York) and WINPEPI version 11.15 (freeware; <http://www.brixtonhealth.com/pepi4windows.html>). Averages for medication adherence were compared with the *t* test. Proportions of nonadherent patients by each measure were compared using  $\chi^2$  test. Fractional differences in LDL were compared by analysis of

variance. ROC curves were generated using standard methodology, and areas under the ROC curve were compared using the Hanley-McNeil method.<sup>21</sup>

## RESULTS

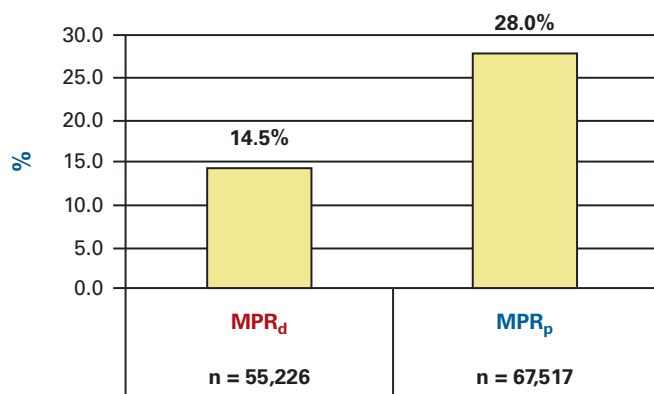
A total of 67,517 members of CHS fulfilling all inclusion criteria received a total of 1,386,270 written prescriptions for a statin over the 3-year study period. The average age of the study population was 55.3 ± 12.9 years and 47.2% were male. Approximately half (47.6%) the patients were characterized as of low socioeconomic status. Patients took an average of 3.3 ± 2.9 distinct concomitant medications in the month up to and including the day of index prescribed statin. In the year before study enrollment, 3.7% of patients had sustained an acute coronary event. The average length of study participation was 692.8 ± 332.0 days. A total of 13,667 (20.2%) patients were hospitalized for a median of 4 days (interquartile range 2-8 days). The average number of acute hospitalization days for the whole study population was 1.5 (Table).

Average adherence was 59.0% as measured by MPR<sub>d</sub> and 50.9% as measured by MPR<sub>p</sub>. Thus, adherence as measured by MPR<sub>d</sub> was 15.9% higher than adherence as measured by MPR<sub>p</sub> (*P* < .001). A far higher proportion of patients were identified as nonadherent by MPR<sub>p</sub> than by MPR<sub>d</sub> (28.0% vs 14.5%, 93% more; *P* < .001). Whereas our entire study population was available for nonadherence analysis using MPR<sub>p</sub>, 12,291 patients (18.2% of our sample) were not available for analysis using MPR<sub>d</sub> because these patients filled no prescriptions during the study period (Figure 1).

A total of 49,325 patients (73.1% of our population) had both prestudy and poststudy LDL tests and were thus available for LDL analysis. The average prestudy LDL for the entire study population was 151.4 ± 30.3 mg/dL and decreased to 111.4 ± 36.7 mg/dL at the end of the study, indicating a 25.1% fractional decrease in LDL. Patients identified as nonadherent by MPR<sub>d</sub> had an 8.2% drop in LDL (153.6 ± 29.4 mg/dL to 139.3 ± 35.1 mg/dL), while those identified as nonadherent by MPR<sub>p</sub> had only a 6.8% drop (149.6 ± 31.1 to 136.9 ± 35.1 mg/dL; *P* < .001). Thus, patients identified as nonadherent by MPR<sub>p</sub> were treated less effectively than those identified as nonadherent only by MPR<sub>d</sub> (*P* < .001).

The area under the curve for the ROC curve for MPR<sub>p</sub> as a predictor of a 24% decrease in LDL was 0.815 (95% confidence interval [CI] 0.812-0.819), whereas that for MPR<sub>d</sub> was 0.770 (95% CI 0.765-0.774; *P* < .001 for the comparison), indicating that MPR<sub>p</sub> was a better predictor of LDL change than

■ **Figure 1.** Nonadherence by MPR<sub>d</sub> and MPR<sub>p</sub><sup>a</sup>



MPR indicates medication possession ratio.

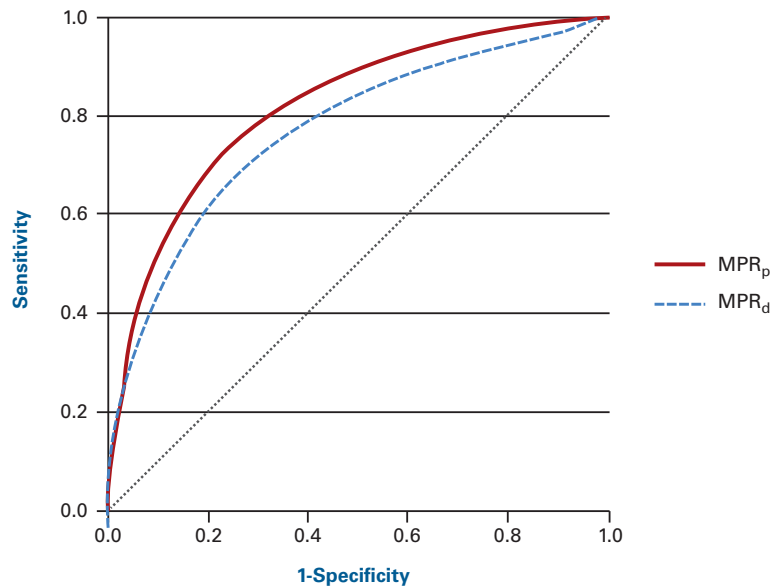
<sup>a</sup>Nonadherence was defined as an MPR<sub>d</sub> of less than 20% for dispensary-only measures and as an MPR<sub>p</sub> of less than 20% for measures integrating prescribed with dispensed medication data. A total of 12,291 patients, 18.2% of our population, were unavailable to analysis by MPR<sub>d</sub>. *P* < .001.

MPR<sub>d</sub>. In sensitivity analysis, area under the curve values changed only slightly when the LDL cutoff was set at 20% or at 30% and when only patients with prestudy LDL values higher than 100 mg/dL were included (Figure 2). Limiting the analysis to patients who had been in the study for more than 90 days or to patients receiving at least 1 dispensed statin did not alter the primary outcome (data not shown).

## DISCUSSION

Because nonadherence to medications is associated with adverse clinical outcomes, a major concern of clinicians and health plan managers is to identify and manage nonadherent patients. In this study, we demonstrate that a measure of medication adherence integrating written prescription information with dispensed medication data better identifies patients who are nonadherent to their medication and more accurately predicts changes in LDL than a commonly used dispensed-only measure. Compared with the integrated measure, the dispensed-only measure overestimated adherence by 16% and failed to identify nearly half of nonadherent patients. In particular, patients filling no prescriptions were identified as nonadherent by the integrated measure, but were invisible to the dispensed-only measure. Comparison of fractional decreases in LDL verified that patients identified as nonadherent by the integrated measure were indeed undertreated and were justly labeled as nonadherent. ROC curve analysis demonstrated that the integrated measure was significantly superior to the dispensed-only measure in predicting changes in LDL over the course of the study. Sensitivity analysis found our results robust when different LDL cutoffs were used, when limited to patients with a pretrial LDL above 100 mg/dL, and even when limited only to those patients who had filled a prescription (ie, including only patients who were “visible” to both measures). Our integrated measure not only uncovered a large

■ **Figure 2.** Predictive Value of MPR<sub>p</sub> and MPR<sub>d</sub> on a 24% Decrease in LDL Over the Study Period, All Patients<sup>a</sup>



Variable	Area Under the Curve (95% CI)		P
	MPR <sub>p</sub>	MPR <sub>d</sub>	
<b>Primary outcome</b>			
Entire population 24% cutoff <sup>b</sup>	0.815 (0.812-0.819)	0.770 (0.765-0.774)	<.001
<b>Sensitivity analysis</b>			
Entire population 20% cutoff	0.820 (0.817-0.824)	0.776 (0.771-0.780)	<.001
Entire population 30% cutoff	0.798 (0.794-0.802)	0.754 (0.750-0.758)	<.001
LDL >100 mg/dL <sup>c</sup>	0.821 (0.818-0.825)	0.779 (0.774-0.783)	<.001

CI indicates confidence interval; LDL, low-density lipoprotein; MPR, medication possession ratio.  
<sup>a</sup>MPR<sub>p</sub> integrates prescribed with dispensed medication data; MPR<sub>d</sub> is a standard dispensed-only adherence measure.  
<sup>b</sup>Primary outcome.  
<sup>c</sup>Analysis limited to patients with prestudy LDL values greater than 100 mg/dL.

population of previously undetected nonadherent patients, but it also was a better predictor of changes in LDL, even among patients visible to both measures.

In our search of the literature, we were able to identify very few studies attempting to integrate written-prescription data into estimates of medication adherence. Four of these studies dealt only with primary (first-fill) nonadherence (ie, failure to fill a first prescription for a new medication) and not with overall measures of adherence as such. Shah and colleagues identified 30-day nonfillers (ie, patients who failed to fill an initial prescription for the study medication within 30 days, and by inference did not fill the prescription at all) separately for antihypertensive and antidiabetic medications.<sup>12,13</sup> They found 17% and 15% nonfillers, respectively, closely paralleling our rate of patients eluding identification

by the dispensed-only measure. In 2 separate settings, Fischer and colleagues in 2010<sup>14</sup> and 2011<sup>15</sup> found 28.2% and 25.2% of patients, respectively, with primary nonadherence to antihyperlipidemic medications in 2 large community cohorts. Those rates are considerably higher than the 18.2% rate of primary nonadherence in our study. Karter et al<sup>22</sup> expressed concern about the potential for missed new fills and the resulting differential misclassification bias in the 2010 study by Fischer et al. We lack information on the characteristics of Fischer and colleagues' study population that would allow an understanding of the marked difference in primary adherence rates. The 2009 study by Karter et al is the work most closely related to our own.<sup>16</sup> His group created a novel algorithm to estimate adherence that integrated written-prescription data, although it was based on a methodology measuring "gaps" (periods not covered by supply of medication). In their study population of diabetic patients, they found that 8.5% never filled a prescription for a cholesterol-lowering therapy.<sup>16</sup> It is conceivable that patients appearing in a diabetes registry are more adherent than the general population evaluated in our study. Their methodology was not found superior to an existing gap measure in predicting changes in LDL.

Our work has several limitations, some of them common to all pharmaceutical database research. Our data could indicate that a medication was prescribed or dispensed, but we were unable to determine whether that medication had in fact been taken as prescribed. Additionally, our study was not immune to the possibility of patients obtaining medications, and possibly prescriptions, outside the health plan's system. However, because in the CHS system visits to primary care physicians are free of charge and pharmacy copayments are low and capped, patients have a strong incentive to receive treatment within the system. These considerations may be of lesser consequence to patients of high socioeconomic status; however, poor adherence has repeatedly been found to be positively associated with lower socioeconomic status.<sup>23,24</sup> Our investigations confirm this association (data not shown). A substantial proportion of our patients did not have the 2 LDL tests necessary to enter LDL analysis. Examining this question, we found that poor compliance and short study duration were strongly associated with missing LDL data. This finding suggests that full data would in fact strengthen the association observed between adherence measures and changes in LDL (data not shown).

Issue may be taken with our decision to base our primary estimate of nonadherence on a measure censoring follow-up on the day before the last written prescription. We found this to be the closest parallel to the common practice of truncating dispensary data before the last refill.<sup>25</sup>

We have generated a novel algorithm for estimating medi-

cation adherence, integrating written-prescription data with dispensed data. This measure identified a far higher proportion of nonadherent patients in our population, including those who never filled a prescription, and we provide evidence that these patients were indeed undertreated. This new measure was also more strongly associated with LDL changes than the dispensed-only measure; thus, it is likely to better predict medical outcomes associated with hyperlipidemia. A common dispensed-only measure of adherence markedly underestimated the scope of the medication adherence problem and failed to identify nearly half of nonadherent patients—those procuring no prescribed medication at all.

With the rapid and accelerating adoption of electronic medical records, prescription data are likely to become available to a wide range of providers. We have shown that integrating these data into dispensary-based adherence measures would more accurately identify nonadherent patients and those unlikely to achieve clinically important LDL reductions, and would provide a superior predictor of LDL reduction. This information should prove important to both clinicians treating patients and to healthcare managers attempting to assess the extent of medication nonadherence and the resources necessary to address it.

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