Effect of Medication Nonadherence on Hospitalization and Mortality Among Patients With Diabetes Mellitus

P. Michael Ho, MD, PhD; John S. Rumsfeld, MD, PhD; Frederick A. Masoudi, MD, MSPH; David L. McClure, PhD, MSc; Mary E. Plomondon, PhD, MSPH; John F. Steiner, MD, MPH; David J. Magid, MD, MPH

Background: Medication nonadherence may reduce the effectiveness of therapies. To our knowledge, the association between medication nonadherence and mortality remains unexplored outside the context of clinical trials.

Methods: A retrospective cohort study of 11,532 patients with diabetes mellitus in a managed care organization. Medication adherence was calculated as the proportion of days covered for filled prescriptions of oral hypoglycemics, antihypertensives, and statin medications. The primary outcomes of interest were all-cause hospitalization and all-cause mortality. Multivariable regression analyses were performed to assess the independent association between medication adherence and outcomes.

Results: Nonadherent patients (proportion of days covered, <80%; prevalence, 21.3%) were younger and had fewer comorbidities compared with adherent patients. During follow-up, nonadherent patients had higher glycosylated hemoglobin, systolic and diastolic blood pressure, and low-density lipoprotein cholesterol levels. In unadjusted analyses, nonadherent patients had higher all-cause hospitalization (23.2% vs 19.2%, P < .001) and higher all-cause mortality (5.9% vs 4.0%, P < .001). In multivariable analyses, medication nonadherence remained significantly associated with increased risks for all-cause hospitalization (odds ratio, 1.58; 95% confidence interval, 1.38-1.81; P < .001) and for all-cause mortality (odds ratio, 1.81; 95% confidence interval, 1.46-2.23; P < .001). The findings were consistent across patient subgroups and using different cutoffs for the proportion of days covered.

Conclusions: Medication nonadherence is prevalent among patients with diabetes mellitus and is associated with adverse outcomes. Interventions are needed to increase medication adherence so that patients can realize the full benefit of prescribed therapies.

Arch Intern Med. 2006;166:1836-1841

Clinical trials demonstrated the efficacy of medications such as oral hypoglycemics, angiotensin-converting enzyme inhibitors, and 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors (statins) among patients with diabetes mellitus (DM). According to national clinical practice guidelines, glycemic, blood pressure (BP), and cholesterol control are key components to preventing complications of DM. Despite these recommendations, only 43%, 29%, and 52% of patients with DM achieved guideline targets for glycosylated hemoglobin (HbA1c), BP, and low-density lipoprotein cholesterol (LDL-C) levels, respectively. Medication nonadherence may explain the suboptimal achievement of therapeutic targets. One study found that fewer than 50% of patients prescribed statin medications were adherent 12 months after initiating treatment. In addition, nonadherence to oral hypoglycemics and antihypertensive medications has been associated with higher HbA1c and BP levels, respectively. To date, studies in clinical practice have not evaluated the association between medication nonadherence and outcomes such as mortality, to our knowledge.

See also pages 1802, 1822, 1829, 1842, 1848, and 1855

The objective of this study was to evaluate the association between medication nonadherence and clinical outcomes in a large community cohort of patients with DM. We evaluated the association between medication nonadherence and achievement of treatment targets, including HbA1c, BP, and LDL-C levels. Then, we assessed the association between medica-
tion nonadherence and all-cause hospitalization and all-cause mortality.

METHODS

STUDY SETTING

Kaiser Permanente of Colorado (KPCO) is an integrated, nonprofit managed care organization that provides medical services to more than 400,000 members in the Denver metropolitan area. A diabetes registry was established on September 17, 2002. Patients with DM who are 18 years or older are initially identified using an algorithm applied to KPCO automated databases consisting of pharmacy records, laboratory data, hospitalization records, and outpatient diagnoses. Once a potential patient is identified, the diagnosis of DM is validated by medical record review before inclusion in the registry.

PATIENTS

We conducted a retrospective cohort study of patients in the KPCO diabetes registry. Patients who were in the registry as of September 17, 2002, and had continuous enrollment through December 31, 2003, were included. Patient adherence to medications was assessed during 2003. The outcomes were ascertained from January 1, 2004, through April 30, 2005, which was the most recent date for which follow-up data were available. Baseline patient demographics, comorbidities, vital signs, and laboratory data were derived from automated KPCO databases. Comorbidities were defined using diagnosis related group system, Current Procedural Terminology, or International Classification of Diseases, Ninth Revision codes within the automated databases. The baseline HbA1c and LDL-C levels were defined as the most current measurement during 2002. For BP, if 2 or more measurements were available in 2002, the 2 most recent measurements were averaged. Patients were followed up until death or disenrollment from the health plan. As of April 30, 2005, 96.6% of the patients were still enrolled or had died. The mean follow-up was 474 days.

MEDICATION ADHERENCE

The automated pharmacy records at KPCO include all medications dispensed at each outpatient facility. Almost all patients (>98%) have prescription drug coverage for a nominal copayment. The nominal copayment and the location of pharmacies at the same site as the clinic offices serve as incentives for patients to fill their prescriptions within the system. Medication adherence was calculated as the proportion of days covered (PDC), based on the total number of days supplied for filled prescriptions during the observation interval. We defined this interval as a minimum of 240 days and a maximum of 365 days to ensure stable estimates for refill adherence in our primary analysis.

A PDC was derived for each of the 3 categories of medications important to patients with DM, including oral hypoglycemics, antihypertensives, and 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors (statins). For oral hypoglycemic agents, the PDC was based on filled prescriptions for sulfonylureas, metformin hydrochloride, or thiazolidinediones. A PDC was not derived for insulin because of the difficulty in measuring adherence to injectable medications from pharmacy data; however, patients requiring insulin only as a hypoglycemic agent were included in the cohort based on adherence to antihypertensive or statin medications. Similarly, patients with diet-controlled DM were included based on adherence to the other 2 categories of medications.

The antihypertensive medication PDC was based on filled prescriptions for angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, B-blockers, diuretics, or calcium channel blockers. Because antihypertensive medication regimens are often changed for different reasons (ie, adverse effects or inadequate control) and because patients often require more than 1 agent to control BP, adherence was averaged across the different classes of medications. Therefore, the antihypertensive medication PDC reflects general adherence to the overall antihypertensive medication regimen.

For 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors, the PDC was based on filled prescriptions for statin medications. For patients prescribed medications from multiple categories, a summary PDC measure was calculated as the averaged PDC of any 1 or more categories of medications.

Next, patients were classified as nonadherent based on a summary PDC less than 80%, consistent with the dichotomization of medication adherence in the literature.9,10,13-15 This medication nonadherence variable was the primary predictor variable in the multivariable analyses. Applying this algorithm, we calculated a summary PDC for 11,532 patients in the KPCO diabetes registry, and these patients constituted the study cohort.

DEPENDENT OR OUTCOME VARIABLES

The primary outcomes were all-cause hospitalization and all-cause mortality during the follow-up period (January 1, 2004, through April 30, 2005). Data on hospitalization and mortality were derived from the KPCO automated databases and were validated by comparison with internal KPCO data sources.

Secondary outcomes were achievement of treatment targets for HbA1c, BP, and LDL-C levels. Consistent with baseline data, the most recent measurements for HbA1c and LDL-C levels in 2004 and the mean of the 2 most recent BP measurements in 2004 were used to define these secondary outcomes.

STATISTICAL ANALYSIS

Using \( \chi^2 \) test for categorical variables and t test for continuous variables, we compared the baseline demographic factors, comorbidities, and proportions of patients attaining HbA1c, BP, and LDL-C guideline-indicated levels between adherent and nonadherent patients. The achievement of treatment targets (ie, HbA1c, BP, and LDL-C levels) was compared between the 2 groups by using the 2-tailed t test. Unadjusted all-cause hospitalization and all-cause mortality were compared using the \( \chi^2 \) test.

In multivariable analysis, separate logistic regression models were constructed to evaluate the association between medication nonadherence and all-cause hospitalization and mortality. Unselected multivariable models were constructed to maximally adjust for confounding and included all variables in Table 1. Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated for each independent variable in the multivariable models.

In secondary analysis, the association between medication nonadherence and outcomes was first evaluated across different patient subgroups, including the following: patients with diet-controlled DM; patients requiring insulin only; patients requiring oral hypoglycemics only; older patients (\( \geq 65 \) years), patients with hypertension, heart failure, hyperlipidemia, or coronary artery disease; and patients at target HbA1c, BP, and LDL-C level goals at baseline. Second, we constructed multivariable Cox proportional hazards regression models to assess the relationship between medication nonadherence and time to event. Separate models were constructed for time to hospitalization due to any cause and...
for time to death due to any cause, controlling for all variables in Table 1. Hazard ratios and 95% CIs were calculated for each independent variable in the multivariable models. Third, we evaluated the incremental benefit of every 25% increase in medication adherence with respect to the primary and secondary outcomes. For the treatment targets, multivariable linear regression models were constructed to determine the magnitude of change in the antihypertensive medication PDC. Similar models were constructed to determine the magnitude of change for percentage HbA1c and for LDL-C level (in milligrams per deciliter) for every 25% incremental change in the PDC of oral hypoglycemics and of statins, respectively. For all-cause hospitalization and all-cause mortality, separate multivariable logistic regression models were constructed to determine the relative benefit of a 25% incremental change in the summary PDC for each of the outcomes.

To further assess the robustness of our findings, we performed additional analyses using alternative definitions of adherence, including the following: (1) changing the observation interval for deriving the PDC to anywhere from 60 to 300 days, (2) using the PDC for individual categories of medications rather than the summary PDC, (3) using the summary PDC as a continuous variable, and (4) varying the PDC cut-offs for medication nonadherence (to <50%, <60%, <70%, <90%, or <100%). The results of these additional analyses were consistent with our primary findings.

The study was approved by the institutional review board of KPCO. All analyses were performed using the SAS statistical package version 9.1 (SAS Institute Inc, Cary, NC).

Baseline characteristics of the study population are listed in Table 1. For the overall cohort of patients with DM, 20.4% had diet-controlled DM, 9.7% required insulin only, 57.0% required hypoglycemic agents only, and 13.0% needed insulin and an oral hypoglycemic agent. Based on the summary PDC, 2456 patients (21.3%) were categorized as nonadherent. Nonadherent patients were younger and had fewer comorbidities compared with adherent patients.

At baseline, the proportions of adherent and nonadherent patients at HbA1c, BP, and LDL-C level goals were similar. However, during follow-up, nonadherent patients had higher HbA1c, BP, and LDL-C levels compared with adherent patients (Table 2). In unadjusted analyses, nonadherent patients had higher all-cause hospitalization (23.2% vs 19.2%, \( P < .001 \)). In unadjusted analyses, nonadherent patients also had higher all-cause mortality (5.9% vs 4.0%, \( P < .001 \)).

In multivariable analyses, medication nonadherence was associated with an increased risk for all-cause hospitalization (OR, 1.58; 95% CI, 1.38-1.81; \( P < .001 \)) (Table 3). Medication nonadherence was associated with an increased risk for all-cause mortality (OR, 1.81; 95% CI, 1.46-2.23; \( P < .001 \)). These findings were consistent when the PDC for the individual category of medication (ie, oral hypoglycemics, antihypertensives, or statin medications) was used rather than the summary measure, across different patient subgroups (Table 4) and using different PDC cutoffs (Table 5).

Using Cox proportional hazards regression models, medication nonadherence was associated with significantly higher risk for hospitalization due to any cause (hazard ratio, 1.37; 95% CI, 1.25-1.51; \( P < .001 \)) and for death due to any cause (hazard ratio, 1.77; 95% CI, 1.45-2.15; \( P < .001 \)).
Incremental increases in medication adherence were associated with improved outcomes. Each 25% increase in adherence to antihypertensive medication was associated with \(-1.0\) mm Hg (95% CI, \(-1.5\) to \(-0.6\) mm Hg) and \(-1.2\) mm Hg (95% CI, \(-1.4\) to \(-0.9\) mm Hg) reductions in systolic and diastolic BPs, respectively. Similarly, each 25% increase in adherence to oral hypoglycemics and statins was associated with \(-0.05\%\) (95% CI, \(-0.08\%\) to \(-0.01\%\)) and \(-3.8\) mg/dL (\(-0.10\) mmol/L) (95% CI, \(-4.5\) to \(-3.0\) mg/dL \([-0.12\) to \(-0.08\) mmol/L]) reductions in HbA\(_1c\) and LDL-C levels, respectively. Furthermore, 25% increases in medication adherence were associated with significant reductions in all-cause hospitalization (OR, 0.83; 95% CI, 0.79-0.88; \(P<.01\)) and in all-cause mortality (OR, 0.75; 95% CI, 0.68-0.83; \(P<.01\)).

### Table 3. Association Between Medication Nonadherence and Outcomes

<table>
<thead>
<tr>
<th>Nonadherence Measure</th>
<th>Nonadherent Patients, %</th>
<th>No. of Patients</th>
<th>All-Cause Mortality</th>
<th>All-Cause Hospitalization</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Unadjusted</td>
<td>Adjusted*</td>
<td>Unadjusted</td>
<td>Adjusted*</td>
</tr>
<tr>
<td>Summary measure</td>
<td>21.3</td>
<td>11,532</td>
<td>1.49 (1.22-1.81)</td>
<td>1.81 (1.46-2.23)</td>
</tr>
<tr>
<td>Antihypertensives</td>
<td>19.1</td>
<td>6217</td>
<td>1.54 (1.20-1.97)</td>
<td>1.58 (1.22-2.05)</td>
</tr>
<tr>
<td>Statins</td>
<td>24.8</td>
<td>6486</td>
<td>1.60 (1.21-2.13)</td>
<td>2.07 (1.54-2.80)</td>
</tr>
<tr>
<td>Oral hypoglycemics</td>
<td>20.3</td>
<td>7883</td>
<td>1.25 (0.97-1.62)</td>
<td>1.39 (1.07-1.82)</td>
</tr>
</tbody>
</table>

*Adjusted for all variables in Table 1.

The objectives of this study were to evaluate the association between medication nonadherence and outcomes in clinical practice. Medication nonadherence was present in more than 1 of every 5 patients and was associated with higher HbA\(_1c\), BP, and LDL-C levels. In addition, nonadherent patients had significantly increased risk for all-cause hospitalization and all-cause mortality. The risk associated with medication nonadherence was consistent across patient subgroups and using different cutoffs for nonadherence.

Previous investigations assessing medication adherence among patients with DM focused mainly on the association of adherence with intermediate outcomes. The rates of adherence ranged from 36% to 93%, depending on the type of medication studied, the population examined, and the method of adherence assessment used.\(^{11}\) Higher adherence to oral hypoglycemic and statin medications was associated with improvements in glycemic control and LDL-C levels, respectively,\(^{12}\) consistent with our findings. In addition, some studies\(^{17-19}\) found an association between increasing levels of adherence and lower medical care costs. Our finding of links between medication adherence and hospitalization and mortality expands the literature on adherence and emphasizes the importance of medication nonadherence in clinical practice.

The results of this study suggest that the association between medication adherence and outcomes such as hospitalization and mortality is mediated in part through improvements in treatment targets important to patients with DM. Each 25% increase in medication adherence was associated with reductions in HbA\(_1c\), BP, and LDL-C levels. However, the magnitude of reduction for hospitalization and mortality was greater than expected given the changes in the intermediate measures, suggesting that medication adherence may also be correlated with self-care behaviors that are directly or indirectly related to outcomes.\(^{20-26}\) For example, medication adherence has been associated with better outcomes regardless of treatment assignment in randomized controlled clinical trials.\(^{20-23}\) Adherent patients may be more likely to follow lifestyle recommendations and other healthy behaviors, leading to improved outcomes, and nonadherence has conversely been associated with factors such as depression, cognitive impairment, and missed appointments, which may be linked to adverse outcomes.\(^{3,9}\) These findings suggest that the association between medication adherence and outcomes may be mediated directly through achievement of intermediate targets important to patients with DM and indirectly through its correlation with other adherence behaviors that affect outcomes.

### Table 4. Association Between Medication Nonadherence Based on the Summary Proportion of Days Covered and Outcomes Across Different Patient Subgroups

<table>
<thead>
<tr>
<th>Patient Subgroup</th>
<th>No. of Patients</th>
<th>All-Cause Mortality</th>
<th>All-Cause Hospitalization</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diet-controlled diabetes mellitus</td>
<td>2347</td>
<td>2.23 (1.35-3.69)</td>
<td>1.62 (1.24-2.12)</td>
</tr>
<tr>
<td>Insulin only</td>
<td>1302</td>
<td>1.95 (1.25-3.04)</td>
<td>1.37 (1.02-1.84)</td>
</tr>
<tr>
<td>Oral hypoglycemics only</td>
<td>6575</td>
<td>1.73 (1.27-2.36)</td>
<td>1.39 (1.18-1.64)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>9401</td>
<td>1.74 (1.39-2.18)</td>
<td>1.47 (1.29-1.66)</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>3655</td>
<td>1.79 (1.33-2.40)</td>
<td>1.55 (1.29-1.86)</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>7464</td>
<td>2.04 (1.58-2.63)</td>
<td>1.53 (1.32-1.76)</td>
</tr>
<tr>
<td>Heart failure</td>
<td>1754</td>
<td>1.68 (1.19-2.38)</td>
<td>1.40 (1.09-1.79)</td>
</tr>
<tr>
<td>Age (\leq65) y</td>
<td>6427</td>
<td>1.91 (1.51-2.40)</td>
<td>1.41 (1.22-1.64)</td>
</tr>
<tr>
<td>Baseline levels at goal</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glycosylated hemoglobin</td>
<td>5273</td>
<td>2.09 (1.56-2.80)</td>
<td>1.36 (1.15-1.62)</td>
</tr>
<tr>
<td>Blood pressure</td>
<td>3924</td>
<td>1.41 (0.98-2.03)</td>
<td>1.44 (1.18-1.75)</td>
</tr>
<tr>
<td>Low-density lipoprotein cholesterol</td>
<td>7782</td>
<td>1.74 (1.37-2.22)</td>
<td>1.47 (1.28-1.69)</td>
</tr>
</tbody>
</table>

*Adjusted for all variables in Table 1.
The association between poor medication adherence and increased mortality has been demonstrated previously (to our knowledge) only in randomized controlled trials.\(^2\) Among those randomized to active treatment, nonadherent patients had higher mortality compared with adherent patients. For example, in the \(\beta\)-Blocker Heart Attack Trial, patients nonadherent to propranolol hydrochloride were 2.6 times more likely to die within a year compared with adherent patients.\(^2\) We are unaware of any previous investigations that demonstrated an association between adherence and mortality in unselected populations. The finding in our study of an association between medication nonadherence and increased mortality outside the context of a randomized controlled trial further supports the clinical importance of nonadherence as a risk marker for adverse outcomes.

Medication nonadherence is common and often is not directly assessed by clinicians. The underrecognition of medication nonadherence can have adverse consequences.\(^2\) For example, patients may have poor glycemic control related to medication nonadherence. However, clinicians may attribute poor glycemic control to therapeutic ineffectiveness and may increase the dosages of current medications or add medications to the regimen. This can potentially lead to adverse consequences such as hypoglycemia. Because of its high prevalence and association with negative outcomes, medication nonadherence should be routinely assessed. Once identified, clinicians should engage the patient in a discussion of the reasons for nonadherence and promote ways of improving adherence to prescribed medications. Future studies are needed to better understand the natural history of nonadherence so that interventions can be developed to target modifiable factors.

Several potential limitations of this study should be recognized. First, this was a single managed care organization study using administrative data. However, it was a population-based study of a large integrated health care delivery organization. Second, similar to other investigations of adherence using pharmacy fill rates,\(^2\) medication consumption was assumed, and the timing of the doses of medications was unknown. Nevertheless, pharmacy refill records are correlated with electronic adherence monitoring and a wide array of clinical outcomes.\(^2\) In addition, the act of refilling a medication is the first step toward taking a medication and reflects a patient’s active decision to continue with therapy.\(^2\) Third, the primary categorization of adherence based on a PDC 80% or higher vs less than 80% was arbitrary. However, this is the most commonly used cut point for medication adherence using pharmacy refill records. In addition, we examined the effect of medication adherence on outcomes using multiple definitions of adherence (ie, using the summary measure and the individual categories of medications). Furthermore, the association between nonadherence and outcomes was consistent for a wide range of PDC cutoffs. Fourth, patients who are nonadherent may have other traits that contribute to worse outcomes, including factors such as depression, lower socioeconomic status, and associated adverse health behaviors.\(^2\) Although we were unable to measure these factors in our study, our findings of a link between nonadherence and adverse outcomes should serve as the impetus for future studies to better understand mediators of medication nonadherence.

Medication adherence was associated with small incremental changes in the intermediate treatment targets. One potential explanation is that we assessed the effect of adherence at a single interval among patients prescribed medications over a longer term and may not have seen the full effect of these medications on the treatment targets. Furthermore, when applied on a population-wide basis, the differences in the treatment targets between adherent and nonadherent patients may translate into significant reductions in morbidity and mortality.\(^2\) Finally, clinical trials demonstrated the efficacy of oral hypoglycemics, antihypertensives, and statin medications among patients with DM.\(^2,3\) Because these medications were shown to be efficacious compared with placebo in the clinical trials, the present study was intended to assess the effectiveness of these medications in clinical practice and, in particular, to focus on the effect of medication nonadherence.

In conclusion, medication nonadherence is prevalent among patients with DM and is associated with adverse clinical outcomes. The assessment of medication nonadherence should be incorporated into routine clinical practice. Patient adherence to therapies has been touted as the next frontier in quality improvement.\(^2\) Interventions are urgently needed to increase medication adherence so that patients can realize the full benefit of prescribed therapies.\(^2,3\)
Accepted for Publication: May 18, 2006.

Correspondence: P. Michael Ho, MD, PhD, Denver Veterans Affairs Medical Center, 1055 Clermont St (111B), Denver, CO 80220 (michael.ho@uchsc.edu).

Author Contributions: Dr Ho had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Financial Disclosure: None reported.

Funding/Support: This study was supported in part by grant 0535086N from the American Heart Association, by Advanced Research Career Development Award RCD 98341-2 from the Veterans Affairs Health Services (Dr Rumsfeld), and by Research Career Award K08-AG01011 from the National Institutes of Health (Dr Masoudi).

Previous Presentation: This study was presented at the 55th Annual Scientific Session of the American College of Cardiology; March 14, 2006; Atlanta, Ga.

REFERENCES


