Impact of Medication Therapy Discontinuation on Mortality After Myocardial Infarction

P. Michael Ho, MD, PhD; John A. Spertus, MD, MPH; Frederick A. Masoudi, MD, MSPH; Kimberly J. Reid, MS; Eric D. Peterson, MD, MPH; David J. Magid, MD, MPH; Harlan M. Krumholz, MD, SM; John S. Rumsfeld, MD, PhD

Background: Nonadherence to medications is common, but the determinants and consequences are poorly defined. The objectives of this study were to identify patients and myocardial infarction (MI) treatment factors associated with medication therapy discontinuation and to assess the impact of medication discontinuation 1 month after MI on 12-month mortality.

Methods: This was a multicenter prospective cohort of patients with MI enrolled in the Prospective Registry Evaluating Myocardial Infarction: Event and Recovery study. The outcomes were use of aspirin, β-blockers, and statins at 1 month after MI hospitalization among patients discharged with all 3 medications as well as 12-month mortality.

Results: Of 1521 patients discharged with all 3 medications, 184 discontinued use of all 3 medications, 56 discontinued use of 2 medications, 272 discontinued use of 1 medication, and 1009 continued taking all 3 medications, 184 discontinued use of all 3 medications, 56 discontinued use of 1 medication, and 1009 continued taking all 3 medications at 1 month. In multivariable analyses, patients not graduating from high school (odds ratio [OR], 1.76; 95% confidence interval [CI], 1.20-2.60) were more likely to discontinue use of all medications. The effect of increasing age on medication therapy discontinuation was greater for females (OR, 1.77; 95% CI, 1.34-2.34) than males (OR, 1.23; 95% CI, 1.02-1.47). Patients who discontinued use of all medications at 1 month had lower 1-year survival (88.5% vs 97.7%; log-rank P<.001) compared with patients who continued to take 1 or more medication(s). In multivariable survival analysis, medication therapy discontinuation was independently associated with higher mortality (hazards ratio, 3.81; 95% CI, 1.88-7.72). Results were consistent when evaluating discontinuation of use of aspirin, β-blockers, and statins separately.

Conclusions: Medication therapy discontinuation after MI is common and occurs early after discharge. Patients who discontinue taking evidence-based medications are at increased mortality risk. These findings suggest the need to improve the transition of care from the hospital to outpatient setting to ensure that patients continue to take medications that have mortality benefit.

Arch Intern Med. 2006;166:1842-1847

See also pages 1802, 1822, 1829, 1836, 1848, and 1855

found that 12% were no longer taking the medication 6 months later. Moreover, medication nonadherence in randomized controlled trials has been associated with increased mortality regardless of treatment assignment. To date, however, the impact of medication therapy discontinuation early after MI on outcomes such as mortality remains unknown in community-based populations.

Accordingly, we evaluated rates of aspirin, β-blocker, and statin use at hospitalization.
nal discharge and 1, 6, and 12 months after MI in a large multicenter prospective cohort study of patients with acute MI. We identified the patient (demographics, clinical, and psychosocial) and MI treatment factors associated with medication therapy discontinuation. Finally, we evaluated the association between medication therapy discontinuation 1 month after MI and 12-month mortality. The results of this study may have important implications for improving the transition of care from the hospital to the outpatient setting, as well as the development and testing of new post-MI quality performance measures and interventions.

**METHODS**

**PATIENT SAMPLE**

Between January 1, 2003, and June 28, 2004, a total of 2498 patients with acute MI were recruited into the Prospective Registry Evaluating Myocardial Infarction: Event and Recovery (PREMIER) study from 19 US hospitals. The hospitals in the PREMIER study represented a broad spectrum, including academic centers, inner-city hospitals, several single-payer systems, and nonuniversity hospitals. Additional details of the study methods have been published previously. In brief, all patients with biomarker evidence of myocardial necrosis during the initial 24 hours of admission were screened for possible inclusion. According to standard criteria, patients were eligible if they were 18 years or older and had other evidence that supported the diagnosis of acute MI, such as prolonged (> 20 minutes) ischemic signs or symptoms or electrocardiographic ST changes. Patients who did not present initially to the enrolling institution were eligible only if they were transferred within the first 24 hours of symptom onset, ensuring that the primary decision making occurred at the enrolling site. Institutional review board approval was obtained at each participating institution, and patients signed informed consent forms for baseline and follow-up interviews.

**DATA COLLECTION**

Three sources of data were used at baseline. First, a medical record abstraction was performed by trained data collectors, which included data regarding patients’ presentation, clinical history, admission medications, presenting electrocardiogram, and treatments during the first 24 hours. Second, a detailed baseline patient interview was administered. Third, at discharge, data on patients’ diagnostic findings (including the results of angiography and electrocardiography), in-hospital treatments, in-hospital complications, discharge recommendations, discharge medications, plans for follow-up, and final diagnoses were collected. Where possible, all data collection elements conformed to the American College of Cardiology Clinical Data Standards for Acute Coronary Syndromes.

**OUTCOMES ASSESSMENT**

The outcomes for this analysis were (1) medication therapy discontinuation at 1 month among patients discharged with aspirin, β-blockers, statins, and the combination of all 3 medications at hospital discharge and 1, 6, and 12 months after MI for the overall cohort using the χ² test. For the primary analyses, we focused on patients discharged with all 3 medications who completed the 1-month telephone interview. Baseline demographic factors; comorbidities; and psychosocial, socioeconomic, and treatment factors were compared between patients discontinuing use of all medications at 1 month and patients continuing use of 1 or more medications using the χ² test for categorical variables and t test for continuous variables.

To identify baseline patient and MI treatment factors independently associated with medication therapy discontinuation at 1 month, parsimonious multivariable hierarchical logistic regression models were developed that sequentially evaluated demographic variables (age, sex, race, and marital status), clinical history (diabetes, heart failure, hypercholesterolemia, hypertension, and coronary disease), MI treatment variables (coronary revascularization during index hospitalization and type of MI), psychosocial variables (social support and avoidance of medications because of cost), patient’s educational level (completed high school education), and site of patient enrollment. Variables permitted to enter the model were required to have a statistically significant bivariate association with medication therapy discontinuation (Table) or were considered clinically important (eg, age, race, sex, or coronary revascularization) so that they were included in the model regardless of the statistical association with medication therapy discontinuation. Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated for each independent variable in the multivariable models.

To define the prognostic importance of medication therapy discontinuation, survival was compared between patients discontinuing use of all medications at 1 month and patients continuing use of 1 or more medications using the Kaplan-Meier method. The differences in survival were evaluated with the log-rank test. To determine the independent association between medication therapy discontinuation at 1 month and 12-month mortality, hierarchical proportional hazards regression models were constructed, adjusting for all variables shown in the Table, including the clustering of patients by site. Hazard ratios (HRs) and 95% CIs were calculated for each independent variable in the multivariable models.

To further assess the robustness of our findings, first we performed additional analyses with alternative definitions for medication use, including categorization of medication therapy discontinuation as a 3-level variable: discontinuing use of all medications, continuing use of 1 or 2 medications, and continuing use of all 3 medications. Second, we compared survival between patients continuing 0, 1, 2, and 3 medications at 1 month among patients discharged with all 3 medications using the Kaplan-Meier method. Third, patients were evaluated based on the individual medications. Among patients discharged with aspirin, β-blockers, or statins, we compared survival between patients who discontinued use of the medication at 1 month and those who continued use of the medication. Multivariable analyses were repeated to evaluate the association between medication therapy discontinuation and mortality. Fourth, first-level interactions between each of the significant independent predictor variables and medication therapy discontinuation were evaluated.

**STATISTICAL ANALYSIS**

We compared rates of medication use for aspirin, β-blockers, statins, and the combination of all 3 medications at hospital discharge and 1, 6, and 12 months after MI for the overall cohort using the χ² test. For the primary analyses, we focused on patients discharged with all 3 medications who completed the 1-month telephone interview. Baseline demographic factors; comorbidities; and psychosocial, socioeconomic, and treatment factors were compared between patients discontinuing use of all medications at 1 month and patients continuing use of 1 or more medications using the χ² test for categorical variables and t test for continuous variables.

To identify baseline patient and MI treatment factors independently associated with medication therapy discontinuation at 1 month, parsimonious multivariable hierarchical logistic regression models were developed that sequentially evaluated demographic variables (age, sex, race, and marital status), clinical history (diabetes, heart failure, hypercholesterolemia, hypertension, and coronary disease), MI treatment variables (coronary revascularization during index hospitalization and type of MI), psychosocial variables (social support and avoidance of medications because of cost), patient’s educational level (completed high school education), and site of patient enrollment. Variables permitted to enter the model were required to have a statistically significant bivariate association with medication therapy discontinuation (Table) or were considered clinically important (eg, age, race, sex, or coronary revascularization) so that they were included in the model regardless of the statistical association with medication therapy discontinuation. Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated for each independent variable in the multivariable models.

To define the prognostic importance of medication therapy discontinuation, survival was compared between patients discontinuing use of all medications at 1 month and patients continuing use of 1 or more medications using the Kaplan-Meier method. The differences in survival were evaluated with the log-rank test. To determine the independent association between medication therapy discontinuation at 1 month and 12-month mortality, hierarchical proportional hazards regression models were constructed, adjusting for all variables shown in the Table, including the clustering of patients by site. Hazard ratios (HRs) and 95% CIs were calculated for each independent variable in the multivariable models.

To further assess the robustness of our findings, first we performed additional analyses with alternative definitions for medication use, including categorization of medication therapy discontinuation as a 3-level variable: discontinuing use of all medications, continuing use of 1 or 2 medications, and continuing use of all 3 medications. Second, we compared survival between patients continuing 0, 1, 2, and 3 medications at 1 month among patients discharged with all 3 medications using the Kaplan-Meier method. Third, patients were evaluated based on the individual medications. Among patients discharged with aspirin, β-blockers, or statins, we compared survival between patients who discontinued use of the medication at 1 month and those who continued use of the medication. Multivariable analyses were repeated to evaluate the association between medication therapy discontinuation and mortality. Fourth, first-level interactions between each of the significant independent predictor variables and medication therapy discontinuation were evaluated.
variables for medication therapy discontinuation at 1 month were evaluated in the multivariable models.

Propensity scores were computed using logistic regression analyses to predict the likelihood of unsuccessful follow-up. From these models, a probability of failure to complete an interview was calculated. The reciprocal of this probability was then assigned to those patients’ scores in the multivariable regression analyses to appropriately weight patient scores in the analysis to remove the lost-to–follow-up bias. Statistical analyses were performed and graphs were constructed with SAS statistical software, version 9.1.3 (SAS Institute Inc, Cary, NC) and R version 2.1.1.

RESULTS

MEDICATION CONTINUATION

Among the entire cohort of 2498 patients, most patients were prescribed aspirin (90.9%), β-blocker (86.6%), and statin (80.4%) medications at hospital discharge (Figure 1). During follow-up, the largest decline in rates of medication use occurred between hospital discharge and 1 month ($P<.001$ for trend between hospital discharge and 1, 6, and 12 months after MI hospitalization for each of the medications). Thereafter, medication use rates remained relatively stable, although a steady attrition of patients continuing to take β-blockers was observed.

A total of 1754 patients (70.2%) were discharged with all 3 medications (aspirin, β-blockers, and statins). However, 233 patients did not complete the 1-month interview. The reasons for missing the 1-month interview included the following: deceased (15), lost to follow-up (155), refused contact (9), and too ill (54). Of the patients completing the 1-month interview ($n=1521$), 1009 patients (66.3%) continued taking all 3 medications, 184 patients (12.1%) discontinued use of all medications, 56 (3.7%) discontinued use of 2 medications, and 272 (17.9%) discontinued use of 1 medication. Patients discontinuing use of all medications were older, less likely to be married, less likely to have completed high school, and less likely to be white (Table). In addition, patients continuing use of medications had more comorbid...
ties and were less likely to have coronary revascularization during the index hospitalization.

In multivariable analysis, those who had not completed high school (OR, 1.76; 95% CI, 1.20-2.60) remained at increased risk for discontinuing use of all medications at 1 month. In addition, a significant interaction was found between age and sex, whereby the effect of increasing age on medication therapy discontinuation was greater for women (OR, 1.77; 95% CI, 1.34-2.34, per 10-year increment) than men (OR, 1.23; 95% CI, 1.02-1.47; per 10-year increment).

ASSOCIATION BETWEEN MEDICATION THERAPY DISCONTINUATION AND MORTALITY

In unadjusted analysis, patients who discontinued use of all medications at 1 month had lower 1-year survival (88.5% vs 97.7%; log-rank test, P<.001) compared with patients continuing use of 1 or more medications (Figure 2). In multivariable analysis, patients who discontinued use of all medications remained at significantly increased risk of death during follow-up (HR, 3.81; 95% CI, 1.88-7.72); the mortality risk was similar for patients who discontinued use of all medications compared with patients who continued use of 1 or 2 medications (HR, 5.00; 95% CI, 1.85-13.5) or who continued use of all 3 medications (HR, 3.33; 95% CI, 1.52-7.14) (Figure 3).

In addition, propensity score analyses assessing for bias because of missing follow-up interviews did not alter our primary findings.

In the secondary analysis, survival was compared for patients who continued taking 0, 1, 2, and all 3 medications at 1 month among patients discharged with all 3 medications. Patients continuing use of none of the medications had a lower 1-year survival (88.5% vs 96.4% vs 97.8% vs 97.8%) for continuation of 0, 1, 2, or 3 medications; log-rank P<.001) compared with patients continuing use of 1, 2, or all 3 medications (Figure 4). Next, aspirin, β-blocker, and statin discontinuation were evaluated separately. Among patients discharged with aspirin, those discontinuing use of the medication at 1 month had lower 1-year survival (91.0% vs 97.0%; log-rank P<.001) compared with those continuing use of the medication. In multivariable analysis, aspirin therapy discontinuation (HR, 1.82; 95% CI, 1.09-3.03) remained associated with increased 1-year mortality (Figure 3). Among patients discharged with β-blockers, those discontinuing use of the medication at 1 month had lower 1-year survival (91.6% vs 97.2%; log-rank P<.001). In multivariable analysis, β-blocker therapy discontinuation (HR, 1.96; 95% CI, 1.10-3.45) remained associated with higher mortality. Finally, among patients discharged with statins, those discontinuing use of the medication at 1 month had lower 1-year survival (91.2% vs 97.8%; log-rank P<.001).

In this study that assessed the rates of cardioprotective medication therapy discontinuation, we found that more than 1 in 5 patients discontinued use of aspirin, β-blockers, or statins and 1 in 8 discontinued use of all 3 medications within 1 month after MI. On average, patients who discontinued use of medications were older and did not complete high school. During 1-year follow-up, these patients had significantly higher rates of death, even after ad-

Figure 2. Kaplan-Meier survival curve comparing patients discontinuing use of all medications at 1 month with patients continuing use of 1 or more medications among patients discharged with all 3 medications (log-rank test, P<.001).

Figure 3. Adjusted (for all Table 1 variables) hazards ratios for patient subgroups. Statins include 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitor medications. Error bars indicate 95% confidence intervals.

Figure 4. Kaplan-Meier survival curve comparing patients discontinuing use of all medications at 1 month with patients continuing use of 1, 2, or all 3 medications among patients discharged with all 3 medications (log-rank test, P<.001).

©2006 American Medical Association. All rights reserved.
justment for demographics, clinical history, psychosocial factors, and MI treatment variables. The results were consistent in analyses of discontinuation of use of the individual medications.

Discontinuation of use of cardioprotective medications is common after MI hospitalization. In the Global Registry of Acute Coronary Events (GRACE), 8%, 12%, and 13% were no longer taking aspirin, β-blockers, and statins, respectively, 6 months after MI hospitalization despite being discharged with the medication.8 Among patients with insurance in a national study, 45% of patients discharged with β-blocker prescriptions were no longer taking the medication 3 months after hospital discharge for MI.13 Rates of medication therapy discontinuation in our study were consistent with prior findings; however, we found that medication therapy discontinuation occurred much earlier than previously reported, and we linked medication therapy discontinuation to increased mortality risk. These findings suggest that the transition period from hospital discharge to the outpatient setting is a critical period to ensure that patients continue to take medications that improve outcomes after MI.

Several prior studies9,14 have reported on factors associated with medication use after MI. In GRACE, variables including history of hypertension, history of heart failure, acute coronary syndrome presentation with MI compared with unstable angina, and care provided by cardiologists compared with nonspecialists were associated with medication use 6 months after MI.8 In contrast to prior studies, factors associated with medication use in our study were either demographic or socioeconomic characteristics rather than clinical. Given the multitude of factors that are associated with medication use in our study and the existing literature, quality improvement interventions to increase medication persistence should probably target all patients who have had MI, but the results of our study highlight the importance of socioeconomic status as a cofactor in medication therapy continuation.

The association between medication therapy discontinuation and mortality may be mediated through direct and indirect mechanisms. In clinical trials of individual medications, aspirin, β-blocker, and statin medications have been demonstrated to benefit patients after MI.15,16 However, the magnitude of mortality benefit seen in our study was greater than the benefit demonstrated in clinical trials. This finding may suggest a direct synergistic effect of combinations of post-MI medications. Alternatively, medication therapy discontinuation may also be correlated with self-care behaviors that are directly or indirectly related to outcomes.17-19 For example, medication nonadherence has been associated with worse outcomes regardless of treatment assignment in randomized controlled clinical trials.9,20-22 In addition, nonadherence has been associated with factors such as depression, which is linked to adverse outcomes.8 Conversely, adherent patients may be more likely to follow lifestyle recommendations and other healthy behaviors, leading to improved outcomes. The association between medication therapy discontinuation and adverse outcomes is likely multifactorial, and future studies should evaluate whether interventions to improve medication persistence will also affect self-care behaviors.

Recent advances in the treatment of MI have decreased in-hospital mortality rates; however, the risk of a recurrent event after the index hospitalization remains substantial in the following year.9 One potential contributor is the discontinuation of use of cardioprotective medications early after hospital discharge. In the Beta-Blocker Heart Attack Trial, patients nonadherent to propranolol hydrochloride treatment were 2.6 times more likely to die within 1 year of follow-up compared with adherent patients.9 In our study, patients who discontinued use of medications at 1 month had higher mortality (11.5%) in the subsequent 11 months compared with patients continuing use of their medications (2.3%). These findings suggest that the assessment of medication use should be performed early after hospital discharge and routinely as part of the usual processes of care for patients after MI. Once medication therapy discontinuation has been identified, health care professionals should approach the problem like an elevated blood pressure reading: a risk marker for adverse outcomes that requires intervention and follow-up.

Current quality improvement efforts for MI care are mainly focused on the inpatient setting. In addition, performance measures treat the inpatient and outpatient setting separately and do not focus on the transition from one setting to the other.23-24 The findings of this study suggest that an important quality gap in current MI care may not occur during the hospitalization. Rather, an important gap with regard to medications occurs in the immediate follow-up period after hospital discharge, when patients are most likely to discontinue use of beneficial medications. Therefore, the assessment of medication use should be an integral component of the first post-MI outpatient visit to ensure that patients continue to take indicated cardioprotective medications. For situations in which follow-up cannot occur early after hospital discharge, innovative strategies, such as the use of telehealth technologies, should be explored as an alternative for patient follow-up.25 Finally, to further improve the quality of care and outcomes for patients with MI, interventions are needed that specifically focus on this critical transition period from the inpatient setting to outpatient care.

Several potential limitations of this study should be considered. First, medication use was assessed by patient self-report, but medication use based on self-report is highly specific and has been correlated with pill counts and blood pressure control.26-28 Second, there is the potential for misclassification bias regarding medication use; however, this would tend to bias the results toward the null. Third, patients may have experienced adverse effects that led to medication therapy discontinuation. However, it is unlikely that patients developed significant adverse effects to all 3 cardioprotective medications. Fourth, we cannot determine if patients were advised by their physician to discontinue use of medications, but it is unlikely that a recommendation was made to discontinue use of all 3 medications within 1 month of being discharged with these medications given the wealth of evidence supporting the benefit of these therapies after MI. Future studies should investigate reasons for medication therapy discontinuation after MI so that interventions can be designed to specifically address these factors. In the interim, additional efforts are needed to educate patients regarding the importance of these medications.
Fifth, we adjusted for more than 20 variables in our multivariable models, including patient demographics, comorbidities, MI treatment, and psychosocial factors; however, unmeasured confounding is always a potential limitation in observational studies. Sixth, we assessed the association between medication therapy discontinuation and all-cause mortality but did not have reliable data on cause-specific mortality. Finally, we did not identify specific combinations of medications associated with improved survival. The objectives of the study were to emphasize that a sizable proportion of patients discontinue use of all 3 prescribed cardioprotective medications early after MI and that these patients have worse outcomes rather than to reestablish the efficacy of the specific medications.

In conclusion, we found that among patients discharged with aspirin, β-blockers, and statin medications, 1 in 8 discontinued use of all medications within 1 month of hospital discharge. Patient factors associated with medication therapy discontinuation included older age and lack of a completed high school education. Patients discontinuing use of medications had significantly increased mortality during the subsequent 11 months. These findings highlight the need to improve the care of patients in the transition from the hospital setting to outpatient care to ensure that patients continue to take medications that have demonstrated mortality benefit after MI.

Accepted for Publication: June 7, 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 Rumsfeld 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 project was principally supported by CV Therapeutics Inc.
Role of the Sponsor: CV Therapeutics Inc had no involvement in the design and conduct of the study; collection, management, analysis, and interpretation of the data; and preparation, review, or approval of the manuscript.

REFERENCES