Patient-Centered Adherence Intervention After Acute Coronary Syndrome Hospitalization

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Background—Adherence to cardioprotective medications in the year after acute coronary syndrome hospitalization is generally poor and is associated with increased risk of rehospitalization and mortality. Few interventions have specifically targeted this high-risk patient population to improve medication adherence. We hypothesize that a multifaceted patient-centered intervention could improve adherence to cardioprotective medications.

Methods and Results—To evaluate this intervention, we propose enrolling 280 patients with a recent acute coronary syndrome event into a multicenter randomized, controlled trial. The intervention comprises 4 main components: (1) pharmacist-led medication reconciliation and tailoring; (2) patient education; (3) collaborative care between pharmacist and primary care provider/cardiologist; and (4) 2 types of voice messaging (educational and medication refill reminder calls). Patients in the intervention arm will visit with the study pharmacist 1 week post-hospital discharge. The pharmacist will work with the patient and collaborate with providers to reconcile medication issues. Voice messages will augment the educational process and remind patients to refill their cardioprotective medications. The study will compare the intervention versus usual care for 12 months. The primary outcome of interest is adherence using the ReComp method. Secondary and tertiary outcomes include achievement of targets for blood pressure and low-density lipoprotein, and reduction in the combined cardiovascular end points of myocardial infarction hospitalization, coronary revascularization, and all-cause mortality. Finally, we will also evaluate the cost-effectiveness of the intervention compared with usual care.

Conclusions—If the intervention is effective in improving medication adherence and demonstrating a lower cost, the intervention has the potential to improve cardiovascular outcomes in this high-risk patient population. 

Key Words: acute coronary syndromes ■ adherence ■ medication adherence ■ cost-effectiveness ■ treatment effectiveness

Adherence to cardioprotective medications (eg, β-blockers, statins, clopidogrel) in the year after acute coronary syndrome (ACS) hospitalization is generally poor.1-5 After acute myocardial infarction (AMI) hospitalization, almost one quarter (≈24%) of patients do not fill their cardiac medications within 7 days of discharge, and among those who are taking their cardiac medications, one third of patients stop at least 1 medication by 1 month.2,3 Longer-term adherence continues to decline, and at 1 year after the index cardiac event, ≈60% of patients are found to still take statin medications.1,6 More importantly, multiple studies have shown that nonadherence to cardioprotective medications after AMI hospital discharge is associated with increased risk of subsequent cardiac hospitalizations and mortality.4,7,8

Despite the prevalence of medication nonadherence and the benefits of these cardioprotective medications for reducing recurrent events among ACS patients, few interventions to date have specifically targeted this high-risk patient population to improve medication adherence. A recently published study, Postmyocardial Infarction Free Rx Event and Economic Evaluation Trial (Post-MI FREEE),9 demonstrated improved medication adherence with the elimination of patient copayments. A cluster randomized, controlled trial also demonstrated a small but statistically significant improvement in β-blocker adherence with educational mailings to
patients after AMI hospitalization. In contrast, most of the earlier interventions to improve medication adherence in cardiovascular populations have produced mixed results and have primarily focused on patients with chronic cardiovascular disease rather than those with a recent hospitalization for ACS. Together, these studies suggest that there are still significant opportunities to improve medication adherence after ACS hospitalization, and an intervention focused on adherence to cardioprotective medications has significant potential to improve outcomes given the clear benefit of these secondary prevention medications, the high prevalence of nonadherence after hospital discharge, and the potentially fatal consequences of nonadherence.

The present study assesses the effectiveness of a multifaceted, patient-centered intervention to improve medication adherence and outcomes. This intervention builds on 2 complementary conceptual models: (1) Wagner chronic care model; and (2) the Medication Adherence Model (MAM). It adapts components of earlier successful adherence interventions and will be delivered for 12 months after hospital discharge and compared with usual care. The components of the intervention include (1) medication reconciliation and tailoring; (2) patient education; (3) collaborative care between pharmacists and providers (primary care providers [PCPs] or cardiologists); and (4) voice messaging reminders. The study will assess the effectiveness of the intervention (1) to improve adherence to cardioprotective medications (ie, β-blockers, statins, clopidogrel, and ACE inhibitors/ARB; primary outcome); (2) to achieve targets for blood pressure and low-density lipoprotein (LDL) cholesterol (secondary outcome); (3) to reduce the combined cardiovascular end points of MI hospitalization, coronary revascularization, and all-cause mortality (tertiary or exploratory outcomes); and (4) to increase the incremental cost-effectiveness of the intervention compared with usual care.

Methods

Study Population and Recruitment

This prospective multicenter clinical trial is being conducted at 4 Veterans Affairs (VA) Medical Centers (Denver, CO; Little Rock, AR; Durham, NC; and Seattle, WA). The recruitment phase of the study began on July 1, 2010, in Denver and Seattle; September 1, 2010, in Little Rock; and July 1, 2011, in Durham. All patients who were admitted with ACS as the primary reason for hospital admission and who used the VA for their usual source of care were screened for eligibility to participate. ACS is defined as AMI (both ST-elevation MI and non-ST elevation MI) or unstable angina using standard definitions from an international consensus statement. Exclusion criteria included (1) patients admitted for primary noncardiac diagnosis who developed ACS as a secondary condition (eg, perioperative MI); (2) planned discharge to a nursing home or a skilled nursing facility; (3) inclusion of patients admitted with ACS as the primary reason for hospital admission and non-ST elevation MI or unstable angina using standard definitions from an international consensus statement.

Data and Safety Monitoring

Data are collected using a software application with a web-based graphical user interface. The database allows tracking of number of patients enrolled/enrollment visits completed and the number of patients due for 12-month assessment/final visits completed. Data are entered directly into study forms in the software application. The Coordinating Center in Denver monitors compliance with data acquisition protocols, maintains quality of data entered, and reviews data accuracy. Site pharmacists and research assistants enter data from the enrollment visit, summary of telemonitoring data, adverse events, and final visit data into the database.

To ensure adherence to the study protocol, we have bimonthly conference calls to discuss project progress and to address barriers to delivery of the intervention. In addition, the pharmacists and research assistants record in the database components of the intervention delivered as well as the time spent. This allows for careful tracking of process delivery across all study sites and also ensures intervention fidelity.

An Internal Safety Committee comprised of the study site principal investigators (P.M.H., E.J.D., I.E.F., C.L.B., S.D.M.) meets quarterly to review all adverse events. In these meetings, the committee reviews details of each adverse event to determine whether the event is related to the study and also ensures compliance with all reporting requirements for each of the local Institutional Review Board. Further, oversight is provided by the VA HSR&D National DSMB, which convenes yearly, to review study progress including overall study progress, recruitment, and adverse events.

Intervention Components

The multifaceted intervention is comprised of 4 main components that are described in detail below and are not the standard of care procedures at any of the sites in this study:

1. Medication reconciliation and tailoring: Within 7 to 10 days of hospital discharge, a pharmacist meets with the patients via an in-person clinical visit or through telephone to address any medication problems or side effects and reconciles any differences in medications between the prehospital and the postdischarge regimens. The pharmacist also provides patients with a pill box for those who do not have one and instructs the patient on how to fill the pill box. One month later, the pharmacist calls the patient to assess for any interim new medications as well as any side effects to medications and/or adherence issues. At that point, the pharmacist attempts to synchronize the refill dates of the cardiac medications so that they all occur on the same date and/or as close as possible instead of usual practice where medication refill dates can vary tremendously. The pharmacist answers any other question related to medications, emphasizing the importance of continuing to take medications as prescribed. If questions arise about a specific medication and/or if the indication for a medication is unclear based on the discharge instructions, the pharmacist contacts the patient’s PCP to resolve discrepancies.

2. Patient education: Patients not only receive education about medications at the point of hospital discharge but also continue to receive education after hospital discharge to ensure retention of the information. This occurs at the 1-week and 1-month visit after discharge during the pharmacist’s telephone call with the patients. Thereafter, educational messages are provided through the voice messaging system and pharmacist telephone calls when requested by the patient. As part of the telephone calls, the pharmacist follows a basic script that addresses any new medication(s) since last contact, patient’s knowledge regarding new medication(s), and any new or recurrent problems/side effects with medications. Based on any knowledge gaps identified, the pharmacist provides education addressing these gaps.

3. Collaborative care: The pharmacist notifies the patient’s PCP and cardiologist (if the patient has one) that the patient is enrolled in the adherence intervention by having them cosign the
pharmacists’ initial enrollment note in the computerized medical record. This enrollment note includes the pharmacists’ contact information so that the PCP and/or cardiologist can reach the pharmacist for questions or clarifications. The electronic medical record serves as the primary method of communication between the pharmacist and the clinicians. Clinicians are also able to reach the pharmacist via telephone and/or e-mail depending on their preference. Furthermore, clinicians can contact the pharmacist to notify them of newly prescribed medications or changes to dosing of current medications so that medication refill reminder calls can be set up.

4. **Voice messaging:** The voice messaging system contacts patients at regularly scheduled intervals. There are 2 types of calls: medication reminder and medication refill calls. The medication reminder calls occur monthly. During these calls, patients receive reminder messages about the importance of taking medications as prescribed and are instructed to call the pharmacist if needed to address problems/questions related to their medication regimen. The medication refill calls are synchronized to when a medication refill is due. The calls occur 14 days before the refill due date, 7 days before the refill due date, and on the due date. Before day 7 and due date medication refill calls, the pharmacist reviews the medical record and makes sure that the medication has not been discontinued by a clinician and assesses whether the medication has been refilled. If the medication has not been refilled, the pharmacist or a member of the study staff calls the patient to determine whether they have run out of their medications and addresses any medication problems. If the pharmacist is unable to contact the patient via telephone, a letter will be sent out to the patient informing him or her of the need to refill the medication. If the medication has been refilled, the reminder call is stopped, and the patient does not receive the refill call. During months 2 to 6 of the intervention, patients receive both a medication reminder (monthly) and medication refill calls (timed to refill due dates). During months 7 to 12 of the intervention, patients only receive medication refill calls.

### Study Visit Overview

**Baseline visit before hospital discharge (patients randomized to intervention and usual care)**

After signing of informed consent, both intervention and usual care patients are administered the following surveys: the Saint Louis University Mental Status Exam, the Patient Health Questionnaire, and the Rapid Estimate of Adult Literacy in Medicine (revised; Table 1 and Figure).24–26 The Saint Louis University Mental Status Exam is a 30-point screening test validated against the minimental status exam used to assess for mild neurocognitive dementia.24 The Rapid Estimate of Adult Literacy in Medicine (revised) is a validated and reliable tool that assesses a patient’s literacy or the ability to read and pronounce common medical terminology and lay terms for body parts and illnesses.25 The Patient Health Questionnaire is a validated and reliable short version of the PRIME-MD that assesses for mild, moderate, moderately severe, and severe depressive symptoms.25 After the administration of these surveys, patients are told of the 12-month follow-up study clinic visit. Consistent with usual practices at each of the sites, patients also receive standard ACS discharge instructions (eg, numbers to call, follow-up appointments, diet, exercise advice), a discharge medication list, and educational information about cardiac medications. For patients randomized to the intervention, an appointment for an in-person or phone visit with a pharmacist is scheduled by the study personnel within 7 to 10 days of discharge.

### Table 1. Study Activities

<table>
<thead>
<tr>
<th>Visits and Activities</th>
<th>Intervention</th>
<th>Usual Care</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline (in-hospital)</td>
<td>SLUMS, PHQ-9, REALM-R</td>
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</tr>
<tr>
<td>1-Week visit with pharmacist</td>
<td>Medication Knowledge Tool</td>
<td>X</td>
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<tr>
<td>Medication reconciliation</td>
<td>1-Month telephone visit with pharmacist</td>
<td>Synchronizing medication refills</td>
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<tr>
<td>Medication reminder calls (months 1–6)</td>
<td>Medication refill calls (months 1–12)</td>
<td>X</td>
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<tr>
<td>12-Month visit: BP, LDL</td>
<td>X</td>
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SLUMS indicates Saint Louis University Mental Status Exam; PHQ-9, Patient Health Questionnaire; REALM-R, Rapid Estimate of Adult Literacy in Medicine, revised; BP, blood pressure; and LDL, low-density lipoprotein.

Week 1 visit (intervention only): This in-person clinical visit occurs within 7 to 10 days of hospital discharge or via telephone if a patient is unable to attend in person. Patients are asked to bring in all of their medications to this visit including all pre- and posthospitalization medications that they have at home. The pharmacist administers the medication knowledge assessment,27 which is a tool that assesses the patient’s knowledge and ability to read and comprehend information necessary for appropriate medication use. In addition, the
pharmacist reviews the results of the surveys performed before hospital discharge to identify potential barriers to medication adherence. Once a barrier is identified, the pharmacist provides potential solutions to address the barrier. Examples of potential barriers and possible interventions are listed in Table 2. Further, the pharmacist confirms current medications and review purpose, dosing frequency, and side effects of all medications before the reconciliation process, the pharmacist answers any other questions related to medications, emphasizing the importance of continuing to take medications as prescribed. If questions arise about a specific medication and/or if the indication for a medication is unclear based on the discharge instructions, the pharmacist contacts the patient’s PCP to resolve discrepancies.

Month 1 visit (intervention only): This is a telephone visit. The pharmacist reviews current medications and addresses any interim medication problems. In addition, if a new cardiovascular medication has been prescribed, the pharmacist reviews the purpose, dosing frequency, and side effect of the medication and synchronizes the refill date with other cardiac medications. During this visit, the pharmacist reminds patients to contact them as medication problems arise.

Month 12 visit (intervention and usual care groups): Both intervention and usual care patients are scheduled for a 12-month clinical visit. At this visit, 3 blood pressure measurements are taken by a nurse or cardiovascular technician, trained to perform blood pressure assessments (eg, after 5 minutes of rest and 2 minutes apart between measurements) and blinded to the randomization group of the patient. The final blood pressure is based on the average of the latter 2 measurements. In addition, patients are referred for a laboratory blood draw to assess LDL cholesterol levels. If a patient has had a value checked within the prior month and the dosing of the anti-lipemic medication(s) has not changed, this value is used as the end of study LDL cholesterol for outcomes assessment.

Patients are asked about interim procedures and/or hospitalizations outside of the VA, and if an event has occurred, information is requested for review. Finally, patients are asked to participate in a qualitative interview to provide feedback about the study.

Variables
Baseline in-hospital patient data including demographics, comorbidities, ACS presentation characteristics, in-hospital treatment, and procedural results will be collected via chart review, consistent with variables and definitions of national AMI registries such as the NCDR ACTION Registry-GWTG.28 All outcome measures will be collected from both intervention and usual care participants at identical time points. The primary outcome of the study is the proportion of patients who are adherent with cardioprotective medications (β-blockers, statins, clopidogrel, and ACE inhibitors) in the year after ACS hospitalization among those prescribed the medication using pharmacy refill data. Adherence to aspirin will not be assessed because the majority of veterans obtains medication over the counter. Adherence will be calculated using the ReComp method, which is a modification of a medication possession ratio, and is calculated by the number of days supplied over the observation time interval, which will be 365 days. Adherence will be calculated for each medication class and then averaged across all classes of medications to derive the summary ReComp score.29 Adherent patients will be defined based on a summary ReComp score of ≥20.80 consistent with the literature.

The secondary outcomes will be the proportion of patients reaching goals for blood pressure <140/90 mm Hg (<130/80 mm Hg for patients with diabetes mellitus or chronic kidney disease) and LDL cholesterol <100 mg/dL at 12 months after ACS hospital discharge. These goals are consistent with national guidelines among patients with a prior cardiac event. Tertiary outcomes include hospitalization for MI, coronary revascularization, and all-cause mortality. The occurrence of an MI hospitalization will be based on the same criteria used to identify patients for the study. Coronary revascularization procedures (ie, percutaneous coronary intervention [PCI] with or without stenting and coronary artery bypass graft surgery) that were not planned prior to the index ACS hospital discharge will count as an outcome. Mortality will be obtained from the new VA vital status file, which has a sensitivity of 98.3% and 97.6% of exact agreement with Vital Status Inquiry, respectively.29,30

Sample Size
Power was estimated based on prior studies that demonstrated that a ≥50% to 70% of patients will be adherent 12 months after ACS hospital discharge.31 Therefore, to detect an anticipated ≥15% improvement in the proportion of adherent patients relative to usual care, utilizing a power of 80% and an α of 5%, enrollment will target 280 patients (140 patients in each group). Even with 10% lost to follow-up, there will still be 252 patients (126 patients in each group) at the end of study, which is more than sufficient to assess the primary outcome of interest. Power was not evaluated for the secondary outcomes to avoid multiple comparison issues or for tertiary or exploratory outcomes because of their expected low frequency. Because our primary study outcome is based on pharmacy refill data, we expect that loss to follow-up will be minimal or nonexistent because we will still be able to assess adherence to cardioprotective medications using pharmacy refill data among patients who do not return for the 12-month study visit. We will still be able to evaluate pharmacy refills for all patients who obtain their medications through the VA pharmacy system.

Analysis
Baseline patient characteristics (eg, demographics, comorbidities) of the intervention and usual care groups will be compared using the χ² test and t test. For the primary and secondary outcomes, the analyses will
compare dichotomous outcome variables measured at the 12-month follow-up visit. Primary analyses will be completed on an intention-to-treat basis and all persons initially enrolled will be considered as non-adherent if they do not have evidence of ≥0.80 based on the summary ReComp measure at 12 months. The dichotomous adherence outcome variable (<0.80 versus ≥0.80) will be compared for intervention and usual care arms using unadjusted logistic regression analysis. If needed, baseline characteristics will be adjusted for, if not balanced by randomization. Both unadjusted and adjusted analyses will be reported with an explanation of the adjustment. In secondary analyses, unadjusted linear regression models will estimate the difference in adherence, systolic and diastolic blood pressure, and LDL levels by study arm.

Cardiovascular end points (ie, subsequent MI hospitalization, coronary revascularization, or mortality) are tertiary outcomes that will be explored using Kaplan–Meier curves and Cox proportional hazards models. We plan to provide hazard ratio estimates and 95% confidence intervals comparing the intervention to usual care arms but recognize that these analyses will be exploratory as we are not likely to have power to detect differences for these end points.

Missing data will be relevant for patients who die during the study period. We will compare mortality across treatment groups, and if it is comparable, we will exclude these patients in the intention-to-treat analysis of the primary outcome of medication adherence. If there is a difference in mortality rates, we will carry out sensitivity analyses by assuming various levels of adherence for intervention and control patients who died. \(^{33}\) If substantial differences in mortality between arms are noted, we will consider joint models for the potentially correlated measures of adherence and mortality. \(^{33}\)

**Economic Analysis**

Measures of both costs and outcomes of the intervention from the health system (VA) perspective will be captured alongside the main trial. A descriptive cost analysis will report the annual overall medication, intervention delivery costs, and VA service utilization costs per patient in both the usual care and intervention groups. Medication and VA utilization costs (including hospitalization, emergency department use, other cardiac care, and other VA services) for each study participant will be derived from the Decision Support System (DSS) pharmacy data and electronic medical records (Computerized Patient Record System [CPRS]). Intervention delivery costs will be collected by the study team through brief interviews with pharmacists and process flow mapping of pharmacist intervention activities. Pharmacists at each study site will be asked to include typical process time, optimistic (shortest) process time, and pessimistic (longest) process time for each intervention activity related to the 1-week patient visit and subsequent intervention activities. Once the process flow maps and time estimates are drafted, the pharmacists will verify the resulting flow diagram, and the team will identify any systematic differences in time estimates across sites. Time costs for the VA staff to provide the intervention will be estimated using the VA pay scale data using a normalized (or median) wage value by type of clinician, shift, and geographic area (VA site). Costs of the intervention compared with usual care will be measured for sensitivity using low, typical, and high-cost cases at each of the 4 study sites. Combined costs of VA services, medication, and the intervention will be estimated for each participant and reported as means with standard deviations. Regression models to predict 12-month costs may also be estimated to determine whether participation in the intervention has a positive or negative impact on overall or various component costs (medication, hospitalization, other utilization), holding other factors fixed. \(^{32}\)

The effectiveness component will primarily include the measures of medication adherence described above. Assuming that a higher proportion of patients in the intervention group will be adherent (ReComp measure ≥0.80), the cost-effectiveness analysis will measure the difference in overall annual costs for the intervention versus usual care group as the numerator and the difference in adherence proportions for the 2 groups as the denominator. For secondary analyses, we will analyze costs per (prevented) death, rehospitalization, or ED visit to determine whether the cost outcome results are sensitive to clinical outcome specification. A prevented death, hospitalization, or ED visit will be measured as the difference between observed and expected hospitalization rates for VA patients during the first 12 months after ACS hospitalization. Expected rates will be estimated from VA national in-patient and vital statistics databases. To construct the cost outcomes measures, costs and outcomes will be calculated for each patient’s refill period (eg, 90 days) to ascertain whether there are differences in these measures over time. Results will be assessed for sensitivity to underlying assumptions and costs will be discounted to reflect the value of time preferences. Findings from the economic evaluation will be gauged in relation to similar program interventions for secondary prevention to determine whether the intervention compares favorably with options for distributing or investing VA health system resources.

**Conclusions**

The MEDICATION study will refine the current state of knowledge on improving medication adherence in multiple ways. First, it uniquely combines multiple interventions that have been separately shown to be effective rather than using untested interventions. Second, the intervention focuses on a novel setting (ie, patients discharged following ACS hospitalization and transitioning to outpatient care) in contrast to prior adherence interventions that have focused mainly on patients with stable chronic diseases (eg, hypertension). Third, the targeted medications in this study have demonstrated short-term benefits and where nonadherence can have immediate adverse outcomes (eg, stent thrombosis with discontinuation of clopidogrel). Prior studies have focused on medications (eg, hypertension medications) where nonadherence leads to problems in the long term rather than in the short term. Finally, the study utilizes existing resources (ie, VA pharmacists) to implement the intervention; as such, it is an effectiveness intervention, which is a novel contribution. Prior adherence interventions have generally required significant additional resources, and the majority of quality improvement interventions are not continued following the end of the research project. This study will extend the current state of knowledge on medication adherence by demonstrating that a successful intervention will need multiple evidence-based components and designed with plans for eventual widespread implementation in mind.

**Potential Limitations**

Several potential limitations of this study should be acknowledged. The VA is an integrated healthcare delivery system with a comprehensive electronic medical record. Accordingly, the collaborative care proposed in this study comprised of pharmacists, PCPs, and cardiologists may be unique to the VA, thus potentially limiting the generalizability of our findings if the results are positive. However, the findings would still be relevant to the large number of veterans who receive care in the VA as well as the large populations of patients who receive care within integrated healthcare delivery systems. Next, given that this is a patient randomized trial, there is the potential for contamination, albeit low, because a study pharmacist may interact with patients in both intervention and usual care arms. Patients in usual care are generally not referred to pharmacists following hospitalization discharge for ACS. Even if a given usual care patient is referred to a pharmacist, the chances that the patient is referred to the study pharmacist would be low. However, if any contamination does take place, it would bias the results toward the null and would not invalidate any differences detected in outcomes. We will
closely monitor processes of care of usual care patients to allow for examination of possible contamination, although we feel that the set-up of the intervention minimizes the likelihood of this being a problem.

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