Rationale and Design of the Pharmacist Intervention for Low Literacy in Cardiovascular Disease (PILL-CVD) Study

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Background—Medication errors and adverse drug events are common after hospital discharge due to changes in medication regimens, suboptimal discharge instructions, and prolonged time to follow-up. Pharmacist-based interventions may be effective in promoting the safe and effective use of medications, especially among high-risk patients such as those with low health literacy.

Methods and Results—The Pharmacist Intervention for Low Literacy in Cardiovascular Disease (PILL-CVD) study is a randomized controlled trial conducted at 2 academic centers—Vanderbilt University Hospital and Brigham and Women’s Hospital. Patients admitted with acute coronary syndrome or acute decompensated heart failure were randomly assigned to usual care or intervention. The intervention consisted of pharmacist-assisted medication reconciliation, inpatient pharmacist counseling, low-literacy adherence aids, and tailored telephone follow-up after discharge. The primary outcome is the occurrence of serious medication errors in the first 30 days after hospital discharge. Secondary outcomes are health care utilization, disease-specific quality of life, and cost-effectiveness. Enrollment was completed September 2009. A total of 862 patients were enrolled, and 430 patients were randomly assigned to receive the intervention. Analyses will determine whether the intervention was effective in reducing serious medication errors, particularly in patients with low health literacy.

Conclusions—The PILL-CVD study was designed to reduce serious medication errors after hospitalization through a pharmacist-based intervention. The intervention, if effective, will inform health care facilities on the use of pharmacist-assisted medication reconciliation, inpatient counseling, low-literacy adherence aids, and patient follow-up after discharge.

Clinical Trial Registration—clinicaltrials.gov. Identifier: NCT00632021.

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Key Words: coronary disease ■ heart failure ■ patients
Potential ADEs include unintentional medication discrepancies (differences between what patients think they should be taking and the actual regimens ordered by physicians) and medication nonadherence (differences between what patients think they should be taking and what they actually take). We define “serious medication error” (SME) as any preventable or ameliorable ADE, or a potential ADE caused by nonadherence or an unintentional discrepancy.

ADEs occur in 13% to 17% of patients after hospital discharge. Studies suggest that improvements in provider communication could prevent or ameliorate 50% to 72% of ADEs. Potential ADEs are also common and arise from unintentional discrepancies between admission and discharge regimens, such as changes in dose, route, or frequency, and/or introduction of new medications. Consequently, patients may have difficulty reconciling their new and old regimens on returning home. In fact, drug additions/deletions or errors in dosing occur in 50% to 90% of patients 1 month after discharge.

Patients with cardiovascular diseases may be particularly prone to SMEs. These patients are often elderly and prescribed complex medication regimens. Cardiovascular drugs are commonly implicated in adverse events, comprising 14% of all postdischarge ADEs. The consequences of poor medication management in cardiovascular disease, particularly acute coronary syndrome and heart failure, can lead to readmission and complications. Often these complications are caused by nonadherence to and early discontinuation of cardiac medications.

Health literacy is “the degree to which individuals have the capacity to obtain, process, and understand basic health information and services needed to make appropriate health decisions.” Patients with low health literacy may have increased risk of SMEs related to difficulty understanding prescription drug information, maintaining adherence, and other barriers.

Pharmacist-based interventions are effective in promoting safe and effective use of medications during and after hospitalization. Moreover, multifactorial interventions which include patient education and follow-up regarding medications have demonstrated a decrease in hospital readmission. To date, however, few multisite studies have rigorously evaluated a standard pharmacist-based educational intervention to improve medication safety, nor have many programs specifically targeted patients with low health literacy. No such interventions have been evaluated in an era in which medication reconciliation is standard (Note: Medication Reconciliation is “the process of creating the most accurate list possible of all medications a patient is taking—including drug name, dosage, frequency, and route—and comparing that list against the physician’s admission, transfer, and/or discharge orders, with the goal of providing correct medications to the patient at all transition points within the hospital.”) This is important because at least some of the benefit of past pharmacist interventions may be attributed to their role in reconciling medications.

This report describes the design of the Pharmacist Intervention for Low Literacy in Cardiovascular Disease (PILL-CVD) study. PILL-CVD is a randomized controlled trial conducted at 2 academic medical centers—Vanderbilt University Hospital (VUH) and Brigham and Women’s Hospital (BWH). Our hypothesis is that an intervention consisting of pharmacist-assisted medication reconciliation, inpatient pharmacist counseling, low-literacy adherence aids, and tailored telephone follow-up will decrease the incidence of SMEs in the first 30 days after hospital discharge compared with usual care. We will also study the effect of patient health literacy on the effectiveness of the intervention as well as the effect of the intervention on health care utilization, disease-specific quality of life, and costs.

Methods

Patient Enrollment

Patient enrollment began in May 2008 and ended in September 2009. Eligible patients were at least 18 years of age and admitted for acute coronary syndrome (ACS) or acute decompensated heart failure (ADHF). ACS was defined according to national guidelines. ADHF was determined by the presence of at least 2 major, or 1 major and 2 minor, Framingham criteria. Patients with volume overload caused by sepsis, arteriovenous shunts, renal failure, or administration of intravenous fluids or blood products were not considered to have ADHF.

Patients were excluded if they were receiving intravenous cardiac inotropic medications at home; intravenous pressors, a ventricular assist device, intra-aortic balloon pump in the hospital; aggressive medication management as a result of recent or imminently planned transplantation; or another medication management program. Patients were excluded in the presence of corrected visual acuity worse than 20/200, severe hearing impairment, unintelligible speech, inability to communicate in English or Spanish, severe mental illness (psychosis or bipolar disorder)
Patients admitted with acute coronary syndrome (ACS) or acute decompensated heart failure (ADHF) and eligibility confirmed

Exclusion criteria
- Age younger than 18 years
- Delirium/severe dementia
- Psychotic or manic illness
- Corrected visual acuity worse than 20/200
- Severe hearing impairment
- Not discharging patient to home
- Not fluent in English or Spanish
- Unintelligible speech
- Caregiver manages medications
- Police custody
- No regular telephone number
- Too ill to participate
- Unable to provide intervention

Informed consent, baseline interview
- Demographics
- Health literacy (s-TOFHLA)
- Cognitive function (Mini-Cog)
- Medication understanding
- Medication self-management strategies
- Medication adherence

Randomization
- Stratified by site & diagnosis

Usual Care

Pharmacist Intervention
- Medication reconciliation
- Initial counseling
- Discharge counseling
- Follow-up phone calls after discharge

Follow-up interview (25-35 days post discharge)
- By phone:
  - Review of symptoms with follow-up questions for association with medications
  - Medication review with assessment for discrepancies and non-adherence
  - Utilization of health care services
  - Social support
- By mail or by phone:
  - Quality of life questionnaires

Adjudication
- By two independent, blinded physicians using discharge documents, medical records within 30 days of discharge, and follow-up interview:
  - Preventable or ameliorable ADEs
  - Discrepancies or non-adherence with potential for harm (PADEs)

Random Assignment
Consented patients were randomly assigned to receive usual care or usual care plus the intervention (Figure 2). The randomization sequence was computer-generated in permuted blocks of 2 to 6 patients, stratified by study site and diagnosis (ACS or ADHF). Random assignment was managed with concealment of treatment allocation by a member of the study team at each site who was unblinded to patient assignment and had no role in outcome assessment. All investigators and outcome assessors were blinded.

Intervention
There were 4 intervention components (Table 1), developed according to the following principles:

1. Pharmacist oversight can mitigate the potential harm caused by medication errors during care transitions, even with mandated medication reconciliation, because many institutions have difficulty implementing reconciliation and errors still remain. Pharmacists can provide medication reconciliation and improve medication use. Educational interventions may benefit patients with low health literacy if they adhere to clear health communication guidelines.

2. Tailored patient education can increase knowledge of medications and improve medication use. Educational interventions may benefit patients with low health literacy if they adhere to clear health communication guidelines.

3. Phone calls within 72 hours of discharge can identify and mitigate problems related to filling prescriptions, early side effects, and misunderstanding of the regimen. A team-based approach leveraging nonclinical personnel can reduce program costs while maintaining effectiveness, reserving hospital pharmacists for specific activities that require a higher level of skill and training.
1. Medication reconciliation
- Obtains preadmission medication information and evaluates validity of medical team’s preadmission medication history
- Identifies and communicates with medical team to resolve discrepancies between the preadmission medication history, current inpatient medications, and discharge orders

2. Initial counseling
- Reviews and assesses: understanding of preadmission regimen, social support, adherence with filling and taking medicines, and barriers to medication use, including costs, transportation, and side effects
- Contacts social worker if needed
- Tailors counseling on the basis of patient’s needs

3. Discharge counseling
- Reviews updated discharge medication list with the patient, with an emphasis on changes from preadmission medication list
- Provides patient with a personalized medication schedule
- Tailors counseling and uses teach-back method during counseling
- Offers a pill box and demonstrates how to fill it, using the personalized medication schedule as a guide

4. Follow-up phone calls
- Inquires about general health and any symptoms since discharge and ability to obtain all of his/her medications
- Notes symptoms, medication discrepancies, nonadherence, and issues related to follow-up
- Communicates significant findings to the study pharmacist
- Pharmacist (if needed):
  - Contacts the patient and explores significant issues in further detail
  - Takes action as needed to address any issues, including patient education and communication with the patient’s outpatient providers
  - Follows up with additional phone calls as needed, depending on the nature of the problem(s)

4. Understanding the patient subgroups that benefit most from the intervention, as well as program costs, will enable hospitals to use resources more judiciously.

### In-Hospital Components
Pharmacists performed medication reconciliation on enrollment, at discharge, and during in-hospital transfers. When unintentional discrepancies were identified, the pharmacist contacted the patient’s inpatient team to resolve the differences.

Intervention patients received tailored counseling by a pharmacist at enrollment and discharge. Pharmacists were informed of the patient’s health literacy and cognitive function so they could tailor their approach. During the initial counseling session, the pharmacist assessed the patient’s understanding of the preadmission regimen and medication labels; medication adherence; barriers to adherence; and level of social support. A hospital social worker was notified if it appeared that the patient might need assistance obtaining discharge medications.

During the discharge counseling session, the pharmacist provided tailored counseling based on the initial assessment of that individual’s medication management needs and the discharge regimen determined by the treating physicians. The pharmacist emphasized differences between the preadmission medication regimen and the one prescribed at discharge and reviewed strategies to enhance medication adherence and techniques to prevent or ameliorate side effects. Extra counseling was provided for medications with special instructions (eg, warfarin).

Patients received a personalized, illustrated medication schedule demonstrating why, when, and how they should take their medications, as well as major and common side effects (Figure 3). The medication schedule facilitated the pharmacist-patient interaction and served as a take-home educational aid. The schedule was prepared by a pharmacist using a master template created by the study team that contained pictures for indications, standard directions, and common side effects. Patients were asked to “teach-back” key aspects of their medication regimen to confirm understanding.

Patients were offered a pill box and taught to fill it using the medication schedule as a guide. When discharge occurred on the day of enrollment, the admission and discharge counseling sessions were combined, with an emphasis on discharge elements.

### Postdischarge Components
At each site, the unblinded project coordinator called each intervention patient 1 to 4 days after hospital discharge. The coordinator (1) reviewed the medications to identify any discrepancies from the discharge medication list, confirm that prescriptions had been filled, and verify that the patient understood how to take each medication; (2) performed a review of systems with follow-up questions to screen for early medication side effects; (3) documented discrepancies, nonadherence, new or worsening symptoms, and issues related to physician follow-up; and (4) communicated significant information to the study pharmacist. Pharmacists managed any significant issues in collaboration with the patient’s treating physicians, and made additional phone calls as needed with a frequency determined by the nature of the issue.

If the study pharmacist was unavailable at the time of discharge (ie, evenings or weekends), the pharmacist called the patient at home within 1 to 4 days to perform discharge counseling and the follow-up call. In these situations, the personalized medication schedule and pill box were mailed.

### Intervention Fidelity
Pharmacists helped develop the content and delivery of the intervention, from which a procedure manual and reference sheet were created. Pharmacists were trained to deliver the intervention in a standardized fashion, while tailoring it to the patient’s needs. This training included one-on-one feedback using practice patients. Pharmacists and study staff received training in clear verbal communication using previously developed educational programs. Finally, with patient permission, we audiorecorded a sample of counseling sessions at each site and provided pharmacists with individual feedback.

### Usual Care
Patients in the usual care arm received routine counseling by the nurse and treating physicians at hospital discharge. In accordance with Joint Commission requirements, each hospital has a protocol for performing medication reconciliation within 24 hours of admission, at transfers of care, and discharge. In these academic centers, medical residents are responsible for medication reconciliation, although they can consult a nurse or clinical pharmacist for assistance. Nurses routinely verify reconciled medication information at hospital discharge in preparation to counsel patients on their discharge prescriptions. The process of obtaining a medication history for reconciliation at each hospital is facilitated by electronic medication records that contain complete prescribing information from the hospital and affiliated outpatient clinics. BWH also benefits from an internally developed medication reconciliation application, which has been shown to decrease potential ADEs.
Outcome Assessment

Primary and secondary outcomes are shown in Table 2. Outcomes were based on patient responses to a follow-up telephone interview conducted by research staff approximately 30 days (range, 25 to 35 days) after discharge and a review of all available medical records during the 30 days after discharge. Up to 10 call attempts were made, primarily at times that each patient had previously indicated would be most convenient. The follow-up interview included a detailed review of symptoms, a medication review, an assessment of planned and unplanned health care utilization, and a quality-of-life evaluation. For new or worsening symptoms, follow-up questions elicited details such as the onset, duration, and effect on the patient. The interviewer inquired if symptoms were related to medications, if a physician implicated a medication, and if symptoms responded to any adjustments in the medication regimen. RAs asked patients to state which medications they were supposed to be taking and then compared this with the discharge medication list (or a more recent list, if available). Discrepancies (eg, change in dose or frequency, omissions, additional medications) were noted and reasons for these discrepancies were explored with the patient to determine whether they were intentional or unintentional. Intentional medication changes were those reportedly made by a physician or due to completion of a prescribed course; physician changes to a regimen were confirmed with medical record review when possible. Finally, RAs assessed adherence by asking the number of days in the previous week that each medication was not taken as prescribed. This method of assessing self-reported adherence has been validated previously and associated with cardiovascular risk factor control.

Primary Outcome: SMEs

The primary outcome is the occurrence of SMEs within 30 days after hospital discharge. SME is a composite of (1) preventable or ameliorable ADEs and (2) potential ADEs as previously defined. To determine the presence of a SME, 2 blinded physician adjudicators independently reviewed the discharge summary and medication orders from the index hospitalization, the final 30-day interview report, and all available medical records within 30 days after discharge. The adjudicators followed a standardized procedure based on previously validated methods. Differences between adjudicators were resolved by discussion or with assistance from a third adjudicator when needed. Early adjudication sessions were supervised to ensure consistency in adjudication practices, with teaching points documented and communicated to all adjudicators across sites.

ADEs

The presence of ADEs was based on the 30-day review of symptoms and chart review. For each adverse event, adjudicators decided whether the injury was related to a medication using a...
6-point confidence scale, based on clinical judgment and the Naranjo algorithm, a validated scoring system to assess causality. For all ADEs (ie, >50% confidence that the injury was caused by a medication), clinicians determined the likelihood that it could have been prevented or ameliorated by any change in management. “Probably” or “definitely” preventable and/or ameliorable ADEs were counted in the outcome. Severity of ADEs was determined using 2 definitions: (1) “significant,” “serious,” “life-threatening,” or “fatal,” using previously established definitions, and (2) serious ADEs as defined by the Food and Drug Administration.

Potential ADEs
Based on their review of the 30-day medication history and patient chart, adjudicators noted the presence of unintentional medication discrepancies and self-reported nonadherence. Based on the medication involved and the degree of deviation from what was prescribed, adjudicators determined the likelihood of it potentially causing harm. Cases with at least a 50% likelihood of potential harm were considered potential ADEs, and the severity of potential ADEs was graded as “significant,” “serious,” “life-threatening,” or “potentially ameliorable” using definitions analogous to the severity of ADEs.

Secondary Outcomes
Quality of Life
Quality-of-life questionnaires were mailed to all patients before the 30-day follow-up call. Questionnaires could be completed by mail or, if preferred, administered by phone during the follow-up call. All patients admitted with ADHF received the Kansas City Cardiomyopathy Questionnaire for all patients admitted with ADHF.

Excess Health Care Utilization
Health care utilization will be assessed as the number of emergency department visits and unplanned hospital readmissions within 30 days of discharge, including care received at the study hospitals and other facilities. Utilization rates will be based on all available hospital and emergency department records as well as self-report.

Cost-Effectiveness
We will estimate program replication costs for potential adopters of the intervention, as well as the program cost per SME averted.

**Power and Sample Size**
We based the initial sample size calculations on achieving a 25% reduction in the percentage of patients who would experience at least 1 SME after discharge. Assuming a control event rate of 40%, 80% power, α of 0.05, and a 15% loss to follow-up, we planned to enroll 862 patients. Before study initiation, we reframed the primary outcome as the number of SMEs per patient rather than the percentage of patients with at least 1 SME. A review of the frequency of SMEs among 50 patients demonstrated that the number of SMEs per patient is an overdispersed count, with a mean of 1.0 (95% CI, 0.63 to 1.37). Using simulations, we determined that with 862 patients we will be able to detect a 30% reduction in the primary outcome, with 80% power and a of 0.05.

**Statistical Analysis**
Data will be analyzed on the basis of intent to treat. We will also perform a sensitivity analysis (per protocol “as treated” analysis). We will examine patient characteristics in the 2 study arms using proportions for categorical variables and means and standard deviations or medians and interquartile ranges for continuous variables, depending on their distribution. For univariable comparisons of the primary outcome, we will assess whether the number of SMEs per patient differs between the intervention arm and usual care using the Wilcoxon rank sum test. To adjust for potential confounding, we will conduct multivariable analysis using Poisson or negative binomial regression, depending on the characteristics of the outcome variable. Potential confounders, chosen a priori, will include health literacy, age, cognition, number of preadmission medications, number of high-risk medications, and medication understanding score. The model will also include an interaction term of the intervention and health literacy to examine whether health literacy modifies the effect of the intervention. Other intervention effect modifiers to be evaluated using interaction terms will include number of preadmission medications, number of high-risk medications, and medication understanding score. Secondary outcomes—including each component of SMEs (preventable or ameliorable ADEs, and potential ADEs), quality of life, and health care utilization—will be modeled similarly, with model type determined by characteristics of the outcome variable. All analysis will be performed in statistical language R, version 2.6.0 (http://www.r-project.org). We will use a 2-sided 5% significance level for all statistical inferences.

**Intervention Fidelity and Follow-Up**
A total of 430 patients (200 of 403 enrollees at VUH, and 230 of 459 at BWH) were randomly assigned to receive the intervention. The majority (n=402, 93.5%) received tailored pharmacist counseling that included review of discharge medications, either in person or by phone (Table 3). Most patients (n=367, 85.3%) received the follow-up phone call to review medications and symptoms. Three patients withdrew from the study and 6 died in the hospital before entering the follow-up period. A total of 690 (80.0%) were successfully contacted for 30-day follow-up.

**Summary**
The PILL-CVD study was designed to reduce SMEs after hospital discharge through a pharmacist-based intervention. If effective, the intervention will serve as a basis for developing guidelines for hospitals and health care facilities on pharmacist-assisted medication reconciliation, inpatient pharmacist counseling, low-literacy adherence aids, and patient follow-up after discharge. Cost-effectiveness analysis, coupled with identification of patients most likely to benefit from this intervention, will inform hospitals about how to improve medication safety while using resources judiciously.
Table 3. Intervention Fidelity Among the 430 Patients Randomly Assigned to Intervention Arm

<table>
<thead>
<tr>
<th>Patient Intervention Delivery</th>
<th>Total (n=430)</th>
<th>VH (n=200)</th>
<th>BWH (n=230)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 Separate counseling sessions (initial and discharge in hospital)</td>
<td>247 (57.4)</td>
<td>106 (53.0)</td>
<td>141 (61.3)</td>
</tr>
<tr>
<td>1 Combined counseling session in hospital</td>
<td>45 (10.5)</td>
<td>14 (7.0)</td>
<td>31 (13.5)</td>
</tr>
<tr>
<td>Initial counseling in hospital and discharge counseling by phone</td>
<td>95 (22.1)</td>
<td>60 (30.0)</td>
<td>35 (15.2)</td>
</tr>
<tr>
<td>Both initial and discharge counseling by phone</td>
<td>15 (3.5)</td>
<td>5 (2.5)</td>
<td>10 (4.3)</td>
</tr>
<tr>
<td>Initial session in hospital and no discharge counseling*</td>
<td>16 (3.7)</td>
<td>11 (5.5)</td>
<td>5 (2.2)</td>
</tr>
<tr>
<td>No intervention†</td>
<td>12 (2.8)</td>
<td>4 (2.0)</td>
<td>8 (3.5)</td>
</tr>
<tr>
<td>Postdischarge follow-up phone call completed (1 to 4 d after discharge)</td>
<td>367 (85.3)</td>
<td>181 (90.5)</td>
<td>186 (80.9)</td>
</tr>
</tbody>
</table>

Values are presented as n (%).

*Pharmacist unable to reach patients due to early discharge, inability to reach patient by phone, patient withdrawal from study, death, or patient not having any medications ordered at discharge.
†Among these, 2 died in hospital, 2 withdrew consent, and 8 did not receive intervention for logistical and/or clerical reasons (eg, pharmacist unavailable).

Disclosures

Dr Kripalani is a consultant to and holds equity in PictureRx, LLC, which makes patient education tools to improve medication management. PictureRx did not provide materials or funding for this study.

References


Appendix

The PILL-CVD study group includes the following.

Investigators: Sunil Kripalani, MD, MSc (principal investigator); Jeffrey L. Schnipper, MD, MPH (BWH site principal investigator); Christiane L. Roumie, MD, MPH; Anuj K. Dalal, MD; Terry A. Jacobson, MD; Kimberly J. Rask, MD, PhD; Viola Vaccarino, MD, PhD; Tejal K. Gandhi, MD, MPH; and David W. Bates, MD, MSc.

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