Annals of Internal Medicine | ORIGINAL RESEARCH

Effect of a Pharmacist Intervention on Clinically Important Medication Errors After Hospital Discharge

A Randomized Trial

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Background: Clinically important medication errors are common after hospital discharge. They include preventable or ameliorable adverse drug events (ADEs), as well as medication discrepancies or nonadherence with high potential for future harm (potential ADEs).

Objective: To determine the effect of a tailored intervention on the occurrence of clinically important medication errors after hospital discharge.

Design: Randomized, controlled trial with concealed allocation and blinded outcome assessors. (ClinicalTrials.gov registration number: NCT00632021)

Setting: Two tertiary care academic hospitals.

Patients: Adults hospitalized with acute coronary syndromes or acute decompensated heart failure.

Intervention: Pharmacist-assisted medication reconciliation, inpatient pharmacist counseling, low-literacy adherence aids, and individualized telephone follow-up after discharge.

Measurements: The primary outcome was the number of clinically important medication errors per patient during the first 30 days after hospital discharge. Secondary outcomes included preventable or ameliorable ADEs, as well as potential ADEs.

Results: Among 851 participants, 432 (50.8%) had 1 or more clinically important medication errors; 22.9% of such errors were judged to be serious and 1.8% life-threatening. Adverse drug events occurred in 258 patients (30.3%) and potential ADEs in 253 patients (29.7%). The intervention did not significantly alter the per-patient number of clinically important medication errors (unadjusted incidence rate ratio, 0.92 [95% CI, 0.77 to 1.10]) or ADEs (unadjusted incidence rate ratio, 1.09 [CI, 0.86 to 1.39]). Patients in the intervention group tended to have fewer potential ADEs (unadjusted incidence rate ratio, 0.80 [CI, 0.61 to 1.04]).

Limitation: The characteristics of the study hospitals and participants may limit generalizability.

Conclusion: Clinically important medication errors were present among one half of patients after hospital discharge and were not significantly reduced by a health-literacy–sensitive, pharmacist-delivered intervention.

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* For members of the PILL-CVD study group, see the **Appendix** (available at www.annals.org).

After returning home from the hospital, patients commonly have problems with their medication regimen (1), and many have adverse outcomes (2). Adverse drug events (ADEs), defined as injury due to a medication (3), affect 11% to 17% of patients during the first few weeks after hospital discharge (4–6). Previous research indicates that many of these events could be prevented (preventable ADEs) (6). Many others are not entirely preventable, but their duration or severity could be reduced (ameliorable ADEs) (6). In addition to ADEs, other medication-related problems may be present after discharge, which have not yet caused injury but may cause harm in the future if not corrected. These potential ADEs include discrepancies in the patient's medication regimen (7, 8) or episodes of nonadherence (9), with a high likelihood of potential future harm. Together, preventable or ameliorable ADEs and potential ADEs comprise clinically important medication errors, a meaningful target for patient safety interventions.

Certain patients seem to be at higher risk for clinically important medication errors, including elderly patients, patients with impaired cognitive function or low health literacy (10), or those prescribed numerous or high-risk medications (11, 12). Interventions that use pharmacists are generally effective in reducing medication errors and adverse events among hospitalized patients (13). Research is needed to determine the extent to which a pharmacist-delivered intervention can reduce clinically important medication errors during the vulnerable period after hospital discharge, particularly in an era where medication reconciliation is the expected standard of care.

The PILL-CVD (Pharmacist Intervention for Low Literacy in Cardiovascular Disease) study was done to evaluate the effect of a tailored intervention, consisting of

See also:

Print
Summary for Patients I-32

Web-Only
Supplement

Context

Many patients have problems with their medications after hospital discharge.

Contribution

In this study of adults with acute coronary syndromes or decompensated heart failure, one half of the patients had a clinically important medication error during the month after discharge, which persisted when pharmacists made special efforts to ensure prescribing accuracy, discussed medication use with patients during hospitalization and at discharge using patient education aids, and called patients after discharge.

Caution

These results are from patients who were relatively well-educated, literate, and cognitively intact and from academic hospitals that already had strong medication-use programs.

Implication

Not all pharmacist-led interventions to improve medication use after discharge are effective.

—The Editors

pharmacist-assisted medication reconciliation, inpatient pharmacist counseling, low-literacy adherence aids, and individualized telephone follow-up, on the number of clinically important medication errors after hospital discharge.

METHODS

Design Overview

PILL-CVD was a randomized, controlled trial done at 2 academic medical centers in Nashville, Tennessee, and Boston, Massachusetts. The study methods are described in detail elsewhere (14). Patients were allocated to intervention or usual care in a 1-to-1 ratio. The Vanderbilt University Institutional Review Board and the Partners Human Research Committee approved the study. Participants provided written informed consent.

Setting and Participants

Adults hospitalized at Vanderbilt University Hospital or Brigham and Women's Hospital for acute coronary syndromes (15) or acute decompensated heart failure (16) were enrolled between May 2008 and September 2009. Patients were excluded if they were being discharged within 3 hours; were too ill to participate; could not communicate in English or Spanish; had active psychosis, bipolar disorder, delirium, or severe dementia; had hearing or vision impairment; did not manage their own medications; were unlikely to be discharged to home; lacked a telephone; or were in police custody.

On patient enrollment, research staff collected demographic information, health literacy (short form of the Test of Functional Health Literacy in Adults) (17), cognitive function (Mini-Cog) (18), self-reported medication adherence (Morisky scale) (19), and understanding of the preadmission medication regimen (Medication Understanding Questionnaire) (20).

Randomization and Interventions

Participants were randomly assigned to receive usual care or usual care plus the intervention. Randomization was stratified by study site and diagnosis (acute coronary syndrome or heart failure), in permuted blocks of 2 to 6 patients, by a computer program that maintained allocation concealment. One unblinded research coordinator at each site administered the randomization, contacted study pharmacists who then delivered the intervention to eligible patients, and participated in the individualized telephone follow-up, as described below. All investigators, statisticians, and outcome assessors were blinded.

The intervention consisted of 4 components: pharmacist-assisted medication reconciliation, tailored inpatient counseling by a pharmacist, provision of low-literacy adherence aids, and individualized telephone follow-up after discharge (14). Eleven study pharmacists performed medication reconciliation at the time of enrollment, discharge, and in-hospital transfers. They communicated with the treating physicians to resolve any clinically relevant, unintentional medication discrepancies.

Intervention counseling was sensitive to the patient's health literacy and cognition. It was typically provided during 2 sessions, or during a single session when discharge occurred on the day of enrollment. During the initial meeting, the pharmacist assessed the patient's baseline understanding of medications and prescription labels, barriers to adherence, and social support. The second meeting generally occurred at discharge and included tailored counseling on the discharge medication regimen and the patient's needs, as previously identified. The pharmacist focused on changes between the preadmission and discharge regimen; strategies to promote adherence and minimize adverse effects; and high-risk medications, such as insulin or warfarin. Pharmacists confirmed understanding by using "teach-back" (21) and provided low-literacy adherence aids, including a pill box and illustrated daily medication schedule (14, 22).

Within 1 to 4 days after discharge, an unblinded research coordinator called intervention patients and used a structured interview to identify medication-related problems. As needed, pharmacists then called to address any identified issues in collaboration with the treating inpatient and responsible outpatient physicians.

For patients randomly assigned to usual care, the patients' treating physicians and nurses performed medication reconciliation and provided discharge counseling. At each hospital, medication reconciliation was facilitated by electronic records from the hospital and affiliated clinics, as well as internally developed interfaces to construct a pre-

admission medication list. At Brigham and Women's Hospital, the program had additional features (such as reminders to complete a preadmission medication list and integration with order entry) and required providers to continue, stop, or change each preadmission medication at admission; this application, combined with process redesign, was previously shown to reduce potential ADEs (8, 23). Patients assigned to usual care were not routinely provided with a pill box, illustrated medication schedule, or telephone follow-up.

Outcomes and Follow-up

The primary composite outcome was the number of clinically important medication errors per patient within 30 days after hospital discharge. This included preventable or ameliorable ADEs and potential ADEs due to medication discrepancies or nonadherence. Secondary outcomes included preventable or ameliorable ADEs; potential ADEs due to discrepancies or nonadherence; and preventable or ameliorable ADEs judged to be serious, life-threatening, or fatal.

Outcomes were determined for each participant by 2 independent clinician adjudicators who were blinded to treatment assignment. Each adjudicator reviewed all available medical records during the 30 days after discharge and the results of a patient follow-up telephone interview conducted by research staff 25 to 35 days after discharge. This interview included a detailed review of new or worsening symptoms (to detect possible medication adverse effects); discharge medications (to detect possible discrepancies and nonadherence); and health care utilization after discharge. The adjudicators followed a standardized approach based on previously validated methods to ascertain the presence of ADEs and to grade severity, preventability, and ameliorability (3, 11, 24, 25). For each medication discrepancy or episode of nonadherence, adjudicators graded the potential for harm if left uncorrected; if the likelihood of potential harm exceeded 50%, it was counted as a potential ADE. A drug implicated in an ADE was not eligible to be adjudicated as a potential ADE in the same patient. For each ADE and potential ADE, adjudicators categorized the severity as significant, serious, or life-threatening, following rules and examples from an adjudication manual (**Supplement**, available at www.annals.org).

Disagreements between the adjudicators about whether a medication was implicated in a study outcome were uncommon (approximately 3% for ADEs and 5% for potential ADEs) and occurred with similar frequency at each site. Disagreements were resolved by discussion or, in approximately 5% of cases, with assistance from a third adjudicator.

Statistical Analysis

Initially, sample size was calculated on the basis of achieving a 25% reduction in the percentage of patients who would have at least 1 clinically important medication error after discharge (13). Assuming a control event rate of 40% (3, 5, 9, 26), 80% power, an α level 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 clinically important medication errors per patient, rather than the percentage of patients with at least 1 clinically important medication error. Using simulations, we determined that, with 862 patients, we would be able to detect a 30% reduction in the primary outcome, with 80% power and an α level of 0.05.

Patient characteristics were described and compared between study groups by using Wilcoxon rank-sum tests for continuous variables and Pearson chi-square tests for categorical variables.

We analyzed outcomes on an intention-to-treat basis, excluding only patients who withdrew consent or died in the hospital and, therefore, did not enter the period of outcome assessment. In the primary analysis, we used unadjusted negative binomial regression to compare the number of clinically important medication errors by treatment group (27, 28). We report the results of between-group comparisons as incidence rate ratios (IRRs) with 95% CIs.

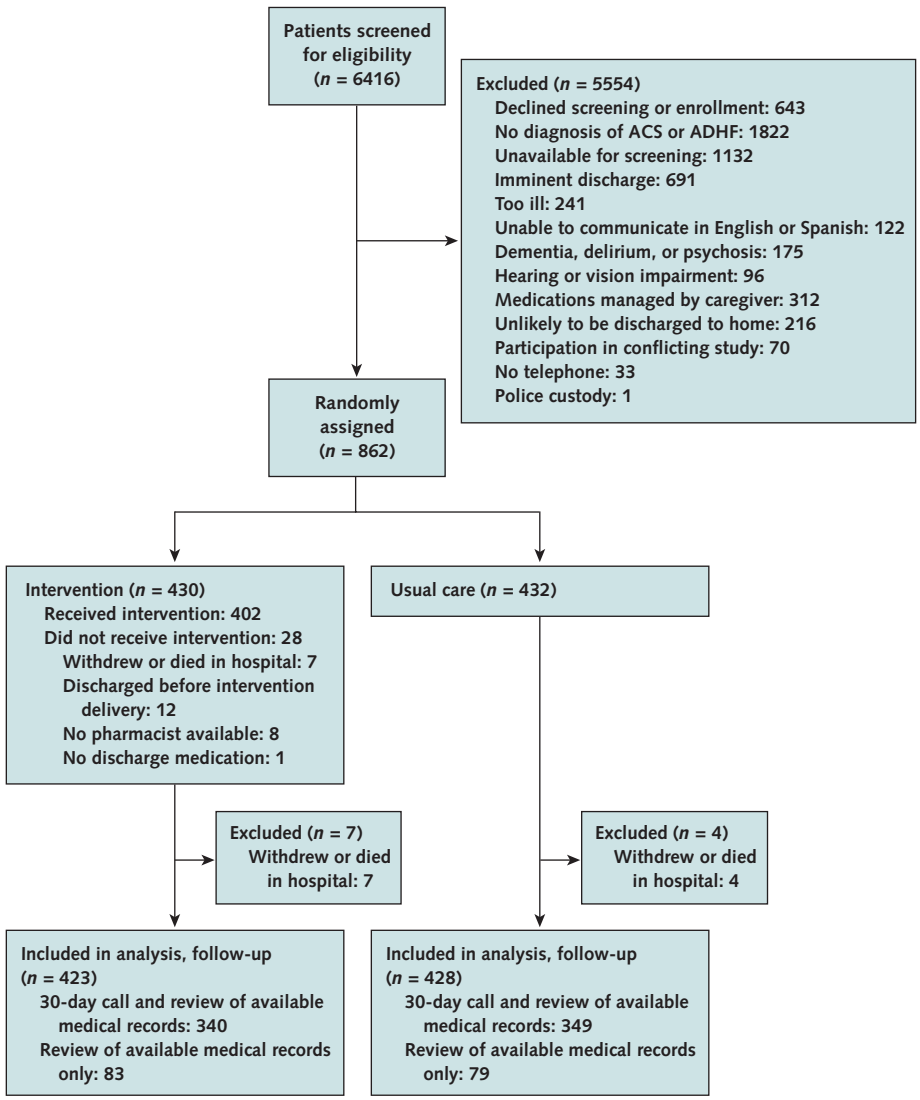
We used negative binomial regression to assess the adjusted effect of the intervention through multivariable analysis. Covariates were chosen a priori and included study site, admission diagnosis (acute coronary syndrome, heart failure, or both), patient age (continuous), marital status (married or cohabitating, or not), insurance type (private, Medicare, Medicaid, or self-pay), health literacy (continuous), cognition (continuous), number of preadmission prescription medications (continuous), medication understanding (continuous), self-reported adherence (continuous), access to a primary care provider, and hospitalization during the previous year. Nonlinearity of the effect of continuous covariates was assessed by inclusion of restricted cubic splines and retained if the P value was less than 0.20. Missing values of health literacy (2.4%), medication understanding (8%), and self-reported adherence (5.2%) were imputed using multiple imputation by chained equations with 10 iterations (29, 30). Similar analyses were done for the secondary outcomes.

Sensitivity and Subgroup Analyses

We did a sensitivity analysis that also adjusted for baseline comorbid conditions, an analysis that excluded patients who received additional medication assistance after discharge (through another medication management program or discharge to a skilled-nursing facility), and an analysis that included only patients who completed a 30-day follow-up call.

Differential effects of the intervention among subgroups of interest were tested by including cross-product terms for interaction in the multivariable model for covariates that were selected a priori (health literacy and number of medications) or post hoc (cognition and site). We graphically display these results using forest plots.

Figure 1. **Study flow diagram.**



ACS = acute coronary syndrome; ADHF = acute decompensated heart failure.

Findings with a 2-sided *P* value less than 0.05 were considered statistically significant. Analyses were done in statistical language R, version 2.6.0 (R Foundation for Statistical Computing, Vienna, Austria).

Role of the Funding Source

The study was funded by the National Heart, Lung, and Blood Institute, which had no role in the design or conduct of the study; collection, management, analysis, or interpretation of the data; or preparation, review, or approval of the manuscript.

RESULTS

Of the 6416 patients who were screened, 862 patients were enrolled and randomly assigned (430 in the intervention group and 432 in the usual care group) (**Figure 1**). Eleven patients (7 in the intervention group and 4 in the usual care group) withdrew consent or died in the hospital, leaving 851 patients in the intention-to-treat analysis. Outcome data were obtained from available charts for all patients. Thirty-day telephone follow-up was available for 81% of patients; this did not differ significantly by site or treatment group.

Participants had a mean age of 60 years and 14 years of education, and 41.4% were women (**Table 1**). Approximately 10% had inadequate and 8.7% had marginal health literacy, and 11.5% had some degree of cognitive impairment. Sixty one percent were hospitalized with acute coronary syndromes only, 31% with acute heart failure only, and 7% with both diagnoses. Age was slightly higher among intervention patients ($P = 0.023$).

Primary Outcome

Among the 851 participants who were analyzed, 432 (50.8%) had 1 or more clinically important medication errors during the 30 days after hospital discharge. Among 777 such errors, 585 (75.3%) were categorized as significant in severity, 178 (22.9%) were serious, 14 (1.8%) were life-threatening, and 0 were fatal (**Table 2**).

The mean number of clinically important medication errors was similar in the intervention (0.87 per patient) and usual care (0.95 per patient) groups. Although the treatment effect favored the intervention, this difference was not statistically significant (unadjusted IRR, 0.92 [95% CI, 0.77 to 1.10]). Models with covariate adjustment and multiple imputation for missing predictors produced similar results.

Secondary Outcomes

A total of 353 preventable or ameliorable ADEs occurred among 258 patients (30.3%). Most ADEs (n = 296 [83.9%]) were categorized as significant; 48 (13.6%) were serious, 9 (2.5%) were life-threatening, and 0 were fatal (**Table 2**). Approximately 13% of ADEs (n = 46) resulted in an emergency department visit or rehospitalization. The drug types most commonly implicated in ADEs were cardiovascular agents, diuretics, opioids, lipid-lowering agents, nutrients, hypoglycemics, and anticoagulants (**Table 3**). **Table 4** provides examples of clinical important medication errors, and the **Appendix Table** (available at www.annals.org) provides patient-level outcomes.

The number of ADEs per patient was similar in the intervention (0.43) and usual care (0.40) groups, as was the number of serious or life-threatening ADEs. The unadjusted and fully adjusted analyses showed no significant treatment effect on ADEs (**Table 2**).

A total of 424 potential ADEs were found among 253 patients (29.7%). Approximately one half were related to medication discrepancies and the other half related to nonadherence. The most common types of discrepancies were omission of a medication (34.5%), incorrect dose (32.9%) or frequency (15.9%), or an additional medication that should not have been on the list (11.9%). Forms of nonadherence included missed doses (48.3%), premature discontinuation of a medication (18.0%), failure to fill (10.0%) or delays in filling (4.7%) a prescription, taking a medication less often (9.0%) or more often (2.4%) than prescribed, and taking smaller (4.3%) or larger (2.4%) doses than prescribed. The potential consequences of discrepancies and nonadherence were rated as significant (n = 289 [68.2%]), serious (n = 130 [30.7%]), or life-threatening (n = 5 [1.2%]) (**Table 2**). Medication types implicated in potential ADEs and examples are provided in **Tables 3** and **4**.

Potential ADEs occurred less often among intervention patients (0.44 per patient) than usual care patients (0.55 per patient). The treatment effect favored the intervention in both unadjusted (IRR, 0.80 [CI, 0.61 to 1.04]) and adjusted (adjusted IRR, 0.79 [CI, 0.61 to 1.01]) analyses, but was not statistically significant.

Sensitivity and Subgroup Analyses

Similar treatment effects were seen in sensitivity analyses that adjusted for baseline comorbid conditions, excluded the 46 patients who received additional medication assistance after discharge, or included only patients who completed a 30-day follow-up call for data collection (data not shown).

Table 1. **Baseline Patient Characteristics***

Characteristic	Usual Care (n = 428)	Intervention (n = 423)
Study hospital		
Vanderbilt University Hospital	200 (46.7)	197 (46.6)
Brigham and Women's Hospital	228 (53.3)	226 (53.4)
Mean age (SD), *y*	59 (13.8)	61 (14.4)
Male sex	249 (58.2)	250 (59.1)
Primary language		
English	425 (99.3)	414 (97.9)
Spanish	3 (0.7)	9 (2.1)
Race		
White	335 (78.3)	319 (75.4)
Black	71 (16.6)	77 (18.2)
Other	22 (5.1)	27 (6.4)
Median length of education (IQR), *y*†	14 (12–16)	14 (12–16)
Annual household income†		
<$10 000	17 (4.3)	20 (5.2)
$10 000–$14 999	24 (6.1)	21 (5.4)
$15 000–$19 999	19 (4.9)	23 (6.0)
$20 000–$24 999	47 (12.0)	56 (14.5)
$25 000–$34 999	49 (12.5)	49 (12.7)
$35 000–$49 999	56 (14.3)	54 (14.0)
$50 000–$74 999	60 (15.3)	58 (15.0)
≥$75 000	119 (30.4)	105 (27.2)
Health literacy†		
Inadequate	39 (9.4)	47 (11.4)
Marginal	38 (9.1)	36 (8.7)
Adequate	340 (81.5)	331 (80.0)
Impaired cognition†	46 (10.8)	52 (12.3)
Has primary care provider	392 (91.6)	386 (91.3)
Median preadmission medications (IQR), *n*	7 (4–11)	8 (4–11)
Comorbid conditions		
Diabetes mellitus	195 (45.6)	140 (33.1)
Hypertension	296 (69.2)	306 (72.3)
Hypercholesterolemia	236 (55.1)	234 (55.3)
Coronary artery disease	211 (49.3)	225 (53.2)
Previous myocardial infarction	73 (17.1)	100 (23.6)
Previous stroke or cerebrovascular event	41 (9.6)	30 (7.1)
Previous coronary revascularization procedure	195 (45.6)	203 (48.0)

IQR = interquartile range.
* Values are reported as numbers (valid percentages), unless otherwise noted.
† Missing responses: education (n = 1), annual household income (n = 74), health literacy (n = 20), and cognition (n = 2).

Table 2. **Number and Severity of Clinically Important Medication Errors, ADEs, and Potential ADEs During the First 30 Days After Hospital Discharge, by Treatment Assignment**

Outcome	Events, *n**		Mean Events per Patient (SD), *n**		IRR (95% CI)	
	Usual Care	Intervention	Usual Care	Intervention	Unadjusted†	Adjusted‡
Clinically important medication errors§	407	370	0.95 (1.36)	0.87 (1.18)	0.92 (0.77–1.10)	0.92 (0.77–1.09)
Significant	298	287	0.70 (1.05)	0.68 (0.96)	–	–
Serious	102	76	0.24 (0.67)	0.18 (0.52)	–	–
Life-threatening	7	7	0.02 (0.17)	0.02 (0.13)	–	–
ADEs	170	183	0.40 (0.75)	0.43 (0.74)	1.09 (0.86–1.39)	1.09 (0.86–1.39)
Significant	141	155	0.33 (0.67)	0.37 (0.67)	–	–
Serious	24	24	0.06 (0.24)	0.06 (0.25)	–	–
Life-threatening	5	4	0.01 (0.16)	0.01 (0.10)	–	–
Potential ADEs	237	187	0.55 (1.07)	0.44 (0.86)	0.80 (0.61–1.04)	0.79 (0.61–1.01)
Significant	157	132	0.37 (0.76)	0.31 (0.68)	–	–
Serious	78	52	0.18 (0.61)	0.12 (0.41)	–	–
Life-threatening	2	3	0.00 (0.07)	0.01 (0.08)	–	–

ADE = adverse drug event; IRR = incidence rate ratio.
* Based on 428 patients in the usual care group and 423 patients in the intervention group. Patients could contribute more than 1 event.
† Unadjusted negative binomial regression comparing the mean count of clinically important medication errors, ADEs, and potential ADEs, by treatment group.
‡ Adjusted negative binomial regression with imputation of missing covariates. Model includes study site, patient age, admission diagnosis, marital status, insurance type, health literacy, cognition, number of prescription medications, understanding of medications, self-reported adherence, access to a primary care provider, and hospitalization during the previous year.
§ Composite of ADEs and potential ADEs.

In prespecified subgroup analyses, the intervention tended to have a greater effect among patients with inadequate health literacy (adjusted IRR for clinically important medication errors, 0.68 [CI, 0.39 to 1.19]) (**Figure 2**, *top*).

Table 3. **Types of Medications Implicated in ADEs and Potential ADEs***

Medication Type	ADEs (*n* = 353)	Potential ADEs (*n* = 424)
Cardiovascular agents (excluding diuretics)	166 (47.0)	181 (42.7)
Diuretics	73 (20.7)	52 (12.3)
Opioids	19 (5.4)	0 (0)
Lipid-lowering agents	17 (4.8)	35 (8.3)
Nutrients (herbs, vitamins, and supplements)	17 (4.8)	18 (4.2)
Hypoglycemic agents	12 (3.4)	35 (8.3)
Anticoagulants	12 (3.4)	7 (1.7)
Antidepressants	6 (1.7)	4 (0.9)
Gastrointestinal agents	6 (1.7)	11 (2.6)
Steroids	5 (1.4)	3 (0.7)
Sedatives	3 (0.8)	7 (1.7)
Gout agents	3 (0.8)	6 (1.4)
Thyroid agents	3 (0.8)	4 (0.9)
Analgesics (nonnarcotic)	3 (0.8)	3 (0.7)
Respiratory agents	1 (0.3)	21 (5.0)
Anti-infective agents	1 (0.3)	11 (2.6)
Other	6 (1.7)†	26 (6.1)‡

ADE = adverse drug event.
* Values are reported as numbers (percentages). Patients could contribute more than 1 event.
† Includes drugs for incontinence ($n = 1$), ophthalmic use ($n = 1$), hormone replacement therapy ($n = 1$), erectile dysfunction ($n = 1$), tobacco cessation ($n = 1$), and electrolyte management ($n = 1$).
‡ Includes drugs for ophthalmic use ($n = 6$), osteoporosis ($n = 4$), incontinence ($n = 3$), immunosuppression ($n = 3$), seizures ($n = 3$), muscle relaxants ($n = 2$), Parkinson disease ($n = 1$), erectile dysfunction ($n = 1$), and electrolyte management ($n = 1$), as well as antipsychotics ($n = 1$) and antihistamines ($n = 1$).

The relationship between the number of preadmission medications and outcomes was nonlinear, with an apparent inflection point at 10 medications. Patients with 10 or more preadmission medications tended to benefit from the intervention (adjusted IRR for clinically important medication errors, 0.80 [CI, 0.61 to 1.05]). In post hoc subgroup analyses, the intervention seemed to benefit patients with impaired cognition and patients enrolled at Vanderbilt University Hospital, particularly by reducing potential ADEs (**Figure 2**).

DISCUSSION

In this randomized, controlled trial, we found that clinically important medication errors were very common, affecting 50.8% of patients during the first 30 days after hospital discharge. Overall, a health-literacy–sensitive pharmacist intervention did not significantly reduce clinically important medication errors or ADEs at the study hospitals. Potential ADEs tended to decline, but this effect was not statistically significant. These results highlight the difficulty of improving medication safety during the transition from hospital to home.

In interpreting the results of this negative trial, a key question is the extent to which its findings are generalizable to other settings. Indeed, as hospitals increasingly implement and evaluate programs to improve care transitions, it is critical to understand contextual factors that may affect the results, as examples of both positive (13, 25) and negative (31) studies exist. PILL-CVD was done at 2 academic hospitals that had resources to support medication recon-

ciliation, including health information technology, at baseline. This made it more difficult to show an incremental benefit from the PILL-CVD intervention. The effect size was smaller than anticipated and smaller than that found in studies conducted before the medication reconciliation era. Even at these 2 relatively similar academic hospitals, we saw a possible difference in treatment effect. Further study is needed to determine whether hospitals with different characteristics, such as less electronic medical record support for medication reconciliation or fewer pharmacist resources, see benefit over usual care from this type of intervention.

Another factor affecting generalizability is that, on average, the study participants were well-educated (median of 14 years of education) and cognitively intact (88%) and had a relatively low prevalence of inadequate health literacy (10%), compared with a 26% prevalence in the medical literature (32). The PILL-CVD intervention, which was designed to accommodate the needs of patients with low health literacy or cognitive impairment, may be more effective among those populations. This also requires further investigation, because the present study was not powered to detect a benefit in these subgroups.

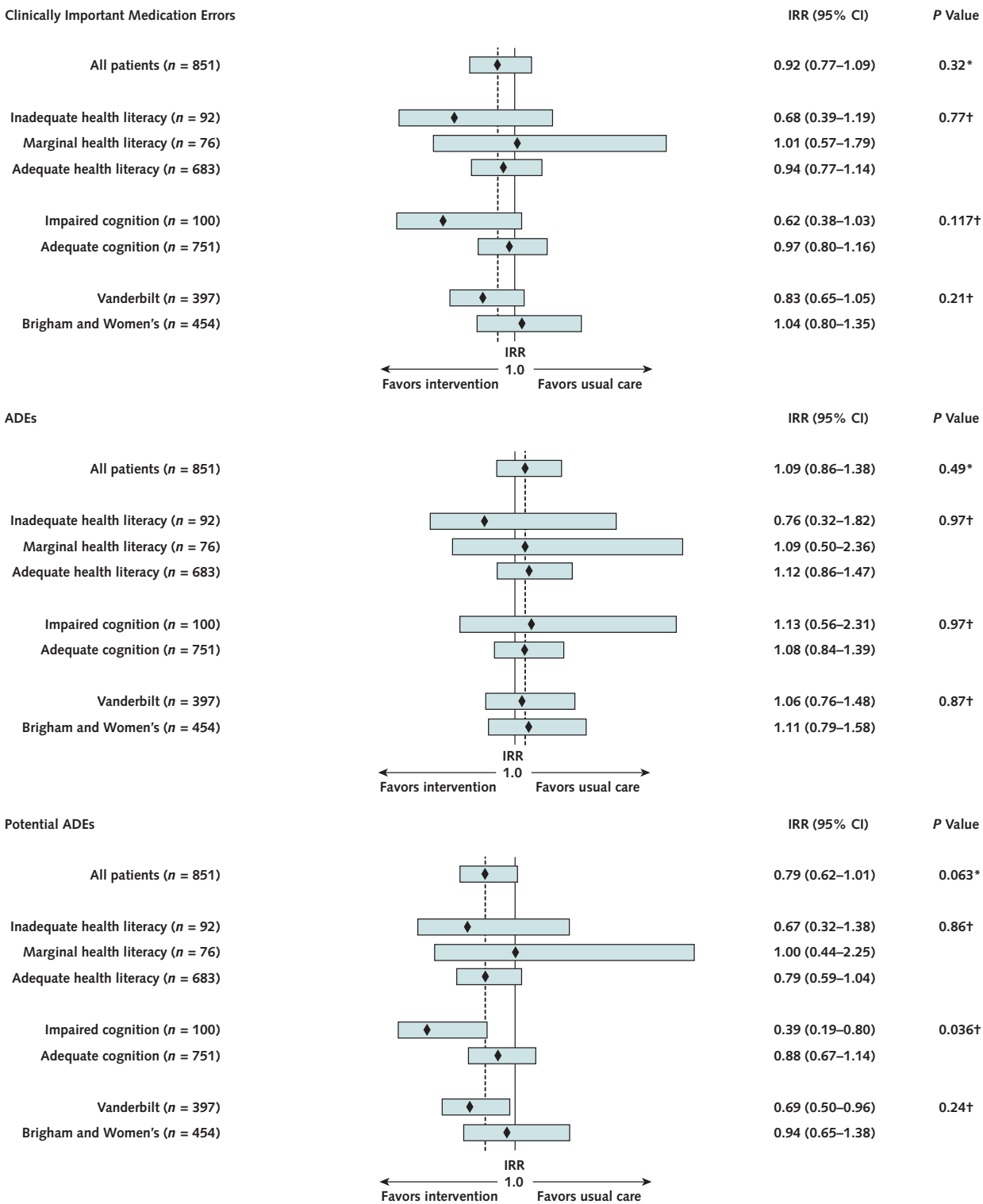
The intervention had no effect on the number of ADEs after discharge. Part of this finding may be artifactual; the adjudication process has some inherent subjectivity. In particular, patients who learn about side effects through the intervention may report symptoms in such a

Table 4. **Examples of Clinically Important Medication Errors**

Potential ADE Type or ADE Preventability	Severity	Description
Potential ADE		
Nonadherence: missed doses	Significant	A middle-aged patient with ischemic cardiomyopathy and peripheral vascular disease complicated by toe osteomyelitis reported frequent nonadherence (at least 2 d/wk) in the month since discharge with aspirin, simvastatin, extended-release metoprolol, isosorbide dinitrate, and hydralazine secondary to intermittent nausea; patient expressed frustration with taking so many medications.
Nonadherence: delay in filling prescription	Serious	A middle-aged patient was hospitalized with several months of progressive dyspnea requiring cardiac bypass surgery complicated by postoperative ischemia. The patient was discharged with several cardiac medications, including atenolol. In the month after discharge, the patient ran out of atenolol and delayed refilling the prescription for several days. Given the patient's recent ischemia, the risk of nonadherence to atenolol causing recurrent ischemia led the adjudicators to judge this potential ADE as serious.
Discrepancy: omission	Significant	An elderly patient with nonischemic cardiomyopathy was hospitalized with a 6.8-kg weight gain and CHF. Although the patient had been receiving sublingual nitroglycerin for years, the patient no longer had it on the medication list (and was not taking it) 1 mo after discharge because of a medication discrepancy. Adjudicators rated this as significant (and not serious) because the cardiomyopathy was nonischemic and nitroglycerin was mainly for symptom control.
Discrepancy: dose	Serious	A middle-aged patient with diabetes mellitus, CAD, and recent coronary stent placement was hospitalized with angina requiring further coronary stenting. The patient was believed to be taking metformin, 500 mg twice daily, and was prescribed that dose at discharge (in addition to insulin). At 1-mo follow-up, the patient reported taking metformin, 1000 mg twice daily, "which is what it has always been." The potential for severe consequences from poorly controlled diabetes led adjudicators to rate this potential ADE as serious.
ADE		
Ameliorable	Significant	A middle-aged patient was hospitalized for STEMI requiring bare-metal coronary stent placement. The hospitalization was complicated by a new diagnosis of atrial fibrillation. The patient was discharged with aspirin, 325 mg/d; clopidogrel for 6 mo; and warfarin. At 1-mo follow-up, the patient reported several weeks of epistaxis, which was finally reported at the regular PCP visit; the PCP then decreased the daily aspirin dose to 81 mg. The ADE was adjudicated as ameliorable because earlier PCP notification could have led to a shorter duration of epistaxis.
Preventable	Serious	An elderly patient with diabetes, CKD, CAD, and diastolic heart failure was hospitalized for unstable angina, heart failure, bradycardia, and hyperkalemia. At 1-mo follow-up, the patient reported several episodes of symptomatic hypoglycemia. The patient's insulin requirements in the hospital had been less than at home. The discharge documentation showed a handwritten change from 80 units of 70/30 insulin to 40 units every morning, but the patient continued to take 80 units and often took the full dose despite not eating. Adjudicators believed that this ADE could have been prevented with better documentation and patient education about correct dosing and dietary practices.
Ameliorable	Life-threatening	An elderly patient with CAD was electively hospitalized for management of persistent atrial flutter and worsening cardiomyopathy. The hospitalization was complicated by intermittent diplopia found to be secondary to basilar artery stenosis, for which the patient was managed conservatively with warfarin and low-dose aspirin. The patient's first INR check was 14.1 at 8 d after discharge. Adjudicators believed that the severity and duration of dangerous overanticoagulation could have been alleviated with earlier and more frequent monitoring.

ADE = adverse drug event; CAD = coronary artery disease; CHF = congestive heart failure; CKD = chronic kidney disease; INR = international normalized ratio; PCP = primary care physician; STEMI = ST-elevation myocardial infarction.

Figure 2. **Adjusted treatment effect on clinically important medication errors, ADEs, and potential ADEs, by subgroups of interest.**



Values less than 1.0 indicate that the mean count of outcomes in the treatment group is smaller than that in the usual care group. Clinically important medication errors are a composite of ADEs and potential ADEs. ADE = adverse drug event; IRR = incidence rate ratio.

* *P* values for the main treatment effect are based on negative binomial regression models, adjusted for covariates, using multiple imputation for missing predictor data.

† *P* values for the interactions assess homogeneity among subgroup-specific treatment effects and are based on the likelihood ratio test that compared models with and without the interaction term.

way that they are more likely to be adjudicated as ADEs, thus altering the apparent effect of the intervention (25). Intervention patients in this study had more significant (that is, symptom-only) ADEs. In addition, reduction of preventable or ameliorable ADEs may require different interventions than those evaluated here, such as closer postdischarge monitoring, clinic-based support, or home visits.

Other findings are noteworthy. The observed incidence of preventable or ameliorable ADEs (30.3%) is more than double that reported by Forster and colleagues (4–6), despite similar adjudication procedures. Possible explanations include the present study having a slightly longer follow-up (30 days vs. a mean of 24 days), more thorough electronic health records for review, and more extensive review of outside medical records (5). Moreover, patients in the present study had specific cardiac conditions, compared with a general medical population (5).

Potential ADEs were also common, affecting 29.7% of patients overall. Here, potential ADEs were defined as medication discrepancies or nonadherence during the first 30 days after discharge, whereas others have focused only on medication discrepancies and used a 72-hour follow-up (7). How elapsed time affects discrepancies is uncertain. Medication discrepancies that are present immediately after discharge could be resolved as patients visit their outpatient physicians, although the incidence remained high in the present investigation. Different definitions, data collection procedures, and follow-up duration make comparison with other studies difficult.

Certain study limitations were present. First, as previously noted, the characteristics of the study hospitals and participants made it more difficult to show incremental benefit and also limit generalizability. Second, the participants had acute cardiovascular conditions; the number of medication-related problems, classes of medications implicated, and efficacy of this type of intervention may differ in other populations. Third, not all patients received the full intervention as intended, although the vast majority did (14).

In conclusion, we found that clinically important medication errors commonly occur during the 30 days after a cardiac hospitalization, and we report a much higher incidence than previously shown for preventable or ameliorable ADEs, as well as potential ADEs. A health-literacy–sensitive pharmacist intervention that included postdischarge telephone follow-up did not improve medication safety overall. Reducing ADEs and potential ADEs in the postdischarge period is becoming more critical as hospitals have increasing financial penalties tied to rehospitalization rates. Further work is needed to develop and test interventions in this setting, including strategies for higher-risk populations, as well as additional methods, such as postdischarge medication reconciliation (33) or closer postdischarge surveillance.

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Appendix Table. **Patients With at Least 1 Clinically Important Medication Error, ADE, or Potential ADE, by Treatment Assignment***

Outcome	Overall (n = 851)	Usual Care (n = 428)	Intervention (n = 423)
Clinically important medication errors†			
≥1	432 (50.8)	219 (51.2)	213 (50.4)
≥1 significant	366 (43.0)	181 (42.3)	185 (43.7)
≥1 serious	132 (15.5)	71 (16.6)	61 (14.4)
≥1 life-threatening	12 (1.4)	5 (1.2)	7 (1.7)
ADEs			
≥1	258 (30.3)	125 (29.2)	133 (31.4)
≥1 significant	223 (26.2)	105 (24.5)	118 (27.9)
≥1 serious	45 (5.3)	23 (5.4)	22 (5.2)
≥1 life-threatening	7 (0.8)	3 (0.7)	4 (0.9)
Potential ADEs			
≥1	253 (29.7)	132 (30.8)	121 (28.6)
≥1 significant	197 (23.1)	102 (23.8)	95 (22.5)
≥1 serious	95 (11.2)	52 (12.1)	43 (10.2)
≥1 life-threatening	5 (0.6)	2 (0.5)	3 (0.7)

ADE = adverse drug event.
* Values are reported as numbers (percentages). Patients could contribute more than 1 event and have events of different severity.
† Composite of ADEs and potential ADEs.