JAMA Internal Medicine | Original Investigation

Effect of Electronic Reminders, Financial Incentives, and Social Support on Outcomes After Myocardial Infarction
The HeartStrong Randomized Clinical Trial

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IMPORTANCE Adherence to medications prescribed after acute myocardial infarction (AMI) is low. Wireless technology and behavioral economic approaches have shown promise in improving health behaviors.

OBJECTIVE To determine whether a system of medication reminders using financial incentives and social support delays subsequent vascular events in patients following AMI compared with usual care.

DESIGN, SETTING, AND PARTICIPANTS Two-arm, randomized clinical trial with a 12-month intervention conducted from 2013 through 2016. Investigators were blinded to study group, but participants were not. Design was a health plan–intermediated intervention for members of several health plans. We recruited 1509 participants from 7179 contacted AMI survivors (insured with 5 large US insurers nationally or with Medicare fee-for-service at the University of Pennsylvania Health System). Patients aged 18 to 80 years were eligible if currently prescribed at least 2 of 4 study medications (statin, aspirin, β-blocker, antiplatelet agent), and were hospital inpatients for 1 to 180 days and discharged home with a principal diagnosis of AMI.

INTERVENTIONS Patients were randomized 2:1 to an intervention using electronic pill bottles combined with lottery incentives and social support for medication adherence (1003 patients), or to usual care (506 patients).

MAIN OUTCOMES AND MEASURES Primary outcome was time to first vascular rehospitalization or death. Secondary outcomes were time to first all-cause rehospitalization, total number of repeated hospitalizations, medication adherence, and total medical costs.

RESULTS A total of 35.5% of participants were female (n = 536); mean (SD) age was 61.0 (10.3) years. There were no statistically significant differences between study arms in time to first rehospitalization for a vascular event or death (hazard ratio, 1.04; 95% CI, 0.71 to 1.52; $P = .84$), time to first all-cause rehospitalization (hazard ratio, 0.89; 95% CI, 0.73 to 1.09; $P = .27$), or total number of repeated hospitalizations (hazard ratio, 0.94; 95% CI, 0.60 to 1.48; $P = .79$). Mean (SD) medication adherence did not differ between control (0.42 [0.39]) and intervention (0.46 [0.39]) (difference, 0.04; 95% CI, −0.01 to 0.09; $P = .10$). Mean (SD) medical costs in 12 months following enrollment did not differ between control ($29 811 [$74 850]) and intervention ($24 038 [$66 915]) (difference, −$5773; 95% CI, −$13 682 to $2137; $P = .15$).

CONCLUSIONS AND RELEVANCE A compound intervention integrating wireless pill bottles, lottery-based incentives, and social support did not significantly improve medication adherence or vascular readmission outcomes for AMI survivors.

TRIAL REGISTRATION clinicaltrials.gov Identifier: NCT01800201

JAMA Intern Med. 2017;177(8):1093-1101. doi:10.1001/jamainternmed.2017.2449
Published online June 26, 2017.

Author Audio Interview

Supplemental content

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Coronary artery disease is the leading cause of death in the United States. Medications including β-blockers, statins, and aspirin and other antiplatelet drugs significantly reduce the rate of cardiovascular events and repeated treatment procedures among patients surviving acute myocardial infarction (AMI). Despite these clinical benefits, the generally low cost, once-a-day schedule, and benign adverse event profile, adherence is low. A large national study of adherence to use of β-blockers, statins, and angiotensin-converting enzyme inhibitors or angiotensin receptor blockers among insured patients in the year following AMI revealed adherence of only 39%, increasing to only 44% when co-payments were waived.[1] Given that atherosclerotic cardiovascular disease kills approximately 400 000 Americans per year and that we have safe and efficacious medications to reduce coronary artery disease sequelae, improved population health depends on their uptake and patient adherence.

Targeted education about the value of medications might be effective if patients do not understand their benefit. Mechanical reminder systems might be effective if patients are forgetful. Social support might be effective if patients need external encouragement. But each of these approaches is already available, suggesting that the underlying explanations for low adherence are different or that these approaches alone do not effectively address them.

Behavioral economics offers promise in improving motivation for desirable but difficult activities, such as weight loss, exercise, or smoking cessation,[2,3] by harnessing pervasive patterns of irrational behavior, rather than patterns of rational behavior typically addressed by traditional economics. New technology, such as wireless pill bottles to measure adherence and platforms to automate communication, allows remote monitoring for large populations at reasonable cost while providing encouragement.[4] In this study, we combined several promising approaches into an automated intervention aiming to reduce repeated cardiovascular events among AMI survivors through improved medication adherence.

Key Points

Question What is the effect of wireless technology and behavioral economic approaches on vascular rehospitalization and medication adherence in a health plan–based intervention for acute myocardial infarction survivors?

Findings In this randomized clinical trial of 1509 patients following acute myocardial infarction, there were no statistically significant differences between study arms in time to first rehospitalization for a vascular event or death, medication adherence, or cost.

Meaning A compound intervention did not significantly improve medication adherence or clinical outcomes.

Methods

Study Design

The HeartStrong study was a 2-arm randomized clinical trial; details of its design have been described elsewhere.[5] The study protocol is available in Supplement 1. All participants randomized to the intervention arm received (1) up to 4 electronic pill bottles (Vitality GlowCaps) used in place of regular pill bottles for cardiovascular medications (β-blockers, statins, aspirin, anti-platelet agents); (2) daily lottery incentives with an approximately 1 in 5 chance of a $5 payout and a 1 in 100 chance of a $50 payout based on medication adherence the previous day; (3) the option of enlisting a friend or family member to support medication adherence who would be automatically notified if participants failed to use the electronic pill bottles 2 out of the 3 previous days, including the previous day; (4) access to social work resources; and (5) a staff engagement advisor to provide close monitoring, feedback, and reinforcement of adherence. The wireless pill bottles electronically monitored openings and transmitted them to Way to Health, a National Institutes of Health–funded software platform that facilitates patient engagement. Patients randomized to the control arm received usual care and had no further contact with study staff following enrollment.

Study Population

Eligible participants were identified via 5 insurance partners (Aetna, Horizon Healthcare of New Jersey, HealthFirst, Humana, and Independence Blue Cross) and through Medicare fee-for-service (for patients in the University of Pennsylvania Health System). Continuous enrollment with health insurers after enrollment was not required. Participants were recruited by University of Pennsylvania research staff from March 2013 through January 2015 and observed for 1 year.

Eligible participants were 18 to 80 years old, were currently prescribed at least 2 of the 4 study medications (statin, aspirin, β-blocker, antiplatelet agent) based on patient self-report at time of enrollment, were hospital inpatients for 1 to 180 days, and were discharged to home with a principal *International Classification of Diseases, Ninth Revision*, diagnosis code of AMI (410.xx excluding 410.x2). Patients could enroll up to 60 days after discharge. Key exclusion criteria included diagnosis of metastatic cancer, end-stage renal disease with requirement of dialysis, dementia, or enrollment in other research studies incorporating electronic pill bottles.

Recruitment and Randomization

All eligible participants received recruitment letters, followed by up to 5 telephone calls from study staff. If eligible, participants were invited to participate and asked to complete the Patient Health Questionnaire-2 (PHQ-2).[6,7] After orally consenting, participants were randomized to intervention or control at a 2:1 ratio using variably sized permuted blocks stratified by insurance provider; the unbalanced randomization enabled the evidence-based evolutionary testing design, in which adjustments to the intervention could be implemented at the study midpoint.[8] Randomization was implemented via the Way to Health platform. All enrolled participants received $25 for participation. Participants in the intervention received an additional $25 for activating the pill bottles. Investigators and data analysts were blinded to arm assignment; patients were not

blinded. The study was approved by the Institutional Review Board of the University of Pennsylvania.

Study Outcomes

The primary outcome was time until first vascular readmission, defined as an inpatient hospitalization with a diagnosis of AMI, unstable angina, stroke, congestive heart failure, or death. Secondary outcomes were time until first all-cause readmission, total number of repeated hospitalizations, medication adherence, and total cost. Each of these measures was collected using claims data from our insurer partners. The study period coincided with a shift from inpatient hospitalizations to shorter "observation" stays; observation stays for myocardial infarction, heart failure, or pneumonia among fee-for-service Medicare beneficiaries nearly doubled from 2007 to 2015.[9] Observation stays are not clearly distinguishable from emergency department visits in claims data, nor are their diagnosis codes as clearly defined. For this reason, in post hoc analyses we also compared time to first readmission or observation stay for any cause and time to first readmission, observation stay, or emergency department visit for any cause.

Statistical Analysis

We measured study outcomes using medical insurance claims. We assessed hospitalization outcomes using place of service, discharge, diagnosis, revenue, and procedure[10] codes.[5,11] For patients on Medicare-type plans from any insurance provider, the Centers for Medicare & Medicaid Services provided a death file[12] to supplement deaths identified from insurance claim discharge codes. To determine lapses in insurance coverage, we used a membership file indicating whether patients had coverage in a given month; participants whose coverage ended were censored. Three insurers also provided deidentified claims data for potential participants who were sent a recruitment letter but did not enroll in our study. We used this reference group to evaluate the potential for selection bias during recruitment.

Medication adherence for medications other than aspirin (which is typically purchased over the counter) was estimated using proportion of days covered (PDC).[13,14] The PDC was calculated for the 12-month study period, including any prescriptions filled after index discharge with a supply extending into the study period. Because we did not know timing of prescription writing by clinicians, we used 3 methods to measure adherence. The strict definition assumed that patients were prescribed all 3 drugs for the entire study period. The relaxed definition assumed that patients were prescribed a medication from time of first fill until the end of the study period. Our intermediate definition assumed that patients had been prescribed a medication for the entire study period if they ever filled that medication after discharge. In addition to PDC for individual drug classes, we calculated a multiple-medication version in which adherence was achieved if a participant was covered by all 3 medication classes on a given day. Annual PDC was compared between arms using 2-sided *t* tests.

Time until first hospitalization or death was estimated using the Kaplan-Meier method[15]; arms were compared using log-rank tests[16] and unadjusted Cox proportional hazards models.[17] Adjusted hazard models included covariates for demographic characteristics, PHQ-2 score, insurer, and baseline Elixhauser scores[18] calculated using the 12 months of claims data prior to index discharge; adjustment was used to control for any small differences in these factors by treatment arm. Analyses incorporating repeated hospitalizations used the Andersen-Gill method.[19] The study was designed to have 80% power to detect a hazard ratio (HR) of 0.70, corresponding to a 6% decrease in the event rate.[5,10] $P \leq .05$ was considered statistically significant. Primary analyses used an intention-to-treat approach. Secondary analyses assessed per-protocol results to investigate the potential impact of nonadherence to intervention activities.

Subgroup analyses were performed assessing intervention impact among those readmitted between index discharge and study enrollment, and with specific demographic characteristics. Given the lack of standardized classification and to allow graphical exploration of effects, a median split was used to determine PHQ-2 and Elixhauser score categories. Annual total medical cost was the summation of allowed costs for the 12 months. Partitioned inversed probability weighting was used in cost analyses to account for data censoring.[20,21]

Analyses were conducted in SAS 9.4 (SAS Institute) and Stata 14.0 (StataCorp).

Results

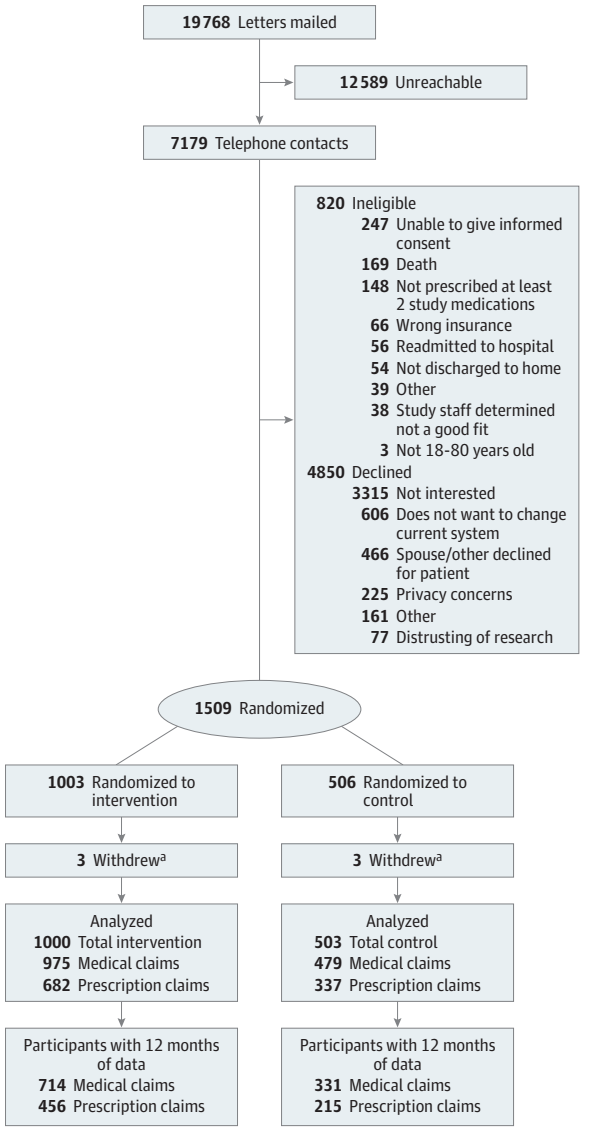
Patient Characteristics

Of 19 678 potentially eligible patients, 12 589 (64.0%) were unreachable, 820 (4.1%) were ineligible, and 4850 (24.5%) declined, leaving an enrolled sample of 1509: 1003 and 506 were randomized to the intervention and control groups, respectively (**Figure 1**). Within the intervention group, 878 (87.5%) set up electronic pill bottles and 701 (69.9%) enlisted a feedback partner. Twelve-month all-cause readmission was similar between the enrolled control population and the eligible but nonenrolled population, suggesting recruitment of a clinically representative population (HR, 0.93; 95% CI, 0.80-1.10; $P = .42$).

The mean (SD) time from index hospital discharge to enrollment was 40.8 (12.3) days. Participants came from 45 states and the District of Columbia; 533 (35.5%) were female; mean (SD) age was 61.0 (10.3) years; 624 (41.5%) were part of a Medicare insurance plan. Participant characteristics were similar across arms (**Table 1**). Six patients withdrew from the study.

Because some participants changed insurance coverage between index discharge and enrollment (making claims data inaccessible), we analyzed postenrollment medical claims for 1454 patients (96.7%); of these, 1045 (71.9%) had continuous insurance coverage for the year. We analyzed adherence among participants receiving prescription drug coverage from the same insurance company as their medical insurance (1019). Of these, 671 (65.8%) had continuous prescription coverage for 12 months after enrollment; 924

Figure 1. Consolidated Standards of Reporting Trials Diagram



[a] Reasons for withdrawal: 2 participants withdrew because they were unhappy that they were placed in the control group; 1 did not want to use the GlowCap device; 2 enrolled but later were concerned about confidentiality and withdrew; 1 was withdrawn by the study investigators due to concern about competency to consent.

Table 1. Patient Demographic Characteristics

Characteristic	Control (n = 503)	Intervention[a] (n = 1000)
Female sex, No. (%)	190 (37.8)	343 (34.3)
Age, mean (SD), y	60.6 (10.2)	61.2 (10.4)
Age group, No. (%), y		
18-34	4 (0.8)	7 (0.7)
35-49	74 (14.7)	147 (14.7)
50-64	254 (50.5)	447 (44.7)
≥65	171 (34.0)	399 (39.9)
Medicare, No. (%)	195 (38.8)	429 (42.9)
PHQ-2 score,[b] mean (SD)	1.3 (1.6)	1.3 (1.6)
Baseline Elixhauser score, mean (SD)	6.1 (9.3)	6.5 (10.0)
Time from index discharge to enrollment, mean (SD), d	41.3 (12.1)	40.6 (12.4)
Region, No. (%)		
Northeast	182 (36.2)	380 (38.0)
Midwest	71 (14.1)	153 (15.3)
South	208 (41.4)	391 (39.1)
West	42 (8.4)	76 (7.6)
With postenrollment claims, No.		
Medical claims	479	975
Prescription claims	337	682
With any study drug claim, No. (%)		
Before index discharge	194 (57.6)	408 (59.8)
Between index discharge and enrollment	309 (91.7)	615 (90.2)

Abbreviation: PHQ-2, Patient Health Questionnaire–2.

[a] There are no statistically significant differences between arms.

[b] Score ranges from 0 to 6. Due to protocol deviation, PHQ-2 scores were collected for only 500 control patients and 995 intervention patients.

(90.7%) filled a study drug between index discharge and enrollment; 762 (74.8%) filled all 3 drug classes (statins, β-blockers, antiplatelet agents) during the study. Data censoring due to insurance changes did not differ significantly by arm (HR, 0.86; 95% CI, 0.70-1.05; $P = .15$). Patients with data censoring were on average younger than patients with full coverage (mean [SD] age, 59.7 [10.2] vs 61.6 [10.4]; $P = .001$) and were less likely to be enrolled in Medicare (122 [29.8%] vs 495 [47.4%]; $P < .001$). They were similar with respect to sex (136 [33.3%] vs 377 [36.1%] female; $P = .31$), mean (SD) PHQ-2 score (1.30 [1.61] vs 1.27 [1.65]; $P = .73$), and mean baseline Elixhauser score (6.94 vs 6.11; $P = .15$).

Hospitalizations

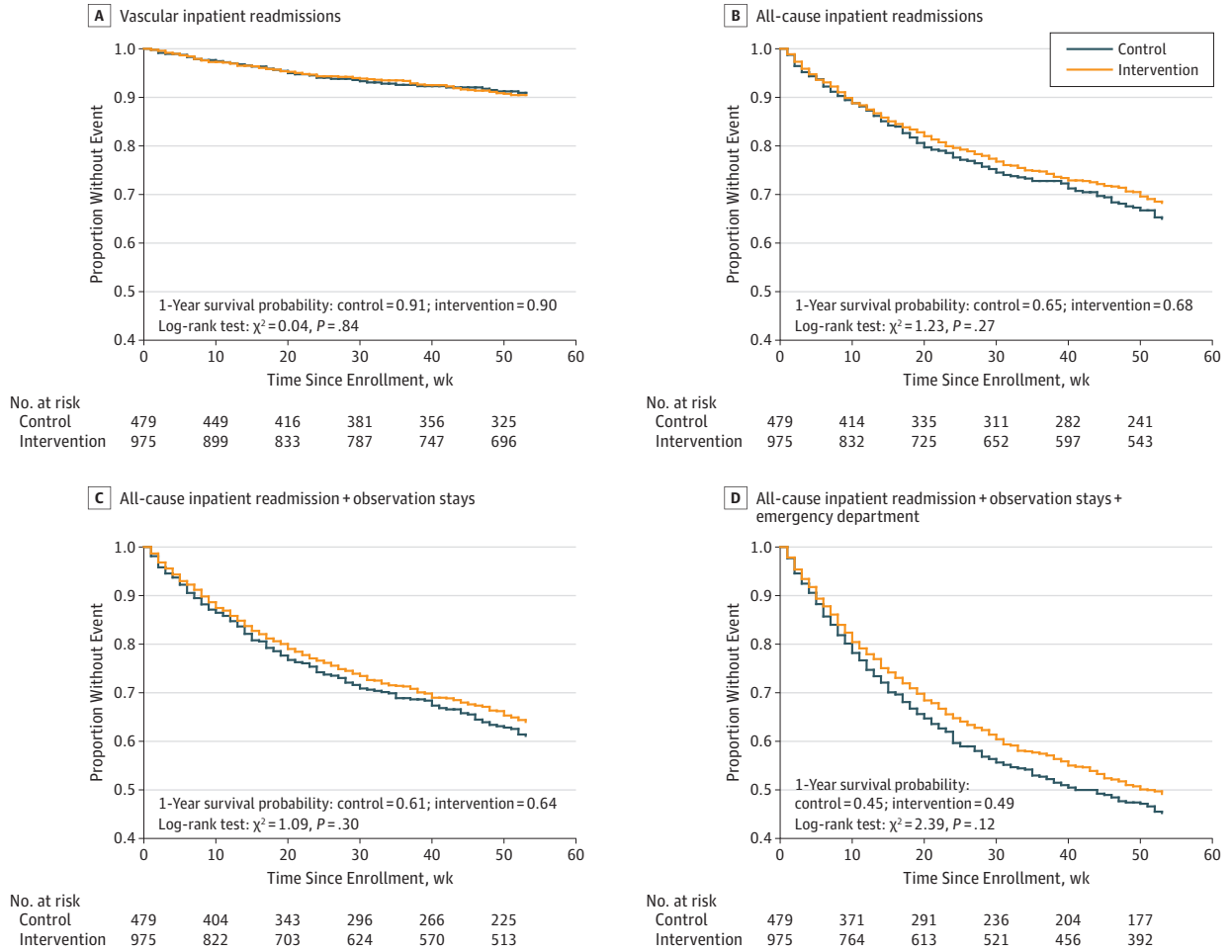
There was no statistically significant difference between arms in the prespecified primary outcome of time to first readmission for a vascular event or death (HR, 1.04; 95% CI, 0.71-1.52; $P = .84$) or the prespecified secondary outcome of time to first all-cause readmission (HR, 0.89; 95% CI, 0.73-1.09; $P = .27$) (**Figure 2**A and B and **Table 2**). There were also no statistically significant differences in time to first event when including observation stays (HR, 0.91; 95% CI, 0.75-1.09; $P = .30$) and emergency department visits (HR, 0.89; 95% CI, 0.76-1.03; $P = .12$) (Figure 2C and D and Table 2). Analyses including repeated primary outcome events showed no difference (HR, 0.94; 95% CI, 0.60-1.48; $P = .79$) (eTable 1 in Supplement 2).

Differences in effect were statistically insignificant for most subgroups, except among patients with low baseline Elixhauser scores. For the more inclusive event definitions, the intervention seemed more effective among patients with low PHQ-2 score, among men, and among those who experienced a readmission between discharge from index hospitalization and study enrollment (Table 2).

Medication Adherence

There were no significant differences in mean multiple-medication PDC between the control and intervention groups

Figure 2. Kaplan-Meier Curves for Hospitalization



using the strict (control = 0.42, intervention = 0.46; difference = 0.04; 95% CI, −0.01 to 0.09; P = .10) or relaxed (control = 0.63, intervention = 0.66; difference = 0.03; 95% CI, −0.02 to 0.08; P = .19) definition. There were no statistically significant differences between the 2 groups for adherence to individual drug classes, nor were there differences by demographic subgroups (**Table 3** and eTable 2 in Supplement 2).

Medical Spending

Mean (SD) annual medical spending in the 12 months following enrollment did not differ significantly between control ($29 811 [$74 850]) and intervention ($24 038 [$66 915]) (difference = −$5773; 95% CI, −$13 682 to $2137; P = .15). There were generally no significant differences by subgroup except among patients with low baseline mean Elixhauser score (difference = −9226; 95% CI, −17 653 to 798; P = .03) (eTable 3 in Supplement 2).

Per Protocol Analysis

A total of 701 intervention participants fully completed the protocol by both setting up electronic pill bottles and enrolling a partner. Per-protocol participants had lower mean (SD) PHQ-2 scores than intervention participants who did not follow protocol (1.19 [1.60] vs 1.44 [1.73]; P = .03) but were similar in terms of sex (228 [32.5%] vs 115 [38.5%] female; P = .07), mean (SD) age (61.5 [10.2] vs 60.7 [10.9] years; P = .30), Medicare enrollment (287 [40.9%] vs 142 [47.5%]; P = .06), and mean (SD) baseline Elixhauser score (6.30 [9.89] vs 6.82 [10.22]; P = .45). As given in eTable 4 in Supplement 2, these participants had superior outcomes to control with respect to both readmissions (all-cause inpatient hospitalization HR, 0.79; 95% CI, 0.63-0.99; P = .03) and mean (SD) adherence (0.48 [0.40] vs 0.42 [0.39]; P = .06). Mean (SD) annual medical spending was also lower compared with control ($21 239 [$57 611] vs $29 810 [$74 842], difference = −$8571; 95% CI, −$16 542 to −$601; P = .04).

Discussion

This study examined the effect of state-of-the-art behavioral economic approaches used in combination on medication adherence and readmissions following AMI.[22,23] We observed no statistically significant effect on medication adherence, hospitalization events of interest, or medical costs.

Table 2. Overall and Subgroup Hazard Ratios (HRs)

	Vascular Inpatient Readmission		All-Cause Inpatient Readmission		All-Cause Inpatient Readmission + Observation Stays		All-Cause Inpatient Readmission + Observation Stays + Emergency Department	
Category	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value
Overall								
Unadjusted	1.04 (0.71-1.52)	.84	0.89 (0.73-1.09)	.27	0.91 (0.75-1.09)	.30	0.89 (0.76-1.03)	.12
Adjusted[a]	0.93 (0.63-1.36)	.70	0.85 (0.70-1.04)	.12	0.88 (0.73-1.06)	.18	0.88 (0.75-1.03)	.11
Sex								
Male	1.23 (0.74-2.06)	.43	0.81 (0.63-1.05)	.12	0.82 (0.64-1.05)	.12	0.80 (0.66-0.98)	.03
Female	0.84 (0.48-1.50)	.56	1.06 (0.78-1.43)	.72	1.08 (0.81-1.43)	.61	1.07 (0.84-1.36)	.60
Age, y								
18-49	1.09 (0.33-3.52)	.89	0.81 (0.46-1.42)	.46	0.82 (0.49-1.39)	.46	0.82 (0.55-1.21)	.32
50-64	1.28 (0.69-2.41)	.43	0.96 (0.72-1.30)	.81	0.95 (0.72-1.25)	.70	0.90 (0.71-1.13)	.36
≥65	0.83 (0.49-1.41)	.49	0.84 (0.62-1.13)	.24	0.87 (0.66-1.16)	.36	0.89 (0.69-1.13)	.33
Medicare								
No	1.28 (0.61-2.68)	.51	0.92 (0.69-1.24)	.60	0.91 (0.69-1.19)	.49	0.90 (0.72-1.12)	.35
Yes	0.88 (0.57-1.38)	.58	0.83 (0.63-1.08)	.17	0.86 (0.67-1.11)	.25	0.84 (0.67-1.04)	.11
PHQ-2 score								
<2	1.06 (0.61-1.86)	.83	0.80 (0.62-1.04)	.10	0.84 (0.66-1.07)	.16	0.80 (0.65-0.98)	.03
≥2	0.99 (0.59-1.66)	.96	1.00 (0.74-1.36)	.98	0.99 (0.74-1.32)	.95	1.01 (0.79-1.29)	.93
Elixhauser score								
Less than median	0.65 (0.30-1.38)	.26	0.64 (0.46-0.90)	.01	0.71 (0.52-0.97)	.03	0.73 (0.57-0.94)	.01
Greater than median	1.17 (0.75-1.83)	.49	1.05 (0.82-1.35)	.69	1.02 (0.81-1.29)	.87	1.00 (0.81-1.22)	.97
Time from discharge to enrollment, d								
<40	1.07 (0.62-1.85)	.80	0.83 (0.63-1.10)	.19	0.83 (0.64-1.07)	.15	0.86 (0.69-1.07)	.17
≥40	1.01 (0.59-1.72)	.98	0.96 (0.73-1.28)	.81	1.00 (0.76-1.31)	.99	0.91 (0.73-1.14)	.42
Readmission prior to enrollment								
No	1.24 (0.77-1.99)	.38	0.94 (0.75-1.18)	.58	0.95 (0.77-1.17)	.64	0.88 (0.75-1.07)	.22
Yes	0.66 (0.34-1.25)	.20	0.68 (0.45-1.01)	.05	0.67 (0.46-0.99)	.04	0.77 (0.54-1.09)	.14

Abbreviation: PHQ-2, Patient Health Questionnaire–2.

[a] The adjusted model includes covariates for sex, age, Medicare enrollment, baseline PHQ-2 score, baseline Elixhauser score, and insurer.

Limitations

At the time of study design, there were many reasons to believe that the intervention might succeed. Aspirin, statins, β-blockers, and platelet blockers are known to reduce repeated vascular events in patients surviving AMI,[24-29] yet adherence to these medications is less than 50%.[10,30,31] Engagement strategies developed from principles of behavioral economics and new technologies have increased medication adherence in other settings,[3,23,32-39] and this study used a combination of the best approaches developed to date. Yet, we found no significant improvement in medication adherence among those assigned to the intervention and no improvement in clinical outcomes. Why not?

One possibility is that these strategies simply do not work in this setting. One lesson emerging from behavioral economics is the importance of subtle differences in framing and context; seemingly small factors, such as whether rewards are framed as gains or losses, often have outsized effects. Perhaps the multiple medications required or use of electronic pill bottles makes adherence daunting. Perhaps the goal of avoiding a subsequent AMI is maximally motivating, so that further efforts toward motivation are ineffective. Perhaps other patient concerns about potential adverse effects of these medications, such as impotence or fatigue, were not targeted by this engagement strategy.[40,41] This intervention was designed to mimic what health plans could do following an AMI hospitalization without any direct involvement of clinicians; perhaps that involvement is needed to better engage the difficult-to-engage patients. The context of post-AMI care may be different in as yet unperceived ways that make medication adherence different in this setting from others.

A second possibility is that the intervention might have worked if implemented earlier. We enrolled patients a mean of 40.8 days following index discharge—a delay necessitated by relying on insurance claims to identify eligible patients. Post hoc analyses suggest that patients who were already readmitted before joining our intervention did achieve lower subsequent readmission rates as a result of this intervention; these high-risk

Table 3. Annual Medication Adherence, Proportion of Days Covered (PDC)

	Control		Intervention			
Medication	No.	PDC, Mean (SD)	No.	PDC, Mean (SD)	Difference (95% CI)	*P* Value
Strict definition						
Statin	337	0.69 (0.36)	682	0.72 (0.35)	0.03 (−0.02 to 0.07)	.23
β-Blocker	337	0.67 (0.37)	682	0.69 (0.36)	0.02 (−0.03 to 0.07)	.38
Antiplatelet agent	337	0.61 (0.41)	682	0.64 (0.40)	0.03 (−0.20 to 0.08)	.25
All 3 medications[a]	337	0.42 (0.39)	682	0.46 (0.39)	0.04 (−0.01 to 0.09)	.10
Intermediate definition						
Statin	298	0.78 (0.27)	611	0.80 (0.26)	0.02 (−0.02 to 0.06)	.26
β-Blocker	297	0.76 (0.30)	606	0.77 (0.29)	0.02 (−0.02 to 0.06)	.38
Antiplatelet agent	267	0.77 (0.30)	558	0.79 (0.29)	0.01 (−0.03 to 0.06)	.54
All 3 medications[a]	246	0.58 (0.35)	516	0.61 (0.33)	0.04 (−0.01 to 0.09)	.16
Relaxed definition						
Statin	298	0.81 (0.26)	611	0.83 (0.25)	0.02 (−0.02 to 0.06)	.27
β-Blocker	297	0.80 (0.28)	606	0.81 (0.27)	0.02 (−0.02 to 0.05)	.43
Antiplatelet agent	267	0.80 (0.29)	558	0.81 (0.28)	0.01 (−0.03 to 0.05)	.50
All 3 medications[a]	246	0.63 (0.34)	516	0.66 (0.33)	0.03 (−0.02 to 0.08)	.19

[a] Calculated by the proportion of days in which a patient has an active medication for all 3 medications. It is not the weighted average of individual medication adherence.

patients might have been helped more had we reached them earlier (Table 2). Recruitment delay could be important if a particularly important time for interventions and follow-up after AMI[42] is in the first 4 to 6 weeks. In the 6 weeks after discharge, 15.9% were already readmitted, a substantial proportion of the 37.6% readmitted by 12 months after discharge.

A third possibility is that we might have seen significant clinical differences with different outcomes. Recent replacements of hospitalizations with shorter observation stays not included in the primary outcome could hide the benefits of the intervention. Indeed, we found that 49% of those patients in the intervention group avoided an inpatient, observation, or emergency department stay within 12 months compared with 45% of patients in the control group, a larger difference than when comparing just inpatient admissions, but one that remained statistically insignificant ($P = .12$). Readmission rates have been declining over time due to a variety of health system efforts nationwide, suggesting that those who are still readmitted may be the toughest cases in which to further lower readmission risk.

A fourth possibility is that current-generation electronic pill bottles need more design evolution to become easier to use to facilitate high rates of ongoing patient engagement.

A fifth possibility is that if everyone had followed our intervention as designed, we would have observed significant effects, as the per-protocol analysis found significant differences in outcomes between the intervention and control arms; an important limitation, however, is that there are likely selection effects in terms of who followed the intervention fully.

A sixth possibility is that the extensive clinical trial enrollment processes would naturally leave behind all but the most motivated AMI survivors—possibly those for whom the added engagement support provided by the intervention would be unnecessary. Nevertheless, clinical event rates among those eligible for the trial but unenrolled did not differ from enrolled patients assigned to the control arm, suggesting no such selection effects.

A final limitation is that we could not design the trial with sufficient power to detect small differences in adherence or costs because of the impracticably large sample size that would have been required.

Each of these considerations represents a possible study or intervention limitation. However, this study also has strengths. It was a large nationwide study with multiple insurance populations and participants from 45 states. It was also highly naturalized. With the exception of the consent procedures required for a research study that would not be required in clinical deployment, it represents a pragmatic trial with a largely untouched control group and clinically meaningful outcomes measured through existing data sources.

Conclusions

This study was undertaken with the promise that new approaches to patient motivation and new wireless technologies could together—in a scalable intervention that a health plan could run—produce improved medication adherence and thereby improve clinical outcomes among survivors of AMI. Despite this promise, the intervention neither significantly increased medication adherence nor significantly reduced the rate of vascular readmission. The fact that this intervention had negative results is important in highlighting that some of the approaches we might expect to significantly improve adherence do not in the context of a health plan–based intervention for patients after AMI. Despite this intervention's lack of success, further investigation in this area remains critical because the population value of therapeutic advances depends fundamentally on identifying ways to improve adherence to them.

ARTICLE INFORMATION

Accepted for Publication: April 23, 2017.

Published Online: June 26, 2017. doi:10.1001/jamainternmed.2017.2449

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Conflict of Interest Disclosures: Drs Volpp and Asch are principals and owners of VAL Health. Dr Volpp has served as a consultant for CVS Caremark and received grants from CVS Caremark, Hawaii Medical Services Association, Humana, Merck, Weight Watchers, and Discovery (South Africa). Dr Troxel serves on the Scientific Advisory Board of VAL Health. The authors who are employed by commercial insurance companies are salaried employees of these companies. Ms Levin and Mr Relish are salaried employees of Humana Inc. Dr Negin is a salaried employee of Horizon Blue Cross Blue Shield of New Jersey. Drs Smith-McLallen and Snyder are salaried employees of Independence Blue Cross. Dr Spettell is a salaried employee of Aetna. No other disclosures are reported.

Funding/Support: This trial was funded with a grant from Center for Medicare & Medicaid Innovation (CMS), Health Care Innovation Award 1C1CMS331009.

Role of the Funder/Sponsor: The funders had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Additional Contributions: Special thanks are due to the HeartStrong staff: Tirza Calderon, MPH, Center for Clinical Epidemiology and Biostatistics, University of Pennsylvania School of Medicine; Victoria Hilbert, MPH, Division of General Internal Medicine, University of Pennsylvania School of Medicine; Amanda Hodlofski, MPH, Medical Ethics and Health Policy, University of Pennsylvania School of Medicine; Christina Jameson, BA, Penn Medicine Center for HealthCare Innovation, University of Pennsylvania Health System; Devon Taylor, MPH, Medical Ethics and Health Policy, University of Pennsylvania School of Medicine. All contributors were research study staff and were compensated from the CMS funding source.

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