Evaluation of a Packaging Approach to Improve Cholesterol Medication Adherence

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ABSTRACT

OBJECTIVES: Elevated low-density lipoprotein cholesterol (LDL-C) is a major modifiable risk factor for cardiovascular disease, a leading cause of death in the United States. Our goal was to evaluate a simple, scalable, and affordable medication packaging method for improving cholesterol medication adherence and subsequently lowering LDL-C levels.

STUDY DESIGN: Mixed-method study.

METHODS: This mixed-method study involved US military veterans with LDL-C levels greater than 130 mg/dL and/or less than 80% refill adherence of cholesterol-lowering medication in the last 12 months; they were randomized to an education-only (control) group or an adherence packaging intervention group. Adherence packaging group participants' statin medication was provided in special blister packaging labeled for daily use that included written reminder prompts. Outcomes included 12-month cholesterol medication possession ratio (MPR) for medication refills; baseline, 6-, and 12-month self-reported cholesterol medication use; LDL-C and high-density lipoprotein cholesterol (HDL-C) levels; and total cholesterol changes over 12 months. Qualitative evaluation of the intervention is presented as well.

RESULTS: We enrolled 240 individuals (120 intervention, 120 control). Overall, 54.2% of the adherence packaging intervention group was adherent per MPR over 12 months compared with 46.6% of the education-only group (difference = 7.6%; 95% confidence interval, −5% to 20%; $P \leq .24$). Both arms reported improvements in self-reported cholesterol adherence at 12 months, and decreases in LDL-C, HDL-C, and total cholesterol were observed, but differences in change between arms were not statistically significant. Qualitatively, patients reported high levels of satisfaction with the blister package.

CONCLUSIONS: In a sample of US veterans, prefilled calendared blister packaging provided an inexpensive method for improving cholesterol medication adherence.

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Elevated low-density lipoprotein cholesterol (LDL-C) is a major modifiable risk factor for cardiovascular disease (CVD).[1] Because of the health implications of hyperlipidemia, developing strategies to reduce LDL-C is critical. CMS established a quality goal for Medicare Part D members who are prescribed statin medications for hyperlipidemia: filling their prescriptions often enough to cover 80% or more of the time they are supposed to be taking the medication.[2] The Department of Veterans Affairs (VA) healthcare system has adopted a similar guideline for pill refill quality.[3] Unfortunately, many veterans do not achieve preferred LDL-C levels.[4]

One strategy to promote better medication adherence is calendared blister packaging. It may make taking medication more convenient for patients by eliminating issues associated with traveling with medication and with forgetting whether medications have been taken on a particular day.[5,6] Additionally, this packaging approach may streamline health professionals' monitoring of patients' statin medication adherence. A patient's provider, caregiver, and/or pharmacy staff could examine a patient's blister packaging and straightforwardly assess whether and when a patient has taken their medication.

We sought to evaluate the efficacy and clinical effectiveness of a relatively inexpensive prescription medication calendared blister packaging approach. We hypothesized that this packaging would improve medication refill rates relative to a control group receiving only cholesterol education.

METHODS

Study Overview

The study included users of the VA healthcare system at risk for CVD, defined as having an LDL-C level greater than 130 mg/dL and/or having less than 80% cholesterol medication refill in the previous 12 months.[7]

Sponsorship was provided by a grant from WestRock/MeadWestvaco and the study was approved by the Durham VA

Medical Center Institutional Review Board (clinicaltrials.gov registration number: NCT01744977).

Sample Identification and Eligibility Criteria

To be eligible for study inclusion, patients had to meet all of the following criteria: enrolled in 1 of 3 primary care clinics affiliated with the Durham VA Medical Center for at least 1 year; had at least 1 visit to their primary care provider in the previous 12 months; had an outpatient diagnostic code for hypercholesterolemia; had uncontrolled LDL-C in the last 12 months (average >130 mg/dL) and/or poor cholesterol medication refill history, defined as lower than 80% medication adherence in the last 12 months; and be prescribed 20- or 40-mg daily doses of simvastatin, rosuvastatin, or pravastatin. The study statistician identified patients meeting initial inclusion criteria and randomly sampled potential participants for additional screening and study recruitment.

TAKEAWAY POINTS

- Overall, 54.2% of the adherence packaging intervention group was adherent per medication possession ratio over 12 months compared with 46.6% of the education-only intervention (difference = 7.6%; 95% confidence interval, $P \leq .24$).
- The potential impact of a relatively inexpensive and highly scalable method for improving adherence should be further considered.
- Packaging interventions provide a mechanism for patients to self-monitor medication consumption and provide a method for remembering whether a given dose has been consumed.
- In a sample of US veterans, pre-filled calendared blister packaging provided an inexpensive method for improving cholesterol medication adherence.

Recruitment and Randomization Procedure

Patient recruitment took place between February 2013 and April 2014. Based on appointment information in the electronic health record, study staff identified participants who had an upcoming medical appointment scheduled in the next 2 to 3 weeks. An introductory recruitment letter, signed by the patient's primary care provider, was sent to potential participants. Approximately 1 week after the introductory letter was mailed, study staff called potential participants to determine whether they met eligibility criteria. For interested and eligible patients, an in-person interview was scheduled. Patients were sent reminder letters up to 3 weeks prior to their scheduled 6- and 12-month follow-up appointments. During the initial in-person interview, patients were presented with full details of the study and provided written informed consent.

The statistician completed the study randomization prior to the study. Once a patient consented and completed the baseline assessment, the research assistant randomized the patient to 1 of the 2 groups: 1) education-only or 2) adherence packaging intervention. A blocked randomization technique was used to ensure rolling balance between study arms. To prevent contamination, research assistants were blinded to block size. A centralized computer process that integrated into the tracking database determined randomization assignments. The study flow is described in the **Figure**.

Baseline Patient Assessment and Follow-up Contacts

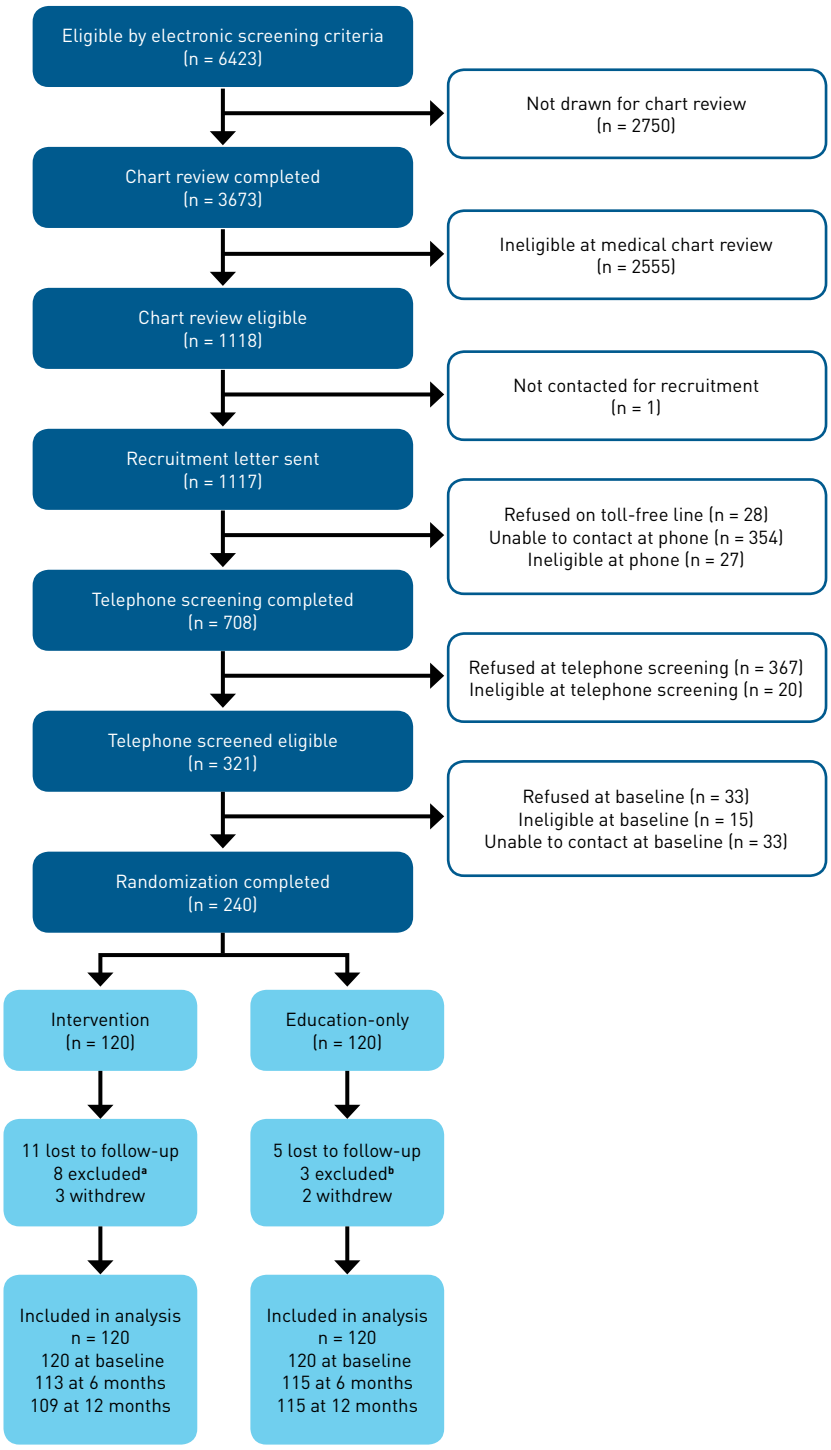
Participants completed assessments at the baseline, 6-month, and 12-month visits, plus during 1 optional qualitative, a telephone-based interview at the conclusion of the study. During the patient assessments, laboratory values (ie, lipids) were obtained. Participants also underwent an in-person baseline interview, which collected each patient's age, race, medical history, self-reported statin medication adherence, health beliefs and knowledge, and understanding about CVD risk. Additionally, during the 12-month visit, 30 of those randomized to the intervention arm were asked about perceptions of the study packaging. In addition to reviewing VA medical records for adverse events, patients were asked about such events at each follow-up visit.

Adherence Packaging Intervention Arm

Adherence packaging participants' medications were provided in a special packaging, the WestRock/MeadWestVaco Corporations' prefilled Dosepak Express with Optilock Technology, which contained standard dose statins. The calendar blister packaging medication flow (ie, prescription fill and refill process) is described in a prior publication.[7] Prepackaged calendar blister packages of 20- or 40-mg tablets of simvastatin, pravastatin, or rosuvastatin were provided to participants in accordance with their existing prescription. If patients were taking a half-tablet of statin medication prior to study enrollment, the investigational drug pharmacy service kept the participant's current dose but provided it in a whole tablet. Over the course of the study, the study staff did not change patients' medications; however, as part of their usual care, a participant's primary care provider may have adjusted medications during the course of the study. In this instance, the calendar blister package contents would change accordingly. Each package was labeled with the preapproved cholesterol education material, and the medication name and dose were labeled for each batch of medication received into pharmacy.

When an adherence packaging participant presented to pharmacy services, they received a 3-month supply of their standard-dose cholesterol medication in the calendar blister package. Following the baseline assessment, adherence packaging patients reported to the VA study pharmacy for their first medication fill, and the pharmacist: 1) counseled the patient on the appropriate use of the calendar blister package (how to open it and use the calendar feature), 2) reviewed the counseling points for statins included on the package, and 3) reviewed how to obtain subsequent refills. Each medication fill

FIGURE. Study Flow



[a]Reasons for exclusion were: no longer receiving care at Durham VA; died; diagnosed with dementia; prolonged hospitalization; no longer on study medication; lost to follow-up; dropped out.

[b]Secondary outcome lab measures were missing for 1 intervention subject at the 6-month follow-up and for 1 education-only subject at baseline. Morisky adherence was missing for 1 intervention subject at both the 6- and 12-month follow-ups.

for enrolled patients was labeled by pharmacy staff, checked for accuracy, and dispensed by a registered licensed pharmacist.

Participants in the adherence packaging group were contacted for an optional telephone-based qualitative interview within 30 days after their final in-person interview. The objective of the qualitative interview was to evaluate participants' perception of the study packaging and evaluate the successes and challenges of the program.

Education-Only Arm

The health education-only (control) group received primary care and management of LDL-C according to the discretion of their regular primary care provider. These patients received generic educational information on LDL-C reduction and had no contact with the research pharmacist. Additionally, the control group received written information on how to obtain medication refills and the importance of taking their cholesterol medications as prescribed. At follow-up study appointments, patients were provided with further educational material addressing issues of hyperlipidemia.

Using a health education group as a control enabled an assessment of the cost benefit of the intervention and is comparable with care typically provided in a traditional VA primary care clinic setting. Patients in the education-only arm did not receive their medication in the special packaging. Veterans randomized to the education group did not have any changes to the way they received their cholesterol medication from the study staff, but healthcare providers made changes as they would ordinarily do, for any medical reasons that arose. Individuals in the education arm typically received a 3-month supply, but they used the standard VA mechanism for refills (centralized mail, not the local VA pharmacy).

Compensation

Participants were paid $20 for participation in each interview (eg, baseline, 6-month, 12-month outcome, and qualitative). Therefore, individuals could receive a maximum compensation of $80.

Measures

Using a single-item measure, participants were asked to describe their household's current financial situation.[7] A binary measure was created. Patients who reported cutting back on their expenditures or having difficulty paying bills were coded as having inadequate financial status.

Health literacy was assessed using the Rapid Estimate of Adult Literacy in Medicine (REALM) test.[8] Low health literacy was defined as a REALM score up to and including 8th grade (≤60 score) versus 9th grade or higher (≥61 score).[9]

Outcomes and Statistical Methodology

The primary analysis examined whether veterans who received the intervention had greater cholesterol medication adherence as measured by medication possession ratio (MPR) at 12 months of follow-up compared with the education group. MPR was calculated as the days supplied divided by the days in the calculation period (ie, 365 days). A Wilcoxon Rank Sum test was used to compare median MPR between the 2 groups. MPR as a continuous measure had a ceiling effect at 1 and spikes in the data distribution at 0.25, 0.50, and 0.75. For this reason, we created a dichotomous categorical variable using MPR at 12 months (adherent [MPR ≥99%] vs nonadherent [MPR <99%]). A c^2 test was used to compare adherence between the 2 groups.[10]

The secondary clinical outcome measures were LDL-C, total cholesterol, and high-density lipoprotein cholesterol (HDL-C) levels obtained from a nonfasting lipid profile. We also measured self-reported medication adherence, specifically to lipid-lowering medications, using a valid, reliable measure.[11] Secondary analyses evaluated whether veterans who received the adherence packaging intervention had improved LDL and total cholesterol levels, as well as self-reported cholesterol medication adherence, compared with the education-only group, over 12 months of follow-up.

Group differences in lipid levels over time were evaluated using general linear mixed model equations. Unconstrained models were initially run for each measure, and the mean baseline measures were compared between the adherence packaging intervention and education-only groups.[11] When nonsignificant, the model was then constrained to make both groups equal at baseline. Dummy-coded variables for time at 6 and 12 months and interactions between time and randomization status were included in each model. An unstructured covariance matrix was selected to account for the correlation between repeated measures on the same subject.

Group differences in self-reported adherence over time were evaluated using a generalized estimating equation with a logit link function and unstructured covariance matrix. As with the general linear mixed model, an unconstrained model was initially run, and when the baseline was found to be not significantly different between the 2 groups, a constrained model was used to obtain estimates.

Qualitative analyses were used to evaluate challenges and successes of the intervention. To formally evaluate the process of implementation of the adherence packaging intervention, we conducted a summative evaluation at 12 months. This was used to gather insights from patients who participated in the intervention program. We randomly selected participants to interview at 12 months and interviewed 10 individuals.

RESULTS

We sent 1117 recruitment letters and completed telephone screening on 708 individuals, which resulted in the identification of 321 eligible potential participants. Five individuals refused to participate at baseline and of the 240 patients who consented for the study, we randomized 120 to each arm and completed the baseline assessment. The sample was, on average, approximately 62 years of age and a majority of individuals were African American, male, married/cohabitating, and had completed 12 or more years of education (**Table 1**). Approximately 30% of participants had a low health literacy level and 20% reported financial strain. At baseline, 68% of the adherence packaging intervention group and 70% of the education-only group reported they had not been adherent with their cholesterol medication in the last month. However, refill rates were greater than 75% for both intervention and controls at baseline.

Adherence

Median MPR at 12 months was greater than or equal to ≥0.99 for the adherence packaging group and 0.94 for the education-only group (P = .30). In terms of the dichotomous measure of MPR adherence, 54% of the adherence packaging intervention group were adherent with their refills over 12 months compared with 47% for the education-only group (**Table 2**). There was a 7.6% greater refill rate by the adherence packaging intervention arm than by the education-only arm (P = .24; 95% confidence interval [CI], −5% to 20%).

Both arms reported improvement in self-reported adherence over the 12 months (**Table 3**). The difference in self-reported adherence by arm was not significant (odds ratio, 0.75; 95% CI, 0.47-1.19) (Table 3).

Clinical Outcomes

Decreases in LDL-C, HDL-C, and total cholesterol were observed for both the adherence packaging intervention arm and the education-only arm, but these differences were nonsignificant (Table 3).

Evaluation of the Blister Package

Among a random subset of individuals who received the adherence packaging intervention and were asked to evaluate aspects of the blister packaging (n = 30), the ratings were high on a scale of 1-10:

TABLE 1. Baseline Characteristics and Primary and Secondary Outcomes at Baseline

Baseline Characteristics[a]	Total (n = 240)	Randomization Group	
		Intervention (N = 120)	Education-Only (n = 120)
Demographics			
Age, years: mean (SD)	62.6 (8.7)	62.4 (8.9)	62.9 (8.6)
Race			
Caucasian	88 (36.7)	47 (39.2)	41 (34.2)
African American or other	152 (63.3)	73 (60.8)	79 (65.8)
Male	219 (91.3)	109 (90.8)	110 (91.7)
Marital status[b]			
Married/living together	134 (55.8)	70 (58.3)	64 (53.3)
Divorced/separated/ widowed/never married	105 (43.8)	50 (41.7)	55 (45.8)
Education			
Completed ≤12 years of school	81 (33.8)	36 (30.0)	45 (37.5)
Low literacy level (REALM score ≤60)			
Yes, low health literacy	82 (34.2)	35 (29.2)	47 (39.2)
Inadequate income[c]			
Yes	51 (21.3)	31 (25.8)	20 (16.7)
No	189 (78.8)	89 (74.2)	100 (83.3)
Primary Outcome			
Medication possession ratio, median (IQR)	0.78 (0.4)	0.76 (0.4)	0.79 (0.4)
Secondary Outcomes[d]			
Total cholesterol, mean (SD)	186.9 (46.5)	185.5 (50.8)	188.3 (42.0)
LDL cholesterol, mean (SD)	110.8 (35.4)	110.1 (38.8)	111.6 (31.7)
HDL cholesterol, mean (SD)	46.8 (16.9)	46.3 (15.6)	47.4 (18.3)
Cholesterol medication self-rated adherence			
Adherent	75 (31.3)	39 (32.5)	36 (30.0)
Nonadherent	165 (68.8)	81 (67.5)	84 (70.0)

HDL indicates high-density lipoprotein; IQR, interquartile range; LDL, low-density lipoprotein; REALM, Rapid Estimate of Adult Literacy in Medicine; SD, standard deviation.
[a]Numbers are n (%) unless otherwise indicated.
[b]One missing value in the education-only group.
[c]Inadequate income was defined as a participant reporting: 1) difficulty paying bills no matter what was done or 2) having money to pay bills only because they cut back on spending.
[d]One education-only subject had missing data for all cholesterol measures.

overall quality of the package (mean = 9.23; standard deviation [SD] = 1.59), ease of opening (mean = 8.43; SD = 2.33), dispensing the cholesterol medication (mean = 9.00; SD = 2.02), and served to help individual to remember if they already took their cholesterol medication (mean = 8.53; SD = 2.52).

Qualitative

The 10 patients interviewed reported that the use of the blister packaging was beneficial and would recommend it to others, noting that the packaging kept the pills from breaking, kept them clean/uncontaminated, and provided a clear reminder of whether they had remembered to take the medication on a given day. Also, patients reported seeing when they were nearing the end of medication, which prompted them to re-order. Individuals also reported appreciating that their medication came in full tablets and that they did not having to worry about possible inaccuracies when splitting tablets.

Three of the 10 participants reported having difficulty in removing the inner medication card from the outer packaging component (American Society for Testing and Material child-resistant feature) and then removing the pill from the blister cavity; they felt they had to push hard and "fight" to remove it, citing arthritis/age as their reason. For some, adherence was more challenging if they used a pillbox for some medications and the calendar blister packaging for the statin medication. Patients liked the convenience of calendar blister packaging, but were not particularly receptive to potentially paying more for it; they felt a small increase might be acceptable but that it really should be about the same cost as standard packaging, or they would want to know the true price of packaging before making a determination.

DISCUSSION

Given the number of individuals at risk for CVD and who have inadequately controlled cholesterol levels[12] and poor refill rates of cholesterol-lowering medications, low-cost interventions that are potentially easy to administer, such as calendar blister packaging, may be useful, especially for those with particular challenges regarding forgetfulness. In the current study, there was a 7.6% improvement in refill rates of the adherence packaging intervention arm over the education-only arm (95% CI, −0.05 to 0.20). However, these improvements in refill rates did not translate to decreases in LDL-C, HDL-C, and total cholesterol.

Our results are consistent with a recent meta-analysis, in which the overall mean weighted standardized difference effect size for 2-group comparisons was 0.593 (favoring treatment over control); this is consistent with the mean of 71% adherence for treatment subjects compared with 63% among control subjects.[5] There are several reasons packaging interventions may be effective at

improving medication adherence. Packaging interventions provide a mechanism for patients to self-monitor medication consumption. Difficulty remembering whether a certain dose had been consumed is an important aspect of forgetting medications—it is the most often patient-reported reason for nonadherence.[13,14] Packaging also allows third parties, such as informal and home-visiting formal caregivers, to use the device to monitor doses taken or not taken.[5] The cost differential of the blister packaging is closely related to volume and typically ranges from $0.10 to $0.25 more than traditional medication bottles.

A key strength of our study was in addressing the efficacy of this innovative prescription calendared blister packaging in a diverse patient population. Selected clinics serve a large African American population, which enabled the recruitment of a racially diverse sample.

Limitations

Although the specific definition of elevated LDL-C and the guidelines for CVD risk reduction continue to evolve, there is growing emphasis on the importance of statin therapy for individuals with high CVD risk.[1] These changing definitions occurred while our study was ongoing—a potential limitation of the study. Despite this definitional change, nonadherence with statin therapy for elevated LDL-C remains a serious issue.

An additional limitation is that during the study enrollment period, the VA National Formulary adjusted its coverage of rosuvastatin. Unless clinically contraindicated, patients prescribed rosuvastatin were converted to atorvastatin. Our study included patients prescribed rosuvastatin, not atorvastatin, potentially reducing the sampling pool of eligible patients. Providers could choose to keep patients on rosuvastatin despite it not being on the formulary. Systemwide conversion of all patients on rosuvastatin limited recruitment or created challenges during study participation. Second, some providers did not acknowledge the Research Clinical Warning (a marker indicating that the individual was participating in a trial) in the medical record. Thus, some providers changed their patients' statin medications without notifying study personnel to see if the study could accommodate medication or dosage change. In addition, some providers separately ordered patients' nonpackaged statin medication, leading to the potential for duplicate orders and confusion for the patient as to which medication they should be taking. Third, cholesterol management guidelines changed from a targeted LDL-C goal level to being on a recommended statin regimen. Fourth, the process for the adherence packaging intervention group to obtain their cholesterol medication may have been more onerous than for those in the education-only arm because adherence packaging patients were required to use a different phone number than the traditional refill number used for their other medications.

TABLE 2. Twelve-Month Outcome Medication Possession Ratio

	Total (n = 238)	Randomization Group		P[a]
		Intervention (n = 120)	Education-Only (n = 118)	
MPR, median (IQR)	0.99 (0.3)	0.99 (0.3)	0.94 (0.4)	.300
MPR ≥99%: n (%)	120 (50.0)	65 (54.2)	55 (46.6)	.244

IQR indicates interquartile range; MPR, medication possession ratio.
[a]*P* value for continuous MPR derived from Wilcoxon Rank Sum test. *P* value for categorical MPR derived from χ^2 test.

TABLE 3. Model Results for Secondary Outcomes

	Intervention	Education-Only		
	Predicted Mean	Predicted Mean	Difference (95% CI)	P[a]
Total cholesterol				
Baseline	186.9	186.9		
6 months	173.7	179.0	−5.4 (−14.7 to 4.0)	.259
12 months	172.5	172.5	−0.0 (−9.2 to 9.2)	.996
LDL cholesterol				
Baseline	110.8	110.8		
6 months	101.4	105.3	−3.9 (−10.4 to 2.7)	.244
12 months	101.3	102.1	−0.7 (−8.0 to 6.5)	.839
HDL cholesterol				
Baseline	46.8	46.8		
6 months	45.3	45.6	−0.3 (−2.5 to 1.9)	.803
12 months	46.3	46.1	0.1 (−2.0 to 2.3)	.905
	Predicted Probability	Predicted Probability	Odds Ratio (95% CI)	P[b]
Cholesterol medication self-rated adherence[11]				
Baseline	.31	.31		
6 months	.41	.33	1.41 (0.90 to 2.23)	.137
12 months	.39	.46	0.75 (0.47 to 1.19)	.219

CI indicates confidence interval; HDL, high-density lipoprotein; LDL, low-density lipoprotein.
[a]Predicted means, mean differences, confidence intervals, and *P* values were derived from general linear mixed models with unstructured covariance matrices.
[b]Predicted probabilities, odds ratios, confidence intervals, and *P* values were derived from a generalized estimating equation with a logit link function.

CONCLUSIONS

The findings of this study may have important clinical implications. Although the impact of the blister packaging seen in this study was less than we anticipated, blister packaging was well accepted. Its potential impact as a relatively inexpensive and highly scalable method for improving adherence should be further considered. ■

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