# Behavioral Nudges as Patient Decision Support for Medication Adherence: The ENCOURAGE Randomized Controlled Trial

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**Background** Medication adherence is generally low and challenging to address because patient actions control healthcare delivery outside of medical environments. Behavioral nudging changes clinician behavior, but nudging patient decision-making requires further testing. This trial evaluated whether behavioral nudges can increase statin adherence, measured as the proportion of days covered (PDC).

**Methods** In a 12-month parallel-group, unblinded, randomized controlled trial, adult patients in Intermountain Healthcare cardiology clinics were enrolled. Inclusion required an indication for statins and membership in SelectHealth insurance. Subjects were randomized 1:1 to control or nudges. Nudge content, timing, frequency, and delivery route were personalized by CareCentra using machine learning of subject motivations and abilities from psychographic assessment, demographics, social determinants, and the Intermountain Mortality Risk Score. PDC calculation used SelectHealth claims data.

**Results** Among 182 subjects, age averaged 63.2±8.5 years, 25.8% were female, baseline LDL-C was 82.5±32.7 mg/dL, and 93.4% had coronary disease. Characteristics were balanced between nudge ($n = 89$) and control arms ($n = 93$). The statin PDC was greater at 12 months in the nudge group (PDC: 0.742±0.318) compared to controls (PDC: 0.639±0.358, $P = 0.042$). Adherent subjects (PDC ≥80%) were more concentrated in the nudge group (66.3% vs controls: 50.5%, $P = 0.036$) while a composite of death, myocardial infarction, stroke, and revascularization was non-significant (nudges: 6.7% vs control: 10.8%, $P = 0.44$).

**Conclusions** Persuasive behavioral nudges driven by artificial intelligence resulted in a clinically important increase in statin adherence in general cardiology patients. This precision patient decision support utilized computerized nudge design and delivery with minimal on-going human input. (Am Heart J 2022;244:125–134.)

Both clinician and patient actions are keys to high-quality, low-cost, effective healthcare. Human behavior constitutes the primary mode for activating improvements in health,[1] including decisions made by a clinician and choices made by a patient. Unfortunately, human decisions are not always perfectly rational.[2] In medical practice, clinician decisions can be gently nudged to improve decision-making by providing an architecture in which optimal default clinical actions are suggested for ease of implementation.[1,3] Outside of controlled environments (eg, intensive care unit or physician clinic), however, patient actions primarily determine health outcomes.[4]

Patient adherence with taking evidence-based prescriptions determines the impact on their health, and medication non-adherence impedes the achievement of optimal health outcomes in a large segment of the population. Furthermore, adherence with medications is further impeded for prescriptions that are not treating acute symptomatic diseases since no event or symptoms have triggered patient concerns. Adherence rates for medications are low: around 40% – 50% for statins, beta-blockers, angiotensin converting enzyme inhibitors, and

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angiotensin receptor blockers.[5-8] Non-adherence hinders clinicians' efforts, the reported benefits of clinical trials, and benefits from other patient choices, whereas adherence to evidence-based medications produces health improvements, reduces major adverse cardiovascular events (MACE), and lowers healthcare costs.[6,9,10]

Many medication management tools exist that were created to aid patients, but as currently proposed and applied may not improve adherence.[11] One meta-analysis suggested that a heterogeneous array of methods may modestly improve adherence,[12] but substantial variation of results exists between the examined studies. Whether any given method consistently improves adherence is unclear and the majority of reported studies used self-reported adherence,[12] which is of questionable reliability. Frequent text messaging may reduce surrogate outcomes such as cholesterol or hemoglobin A1c,[13-15] but what caused those changes is uncertain and may simply be because patients were being observed (the "Hawthorne effect").[16]

A nudge is positive structuring of choice architecture to alter behavior in a predictable way without forbidding alternative choices and that is easy and cheap to avoid.[17] This trial tested whether infrequent persuasive behavioral nudges, personalized to individual needs by psychographic profiling and patient health status, can increase adherence to statins.

## METHODS

The improvEment in medicatioN adherenCe thrOUgh the implementation of peRsonAlized nudGEs (ENCOURAGE) trial was a 12-month unblinded randomized, controlled trial that enrolled adult general cardiology patients who were seen in the outpatient clinics at Intermountain Medical Center. The purpose of the trial was to evaluate whether electronic nudges improved adherence to statin medication prescriptions beyond the standard care process. Qualifying outpatient subjects were randomized 1:1 by permuted block design using sequentially numbered envelopes by a clinical research coordinator to a nudge intervention (including standard medical care) or to a parallel control consisting solely of standard medical care. This trial was registered with ClinicalTrials.gov prior to initiation of enrollment (NCT02490423). Ethics approval for the trial was provided by the Intermountain Healthcare Institutional Review Board. All subjects provided written informed consent to participate and the study was conducted according to the principles of the Declaration of Helsinki. The ENCOURAGE trial was funded by the Intermountain Research and Medical Foundation (#752), an in-kind donation from CareCentra, and internal departmental funds. The authors are solely responsible for the design and conduct of this study, all study analyses, the drafting and editing of the paper and its final contents.

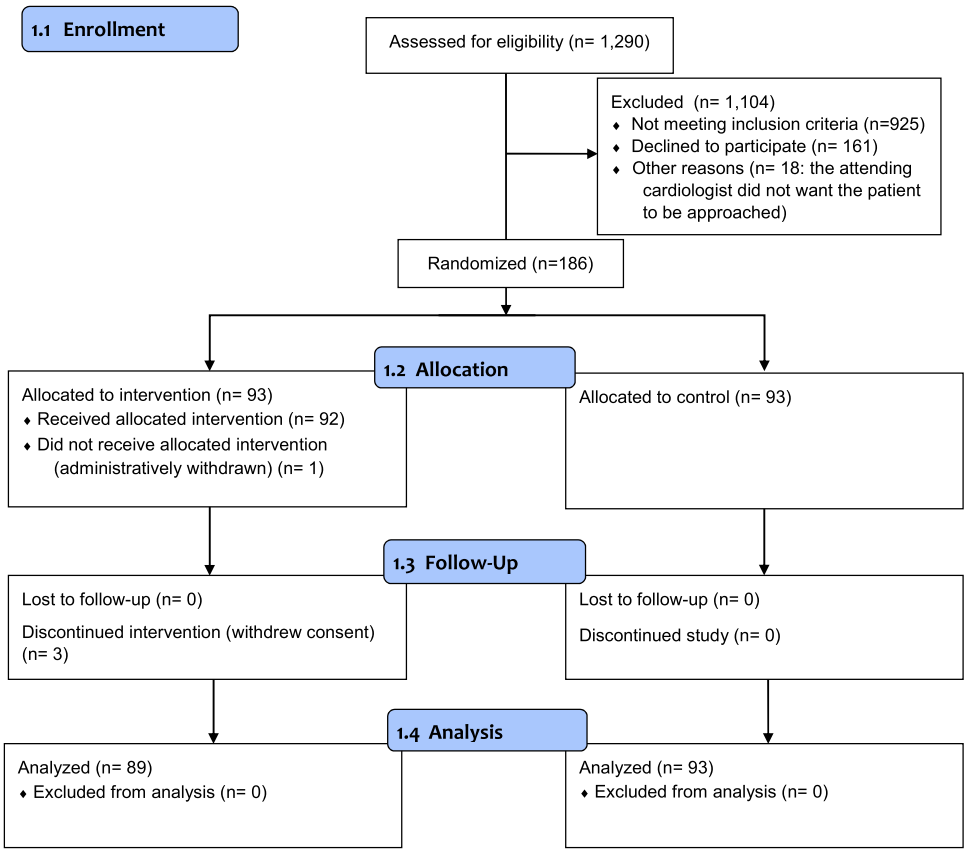
Potential participants were adults aged ≥18 years with a statin indication (regardless of statin use history) who were enrolled in a SelectHealth insurance plan. SelectHealth is the health insurance arm of Intermountain Healthcare and approximately 20% of Intermountain cardiology patients are SelectHealth members. Use of SelectHealth data empowered passive electronic surveillance of medication prescription use through claims data. The study informatician accessed SelectHealth prescription data such as medication name, date of filling of a prescription, refill frequency, and number of pills dispensed for each claim. The primary reason for exclusion from the trial was not having SelectHealth insurance, hence the large ineligible population (Figure 1). As per clinical guidelines,[18] an indication for statins was: 1) having a new or existing coronary artery disease (CAD) diagnosis, 2) having a low-density lipoprotein cholesterol (LDL-C) ≥190 mg/dL, 3) being 40 – 75 years of age and having a diabetes diagnosis and LDL-C =70-189 mg/dL, or 4) being 40 – 75 years of age and free of atherosclerotic cardiovascular disease (ASCVD) and diabetes, or having an LDL-C of 70-189 mg/dL with ≥7.5% 10-year risk of ASCVD.[19] Subject demographics, risk factors, comorbidities, inclusions, and exclusions were collected at enrollment using a combination of patient interview, a study-related physical exam, and verification of data available in the electronic health record. Where necessary, a lipid panel was conducted at baseline to evaluate inclusion criteria. Race and ethnicity were self-reported at enrollment.

Trial exclusions were: contraindication to statin medications, prior diagnosis of dementia, palliative care, discharge to hospice, inpatient rehabilitation, skilled nursing facility, or long-term care. Potential subjects were also excluded if the complete blood count or basic metabolic profile was unavailable for calculating the Intermountain Mortality Risk Score (IMRS).[20] IMRS is a sex-specific clinical laboratory-based decision tool created from the prognostic information in the complete blood count, basic metabolic profile, and age.[20] IMRS provides a quantitative, objective assessment of general health status that is widely validated,[20-22] and clinically utilized.[23]

### Nudge intervention

Subjects randomized to the nudge intervention received standard cardiovascular care from their physician in addition to behavioral nudges. Subjects randomized to the control arm received only standard cardiovascular care and were not contacted by study personnel between enrollment and 12 months. Nudges were developed and delivered by the person-centered engagement platform of CareCentra (New York, NY). Nudge personalization was performed using data from a psychographic profile, baseline IMRS, social determinants of health, and other baseline demographics. The psychographic profile surveyed a subject's beliefs, perceptions, attitudes, pref-

**FIGURE 1**




CONSORT flow diagram for the ENCOURAGE Trial.

erences, and understanding of their health, the healthcare system, and their ability to impact their health as well as social determinants of health (Supplemental Table S1) and was collected electronically using a tablet at the time of enrollment. Nudge personalization was intended to provide a greater level of positive and meaningful contact to achieve the intended effect and to limit the concerns and alert fatigue a contact may induce. Nudges were not personalized to statin medications or any specific therapy, but rather to people by directing modifications of a person's environment at home and elsewhere such that their prescriptions were more integrated into the daily flow of living and, thus, adherence would be easier because following through required less thinking, planning, or action than usual. The nudges were not expected to modify statin adherence better than for other medications and the trial was not powered to find a significant difference between nudge and control for medications prescribed to fewer than the full sample size. However, statins were chosen as the focus for various reasons including to have a large proportion of the general cardiovascular population who qualified for enrollment with a statin indication and as members of SelectHealth, while allowing for adherence evaluation of a single class of medication.

Subjects' barriers to adherence were charted through proprietary recursive machine learning algorithms that mapped subject characteristics (ie, from the psychographic profile, IMRS, social determinants, and demographics) to their motivations and abilities to participate in and modify their own health. The machine learning approach used reinforcement learning state-action-reward-state-action (SARSA) models that were trained on simulated data prior to the study and updated as subjects were enrolled and followed across the study. The adherence barriers were identified as the analyses segmented individuals into homogeneous clusters, with the segmented clusters distinguished by differences in patient motivation and ability values and the number of subjects in each cluster varying based the similarity of those values (targeting 20 clusters in the nudges arm or 4 – 5 subjects per cluster). The clusters were then examined by artificial intelligence to determine the needs and interests of each group by assigning weights of motivation

and ability to each factor that contributed to the creation of the cluster. These analyses targeted general barriers to adherence (not barriers specific to statins such as statin-specific side-effects or the barriers associated with other specific therapies). Through this information, motivation-ability maps (MAM) were created as a landscape of subject needs and how nudging could persuade them in a positive manner.

## Nudge design and delivery

Guided by the MAM, nudges were personalized via augmented intelligence in content, frequency, timing, delivery modality, and feedback metric. Augmented intelligence is the automated calculation and delivery of actionable information that is difficult or impossible to ascertain in the usual course of a process.

A subject usually received multiple distinct nudges and could receive those through different delivery channels. Nudge frequency depended on if it were a primary nudge, which might be a trigger for a behavior or the single event of setting up a process. If it were a secondary nudge, it might be a reminder call to action or a follow-up on an action that should have already happened. Primary nudges were sent once or once per week, and secondary nudges occurred multiple times either on a recurring schedule (eg, monthly) or depending on other needs for personalization. Nudges were not sent often and an attempt was made—where possible—to limit the sending of any of nudges more than once in any given week to avoid alert fatigue (although, for example, a weekly and a monthly nudge might both be sent the same week, and if a nudge reminding about the need for a medication refill was not responded to it might be sent multiple times in the week prior to the quarterly medication refill date). Nudge timing was developed to support or suggest a decision and would be anchored to a calendar event (eg, an anticipated prescription refill date for a 90-day supply, an out of town trip or other event that would interrupt daily routines, or simply the beginning of the month).

Nudge channels were two-way communications with subjects through computer-generated e-mails, text messages, and interactive voice response telephone calls. The content of nudges was determined by the nudge's objective, which objectives included: 1) to attach the action of taking a medication to a subject's existing daily routine, 2) to ameliorate the impact of interruptions in a routine which might arise from a family party, a work holiday, business travel, or an extended vacation, 3) to gather information about and to manage medication aids such as pillboxes or healthcare assistance, such as a family member who was a caregiver, and 4) to deal with interruptions in medication refills. During four of every nine weeks, nudges were selected from a large standard bank of nudges based on individual subject motivations and abilities, while in the other 5 weeks the nudges were individualized further (beyond the clusters used in initial segmentation). The standard bank of nudges was developed by CareCentra psychologists, physicians, and other healthcare professionals based on best practices for addressing common concerns in medication adherence and other issues. The most individualized nudge content could be created using subject survey responses at baseline, responses to prior nudges during the trial, engagement with nudging during the trial, and needs that were discovered during follow-up. As nudge feedback (eg, description of a life change or challenge, or confirmation of an action that was taken) was obtained from each subject, the platform learned from these responses and performed further refinement of the MAM to more precisely configure future nudges (see Supplemental Table S2 for nudge examples and, for 6 subjects' full sets of actual nudges delivered during the trial, see Supplemental Table S3). When feedback was received that had not been encountered previously by the system, hand review of modifications to the nudging content was performed for validation.

As part of the intervention, nudge recipients were contacted on a quarterly basis by telephone by an Intermountain clinical research coordinator to inquire regarding MACE outcomes (mortality, MI, stroke, revascularization), any adverse impact of the nudges, and self-report of medication refills and adherence. These data were used for safety assessments and to aid in redesigning nudges.

## Trial endpoints

The trial's primary outcome was the adherence of individuals to a statin prescription at 12 months after baseline. Adherence was measured as a subject's proportion of days covered (PDC) by a statin prescription at 12 months of participation, as previously defined.[6,7,24] PDC was quantified through the passively-collected SelectHealth pharmacy claims data and calculated as the proportion of days that a subject had their statin available to take (ie, the sum of days that a statin pill was available divided by the total number of days of follow-up). This analysis assumed that subjects took their medication as prescribed when it was available. A non-adherent day, thus, was a day on which the subject did not have a statin to take. PDC was the primary study outcome and for practical purposes the statin adherence during months 10 – 12 were used to assess PDC at the 12-month timepoint. Secondary endpoints, including medications other than statins, are described in the Supplemental Methods.

## Statistical considerations

An expected statin PDC = 0.60 was established from pre-trial SelectHealth data. Using this expected rate for controls, the sample size necessary for 80% power to detect a 13% absolute difference (PDC = 0.73) for those receiving nudges was calculated. A >0.10 PDC improvement was considered clinically meaningful. These calcu-

**TABLE 1.** Baseline Characteristics of the ENCOURAGE Trial Population.

| | Overall ($n = 182$) | Nudges ($n = 89$) | Control ($n = 93$) | *P*-value |
|---|---|---|---|---|
| Age (ys) | 63.2±8.5 | 63.3±8.2 | 63.1±8.7 | 0.88 |
| Sex (female) | 25.8% | 31.5% | 20.4% | 0.09 |
| White | 98.4% | 100% | 96.8% | 0.25 |
| Not Hispanic or Latino | 98.4% | 97.8% | 98.9% | 0.62 |
| Number of medications | 4.6±1.7 | 4.9±1.5 | 4.3±1.8 | 0.02 |
| Past smoker* | 26.4% | 25.0% | 27.8% | 0.74 |
| Current smoker* | 4.5% | 5.7% | 3.3% | 0.49 |
| Body mass index (kg/m$^2$) | 31.3±7.6 | 31.7±8.7 | 30.9±6.4 | 0.46 |
| Systolic BP (mm/Hg) | 128.4±18.4 | 127.6±18.3 | 129.2±18.5 | 0.55 |
| Diastolic BP (mm/Hg) | 73.1±12.6 | 72.3±12.8 | 73.9±12.5 | 0.40 |
| Total Cholesterol (mg/dL)† | 151.6±42.2 | 153.6±42.3 | 149.7±42.2 | 0.55 |
| LDL-C (mg/dL)† | 82.5±32.7 | 84.0±31.5 | 81.0±33.9 | 0.56 |
| HDL-C (mg/dL)† | 40.0±11.6 | 40.1±12.0 | 39.9±11.3 | 0.89 |
| Non-HDL-C (mg/dL)† | 111.6±39.5 | 113.4±38.9 | 109.8±40.3 | 0.55 |
| Total Chol./HDL-C ratio† | 4.2±2.6 | 4.3±3.3 | 4.0±1.6 | 0.41 |
| Triglycerides (mg/dL)† | 147.4±89.9 (median: 125.5) | 148.4±88.8 (median: 126) | 146.5±91.4 (median: 125) | 0.72 |
| IMRS | 9.6±3.1 | 9.6±3.0 | 9.6±3.3 | 0.92 |
| Coronary artery disease | 93.4% | 91.0% | 95.7% | 0.20 |
| Diseased coronary vessels‡ | | | | |
| 0 | 18.8% | 16.7% (3) | 21.4% (3) | 0.55 |
| 1 | 40.6% | 38.9% (7) | 42.9% (6) | |
| 2 | 9.4% | 16.7% (3) | 0% (0) | |
| 3 | 31.3% | 27.8% (5) | 35.7% (5) | |
| History of unstable angina | 8.2% | 6.7% | 9.7% | 0.47 |
| Prior myocardial infarction | 43.4% | 51.7% | 35.5% | 0.03 |
| Heart failure | 8.2% | 9.0% | 7.5% | 0.72 |
| Atrial fibrillation | 14.3% | 16.9% | 11.8% | 0.34 |
| Cardiac valve disease | 8.8% | 5.6% | 11.8% | 0.14 |
| Prior cardiac transplant | 0.5% | 1.1% | 0% | 0.49 |
| Prior cancer diagnosis | 16.5% | 19.1% | 14.0% | 0.35 |
| Prior stroke | 6.0% | 9.0% | 3.2% | 0.13 |
| History of COPD | 3.3% | 5.6% | 1.1% | 0.11 |
| Diabetes | 39.0% | 38.2% | 39.8% | 0.83 |
| Renal failure | 8.8% | 10.1% | 7.5% | 0.58 |
| Peripheral vascular disease | 5.5% | 7.9% | 3.2% | 0.21 |
| Dementia/Alzheimer's | 0.6% | 2.2% | 0% | 0.24 |
| Parkinson's disease | 1.1% | 2.2% | 0% | 0.24 |
| Liver disease | 1.6% | 1.1% | 2.2% | 1.00 |
| History of OSA | 21.4% | 21.3% | 21.5% | 0.98 |

BP, blood pressure; COPD, chronic obstructive pulmonary disease; HDL-C, high-density lipoprotein cholesterol; IMRS, Intermountain mortality risk score; LDL-C, low-density lipoprotein cholesterol; OSA, obstructive sleep apnea.

* n = 178 had smoking data

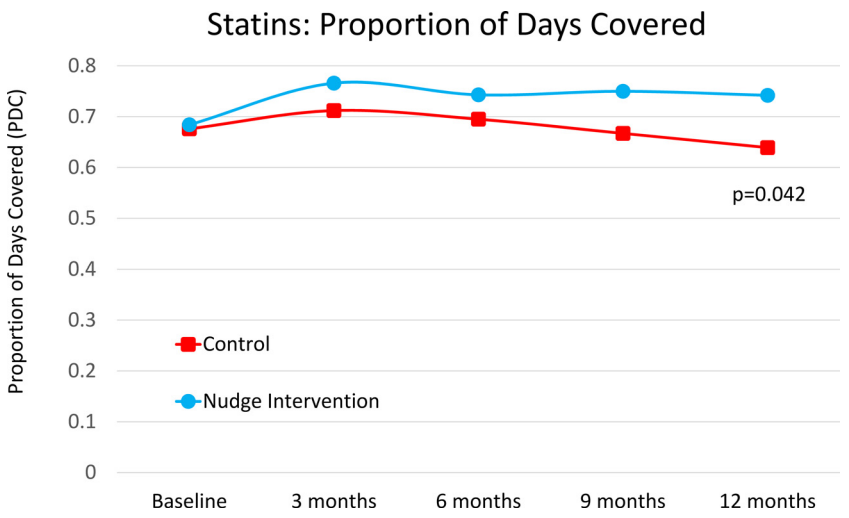
† n = 170 had a lipid panel ordered clinically

‡ n = 32 had a baseline angiogram (vessels with ≥1 lesion of ≥70% stenosis).

lations assumed $\alpha = 0.05$ and two-sided testing using Student's *t*-test. A sample of 182 subjects was required, and a drop-out buffer of 10% was added to yield the initial target sample size of 200. Due to higher-than-expected costs, study funding was exhausted at three-quarters enrollment and departmental funding used to enroll the minimum necessary number of subjects. Due to a low attrition rate (2%), enrollment ended at 186 subjects. The study was not powered to detect PDC differences for adherence to medications where fewer than all subjects had a prescription for them, which included all medications other than statins, thus secondary analyses of other cardiovascular medications were exploratory.

Statistical analyses were performed by a trained statistician who was blinded to trial allocation by a random code (A or B). Comparisons between individuals in the two study arms were performed using the *t*-test or chi-square test, as appropriate, for covariables. Evaluation of statin PDC between subjects in the two trial arms at 12 months was performed using Student's *t*-test under the intention-to-treat approach. Adherent (PDC ≥0.80) was evaluated by the chi-square test and MACE by Fisher's exact test and logistic regression. Statistical analyses used SPSS v.23.0 (IBM SPSS, Inc., Armonk, NY) with $p \leq 0.05$ defined as statistically significant for the primary endpoint.

**FIGURE 2**




The proportion of days covered (PDC) for statins was improved by nudges when compared to the control arm at the 12-month timepoint ($P = 0.042$). No PDC difference between the study arms existed at baseline ($P = 0.88$) and the separation between nudge and control curves appeared over time as differences became progressively greater at the secondary endpoints of 3 months ($P = 0.33$), 6 months ($P = 0.35$), and 9 months ($P = 0.10$).

## RESULTS

A total of 186 subjects were enrolled between March 2016 and February 2018 (Figure 1). Randomization allocated 93 subjects to control and 93 to the nudge intervention. One individual was administratively withdrawn post-randomization when records verification showed that they were not a SelectHealth member, and 3 subjects withdrew consent during the trial; all 4 were in the intervention arm. Subjects ($n = 182$) averaged 63.2±8.5 years of age and 25.8% were female. With respect to statin indications, 93.4% had coronary disease, 39.0% had type 2 diabetes, and baseline LDL-C was 82.5±32.7 mg/dL. Two subjects received a first-time statin prescription at baseline and 180 already had statin prescriptions. Baseline characteristics were well-balanced between nudge ($n = 89$) and control arms ($n = 93$) (Table 1).

For the nudge intervention arm, an average of 56 nudges per person were delivered during the trial, or 1.07 nudges per subject per week. These were delivered via text messaging (78.4%), email (13.4%), and interactive voice response (8.2%). The nudge frequency was weekly for 74.8%, monthly for 8.1%, and one-time for 17.1%. For the primary trial endpoint, the mean statin PDC was greater at 12 months for the nudge intervention at PDC = 0.742 ± 0.318 compared to control PDC = 0.639 ± 0.358 ($P = 0.042$), an absolute 0.103 higher statin PDC for nudges (Figure 2).

Non-significant differences in statin PDC were found at the secondary endpoint times of 3, 6, and 9 months (Table 2), with a trend growing toward the 12-month improvement. Based on data from the 3 months before baseline, no difference existed in statin PDC at baseline (0.684 ± 0.361 for nudges, 0.676 ± 0.365 for controls, $P = 0.88$). Exploratory evaluation of the change score of statin PDC for 12 months minus baseline showed a significant increase ($P = 0.036$) for nudges (ΔPDC= 0.058 ± 0.322) compared to control (ΔPDC= -0.037 ± 0.286), an absolute difference of 0.095. Adherence for the composite of all cardiovascular medications (Table 2) and for other individual medications (Supplemental Table S4) were not significantly different.

Evaluation of the dichotomized secondary outcome of adherent (statin PDC ≥80%) versus non-adherent (statin PDC <80%) found a similar result at 12 months as the primary analysis (Figure 3), with a greater percentage of adherent subjects in the nudges arm (66.3% vs controls: 50.5%, $P = 0.036$). The percentage adherent for nudges vs controls was 73.0% vs 68.8% at 3 months ($P = 0.63$), 67.4% vs 58.1% at 6 months ($P = 0.22$), and 65.2% vs 55.9% at 9 months ($P = 0.23$), respectively.

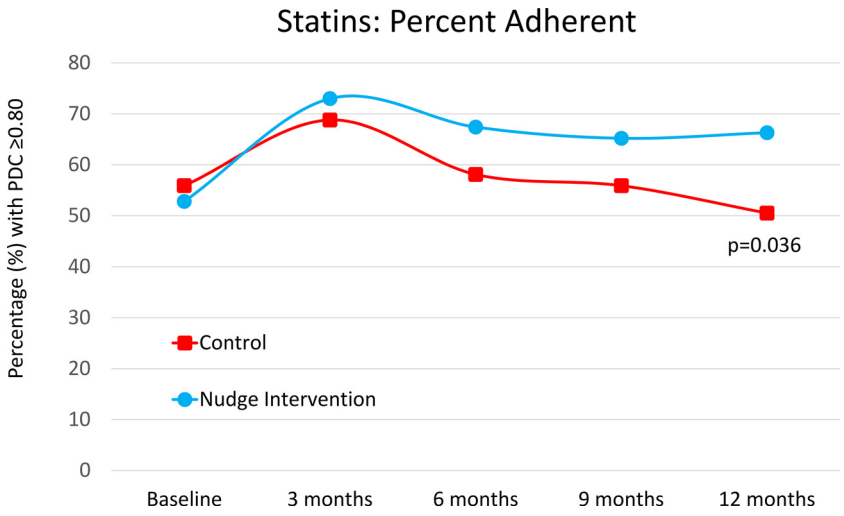
MACE events at 12 months were 6.7% for nudge recipients vs 10.8% of controls ($P = 0.44$; odds ratio = 0.60, 95% confidence interval = 0.21, 1.72). Two nudge subjects experienced multiple events. Mortality was 1.1% in each arm, MIs occurred in 2.2% in nudges and 0% in controls, strokes were 0% in nudges and 2.2% in controls, and coronary revascularizations were 5.6% in nudges and 7.5% in controls. Participant engagement with the nudges rose from just above half of patients responding in the first week to above 70% during months 2-11

**TABLE 2.** Proportion of Days Covered (PDC; Mean ± Standard Deviation) for Statins (primary measure) and for All Other Cardiovascular Medications (Secondary Measure), stratified by Randomization to the Nudge Intervention or to the Standard of Care Control, for The Primary Endpoint of Adherence at 12 Months and for Secondary Endpoints at 3, 6, and 9 Months. For Practical Purposes, PDC at a Timepoint was Measured as Adherence During the Preceding Three Months

| | Nudges | Control | *P*-value |
|---|---|---|---|
| Primary Endpoint | | | |
| Statins, $n = 182$ (nudges, $n = 89$; control, $n = 93$) | | | |
| PDC at 12 ms* | 0.742±0.318 | 0.639±0.358 | 0.042 |
| Key secondary endpoints | | | |
| Statins, $n = 182$ (nudges, $n = 89$; control, $n = 93$) | | | |
| PDC at 3 ms | 0.766±0.354 | 0.712±0.395 | 0.33 |
| PDC at 6 ms | 0.743±0.331 | 0.695±0.364 | 0.35 |
| PDC at 9 ms | 0.750±0.318 | 0.667±0.358 | 0.10 |
| All Cardiovascular Medications, $n = 182$ (nudges, $n = 89$; control, $n = 93$) | | | |
| PDC at 3 ms | 0.619±0.290 | 0.627±0.320 | 0.87 |
| PDC at 6 ms | 0.622±0.276 | 0.599±0.306 | 0.60 |
| PDC at 9 ms | 0.621±0.277 | 0.570±0.298 | 0.23 |
| PDC at 12 ms | 0.611±0.274 | 0.551±0.292 | 0.16 |

* Pre-specified primary endpoint of the trial.

**FIGURE 3**




Adherence, defined as having a statin proportion of days covered (PDC) ≥0.80, was increased at 12 months for nudges ($P = 0.036$). The difference in adherence between study arms appeared over time as subject follow up occurred through 3 months ($P = 0.63$), 6 months ($P = 0.22$), and 9 months ($P = 0.23$).

(Supplemental Figure S1), indicating steadily increasing acceptance of the messaging. No negative feedback regarding the nudging was received during the course of the study and 11 of the nudge recipients provided spontaneous positive feedback during one or more quarterly follow-up call.

## DISCUSSION

After 12 months, the PDC—the primary metric of medication adherence—was increased in subjects receiving a precision nudge intervention compared to a standard of care control. A rise in PDC at 3 months in both groups was likely due to nudging from physicians at baseline clinical exams, but as the enthusiasm of those interactions waned, the 6-, 9-, and 12-month PDC held steady in the nudge group while dropping linearly with time in the controls. The result was an absolute 10.3% higher adherence in favor of nudges. Secondary analyses of "adherent" (PDC ≥0.80) vs "non-adherent" (PDC <0.80) subjects confirmed this. The study was not powered to detect MACE differences, although the MACE rate was

numerically lower at 6.7% in nudges vs 10.8% in controls. This exploratory finding may provide a basis for outcomes trials of nudges to prevent MACE.

Cardiovascular medications reduce MACE in patients with or hospitalized for cardiovascular conditions. Adherence to cardiovascular medications, though, is approximately 40% – 50%.[5-8] Lower adherence is reported for high-dose statins and use of multiple medications.[5,25] Medication non-adherence is estimated to contribute more than $100 billion per year to avoidable expenses in the US health system.[26] Higher adherence may save $294-$868 per patient annually (a 10% – 18% cost reduction) for secondary prevention of CAD and up to $7,823 per patient annually for heart failure, despite the medication costs.[9,27] This includes savings due to the reduction of MACE.[6]

In particular, statins are safe and effective in reducing MACE [28,29] and are a mainstay of modern cardiovascular therapy. In addition to lowering LDL-C, they may have other effects such as reducing vascular inflammation.[30,31] Statins initially faced prescribing barriers in the 1990s,[32,33] but programs including the American Heart Association's Get With The Guidelines program resolved these issues in the early 2000s.[34-36] Statin adherence was subsequently discovered to be lower than in clinical trials,[5-7] with poor adherence associated with lower medication effectiveness in preventing MACE.[6,9] Adherence involves a variety of factors,[5,10,37,38] but nonadherence is not based on drug class and is unlikely to be driven by medication side-effects.[8] Adherence is a complex issue infused with many patient concerns.[37]

Not all such patient challenges can be overcome, but when medication non-adherence is viewed as a diagnosable and treatable medical condition it is more likely that issues will be addressed and resolved.[37] Adherence improvement previously addressed patient education, counseling, intensified care, medication aids, drug regimen simplification, polypills, medication reminders, refill reminders, financial incentives, and collaborative care.[11-13,39,40] While some of these supported patient decision-making, they generally were ineffective.[11]

Specifically, semipersonalized text messaging in prior controlled trials was frequent, with 4 – 6 contacts per week or even twice daily.[13-15,18] But such trials were negative for adherence improvement or, when using changes in LDL-C or hemoglobin A1c as the outcome, led to only mild to no improvement.[13-15,18] For the trials that showed improvements, the cause of changes in LDL-C or hemoglobin A1c was unclear,[13,14] although frequent texting likely induced the Hawthorne effect in which subjects changed their behavior because they were reminded on a daily or near-daily frequency that they were being observed. Eventually, such frequent reminders result in alert fatigue and a consequent long-term lack of effect in part because reminders, unlike nudges, do not change the choice architecture.

Nudging is the formalization of a technique for modifying human behavior in which actions that are immediately gratifying but contrary to personal goals or values are disincentivized by increasing the ease of making an alternative choice that better aligns with a person's long-term goals or values (while not forbidding other choices).[17] Nudging of clinicians—historically called clinical decision support—improves healthcare delivery by designing clinical architectures that help clinicians make evidence-based choices.[1,30,34] In medicine, a nudge aims to present a clinician [3] or patient with positive structuring of a preferred (optimally: evidence-based) choice that more likely will provide the desired long-term health outcomes.

Behavioral nudging may facilitate adherence by positioning patients as the directors of their own health choices and lowering the energy required to make the decision. Personalized support from health professionals could guide patients to establish a nudge-based lifestyle with precise but unobtrusive supportive communications delivered inside the confines of the patient's daily life. To do so, a healthcare professional should first measure the underlying factors by which a patient's life is lived, such as beliefs and perceptions, and utilize those data to persuasively nudge the patient to choose adherent and healthy behaviors.

Patient decision support may improve health outcomes. In this study's nudge intervention, subjects were segmented into homogeneous subsets based on their motivations and abilities to impact their health. Individualized nudges were designed and repeatedly updated to persuade subjects to modify their environment or think about a choice differently to improve their motivation or ability to act. This is similar to how a catalyst lowers the energy of activation for a chemical reaction. A nudge, like a catalyst, can reduce the inputs necessary to achieve an outcome while making it more likely to occur. Reminders, emotional coercion, and shared educational sessions/social modelling (eg, see [41]) are usually not behavioral nudges because they demand, pressure, or coerce a desired choice to be made; to be a nudge, a process or communication must improve the physical or cognitive structure of the health-related choices to persuade the patient to choose the best option.

## Strengths and limitations

The population size studied here was modest. Further, only two subjects were statin naïve and baseline LDL-C was low (mean: 82.5 mg/dL), thus this trial's objective was not to test whether nudges reduced LDL-C. Further, 12-month LDL-C results arose from clinical testing and fewer than half of subjects had a final LDL-C available. The trial was also not designed to determine whether the approximately once-weekly nudges herein were effective due to the use of AI, psychographic profiling, or the Hawthorne effect, thus further research is needed regard-

ing the mechanism of benefit, although the infrequent nudging should inherently be less likely than other methods to induce the Hawthorne effect. Because the nudges were only trained on *in silico* simulated data prior to the study, the nudges may not have been optimally developed at the start of the trial with possible issues with bias and generalizability of the machine learning-derived nudges early in the trial and changes in nudge quality across the study for subjects enrolled toward the end of recruitment. The study population was predominantly non-Hispanic Whites, thus the generalizability of study findings to other races and ethnicities requires further study. The vast majority of subjects also had a prior diagnosis of CAD, thus considerably fewer than half (about 26%) were female and further evaluation of nudging is needed among women.

Strengths of the study included the machine learning-developed, artificial intelligence-driven nudges and objective, passively collected adherence data from SelectHealth insurance claims. Because having SelectHealth insurance was an inclusion and only approximately 20% of Intermountain cardiac patients are SelectHealth members, about 80% of screened patients were excluded because they lacked SelectHealth insurance (Figure 1). Data regarding education and income were not collected by the study; however, because of the SelectHealth inclusion criterion the study population is expected to have a higher socioeconomic profile and be younger than the general population. This is in part because people were excluded if they did not have health insurance or were enrolled in Medicaid. To have SelectHealth insurance, people are often employed and therefore are younger but, for example, the SelectHealth Medicare Advantage plan was eligible for trial inclusion. An issue of generalizability may arise because older patients are less likely to utilize smartphones and text messaging.

## CONCLUSIONS

In a proof of concept trial, precision behavioral nudges driven by artificial intelligence increased statin adherence a clinically important amount and held the gains over a 12-month period in general cardiology patients. The low-frequency patient decision support program relied primarily on computerized nudge design and delivery with minimal on-going human input and measured adherence using objective passively-collected claims data. This persuasive approach may improve health by guiding patient choices in the home, workplace, and other locales where a patient lives their life.

## DATA SHARING STATEMENT

The data underlying this article cannot be shared publicly due to privacy laws that protect the clinical source data of study participants. The data will be shared on reasonable request to the corresponding author.

## Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ahj.2021.11.001.

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