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# Evaluation of the Effectiveness of a Patient Centered Educational Mailer Designed to Improve Statin Adherence: A Pragmatic Trial

John W. Nord
*University Utah SLC VA Medical Center*, john.nord@hsc.utah.edu

Alalia Berry
*University Utah*, alalia.berry@hsc.utah.edu

Barry Stults
*University Utah*, barry.stults@hsc.utah.edu

Zachary Burningham
*University Utah*, zachary.burningham@utah.edu

***See next pages for additional authors***

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## Abstract

**Background:** Patients with high total cholesterol have increased risk of cardiovascular disease. National Cholesterol Education Program (NCEP) and American Hearth Association (AHA) guidelines recommend cholesterol lowering with statin medications; however, statin adherence remains poor. We hypothesized that patient-centered education on the 10-year risk for each of the major constituents of Cardiovascular Disease would increase statin adherence and achievement of low-density lipoprotein cholesterol (LDL-C) goal.

**Methods:** Veterans within the Salt Lake City Veterans Affairs (VA) Medical Center initiating statin therapy during October 2008 to December 2011 were randomized in a pragmatic design to either receive an educational mailer or usual care. The mailer outlined their 10-year global cardiovascular risk, separated into coronary heart disease, stroke, and congestive heart failure. The study was unblinded and followed an intention-to-treat analysis where outcome measures were obtained during normal care process. The primary outcome measure was achievement of LDL-C goal during the 12-month follow-up.

**Results:** Two hundred and seven patients were randomly assigned to either the intervention arm (95) or control arm (112). No differences in the proportion of patients meeting LDL-C goal were detected during 12-months [Relative Risk (RR): 0.95 (95%CI: 0.77-1.17)] or 18-months [RR: 1.03 (95%CI: 0.84, 1.25)]. Patients in the intervention arm had higher adherence on average, e.g., intervention patients were more likely to have 70% or more days of statin therapy compared to patients who received standard care though this did not reach statistical significance. [RR: 1.33(95%CI: 1.00, 1.78)] There were no statistical differences in cardiovascular outcomes or mortality.

**Conclusion:** Patient education mailers sent to patients starting statin treatment did not have a clear impact on LDL-C goal achievement or adherence to statin therapy.

## Authors

John W Nord, *University Utah SLC VA Medical Center*; Alalia Berry, *University Utah*; Barry Stults, *University Utah*; Zachary Burningham, *University Utah*; Srinivasan Beddhu, *University Utah*; Brian C Sauer, *University of Utah*.

# eGEMs
### Generating Evidence & Methods to improve patient outcomes

# Evaluation of the Effectiveness of a Patient-Centered Educational Mailer Designed to Improve Statin Adherence: A Pragmatic Trial

John W. Nord Jr, MD;[i,ii] Alalia Berry, MD;[i,ii] Barry Stults, MD;[i,ii] Zachary Burningham, PhD;[i,ii] Srinivasan Beddhu, MD;[i] Brian C Sauer, PhD[i,ii]

## ABSTRACT

**Background:** Patients with high total cholesterol have increased risk of cardiovascular disease. National Cholesterol Education Program (NCEP) and American Heart Association (AHA) guidelines recommend cholesterol lowering with statin medications; however, statin adherence remains poor. We hypothesized that patient-centered education on the 10-year risk for each of the major constituents of cardiovascular disease would increase statin adherence and achievement of the low-density lipoprotein cholesterol (LDL-C) goal.

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[i]University of Utah, Department of Internal Medicine, [ii]Salt Lake City Veterans Affairs Medical Center

## Introduction

Treatment of elevated cholesterol levels with statin therapy can reduce cardiovascular disease (CVD) morbidity and mortality.[1] Despite large randomized controlled trials demonstrating the benefits of lipid lowering medication,[2–8] many patients do not achieve NCEP LDL-C goals set forth by the Adult Treatment Panel III (ATPIII).[9] Patients who are diagnosed with hyperlipidemia and prescribed statins often struggle with medication adherence.[10–12] While AHA cholesterol treatment guidelines no longer use numeric LDL-C goals, poor adherence remains a significant impediment to reducing the national burden of cardiovascular disease.[13] Batal et al. previously reported that less than 80 percent adherence to statin regimen predicted higher total serum cholesterol (17.23 ± 1.64 mg/dL (0.45 +0.04 mmol/L)), and that less than 90 percent statin-adherence results in a significant increase in nonfatal cardiovascular events, establishing a potential adherence goal for clinicians to target in clinical practice.[14] In addition, historical studies have shown that nonadherent patients experienced more hospitalization and greater mortality. Specifically, nonadherent patients had higher all-cause hospitalizations and higher all-cause mortality.[15–18]

Patient education through the use of mailers may be an effective tool to improve medication adherence. In a 2006 clustered randomized trial, conducted at a single Veteran's Administration Medical Center (VAMC) center, researchers mailed a basic education pamphlet to patients with uncontrolled hypertension (HTN) noting that their blood pressure was inadequately controlled and listing several simple interventions to lower their risk. This intervention showed modest improvement in HTN control rates.[19] In addition, an article published by Grover et al. showed that educating patients on their cardiovascular risk and explaining how lipid-lowering agents reduced that risk resulted in a modest improvement in LDL-C level.[20] A Cochrane review of interventions aimed at enhancing medication adherence concluded that effects were inconsistent from study to study, that very few studies at low risk for bias demonstrated benefit in both adherence and clinical outcomes, and that current methods for enhancing adherence for chronic medical problems were mostly complex and ineffective.[21] Additionally, a systematic review of statin adherence including 29 randomized controlled trials (RCTs) reporting on over 39,000 patients concluded that most of the trials had methodological weaknesses, almost half lacked sufficient power, and most had a risk of bias. Despite these limitations, many trials demonstrated small positive benefits in multiple modalities.[22]

Our study aims were to determine whether patient-centered educational mailers with individualized risk for global CVD, Congestive Heart Failure (CHF), stroke, coronary heart disease (CHD), and calculated cardiac age will increase statin adherence and significantly increase achievement of the LDL-C goal.

## Methods

### Study Design and Study Participants

The University of Utah Institutional Review Board (IRB) and the Salt Lake City (SLC) VAMC Health Services Research and Development Committee approved this study. We employed a pragmatic, randomized, controlled study design with an intention-to-treat analysis. Included patients were veterans ≥ 18 years old who received health care at the SLC VAMC and were recently diagnosed with hyperlipidemia, resulting in a prescription for statin therapy, or a new indication for statin therapy per ATPIII guidelines.[23] Patients were excluded if they lacked evidence of a lipid profile in the Computer Patient Record System (CPRS) or were already receiving statin therapy prior to being enrolled in primary care at the SLC VAMC. Additional exclusion criteria included pregnancy, receiving hospice care, and diagnosis of dementia.

Patients identified as initiating statin therapy during usual care between October 1, 2008 and December 31, 2011 were enrolled and randomly assigned, via coin toss, to receive either a patient-centered, individualized, global cardiovascular-risk assessment (treatment arm) or standard care (control arm). The individualized global cardiovascular-risk assessment was presented to the patient as an educational mailer. A waiver of consent was obtained through the IRB, and subjects who received a mailer were contacted and offered a follow-up visit (only one patient made an appointment to discuss the mailer information). During these visits, patients' primary care provider or study investigator discussed in detail their global cardiovascular risk. This measure was instituted to address the IRB's concern for potential psychological stress induced by learning one's global cardiovascular risk.[24]

### Intervention

The intervention was randomized and consisted of a mailed letter to patients detailing their individual 10-year global cardiovascular risk and calculated cardiovascular age using the D'Agostino[25] algorithm approach.[26] The D'Agostino algorithm is designed to delineate percentage of risk attributed to the various components of the global cardiovascular risk, such as CHD, stroke, risk of developing CHF, and peripheral vascular disease (PVD). The D'Agostino algorithm also predicts heart age, which ultimately reflects vascular age and is determined by the age of another individual with the same predicted risk, but with all other risk factor levels in normal ranges. An example is listed online in Appendix 1.

### Study Data and Variables

All data obtained for this study were generated through usual care, making this a pragmatic trial. Study investigators did not order lipid measurements, provide guidance, or direct care in any way. The SLC Veterans Health Information

Systems and Technology Architecture (VistA) data warehouse and the CPRS were used in obtaining the necessary data for this investigation. First, monthly lists of patients who had been dispensed a statin in the SLC VAMC during October 1, 2008 until December 31, 2011 were provided by staff from the VistA data warehouse.[27] We then reviewed each patient's medical records through CPRS and extracted the data needed to determine whether they met inclusion criteria.

Data were manually extracted from CPRS to compute cardiovascular risk and heart age for the mailer. Specifically, we extracted baseline lipid panel, blood pressure, age, body mass index (BMI), estimated glomerular filtration rate, presence of CVD or CHD equivalents, tobacco use, and presence or absence of lipid lowering or blood pressure lowering medications prescribed in the electronic health record. Data were recorded on a standard form for the study.

Data used to analyze the effectiveness of the intervention were obtained from the local VistA data warehouse and supplemented with VistAWeb in order to track care provided at non-Utah VAMCs. VistAWeb permits retrieval of remote-site patient data, thus allowing us to gather information on patients who received their initial statin therapy from the SLC VA but obtained follow-up care at another location. Patient demographics, outpatient pharmacy, laboratory, vital signs, and condition summaries (inpatient and outpatient) were obtained from the VistA data warehouse and used to evaluate the effectiveness of the educational mailer.

We transformed the data obtained from the local data warehouse and produced an analytic table with baseline data for the variables reported in Table 1 and the outcome measures defined below. The baseline variables were chosen to evaluate cardiovascular risk most proximate to the index date for each person.

**Table 1. Distribution of Baseline Variables among Randomized Treatment Groups**

| BASELINE CHARACTERISTICS | EDUCATIONAL GROUP (N=95) | CONTROL GROUP (N=112) | P-VALUE |
|---|---|---|---|
| Age - year: Mean (SD) | 60.73 (1.30) | 61.95 (1.35) | 0.52 |
| Male: Count (%) | 93 (97.9%) | 108 (96.4%) | 0.69 |
| Smoking: Count (%) | 24 (25.3%) | 34 (30.4%) | 0.44 |
| Body Mass Index: Mean (SD) | 30.13 (0.65) | 29.93 (0.46) | 0.80 |
| Cholesterol - mg/dl: Mean (SD) | | | |
|     Total | 210.40 (4.91) | 211.45 (4.18) | 0.87 |
|     LDL | 138.87 (4.02) | 142.77 (3.83) | 0.49 |
|     HDL | 41.76 (1.01) | 43.31 (1.07) | 0.30 |
|     Triglycerides | 212.91 (10.91) | 181.5 (9.82) | 0.03* |
| Blood Pressure - mm Hg: Mean (SD) | | | |
|     Systolic | 131.02 (1.53) | 131.13 (1.38) | 0.96 |
|     Diastolic | 75.69 (1.20) | 75.44 (0.93) | 0.86 |
| Diabetes mellitus: Count (%) | 31 (32.6%) | 38 (33.9%) | 0.88 |
| Coronary Artery Disease: Count (%) | 21 (22.1%) | 20 (17.9%) | 0.49 |
| Peripheral Vascular Disease: Count (%) | 6 (6.3%) | 4 (3.6%) | 0.52 |
| MI: Count (%) | 2 (2.1%) | 1 (.9%) | 0.60 |
| TIA: Count (%) | 1 (1.1%) | 4 (3.6%) | 0.38 |
| Stroke: Count (%) | 3 (3.2%) | 8 (7.1%) | 0.23 |
| Sleep Disorder: Count (%) | 11 (11.6%) | 12 (10.7%) | 1.00 |
| CKD: Count (%) | 11 (11.6%) | 13 (11.6%) | 1.00 |
| CHF: Count (%) | 7 (7.4%) | 4 (3.6%) | 0.35 |
| Framingham Risk Score: Count (%) | | | |
|     >20% | 58 (61.1%) | 70( 62.5%) | |
|     10–20% | 28 (29.5%) | 31 (27.7%) | |
|     <10% | 9 (9.5%) | 11 (9.8%) | 0.98 |

In some cases the laboratory measures were not captured during the visit that resulted in a new exposure to statin therapy. In these situations, the most proximate laboratory results up to one year prior to the index date or three days after the index date were chosen. Laboratory results reviewed within three days of the index date were thought to be associated with the decision to initiate treatment rather than to monitor response to treatment.

Single-level Healthcare Cost and Utilization Product (HCUP) Clinical Classification System (CCS) codes[28] were used to classify patient medical conditions as descriptive comorbidities for Table 1. The one-year baseline period was also used to identify presence of other disease conditions associated with cardiovascular risk, such as diabetes, HTN, smoking, and known CVD.

### Outcomes

The primary outcome was achievement of the LDL-C goal, as defined per the NCEP ATP III guidelines,[23] during the first year of follow-up. The LDL-C goal was measured in two ways:

1. When any LDL-C measurement during follow-up was within the goal, and
2. When the measurement closest to the end of the follow-up period, i.e., 12 or 18 months, was at goal.

Secondary outcomes included acute coronary syndrome (ACS) (HCUP CCS: 100, 101, 104, 107 or troponin ≥ 1); stroke (CCS: 109, 110, 112); CHF (CCS: 108 or B-type natriuretic peptide (BNP≥500); and deaths. Statin adherence was measured by the proportion of days the patient had statin coverage from the index date until index + 12 months. The proportion of days covered (PDC)[23] was computed using Veterans Health Administration (VHA) outpatient pharmacy-dispensing data. Formulas for patient-level calculations of the PDC and treatment group summary measures are listed in equations 1 and 2, respectively.

### Equations

$$PDC_i = \frac{\text{Observed treatment days}_i}{\text{Observation period}_i}, \text{ where } i \text{ represents unit (patients)} \quad (1)$$

$$\overline{PDC} = \frac{\Sigma_i \, PDC_i}{n}, \text{ where } n = \text{total units} \quad (2)$$

Due to the pragmatic aspect of this trial, the investigators had no control over patient follow-up; for this reason we included an 18-month evaluation as a sensitivity analysis to improve assessment of outcome measures.

### Statistical Analysis

Baseline characteristics were statistically compared with t-tests and Chi-square where appropriate. Relative risk estimation and 95 percent confidence intervals (CI) for primary and secondary dichotomous outcome variables were estimated using generalized linear models with a log link function and a binomial distribution using SAS 9.3.[29]

## Results

### Study Attrition

We screened a total of 454 patients and excluded 247 who did not meet study criteria. Twenty-four patients did not have initial labs in the electronic medical record. Seven patients were not prescribed a statin, though they were prescribed nystatin for fungal infections. Prior statin use was the major issue leading to exclusion; 210 patients were already taking a statin prior to enrollment into the VA health care system or were changed from one statin to another for various reasons—and those were not considered to be new statin prescriptions. Remaining exclusions were due to the following reasons: attempting to conceive, on palliative care, allergies related to statin use, or were already at the LDL goal when statin was initially prescribed.

Two hundred and seven patients met full inclusion criteria, of which 95 were randomized to the

treatment arm and 112 randomized to the control arm (Figure 1). The treatment arm had 68 patients with LDL-C tests within 12 months and 75 within 18 months. The control group had 81 with LDL-C tests within 12 months and 93 within 18 months. Statin adherence was estimated for all 207 patients.

### Baseline Data

Baseline data are presented in Table 1. Overall, 95 percent of the study participants were male veterans, with mean age of 62 years. Randomization effectively balanced all measured covariates except for triglycerides. The mean and standard deviation (SD) of triglyceride levels in the treatment arm was 213 (11) and 182 (10) in the control arm (p value =0.03).

### Assessment of Outcomes

Table 2 presents primary and secondary outcome comparisons between the mailer intervention and usual care arms. No differences in the proportion of patients meeting the LDL-C goal were detected during the 12-month Relative Risk (RR) 0.95 (95 percent CI: 0.77, 1.17)] or 18-month follow-up time

windows RR 1.03 (95 percent CI: 0.84, 1.25). While patients in the educational group had higher adherence to statin therapy on average the results failed to reach statistical significance: PDC ≥ 70 percent 1.33 (95 percent CI: 1.00, 1.78); PDC ≥ 80 percent 1.21(95 percent CI: 0.87, 1.68); PDC ≥ 90 percent 1.22 (95 percent CI: 0.81, 1.84). No other secondary outcome appeared to be affected by the mailer intervention.

## Discussion

Communicating 10-year cardiovascular risk to motivate patients to improve statin adherence and lower LDL-C remains challenging.[30]

Our study compared patient-centered education mailers containing individualized cardiovascular risk and cardiovascular age to usual care. The randomized mailer intervention had no measurable impact on achievement of the LDL-C goal or statin adherence.

Cardiovascular events, including stroke, myocardial infarction (MI), and CHF, represent the most serious direct clinical consequence of uncontrolled

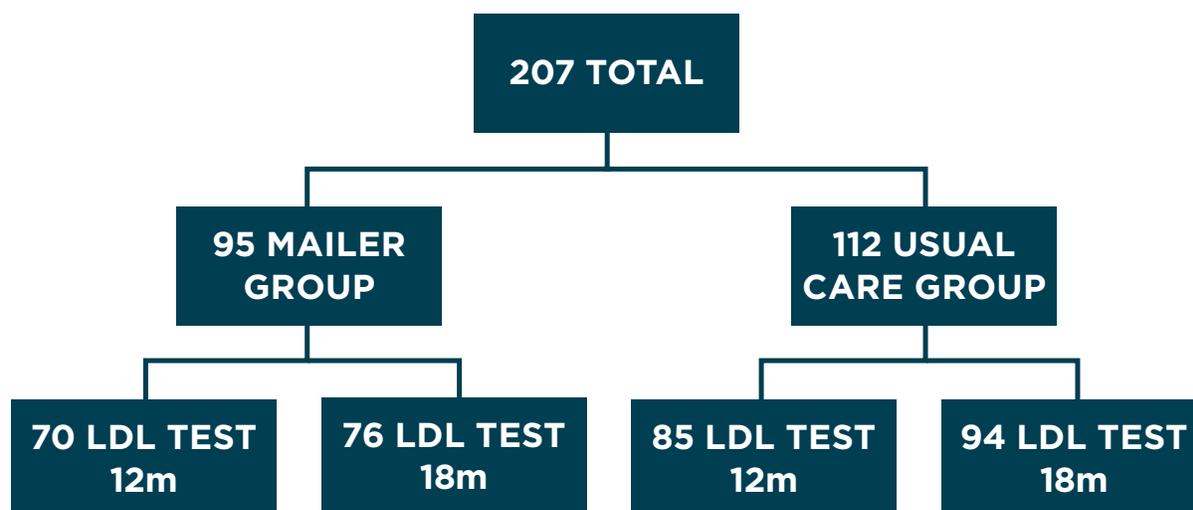**Figure 1. Attrition Figure for Primary Outcomes Asthma**

**Table 2. Primary and Secondary Outcomes**

| PRIMARY AND SECONDARY OUTCOMES | EDUCATIONAL GROUP n=95 | CONTROL GROUP n=112 | RISK RATIO | 95% CONFIDENCE INTERVAL |
|---|---|---|---|---|
| Test within 12m | 68 | 81 | | |
| LDL reach goal in 12m | 47 (69.1%) | 59 (72.8%) | 0.95 | (0.77, 1.17) |
| LDL last test reach goal | 43 (63.2%) | 57 (70.4%) | 0.90 | (0.71, 1.13) |
| Test within 18m | 75 | 93 | | |
| LDL reach goal in 18m | 53 (70.7%) | 64 (68.8%) | 1.03 | (0.84, 1.25) |
| LDL last test reach goal | 46 (61.3%) | 55 (59.1%) | 1.04 | (0.81, 1.33) |
| Secondary Outcomes | 95 | 112 | | |
| >= 90% statin adherence | 32 (33.7%) | 31 (27.7%) | 1.22 | (0.81, 1.84) |
| >= 80% statin adherence | 42 (44.2%) | 41 (36.6%) | 1.21 | (0.87, 1.68) |
| >= 70% statin adherence | 52 (54.7%) | 46 (41.1%) | 1.33 | (1.00, 1.78) |
| ACS | 21 (22.1%) | 21 (18.8%) | 1.18 | (0.69, 2.02) |
| StrokeTIA | 24 (25.3%) | 31 (27.7%) | 0.91 | (0.58, 1.44) |
| CHF | 7 (7.4%) | 5 (4.5%) | 1.65 | (0.54, 5.03) |
| Death | 2 (2.1%) | 5 (4.5%) | 0.47 | (0.09, 2.38) |

hyperlipidemia. The rates of these cardiovascular events were low in our study, at approximately two percent in both groups. Large trials demonstrate that statins can successfully reduce cardiovascular events; however, adherence remains suboptimal and was not improved with our intervention.

A recent meta-analysis demonstrates the value of providing feedback to patients and providing cognitive-educational interventions to improve adherence.[31] Statin adherence rates at one year remain dismal, illustrating the gulf between the perceived need to take these medications by the medical establishment and the lack of perceived benefit or perception of potential harm by those patients to whom the medications are prescribed.

The subjects in this study are predominantly middle-aged white male veterans, and may not be representative of the general population. Nevertheless, the veteran population is important in itself, and systematic improvement in medication adherence and patient outcomes is a national VA priority. Improving cardiovascular disease outcomes in the VA could have a profound effect on VA health care spending, as cardiovascular-related diseases make up the majority of VA discharges.

A stronger intervention would have included scheduled follow-up at 3, 6 and 12 months to ascertain medication use and provide feedback on whether patients reached the LDL-C therapeutic goals. Patients struggling to reach the goal would

receive additional information about cardiovascular risk and therapeutic objectives. The inability of investigators to influence scheduled follow-up and the relatively high proportion of subjects without a follow-up LDL-C measurement were important study limitations that not only limited clinical feedback but may produce selection bias in this type of pragmatic study where follow-up care is not influenced by investigators or study protocol. Methods exist that can be used to remove such biases, and these should be considered when designing and powering pragmatic trials.[32] When designing this study our expectation was that everyone initiating a statin would experience follow-up care and measurement of LDC-C within six months; and we did not account for this variability in practice when designing and powering the study. We did not attempt to develop censoring weights to remove bias due to informative measurement of LDC-C during follow-up because the intervention had little effect on adherence—and the effect of the mailer on LDC-C goals is mediated through adherence.

Strengths of this trial included the use of subjects who represented new statin initiators and the individualized breakdown of each of the components of global cardiovascular risk, including individualized stroke risk and estimated cardiovascular age. Follow-up was at 12 months, an interval that requires several refills and allows for accurate adherence calculations with time for providers to titrate statin medications to a dose that should be adequate to achieve the LDL-C goal, if patients remain adherent to therapy. The primary limitations of the study involved loss to follow-up and the inability to assess the reason for discontinuation of statin therapy. In addition, the study was likely underpowered to detect a clinically meaningful difference for the primary outcome of reaching the LDL target. Even though the mailer was modeled after a successful intervention[19] that found modest improvements in hypertension, the mailer

was not developed based on best practices for consumer health and may not have been optimized for literacy and numeracy for the veteran population.

This study demonstrates the ability to conduct pragmatic RCT in environments with fully electronic health records, such as the VA. It also highlights problems that should be anticipated when designing studies that involve randomization at baseline, but rely on standard care to assess response to the intervention. In a typical protocol-driven study where investigators enrolled subjects and influenced the visit process to systematically assess patient outcomes, there would be an attempt to measure LDC-C at 12 months for all study subjects. Since we did not influence the visit process, we varied the primary outcome measures in two ways to improve determination of whether the mailer affected LDL-C: one measure recorded whether any LDL-C reached the target, and the other recorded whether the measure closest to 12 or 18 months was at target. We included the 18-month measure since only 74 percent of subjects in the intervention arm had an LDL-C within 12 months. Expanding the follow-up period to 18 months increased the total number of subjects with an LDL-C measure by only a few percent. Chart review was conducted on all study subjects without LDL-C measurement, and nearly all patients exhibited evidence of continued system use but did not have LDL-C measures within 12 or 18 months of initiating statin therapy.

Other strategies that involve more proactive panel management through identifying patients not obtaining refills and having a nurse or care manager contact the individual is a reasonable alternative approach to improve medication adherence. This, however, requires functional dashboards designed to track medication management, laboratory findings, and missed visits. Our team is currently developing dashboards that may support such efforts. Additionally, Morrissey et al. have proposed

a hypertension-specific update that, while not related to statin adherence, may inform medication adherence strategies in general when completed.[33]

In conclusion, statin adherence in patients with elevated cardiovascular risk was poor, and the mailer designed to motivate adherence with lipid lowering therapy did not appear to affect medication adherence or patient outcomes. Randomization is an important design feature to remove baseline confounding but bias can also be generated from differential measurement of key outcome variables or loss-to-follow-up when outcomes are assessed during standard care processes. Future studies to improve statin adherence should consider protocols to assess early response to treatment and tailored feedback based on whether patients were at the goal or expected to reach the goal.

## Acknowledgements

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## Appendix 1.

Salt Lake City UT 84148 DEPARTMENT OF
VETERANS AFFAIRS (VA)
Salt Lake City Health Care System
500 Foothill Drive
Salt Lake City, UT 84148

Dear _____,

My name is John Nord and I am an Internal Medicine doctor at the Salt Lake City VA hospital. You were recently diagnosed with high cholesterol and placed on a cholesterol lowering medication. Our clinic recently calculated your 10 year risk of cardiovascular disease. This is the chance that you will have coronary heart disease, stroke, or heart failure within the next 10 years based on your risk factors, clinic visit data, and laboratory data.

Your risk of having coronary heart disease (a heart attack) in the next 10 years is _____%

Your risk of having a stroke in the next 10 years is _____%

Your risk of developing congestive heart failure in the next 10 years is _____%

Your estimated heart age is _____

You will soon receive a phone call from a member of our team to discuss what this risk means for your health. One important way to reduce you risk is to take the cholesterol lowering medication that was prescribed for you every day.

In addition, we will schedule an appointment between you and your primary care provider to discuss this risk.

*d' Agostino et al, Circulation. 2008;117:743-753.*

John Nord, MD
VASLCHCS