Interruptive Versus Non-Interruptive Reminders for Statin tHerApy in Primary Care (INIRSHA-PC)

Statistical Analysis Plan

Leena Choi, PhD

Version 1.0
October 29, 2024
NCT06456658

Principal Investigator: Aileen Wright, MD, MS.

Key Study Personnel:
Cheryl Gatto, PhD, PMP
Todd Rice, MD, MSc
Jennifer Green, MD, MPH
Erin Neal, PharmD
Mary Lynn Dear, PhD
Kylie Nairon, PhD
Sydney Lagalante, MPH
Grace Van Winkle, BA

Leena Choi – Lead Biostatistician

10/29/2024
Date

Introduction

Cardiovascular disease (CVD) remains the leading cause of death in the United States. Lowering low-density lipoprotein cholesterol (LDL-C) can reduce the risk of death from atherosclerotic cardiovascular disease (ASCVD), both in patients without (primary prevention) and those with established CVD, such as after a myocardial infarction (MI) or ischemic stroke (secondary prevention). Statins have been shown to reduce LDL-C and the rate of adverse cardiac events. National guidelines recommend initiation of statin therapy for patients based on LDL-C level and baseline cardiovascular disease risk; however, many patients who are eligible for statins do not receive them. Lack of statin therapy can be caused by providers failing to offer statins, patients declining statins, or patients discontinuing statins due to adverse effects. Previous studies exploring clinical decision support (CDS)-based education delivery and its impact on guideline-concordant prescribing have shown mixed results.

CDS systems which are integrated into the electronic health record (EHR) are now a standard method of improving quality of care, having been incentivized by the Health Information Technology for Economic and Clinical Health (HITECH) Act in 2009, which includes CDS within its core requirements of meaningful use. CDS includes, but is not limited to, interventions such as computerized alerts and reminders, reports, patient summaries, and clinical guidelines embedded within the EHR. Interruptive pop-up alerts, which are the main type of CDS with proven effectiveness, by definition interfere with clinical workflow and can lead to alert fatigue. Introducing more frustrations into the clinician experience with the EHR raises concerns in an age where the rapid adoption of EHRs has been linked to clinician burnout. Non-interruptive reminders, such as those which must be accessed by the clinician in an on-demand manner, may be suggested as an alternative to interruptive pop-up alerts, but the effectiveness of non-interruptive alerts to improve guideline adherence is unclear.

With the widespread use of EHRs and the implementation of reminders, the decision to build an alert as interruptive or non-interruptive is an important one which must balance potential alert fatigue with potential positive effects on adherence to clinical guidelines which improve quality of care for patients. Rigorous studies are needed to gather evidence to help clinical informaticians when making decisions about the design of CDS interventions. Findings from such studies would have implications for the thousands of alerts displayed to clinicians each year. To address this knowledge gap, we will conduct a prospective, randomized trial of reminders delivered to clinicians seeing patients in primary care clinics, comparing interruptive vs. non-interruptive reminders in outcomes of statin prescriptions.

Population and Design Considerations

Study Population:

Adult patients (age ≥ 18 and < 75) who are treated by primary care providers at Vanderbilt University Medical Center and eligible for statin therapy but not currently on a statin are potentially eligible for this study. If a patient presents to a VUMC primary care clinic and meets the below inclusion and exclusion criteria, the patient will be enrolled to the study.

Inclusion Criteria

1. Patients age ≥ 18 and < 75
2. Seen in primary care visit within Vanderbilt University Medical Center

3. Eligible for statin therapy due to: 1) ASCVD 10-year risk ≥ 10%, 2) Type 1 or 2 diabetes and age ≥ 40, or 3) ASCVD diagnosis.

Exclusion Criteria

Patient records within the EMR indicate:

1. Already on statin, ezetimibe, bempedoic acid, or PCSK9 inhibitor
2. Last known LDL-C level < 100 mg/dL
3. Known to be pregnant or lactating
4. Palliative care
5. Statin allergy or adverse effect of statin
6. Rhabdomyolysis
7. Statin contraindicated due to liver disease, defined as 1) Decompensated liver disease, 2) AST or ALT >5 times the upper limit of normal, or 3) Total bilirubin > 1.5 mg/dL.
8. Statin contraindicated due to kidney disease, defined as 1) Dialysis or 2) Estimated glomerular filtration rate < 15 ml/min/1.73 m^2.
9. Has had coronary calcium computerized tomography
10. Less than 3 months since lipid panel resulted
11. Acute visit

Study Design

A pragmatic, single center, randomized, controlled, three-arm trial comparing the effect of interruptive alerts versus non-interruptive alerts versus no alerts recommending guideline-concordant statin prescription on statin prescription rates in primary care clinics.

Randomization and Patients' Enrollment

The study will have three arms: no reminder (routine care) arm, non-interruptive reminder arm, and interruptive reminder arm. A sequence of numbers of 0, 1, or 2, indicating one of the three arms will be randomly generated in a 1:1:1 ratio by a mechanism embedded in the EHR and assigned to patients presenting to a VUMC primary care clinic who are ≥ 18 and < 75 years old. If the patient meets the above statin eligibility criteria and none of the exclusion criteria at the time of the visit, the patient is automatically enrolled in the study and randomized to the study arm assigned by the random number. The provider will receive either an interruptive reminder, a non-interruptive reminder, or no reminder, depending on the patient's assigned arm.

For repeat encounters, the provider will receive the same format of educational intervention (i.e., interruptive, non-interruptive, or no reminder) for a given patient throughout the course of the study. In the interruptive and non-interruptive alert arms, clinicians may or may not still be eligible for a repeat alert depending on how they interacted with the initial alert. If the patient is on a statin at the repeat visit, the clinician will not be shown a repeat alert. If the clinician did not prescribe a statin and chose an acknowledgement reason such as "statin is contraindicated", the alert will not be shown again. If the clinician simply closed or "canceled" the alert during the first visit, or if the clinician did not interact with a non-interruptive alert, the alert will be displayed again at the next visit; however, the patient will not be re-enrolled, and the primary endpoint measurement will not be re-taken relative to the firing of this BPA. Analysis will be

performed on the unique patient level, rather than the visit level, where all eligible visits for an individual patient will be considered a single enrollment.

Sample Size Considerations
Based on baseline rates of eligible patient visits, we estimate a possible sample size of 3,931 over a course of 6 months, and 7,830 over a course of 12 months. If we assume that the statin prescribing rate for the control arm (i.e., no reminder, or routine care) is 3% (an estimate derived from current clinical data) and the statin prescribing rate for the interruptive statin reminder arm is 6% (an estimate based on a clinically meaningful doubling of the current prescribing rate with an active alert), a total of 3,006 patients (1,002 patients per arm) would provide 90% power to detect the difference in the statin prescribing rates between the two arms at a type I error rate of 0.05. With a conventional study design, our planned sample size could be a total of 3,000 patients (1,000 patients per arm).

However, considering that this study is a 3-arm trial with uncertainty on the effect size for both the interruptive statin reminder arm and the non-interruptive statin reminder arm, and potential chance of imbalance across arms, we designed an adaptive clinical trial with sample size adaptation. When the sample size reaches at least 2,250 patients (750 patients per arm), we will conduct an interim analysis to re-estimate the sample size. At the interim, we will calculate the conditional power and allow sample size re-estimation. Should the interim analysis confirm that the originally planned sample size of 3,000 patients (1,000 patients per arm) provides sufficient power, we will proceed without further sample size adjustment and stop recruiting patients when the sample size reaches 3,000 patients (1,000 patients per arm) or the stopping decision is made, whichever occurs later. However, if the interim analysis indicates the need for an increased sample size, we will adjust accordingly based on the re-estimated sample size with the constraint of the maximum sample size of a total of 6,000 patients (2,000 patients per arm).

Interventions
Interruptive reminder arm:

> Providers will receive education via a pop-up alert at the time that the chart is opened for eligible patient visits assigned to the interruptive reminder arm.

Non-interruptive reminder arm:

> Providers will be able to seek out education at their own initiative via an on-demand reminder within a section of the chart for eligible patient visits assigned to the non-interruptive reminder arm.

No reminder arm (routine care):

> No alert recommending a statin will be displayed/available to the provider. The system will record eligibility through triggering a “silent” alert, which is not displayed to the clinician and exists solely for data collection purposes.

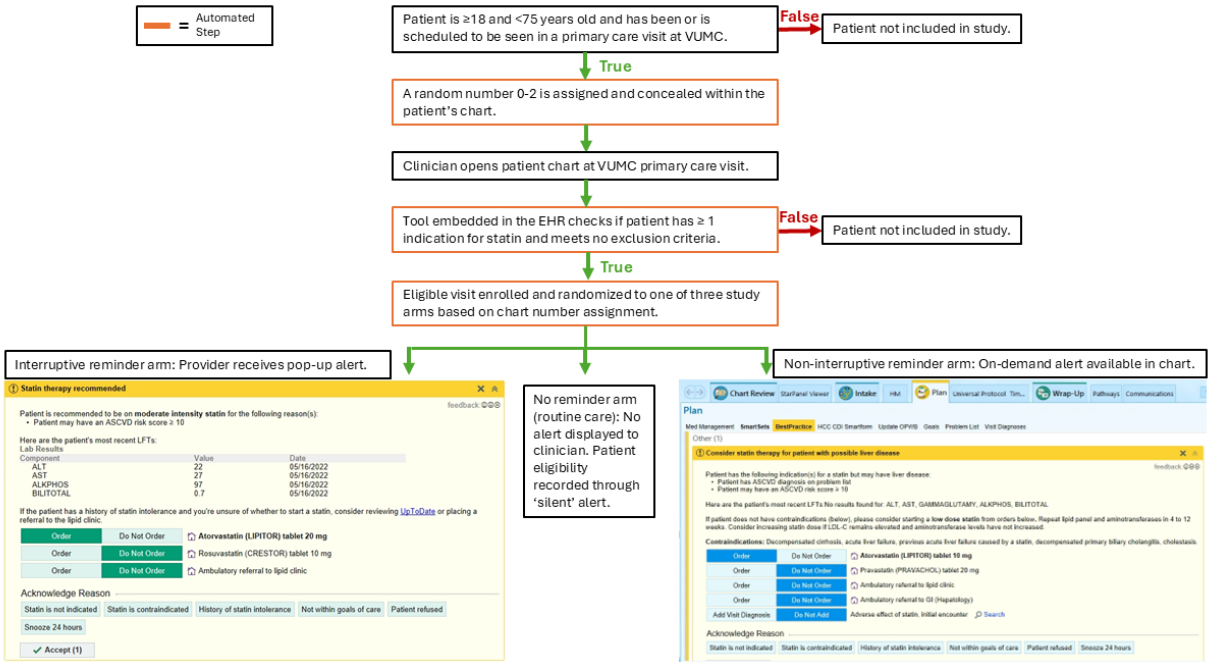

Figure 1: Schematic procedure of arm assignment and enrollment.

Both the interruptive and the non-interruptive alerts will have the same format; only the manner in which it is displayed will differ. The reminder will alert clinicians that a statin is recommended for the patient and list the reasons the statin is indicated. It will give the clinicians a defaulted option for statin prescription as well as alternatives. If the clinician accepts the alert, an order for a statin will be placed in their "shopping cart" for convenience, and the order can be signed to prescribe the medication. If the clinician does not wish to prescribe a statin from the reminder, they can choose an acknowledgement reason.

Endpoints

Primary Endpoint

The primary outcome will be a binary outcome of statin prescription placed within 24 hours after enrollment BPA firing (interruptive, non-interruptive, or no reminder) (Yes/No).

Secondary Endpoints

This trial has two secondary outcomes:

1. A binary outcome of statin prescription placed within 12 months after enrollment BPA firing (Yes/No)
2. The patient's first LDL-C level measured during the follow-up between 30 days and 12 months since the enrollment visit.

Exploratory Endpoints

1. A binary outcome of any non-statin lipid lowering agent prescription placed within 12 months after enrollment BPA firing (ezetimibe, PCSK9 inhibitor, or bempedoic acid) (Yes/No)
2. A binary outcome of any statin prescription filled within 12 months of enrollment BPA firing (Yes/No)
3. A binary outcome of new ASCVD event within 12 months of enrollment BPA firing (Yes/No)
4. Time from enrollment BPA firing to statin prescription

Statistical Approach

Target Population

The target population of the estimand will be the principal stratum that includes all participants meeting the above inclusion/exclusion criteria, for whom the randomization allocated by the EHR embedded tool is executed.

Analysis Dataset

- The analysis set will include all participants in the target population for the analysis of statin prescription placed within 24 hours (the primary endpoint), statin prescription placed within 12 months after enrollment BPA (a secondary endpoint), non-statin lipid lowering agent prescription placed within 12 months after enrollment (an exploratory endpoint), and new ASCVD event within 12 months of enrollment (an exploratory endpoint).
- For the analysis of the first LDL-C level measured during the follow-up (a secondary endpoint), statin prescription filling within 12 months of enrollment (an exploratory endpoint), and time from enrollment to statin prescription (an exploratory endpoint), the analysis set will include participants in the target population who do have the outcome measures but exclude patients whose outcomes are missing even after imputing the outcomes as described in the section, 'Handling Missing Data.'

Descriptive Analysis

General approach:

Categorical variables will be summarized using frequencies and proportions, and continuous variables will be described using means and standard deviations, as well as medians and interquartile ranges. The data also will be described graphically as needed. Missingness will be reported for each variable. No statistical comparisons between arms will be performed for these descriptive analyses.

Characteristics of the study sample:

Patient baseline demographic and clinical data as well as the provider information will be summarized overall and by intervention arm. The following variables will be described at time of enrollment:

- Patient sex (male, female, unknown)

- Patient race (African American, Asian/Pacific Islander, Caucasian, Multiple, Native American, Other, Unknown)
- Patient self-reported ethnicity (Hispanic, Non-Hispanic, Unknown)
- Patient age (years)
- Patient comorbidities:
    - Diabetes (Yes/No)
    - ASCVD diagnosis (Yes/No)
    - Congestive heart failure (Yes/No)
    - Hypertension (Yes/No)
    - Peripheral artery disease (Yes/No)
    - Stroke (Yes/No)
- Patient body mass index (BMI, kg/m^2)
- Patient Charlson comorbidity index
- Type of patient statin therapy recommended to provider (moderate intensity, high intensity, high intensity and potential work up for LDL >= 190, low-dose statin for liver disease)
- Provider role (e.g., physician, physician assistant, resident physician, nurse practitioner)
- Prior statin prescription
- Visit type (in person or telemedicine)

Description of the endpoints:
All the endpoints will be summarized overall and by intervention arm.

Primary Analysis
General approach:
All primary analyses will be performed without covariate adjustment as the study interest lies in estimating the overall intervention effects observed in a diverse patient population in their usual clinical settings. To account for potential imbalance in covariate distribution across arms, secondary analyses will be performed with *a priori* selected covariate adjustment. All analysis results will be reported with point estimates and 95% confidence intervals (CIs). No adjustments for multiplicity will be made.

Analysis of the primary endpoint:
Statin prescription within 24 hours of enrollment BPA firing will be compared between intervention arms using a logistic regression with indicator variables for intervention arms.

Analysis of secondary endpoints:
Statin prescription placed within 12 months after enrollment BPA firing will be analyzed using a logistic regression. For the first LDL-C level measured during the follow-up, a linear regression analysis will be performed with intervention arm indicator variables. If the distribution of LDL-C levels is highly skewed, an ordinal logistic regression analysis will be used in place of a linear regression.

Analysis of the exploratory endpoints:
A logistic regression will be performed to compare the binary outcomes between intervention arms. Time from enrollment BPA firing to statin prescription will be compared between

intervention arms using a Cox proportional hazard model and the differences in the outcome between arms will be visualized using Kaplan-Meier curve.

Secondary Analysis
The covariate adjusted analysis will be performed for the primary and the secondary outcomes using the same regression analysis methods with adjustment of the following covariates.

Covariates for the analysis of statin prescription (the primary endpoint and a secondary endpoint):
Patient age, sex, Charlson Comorbidity Index, type of patient statin therapy recommended to provider, baseline LDL-C level, ASCVD disease, diabetes, chronic kidney disease, prior statin prescription, visit type (in person or telemedicine), and provider role.

Covariates for the analysis of the first LDL-C level measured during the follow-up:
Patient age, sex, Charlson Comorbidity Index, type of patient statin therapy recommended to provider, baseline LDL-C level, ASCVD disease, diabetes, chronic kidney disease, prior statin prescription, visit type (in person or telemedicine), provider role, and time from enrollment to follow-up LDL-C level measurement.

Population-Level Summaries
Odds ratios (ORs) will be used for the analysis of binary (and ordinal) outcomes. For the analysis of the first LDL-C level measured during the follow-up, the estimates of mean differences in LDL-C levels, comparing interruptive reminder vs. no reminder arms, non-interruptive reminder vs. no reminder arms, and interruptive reminder vs. non-interruptive reminder arms will be used if a linear regress model is used. Hazard ratio (HR) will be used for the analysis of time to statin prescription.

Handling Missing Data
We do not expect missingness in our primary outcome and a secondary outcome of statin prescription within 12 months after BPA firing. Some missingness is expected for the first LDL-C level measured during the follow-up. For these missing outcomes, if a prior LDL-C level is available, the outcome will be imputed using the last known LDL-C level prior to the follow-up period; otherwise, the patient will be excluded in this analysis. For the exploratory outcomes, a complete case analysis will be performed without imputing the missing outcomes.

Missing covariates are not expected, or to be small percentage if occurs, which will be imputed using a single imputation. If missing data are substantial, multiple imputation will be used to handle missing covariates.

Intercurrent Events
To handle intercurrent event due to death or switching providers to other institutions, a while-alive strategy will be used.

Differential Treatment Effects
We will explore differential treatment effects for the primary endpoint only. Differential treatment effects will be explored by examining the interaction between the intervention arm

indicators and each variable that could potentially interact with the interventions. The variables we consider include comorbidities (diabetes, ASCVD diagnosis) at time of enrollment, type of patient statin therapy recommended to provider (moderate intensity statin, high intensity statin, high intensity and potential work up for LDL >= 190, low-dose statin for liver disease), and provider role (e.g., physician, physician assistant, resident physician, nurse practitioner). Subgroup analyses will not be performed unless the analysis is suggestive of potential interaction.