Original Protocol

Leveraging the Electronic Health Record to Nudge Clinicians to Prescribe Evidence-Based Statin Medications to Reduce the Risk of Cardiovascular Disease: A Randomized Clinical Trial

September 2020

Outline

1. Abstract
2. Overall objectives
3. Aims
    - 3.1 Primary outcome
4. Background
5. Study design
    - 5.1 Design
    - 5.2 Study duration
    - 5.3 Target population
    - 5.4 Accrual
    - 5.5 Key inclusion criteria
    - 5.6 Key exclusion criteria
6. Subject recruitment
7. Subject compensation
8. Study procedures
    - 8.1 Consent
    - 8.2 Procedures
9. Analysis plan
10. Investigators
11. Human research protection
    - 11.1 Data confidentiality
    - 11.2 Subject confidentiality
    - 11.3 Subject privacy
    - 11.4 Data disclosure

11.5 Data safety and monitoring

11.6 Risk/benefit

11.6.1 Potential study risks

11.6.2 Potential study benefits

11.6.3 Risk/benefit assessment

1. Abstract

Cardiovascular disease (CVD) is the leading cause of mortality in the United States. Statins have been demonstrated to be an effective tool for reducing the risk of CVD-related events and mortality, but statins are often not prescribed for patients that meet evidence-based guidelines. In this study, we will evaluate nudges to clinicians, patients, or both to initiate statin prescriptions for patients that meet the United States Preventive Task Force guidelines, patients with clinical ASCVD condition, and patients with a history of familial hyperlipidemia. In partnership with the health system, this will be conducted as a 4-arm factorial, cluster randomized trial to evaluate the effect of the interventions.

2. Overall objectives

The objective of the study is to evaluate the effect of nudges to clinicians, patients, or both to initiate statin prescriptions for patients that meet national guidelines.

3. Aims

3.1 Primary outcome

The primary outcome measure is percent of patients prescribed a statin medication.

4. Background

Statins have been found to reduce atherosclerotic cardiovascular disease (ASCVD) events and mortality by up to 30% [1]. Statins are affordable and generally well-tolerated [2]. However, less than 50% of eligible patients are prescribed a statin [3]. Previous work has demonstrated how insights from behavioral economics can be used to design nudges to improve statin prescribing by primary care physicians [4].

References

[1] Mozaffarian, D., Benjamin, E. J., Go, A. S., Arnett, D. K., Blaha, M. J., Cushman, M., ... & Huffman, M. D. (2015). Forecasting the future of cardiovascular disease in the United States: a policy statement from the American Heart Association. *Circulation*, *131*(4), e29-e322.

[2] Stone, N. J., Robinson, J. G., Lichtenstein, A. H., Merz, C. N. B., Blum, C. B., Eckel, R. H., ... & McBride, P. (2014). ACC/AHA prevention guideline. *Circulation*, *129*(2), S1-S45.

[3] Salami, J. A., Warraich, H., Valero-Elizondo, J., Spatz, E. S., Desai, N. R., Rana, J. S., ... & Blumenthal, R. S. (2017). National trends in statin use and expenditures in the US adult population from 2002 to 2013: insights from the Medical Expenditure Panel Survey. *Jama cardiology*, *2*(1), 56-65.

[4] Patel, M. S., Kurtzman, G. W., Kannan, S., Small, D. S., Morris, A., Honeywell, S., ... & Volpp, K. G. (2018). Effect of an Automated Patient Dashboard Using Active Choice and Peer Comparison Performance Feedback to Physicians on Statin Prescribing: The PRESCRIBE Cluster Randomized Clinical Trial. *JAMA Network Open*, *1*(3), e180818-e180818.

5. Study design

5.1 Design

This study will be a pragmatic trial to evaluate nudges to clinicians, patients, or both within primary care practices at Penn Medicine over a 6-month intervention period. This will include three interventions tested through a 4-arm, factorial, cluster randomized trial. Patient eligibility for statins will be based on the United States Preventive Services Task Force guidelines, presence of an ASCVD condition, or history of familial hyperlipidemia.

The four-arm factorial trial will randomly assign primary care practices to the following arms: 1) Control with no interventions; 2) Clinician nudge using an active choice prompt in the electronic health record at the time of the patient visit and a monthly peer comparison message on statin prescribing performance relative to peer clinicians at Penn Medicine delivered through the electronic health record; 3) Patient nudge using a text message sent to patients via a Penn Medicine approved platform before an appointment with their primary care clinician that informs them of their eligibility for a statin, the risks and benefits, and asking them to discuss the role of starting a statin with their PCP; 4) Both clinician nudge using peer comparisons and patient nudge using statin message. This trial will have a 12-month pre-intervention period and a 6-month intervention period. Given the uncertainty of patient volume with the COVID-19 pandemic, the trial may be extended until the minimum sample size is met for the specified power calculations.

5.2 Study duration

The study is expected to take 2 years to complete including study preparation, trial intervention, analysis, and dissemination.

5.3 Target population

Patients in primary care practices at Penn Medicine who have a new or return visit with their primary care clinician either in-person or via telemedicine during the intervention period and are eligible for a statin medication based on the United States Preventive Services Task Force guidelines, presence of an ASCVD condition, or history of familial hyperlipidemia.

5.4 Accrual

Patients in this pragmatic trial will accrue based on their eligible visit during the study period.

5.5 Key inclusion criteria

Patients must meet the following criteria to be eligible for the study:

1) Have a primary care provider at one of the study practices at the University of Pennsylvania Health System;
2) Either have an ASCVD condition, history of familial hyperlipidemia, or meet United State Preventive Task Force Guidelines for Statin Therapy which includes age 40-75 years, at least 1 cardiovascular risk factor (e.g. dyslipidemia, diabetes, hypertension, smoking), 10-year ASVCD risk score ≥ 10%

5.6 Key exclusion criteria

Patients will be excluded if any of the following criteria is met: 1) Already prescribed a statin; 2) Allergy to statins; 3) Severe renal insufficiency defined as glomerular filtration rate (GFR) less than 30 mL/min or on dialysis; 4) Adverse reaction to statins including statin-related a) myopathy; b) Rhabdomyolysis; c) hepatitis; 5) Pregnant; 6) Currently breastfeeding; 7) on hospice or at the end-of-life; 8) On a PCSK9 Inhibitor medication

Clinicians (and their respective patients) will be excluded if they have less than 10 patients among their entire panel that are eligible for a statin medication.

6. Subject recruitment

Information on primary care providers and their patients at the University of Pennsylvania Health system will be obtained from the electronic health record using Penn Data Store and Clarity, an Epic reporting database.

7. Subject compensation

No compensation will be offered in this study.

8. Study procedures

8.1 Consent

A waiver of informed consent is requested for the following reasons. First, it is not feasible to consent every patient and clinician and as mentioned this initiative would occur with or without the study of it. Second, if members of the control group were consented, they would know they were being studied and this could change their behavior. This could potential disrupt the design of the study and make interpretation of the findings challenging. Third, clinicians are not being forced to prescribe statins for their patients. Instead, they are being reminded of evidence-based guidelines and offered an opportunity to review pertinent information and prescribe a statin. This is no different than standard of care in which a clinician would review the same information

and decide to prescribe a statin or not. The initiative is simply a reminder for the clinician and makes their standard of care process easier to conduct.

8.2 Procedures

--Interventions--

The clinician nudge using monthly peer comparison messages will be sent as an inbox message through the electronic health record. Clinicians will be told what percent of their eligible patients have been prescribed a statin and how that compares to peer clinicians at Penn Medicine. If the prescribing rate is below the median, the clinician will be compared to the median. If it is above the median, the clinician will be compared to 'top performers' defined as the 90th percentile. If the clinician is a top performer, they will be informed of that.

The clinician nudge using an active choice intervention in the electronic health record will be delivered to the clinician when he or she opens the patient's chart during the patient's visit and is on the test ordering page. This will be through a Best Practice Advisory that describes the guideline criteria for which the patient is eligible for statin therapy, provides preselected options for a statin (based on if the patient meets criteria for a moderate or high dose) with alternative options.

The patient nudge will be a message sent by text message. Patients with a new or return visit with their primary care clinician either in-person or via telemedicine will be identified and sent this message 72 hours prior to their appointment. The message will remind them of the visit, inform them of their eligibility for a statin, describe the benefits and risks of statin therapy, provide a link to a shared decision-making tool for statin therapy, and ask the patient to discuss statin therapy with their primary care clinician during the visit.

--Data--

Data on primary care clinicians and their patients at Penn Medicine will be obtained from Penn Data Store and Clarity (Epic's data reporting database). Clinician data includes demographic information (age, race, gender, type of medical degree, etc.) and may be also obtained from publicly available databases or websites online. Patient information includes demographic information, information about comorbid conditions (including diabetes, hypertension, and chronic kidney disease, and comorbid conditions needed to calculate the Charleston Comorbidity Index), laboratory test results (total cholesterol, triglycerides, LDL-C, HDL-C, liver function tests, creatinine, and glomerular filtration rate), and any contraindications to statin prescription (allergies or history of adverse reactions).

--Randomization—

Primary care practice level randomization will occur electronically. For the 4-arm parallel trial (4 groups), practices will be randomized using block sizes of 4 and stratifying on 7 groups of 4

practices based on mean statin prescribing rate. This method will ensure that the 4 arms each of 7 practices and are well balanced.

9. Analysis plan

Prior to analyses, we will produce data summaries to assess data quality, data distribution, and randomization success. All analyses will be performed using an intention-to-treat approach. To ensure even comparison across practices and arms, we will classify eligible patients at 72 hours before a scheduled appointment for a new or return visit with their primary care clinician as being in the study sample. Patients who do not show up to the clinician visit will be consider to have not received a statin unless one was prescribed within the 72 hour window prior to the visit.

Using retrospective data from our health system and conducting simulations, we estimate that we have at least 90% power to detect a 5-percentage difference in the statin prescribing rate for the clinician and patient main effects and at least 80% power to detect an 8-percentage point change in the clinician-patient interaction effects. This estimate uses retrospective data on 189 clinicians at Penn Medicine as its baseline and assumes 3000 patient visits over a 6-month period.

The primary analysis will fit mixed effects models with the patient as the unit of analysis to evaluate the odds of statin prescription (or change in other variables), adjusting for time, baseline statin prescription rates in the pre-intervention period, and clustering at the level of the practice and clinician. To obtain the adjusted difference in the percentage of patients prescribed a statin and 95% confidence intervals, we will use the bootstrap method, resampling patients 1000 times. Resampling of patients will be conducted by clinician to maintain clustering at the clinician and practice site level.

We will control for multiple testing using a structured testing approach that is designed for a 2x2 factorial trial in which we will prioritize testing for main effects, followed by interaction effects. We will first test the null hypothesis of either a main effect of clinician nudge or patient nudge at an alpha level of 0.05; if this test is rejected, we will test (i) the null hypothesis of no main effect of clinician nudge; (ii) the null hypothesis of no main effect of patient nudge at an alpha level of 0.05; if both of these tests are rejected, we will test for an interaction at an alpha level of 0.05. This sequential structured testing procedure controls the familywise Type I error rate at a level of 0.05 and has greater power for testing main effects than a Bonferroni approach.

We will perform subgroup analyses using available participant sociodemographic characteristics including age, sex, and race/ethnicity to evaluate for differences in change in statin prescription rates. If differences in outcomes exist, we will fit a fully adjusted model that includes these covariates and interaction terms with the treatment arms to evaluate for statistical significance.

10. Investigators

Mitesh Patel, MD, MBA, MS is the Principal Investigator (PI) and is a the Ralph Muller Presidential Ralph Muller Presidential Associate Professor of Medicine and Health Care Management at the Perelman School of Medicine and The Wharton School at the University of Pennsylvania. He has past experience leading clinical trials to deploy interventions impacting patient care and outcomes. He currently spends 80% of his effort on research and 20% on clinical and teaching activities.

David Asch, MD, MBA is a co-investigator and is a Professor of Medicine and a Professor of Health Care Management at the Perelman School of Medicine and The Wharton School at the University of Pennsylvania and the Executive Director at the Center for Health Care Innovation at the University of Pennsylvania. He has extensive past experience conducting research, designing and leading clinical trials, and implementing new policies to improve patient care.

Srinath Adusumalli, MD, MSc, FACC is a co-investigator and an Assistant Professor of Clinical Medicine at the Perelman School of Medicine, a general cardiologist, echocardiographer, and assistant cardiovascular disease fellowship program director at the Hospital of the University of Pennsylvania. He has previous experience conducting research studies and deploying active choice interventions directed at statin prescription within the electronic health record.

11. Human research protection

11.1 Data confidentiality

Computer-based files will only be made available to personnel involved in the study through the use of access privileges and passwords. Wherever feasible, identifiers will be removed from study-related information. Precautions are already in place to ensure the data are secure by using passwords and HIPAA-compliant encryption.

11.2 Subject confidentiality

Data on clinicians and patients will be obtained from Epic and Penn Data Store. Any information that is obtained will be used for research purposes only. Information on patients will only be disclosed within the study team and to the patient's primary care clinician. All study staff will be reminded of the confidential nature of the data collected and contained in these databases.

Penn Medicine Academic Computing Services (PMACS) will be the hub for the hardware and database infrastructure that will support the project and where the project web portal is based. PMACS is a joint effort of the University of Pennsylvania's Abramson Cancer Center, the Cardiovascular Institute, the Department of Pathology, and the Leonard Davis Institute. PMACS provides a secure computing environment for a large volume of highly sensitive data, including clinical, genetic, socioeconomic, and financial information. Among the

IT projects currently managed by PMACS are: (1) the capture and organization of complex, longitudinal clinical data via web and clinical applications portals from cancer patients enrolled in clinical trials; (2) the integration of genetic array databases and clinical data obtained from patients with cardiovascular disease; (3) computational biology and cytometry database management and analyses; (4) economic and health policy research using Medicare claims from over 40 million Medicare beneficiaries. PMACS requires all users of data or applications on PMACS servers to complete a PMACS-hosted cybersecurity awareness course annually, which stresses federal data security policies under data use agreements with the university. Curriculum includes HIPAA training and covers secure data transfer, passwords, computer security habits and knowledge of what constitutes misuse or inappropriate use of the server.

11.3 Subject privacy

All efforts will be made by study staff to ensure subject privacy. Data will be evaluated in a de-identified manner whenever possible.

11.4 Data disclosure

Information on patients will only be disclosed within the study team and to the patient's primary care clinician (to whom this information is already available).

11.5 Data and safety monitoring

A Data and Safety Monitoring Board (DSMB) is an independent group of experts convened to protect the safety of research subjects and to ensure that the scientific goals for the project are being met. The DSMB will be appointed by and act in an advisory capacity to the National Institute on Aging (NIA) to monitor participant safety, data quality and to evaluate the progress of the study. Adverse events will be tracked during the intervention period via monitoring of the electronic health record.

11.6 Risk/benefit

11.6.1 Potential study risks

There are minimal risks to primary care providers (PCPs) and patients in this trial. Prescribing a statin is a standard of care for these patients. Statins have rare side effects that could impact some patients include muscle pain and damage to muscle cells that could impact renal or liver function. We will minimize risk by removing any patients with an adverse event or allergy related to statins that is documented with the electronic health record (EHR). We will also remove any patients with glomerular filtration rate less than 30 (requires dose reduction for statins) or hepatitis (elevated liver enzymes). While interventions will be targeted to PCPs, it ultimately their decision whether or not to use the platform to review patients and prescribe a statin.

There is a risk of breach of data and confidentiality. To minimize the risk of breach of data and confidentiality, we will use secure, encrypted servers to host the data and conduct the analysis. The Penn Medicine Academic Computing Services (PMACS) will be the hub for the hardware and database infrastructure that will support the project. The PMACS provides a secure computing environment for a large volume of highly sensitive data, including clinical, genetic, socioeconomic, and financial information. All members that access data must complete HIPAA (health insurance portability and accountability act) training including secure data transfer, passwords, computer security habits and knowledge of what constitutes misuse or inappropriate use of the server. Only trained study staff will have access to the code that links the unique identifier to the subject's identity.

11.6.2 Potential study benefits

Statin therapy can reduce the risk of cardiovascular events for eligible patients but it is under-prescribed. The EHR could be utilized to identify eligible patients and to nudge providers to prescribe them. The knowledge gained on how to increase evidence-based statin prescribing rates could be applied to other populations and implemented at other health systems. PCPs may benefit from receiving feedback on their performance and having the EHR proactively remind them when patients are eligible.

11.6.3 Risk/benefit assessment

The risk/benefit ratio is highly favorable given the potential benefit from eligible patients being prescribed a statin, that prescription and monitoring of a statin is within the standards of care in a primary care practice, and that efforts have been put into place to minimize the risk of breach of data.

Final Protocol

No changes from the Original Protocol