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SPECIAL ARTICLE

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Pragmatic evaluation of events and benefits of lipid lowering in older adults (PREVENTABLE): Trial design and rationale

Jacob Joseph MBBS, MD[1] | Nicholas M. Pajewski PhD[2] | Rowena J. Dolor MD, MHS[3] | Mary Ann Sellers RN[3] | Letitia H. Perdue MS[2] | Sheronda R. Peeples AS, CCR[4] | Adam M. Henrie PharmD, MS[5] | Nancy Woolard[2] | W. Schuyler Jones MD[3] | Catherine P. Benziger MD, MPH[6] | Ariela R. Orkaby MD, MPH[7] | Amanda S. Mixon MD, MS, MPH[8] | Jeffrey J. VanWormer PhD[9] | Michael D. Shapiro DO[2] | Christine E. Kistler MD, MASc[10] | Tamar S. Polonsky MD, MSCI[11] | Ranee Chatterjee MD, MPH[3] | Alanna M. Chamberlain PhD, MPH[12] | Daniel E. Forman MD[13] | Kirk U. Knowlton MD[14] | Thomas M. Gill MD[15] | L. Kristin Newby MD, MHS[3] | Bradley G. Hammill DrPH[3] | Mine S. Cicek PhD[12] | Neely A. Williams MDiv, EdD[16] | Jake E. Decker MD[17] | Jiafu Ou MD[18] | Jack Rubinstein MD[19] | Gaurav Choudhary MD[20] | Raúl J. Gazmuri MD, PhD[21] | Kenneth E. Schmader MD[22] | Christianne L. Roumie MD, MPH[8] | Camille P. Vaughan MD, MS[23] | Mark B. Effron MD[24] | Rhonda M. Cooper-DeHoff PharmD, MS[25] | Mark A. Supiano MD[26] | Raj C. Shah MD[27] | Jeffrey C. Whittle MD, MPH[28] | Adrian F. Hernandez MD, MHS[3] | Walter T. Ambrosius PhD[2] | Jeff D. Williamson MD, MHS[2] | Karen P. Alexander MD[3] | on behalf of PREVENTABLE Trial Research Group

Correspondence
Jacob Joseph, Cardiology Section, Room 232, Building 35, Providence VA Medical Center, 830 Chalkstone Avenue, Providence, RI 02908, USA.
Email: jacob.joseph@va.gov

Abstract

Whether initiation of statins could increase survival free of dementia and disability in adults aged ≥75 years is unknown. PREVENTABLE, a double-blind, placebo-controlled randomized pragmatic clinical trial, will compare high-intensity statin therapy (atorvastatin 40 mg) with placebo in 20,000 community-dwelling

Group information appears in the Appendix where principal investigators and site coordinators are listed. Additional information at PreventableTrial.org.

Trial registration: ClinicalTrials.gov Identifier: NCT04262206 (https://clinicaltrials.gov/ct2/show/NCT04262206).

For affiliations refer to page 1709

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adults aged ≥75 years without cardiovascular disease, disability, or dementia at baseline. Exclusion criteria include statin use in the prior year or for >5 years and inability to take a statin. Potential participants are identified using computable phenotypes derived from the electronic health record and local referrals from the community. Participants will undergo baseline cognitive testing, with physical testing and a blinded lipid panel if feasible. Cognitive testing and disability screening will be conducted annually. Multiple data sources will be queried for cardiovascular events, dementia, and disability; survival is site-reported and supplemented by a National Death Index search. The primary outcome is survival free of new dementia or persisting disability. Co-secondary outcomes are a composite of cardiovascular death, hospitalization for unstable angina or myocardial infarction, heart failure, stroke, or coronary revascularization; and a composite of mild cognitive impairment or dementia. Ancillary studies will offer mechanistic insights into the effects of statins on key outcomes. Biorepository samples are obtained and stored for future study. These results will inform the benefit of statins for increasing survival free of dementia and disability among older adults. This is a pioneering pragmatic study testing important questions with low participant burden to align with the needs of the growing population of older adults.

KEYWORDS
cognition, dementia, healthy aging, older adults, statins

INTRODUCTION

With the increasing numbers of people living into their 80s, 90s, and even 100s,[1] clinical trials are needed to inform the use of interventions targeted at healthy aging. In particular, scalable ways to extend health span, time without dementia, disability, and cardiovascular disease (CVD) are needed.[2] Conclusive evidence and guidelines support the use of statins to prevent initial and recurrent atherosclerotic CVD events in people aged <75 years. However, randomized evidence supporting the initiation of statins for primary prevention of CVD as well as cognitive impairment and disability in those ≥75 years is lacking.[3–5]

Statins promote cerebrovascular health and may decrease the incidence of vascular cognitive impairment and risk for Alzheimer's disease and related dementias (ADRD).[6–8] Some data suggest statins have no effect on cognitive impairment, while other data suggest statins contribute to cognitive impairment.[9–12] These observational studies are limited by confounding by indication, bias in outcome ascertainment, and heterogeneity across analytic approaches that render them inconclusive.[13,14] In addition to statins' potential role in ADRD reduction, they may delay the onset of disability. The strong

Key points

- Clinical trials tailored to questions of importance to healthy older adults are urgently needed due to increasing numbers of people living into their 80s, 90s, and even 100s.
- It is unknown if statins could prolong healthy life years without dementia and disability in adults aged ≥75 years.
- PREVENTABLE will be the largest trial conducted in adults ≥75 years in the United States and is tailored to answer key clinical questions while limiting participant burden.

Why does this paper matter?

This pragmatic trial is employing methodologies that limit the burden on participants while also obtaining high-quality evidence in support of the effectiveness of the intervention on key study outcomes. Results will establish whether initiating a high-intensity statin is effective in lengthening health span in older patients without heart disease or dementia.

association between CVD and decline in physical function suggests that statins may be useful to preserve physical function in older adults; however, previous statin trials did not enroll enough participants aged ≥75 years at risk for functional decline, thus the contribution of statins to preserve or benefit physical function in older adults is unknown.[15–18] Recent evidence supports the knowledge that the risk of myalgia with statin use is infrequent, and most muscle symptoms in those on statins were similar to those on placebo.[19,20] High-quality evidence for prescribing statins and other scalable measures directed at optimizing healthy life years is therefore needed.[21]

PREVENTABLE (PRagmatic EValuation of evENTs And Benefits of Lipid-lowering in oldEr adults) will address these knowledge gaps as the first trial to randomize older adults to a statin or placebo and follow them for a non-CVD primary outcome. This pragmatic trial is well underway to enroll participants aged ≥75 years free of atherosclerotic CVD, dementia, or disability at enrollment from the Patient Centered Outcomes Research Network (PCORnet), Veterans Affairs (VA) healthcare system, and other participating health systems. Utilizing a double-blind, placebo-controlled randomized trial design, PREVENTABLE will evaluate the risks and benefits of a high-intensity statin compared with placebo on universally important outcomes for healthy aging. In addition, ancillary studies will offer mechanistic insights into the effects of statins on key outcomes (Appendix S1). Results will guide the evidence-based use of statins and other aging insights to care for this important and expanding segment of the population.

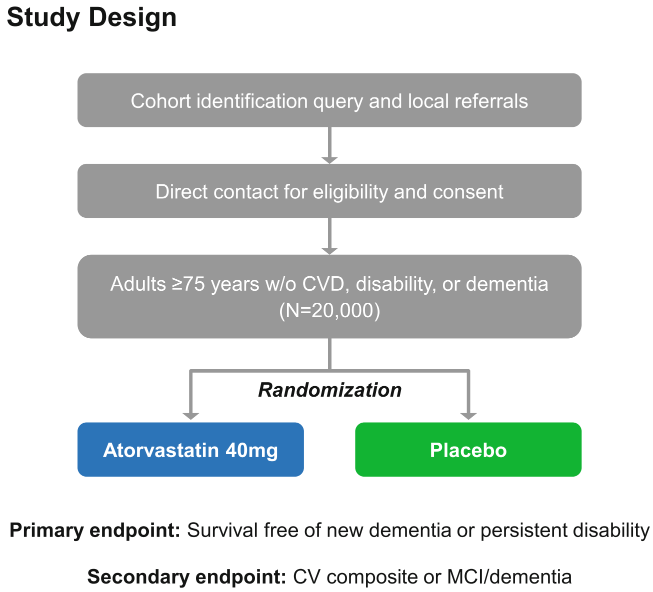

FIGURE 1 PREVENTABLE study design.

METHODS

PREVENTABLE plans to randomize 20,000 community-dwelling adults aged ≥75 years without CVD, dementia, or significant disability at baseline to receive atorvastatin 40 mg daily or matching placebo. Participants will be followed for up to 6 years (estimated median 3.5–4 years). (Figure 1). Participants will be enrolled from approximately 100 health system and VA hospital sites. Potentially eligible participants will be identified from lists generated from electronic health records (EHR) and by engaging community organizations and clinicians serving older adults. Efforts to include Black/African-American and Hispanic/Latinx participants are a high priority to ensure results are meaningful for these groups. The protocol was finalized in May 2020 to allow virtual enrollment during the COVID-19 pandemic. The first participant was enrolled on September 1, 2020.

PREVENTABLE aims to determine the role of a high-intensity statin in preventing dementia and prolonging disability-free survival in a broad and inclusive population of older patients; and secondarily to determine the role of high-intensity statin in preventing cardiovascular hospitalization or CVD-related death and mild cognitive impairment or dementia. The collection of biospecimens at baseline will advance opportunities for precision health in older adults. The PREVENTABLE Trial is similar to the ongoing STAREE trial in patients older than 70 years (A Clinical Trial of STAtin Therapy for Reducing Events in the Elderly in Australia; https://clinicaltrials.gov/ct2/show/NCT02099123).[22] Despite differences in design and implementation, the similarities in the research question have the potential to enhance the understanding of outcomes overall and across subgroups.

Pragmatic features

Trials have key features that can be placed on a continuum from explanatory to pragmatic, based on the requirements of the study. PREVENTABLE has many pragmatic features as assessed by the PRECIS-2 tool to rate domains of trial design using a scale from 1 (very explanatory) to 5 (very pragmatic).[23] Trial domains included are study eligibility, recruitment, setting, organization, flexibility of delivery and adherence to intervention, follow-up, outcomes, and analysis. PREVENTABLE's broad eligibility, flexible adherence and delivery of study drug, primary outcome, and data collection (EHR, National Death Index, and Medicare) are very pragmatic. Features that lean toward explanatory include randomization to study drug, inclusion of large institutional networks, call center collection of cognitive and disability outcomes, and the work of recruitment (Figure 2).

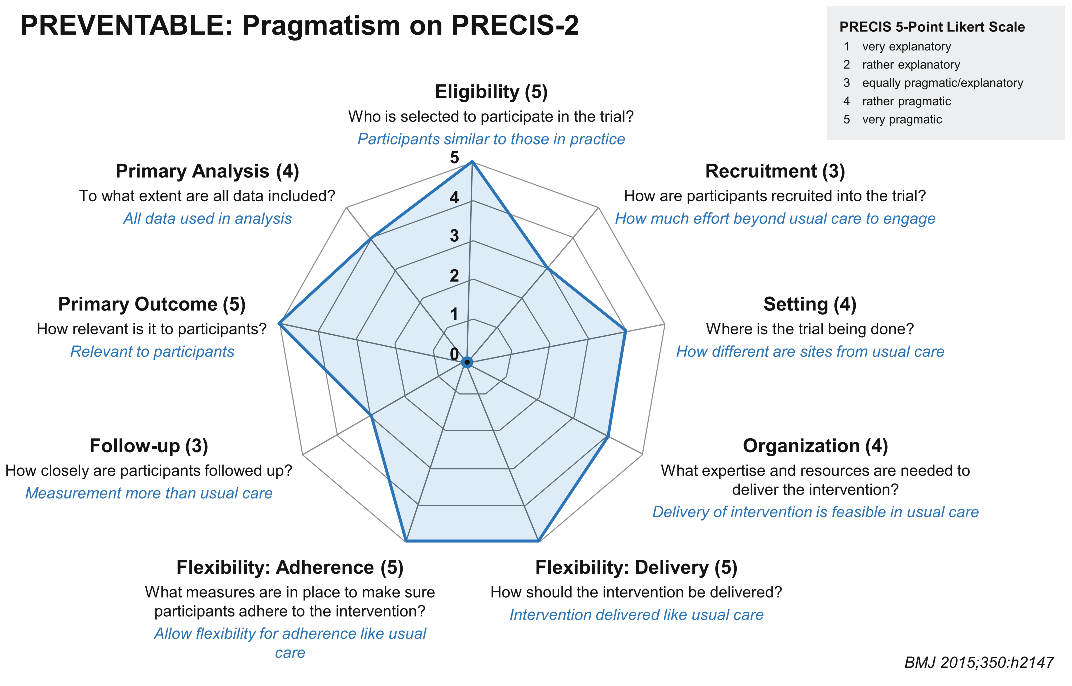

FIGURE 2 PREVENTABLE pragmatism on PRECIS-2.

Patient-stakeholders

Patient-stakeholders are included at every stage with representation on their own committee (the PREVENTERS). The patient perspective is included in other committees to ensure the study remains patient-centered. To promote patient engagement, we employ multiple avenues including newsletters, a website with patient-facing material (https://preventabletrial.org), and social media presence, in addition to the efforts of the PREVENTERS.

Study population and recruitment

Eligibility criteria provide for a broadly inclusive population (Table 1), emphasizing the inclusion of minority populations and older adults with multimorbidity who are traditionally under-represented in clinical trials. Financial supplements were added in recognition of the need to screen higher numbers of potentially eligible participants using multiple recruitment approaches (mail, phone, in-person) for effective recruitment. Resources allocated to support the effort include recruitment materials in English and Spanish including brochures, flyers, postcards, Frequently Asked Questions, posters, self-mailers, greeting cards, social media presence, and weekly Zoom meetings for potential participants.

TABLE 1 PREVENTABLE inclusion and exclusion criteria.

Inclusion criteria	• Community-dwelling adults • Age ≥75 years • English or Spanish as primary language
Exclusion criteria	• Clinically evident cardiovascular disease defined as prior myocardial infarction, prior stroke, prior revascularization procedure, or a secondary prevention indication for a statin (clinician determined) • Hospitalization for a primary diagnosis of heart failure in the prior 12 months (Note: History of heart failure in the absence of recent hospitalization or clinically evident cardiovascular disease is not an exclusion) • Dementia (clinically evident or previously diagnosed) • Dependence in any Katz Basic Activities of Daily Living (with the exception of urinary or bowel continence) • Severe hearing impairment (preventing phone follow-up) • Unable to talk (preventing phone follow-up) • Statin use in the past year or for longer than 5 years previously (participant reported) • Ineligible to take atorvastatin 40 mg (clinician determined) • Documented intolerance to statins • Active liver disease

Intervention

Participants are randomized via a random number generator 1:1 to atorvastatin 40 mg or matching placebo taken once daily. Atorvastatin 40 mg was chosen based on evidence of efficacy and common use. In pivotal clinical trials for regulatory approval, 39,828 patients received atorvastatin doses ranging from 10 to 80 mg, of which 2800 patients (7%) were ≥75 years (Table S1).[24] In these studies, there were no differences in safety or effectiveness of atorvastatin in younger versus older patients. Atorvastatin 40 mg daily is a high-intensity statin dose that leads to a 50% low-density lipoprotein-cholesterol (LDL-C) reduction, is well tolerated, and will avoid the risk of under-treatment as a potential concern.[25,26] In practice, older adults tolerate statins similarly to younger adults supporting this dose selection.[27] PREVENTABLE is exempt from the Investigational New Drug (IND) regulations [21 CFR 312.2 (b)(1)].

The VA Cooperative Studies Program Clinical Research Pharmacy Coordinating Center (Albuquerque, NM) is the central pharmacy. The central pharmacy acquires atorvastatin 40 mg tablets, manufactures matching placebo tablets, and packages products into bottles. Following receipt of an order, study drug is labeled and shipped directly to participants every 90 days via the United States Postal Service (USPS). Orders are renewed either annually (non-VA sites) or every 3 months (VA sites), at which time the site investigator confirms continuing eligibility for study drug. Data integrations between the study database, the VA, the central pharmacy, and USPS facilitate order transmission as well as communication about shipping address changes, discontinuation of study drug, and shipment delivery. Participants, treating clinicians, study team, and personnel involved in endpoint capture are unaware of the treatment allocation.

Schedule of events

PREVENTABLE streamlines work for the participant and study site (Table 2). The site uses a computable phenotype, developed specifically for the study by the Data Coordinating Center and the VA Network Coordinating Center, to identify and generate recruitment lists of potentially eligible participants. The computable phenotype includes code lists and logic that sites use to implement the study eligibility criteria while querying their EHR data. Using in-person or remote contact, the site confirms eligibility and enrolls those who consent. The site is also responsible for annual confirmation of suitability to continue receiving study drug. Data queries on hospitalizations and laboratory testing will be used for safety and endpoint determination. The Geriatrics Outcomes Assessment Center at Wake Forest University School of Medicine (Winston-Salem, NC) is responsible for baseline and annual phone-based assessments of cognitive and physical function.

TABLE 2 Schedule of PREVENTABLE study visits.

Procedures Timeline	Baseline (Visit 1) 0	Baseline call (Visit 2) 2 weeks	Follow-up (Visit 3) 3 months	Follow-up call (Visit 4) 12 months	Follow-up call (Visit 5) 24 months	Follow-up call (Visit 6) 36 months[a]	Final Visit call (Visit 7) EOS
Informed consent	X						
Study enrollment	X						
Randomization		X					
Demographics, medical history	X						
ADL screen	X						
Study blood draw—lipid panel	X[b]		X[c]				
Study blood draw—Biorepository	X[b]						
Use/eligibility of study drug (site)	X			X	X	X	
Review of eligibility for study drug				X	X	X	
Cognitive function		X		X	X	X	X
Physical function (ADL and PROMIS-PF)		X		X	X	X	X
SPPB	X[b]						

Abbreviations: ADL, activities of daily living; EOS, end of study; SPPB, Short Physical Performance Battery.
[a]Then every 12 months until EOS.
[b]For participants enrolled by telehealth, blood draw and SBBP may be obtained separately in-person.
[c]Subset of participants.

During the enrollment visit, a member of the study team reviews study information and collects baseline medical history. If the visit is in-person, they also collect blood and the Short Physical Performance Battery (SPPB). Trained personnel at Wake Forest collect the baseline memory tests. A subset of study participants (approximately 2000) will return for a repeat lipid panel at 3 months. If the participant enrolls virtually, the lipid panel and physical assessments will not be completed. After randomization, all follow-up procedures such as harvesting data from the medical record and phone calls and screening/evaluation for dementia and disability are performed centrally. The study drug is mailed directly to the participant reducing participant burden. Participants are provided a handout and a wallet card that explain what they should do and who to contact if they experience any new symptoms or side effects while participating in the study. The primary clinician is made aware of their patient's participation and are included in clinical management if needed.

Safety

Patient-level meta-analysis from randomized trials and placebo-controlled cross-over studies in statin-intolerant patients support the tolerability of statins.[19,20,28] When safety concerns arise, they will be addressed by the study team with routine healthcare follow-up and treatment. Adverse event data is collected through the EHR, rather than site reported. Reporting is governed by the Common Rule (45 CFR Part 46, Subpart A), as well as International Council for Harmonization Guidelines, institutional review boards (IRBs), and local regulations. In addition, an independent data safety monitoring board (DSMB) appointed by the National Institute on Aging (NIA) reviews aggregate safety events. These include primary and secondary endpoints, reasons for stopping study drug, hospitalizations, events of special interest, and deaths. Events of special interest include new-onset diabetes, hepatic failure, myositis, and cancer. Circumstances that warrant termination or suspension include, but are not limited to, unexpected, significant, or unacceptable risk to participants, inadequate compliance with protocol requirements, incomplete or unevaluable data, or determination of futility by the DSMB.

Biorepository

The Biorepository Core provides coordination and logistical support for collection, processing, and storage of baseline samples from randomized participants and samples from 2000 participants in follow-up. Figure S1 outlines the baseline specimen collection. Each participant able to participate in the biorepository collection provides a total of 20 cc whole blood that will include a 10 cc ethylenediaminetetraacetic acid tube (for plasma and buffy coat) and a 10 cc red top (for serum) for a total of 9 aliquots available for future studies. Participation in the biorepository sample collection is optional for participants enrolled virtually due to the pandemic.

Trial organization

The study is overseen by the Steering Committee, along with its subcommittees, in partnership with the NIA and National Heart, Lung, and Blood Institute (NHLBI). The Steering Committee includes representatives from clinical sites and core operational groups (Biorepository; Recruitment, Retention, and Adherence; Geriatric Outcomes Assessment; Ancillary Studies; Central Pharmacy; and the PREVENTERS). The Clinical Coordinating Center at Duke University (Durham, NC) is responsible for study coordination, site management, communication, single IRB coordination, and financial administration. The Data Coordinating Center is responsible for the treatment allocations, electronic case report forms, study website, receipt and processing of data, quality control programs, coordination and tracking for central units, and statistical analysis and reporting. Committee members are listed in the Appendix S1. In accordance with the NIH's single IRB mandate for multicenter research, the single IRB of record for non-VA sites is the Duke University IRB (Durham, NC) and for the VA sites is the Veterans Affairs Central IRB (cIRB) (Washington, DC).

Outcomes definitions

Primary and secondary outcomes

The primary outcome is survival free of new dementia or persistent disability. The co-secondary outcomes are (1) the composite of cardiovascular death, hospitalization for unstable angina or myocardial infarction, heart failure, stroke, or coronary revascularization; and (2) the composite of mild cognitive impairment (MCI) or dementia.

Cognitive outcomes

Participants will be categorized at baseline and follow-up as having no cognitive impairment (NCI), MCI, or probable dementia. A phone cognitive battery will be administered by the Central Call Center to all participants using the Telephone Interview for Cognitive Status-Modified (TICS-

M)[29,30] which will be repeated annually during follow-up. Participants suspected of having possible cognitive impairment will undergo The Extended Cognitive Assessment Battery (National Alzheimer's Coordinating Center Uniform Data Set Version 3).[31] For more detailed assessment of cognitive functions along with the Patient Health Questionnaire (PHQ)-8,[32] the Functional Assessment Questionnaire (FAQ) will be administered to a trusted contact familiar with the participant's daily function.[33] All tests, questionnaires, and data from the EHR and Medicare claims relevant to cognitive impairment will be submitted to a centralized, web-based system for adjudication by a panel of dementia experts who will assign final study classifications of NCI, MCI, or probable dementia.[34]

At annual follow-up, cognitive assessment will generally use the same process as baseline, with the exception of adding the Dementia Questionnaire (DQ) administered to a previously identified trusted contact if the participant passes away or otherwise cannot be contacted.[33,35] The DQ will be administered if it has been more than 6 months since the participant's last planned cognitive assessment. Annual cognitive assessments will stop after a participant is classified as having probable dementia. Details about the criteria to be used for classifying incident MCI and probable dementia are available in the Appendix S1. Even though an adjudicated event is not equivalent to a clinical diagnosis, the site study team will be notified of probable dementia adjudication; if the participant has given permission, the study team will notify the primary clinician for clinical evaluation.

Functional outcomes

Persistent disability is defined as loss of independence in one or more basic activities of daily living (ADL), except for urinary or bowel continence, at 2 visits at least 3 months apart (to exclude transient loss of function), reported by the participant or trusted contact.[36,37] Since muscle-related limitation due to statin use is a concern in this trial, we administer the Short Performance Physical Battery (SPPB) at baseline that includes assessment of lower extremity function if possible.[38] Functional assessment will also include telephone screening for physical function and disability using the PROMIS 20-item physical functioning scale at baseline and annually thereafter or until a participant is classified as having a persistent disability.[39] A decline in PROMIS physical functioning scale of ≥2 points is associated with subsequent disability. Similar to cognitive outcomes, the Katz ADL will be administered to a trusted contact and used to assess disability if other methods are not possible. Any report of new dependence ≥1 Katz ADL will be confirmed 3 months later in order to classify as new persistent disability.

All-cause mortality

Mortality data will be captured from the site death report form, Medicare beneficiary status change, and National Death Index (NDI). If the central study teams are the first to learn of a participant's death, that information will be relayed to the site.

Cardiovascular outcomes

Deaths will be captured and classified as cardiovascular or non-cardiovascular (malignancy or "other") using site death report form and NDI data, complemented by hospitalization records as necessary and available. Cardiovascular hospitalizations (myocardial infarction, unstable angina, coronary revascularization, heart failure, and stroke) will be captured from EHR databases complemented by Medicare claims data.

Other outcomes

We will capture all-cause hospitalizations and days spent at home.[40,41] Individual components of the primary outcome such as self-reported physical function derived from PROMIS-PF and cognitive function based on TICS-M will also be evaluated as independent secondary endpoints.

Statistical analysis

Primary outcome

Based on the intention-to-treat principle, we will compare treatment groups using a Cox proportional hazards regression model, stratifying the baseline hazard function by site.[42] The hazard ratio from this model, with associated 95% confidence intervals, will be our primary measure of treatment effect. We will not formally test the proportional hazards assumption of the Cox model,[43] instead we will compute complementary treatment group estimates using the restricted mean survival time, calculated at 2 and 4 years of follow-up.[44]

Secondary outcomes

Given the competing risk of non-cardiovascular death, analyses for the cardiovascular secondary outcome will be based on the subdistribution hazard model of Fine–Gray,[45] stratified by clinic site. We will follow recommendations for the reporting of such analyses,[46] describing hazard ratios from the Fine–Gray model with respect to the cumulative incidence function for the event of interest. The secondary outcome of MCI or probable dementia is subject to both interval-censoring due to intermittent ascertainment, as well as the competing risk of death. We will therefore utilize the same framework of the Fine–Gray subdistribution hazard model, combined with sensitivity analyses using multiple imputation to address the influence of interval-censoring.[47,48] Hypothesis tests for secondary endpoints will be 2-sided, employing an unequal allocation of the alpha level to control the type I error rate for the secondary hypotheses. Because we expect a higher event rate for the composite of MCI or probable dementia versus CVD, the alpha level for the secondary endpoints will be partitioned unevenly as 4% for CVD and 1% for MCI/probable dementia.

LDL-C reductions

Adherence will be determined in a pragmatic manner utilizing the number of days a participant had medication available during the study period. We will also estimate the magnitude of achieved reductions in LDL-C with atorvastatin 40 mg by comparing changes in LDL-C levels between baseline and 3 months of follow-up in the lipid panel subgroup ($n = 2000$). These analyses will be based on linear mixed models using 3-month LDL-C as the outcome, incorporating site-specific random effects, and adjusting for baseline LDL-C levels. We will report absolute and percent reductions in LDL-C.

Subgroups

Recognizing that analyses of treatment effect heterogeneity are typically underpowered, a limited number of pre-specified subgroup analyses will be conducted for the primary and secondary outcomes. Analyses will include formal tests of interaction within Cox regression or Fine–Gray subdistribution hazard models as appropriate. The nominal *p*-value for the interaction term using a likelihood ratio test will be reported along with within subgroup estimates of the intervention effect and associated nominal 95% confidence intervals. Subgroups of interest, defined according to baseline characteristics, will include: sex; race; ethnicity; estimated life expectancy based on the modified Lee Index[49] (≤7 [<20% risk of 5-year mortality], 8–12 [20 to ≤50% 5-year mortality risk], or > 12 [≥50% 5-year mortality risk]); baseline physical function (if available) based on the SPPB (<10 vs. ≥10)[38]; multimorbidity (median split); baseline LDL-C (median split); and diabetes at baseline. Finally, to control for multiplicity among the pre-specified subgroups, we will also report adjusted p-values based on the Holm sequential procedure.[50]

Sample size and statistical power

Primary outcome

Power calculations were informed by data in adults ≥75 years without a history of CVD from the Systolic Blood Pressure Intervention Trial (SPRINT)[51] and the Aspirin in Reducing Events in the Elderly (ASPREE) trial.[52] These trials indicated an expected CVD rate of roughly 30–40 events per 1000 person-years. We further assumed that atorvastatin 40 mg would lead to a 20% reduction in the primary outcome in a hypothetical scenario with full adherence. However, non-negligible cross-over between the treatment groups is certainly expected, driven by statin intolerance and placebo participants experiencing CVD events that would warrant a statin for secondary prevention. Medication data from Australia indicated that in adults ≥75 years, approximately 27.3% of those initiating a statin will discontinue use of the medication over a mean follow-up of 5 years.[53] However, among those who discontinue, about 25% will reinitiate statin treatment. Based on these estimates, we assumed that 20% of participants randomized to atorvastatin would discontinue and not reinitiate statin treatment. Similarly, we assumed that 10% of participants randomized to placebo would initiate statin treatment during follow-up. These assumptions imply that cross-over would reduce the assumed treatment effect of a 20% reduction to 14.3% (hazard ratio $= 0.857$).[54] Assuming a total study length of 5 years, a 2-year recruitment period, and 3% loss to follow-up per year, we estimated that 20,000 participants would provide 94.2% power (assuming an event rate of 32.6 per 1000 person-years based on ASPREE). These estimates were subsequently updated to reflect a longer anticipated recruitment window (~54 months [4.5 years]), with a total study length of 6.5 years, which increases the power estimate to 95.1%. We have considered sensitivity estimates examining higher rates of statin discontinuation. If the discontinuation rate in those randomized to atorvastatin increases to 25%, this reduces the assumed treatment effect to a hazard ratio of 0.867, and decreases power to 91.7%. Similarly, increasing the discontinuation rate to 30% decreases the assumed hazard ratio to 0.877, and reduces power to 86.9%.

Secondary outcomes

Power for the composite secondary outcome of MCI or probable dementia used analogous calculations, with two primary changes to the assumptions. First, the inclusion of MCI implies a higher expected event rate, estimated to be 61.2 events per 1000 person-years based on SPRINT. Second, this event rate was approximately double what we expected to observe for the secondary cardiovascular endpoint. Therefore, we planned an unequal partition of the type I error rate, allocating 1% to the MCI/probable dementia composite and 4% to the CVD endpoint. Based on these assumptions, we estimated that 20,000 participants would have 98.3% power to detect a 14.3% reduction in the combined incidence of MCI or probable dementia.

With respect to CVD, meta-analyses indicate an approximate 22% reduction in the risk of major atherosclerotic CVD events per 1 mmol/L (39 mg/dL) reduction in LDL-C.[25,55] We estimated that the baseline LDL-C levels in the cohort would be 110–120 mg/dL (2.84–3.10 mmol/L). Assuming a 50% LDL-C reduction with atorvastatin 40 mg (i.e., mean decreases of 1.42–1.55 mmol/L), this would correspond to about a 30% relative risk reduction (hazard ratio = 0.70). With similar assumptions for cross-over as for primary outcome (20% statin discontinuation and 10% cross-over from placebo), this reduces the assumed effect to a hazard ratio of 0.783. There is some uncertainty about the expected incidence of CVD in this population, as estimates vary widely from trials like ASPREE (14.1 events per 100 person-years) versus SPRINT (31.2 events per 100 person-years).[34] A sample size of 20,000 participants would provide >99.0% power. Using the rate from SPRINT, though this is reduced to 95.6% assuming the lower assumed rate from ASPREE. If the strength of the assumed treatment effect is reduced to a hazard ratio of 0.857 (consistent with the primary outcome), then power is reduced to 95.01% (SPRINT rate) or 64.7% (ASPREE) rate.

Changes as a result of COVID-19

The trial adapted to the significant challenges due to COVID-19 by rapidly facilitating the adoption of remote consenting. The requirement for baseline labs and SPPB was waived, and additional payment was provided to acknowledge the additional effort needed to obtain labs and SPPB. In addition to an e-consent platform for enrolling participants at non-VA sites, new methods were added for remote consenting at VA sites. Novel approaches included phone consenting and the use of DocuSign for remote consenting, the use of VA Video Connect for virtual study visits, and Rights Management System (RMS) Outlook encryption to enable electronic communication with participants and family members. To mitigate the effects of study staff turnover at sites, the VA National Network provided support for regulatory activities.

CONCLUSION

PREVENTABLE is a landmark initiative to address a question of vital importance to old and very old US adults with multiple stakeholders including the participants themselves. This study will inform the benefit of initiating a high-intensity statin for the primary prevention of death, dementia, and physical disability as well as MCI and CVD in adults older than 75 years, especially in those with concomitant multimorbidity and frailty. The biorepository and ancillary studies provide opportunities for knowledge generation for dementia and cardiovascular science in older adults to inform which subgroups may benefit the most. The trial combines the rigor of traditional randomized controlled trials, with randomization, a double-blind and placebo-controlled intervention, and centralized primary outcome ascertainment with more pragmatic elements with real-world data for outcomes and study drug adherence. The primary study question seeks to identify a foundational and scalable way to increase independent life years among older adults without dementia or cardiovascular disease at baseline.

AUTHOR CONTRIBUTIONS

Study concept and design: Jacob Joseph, Nicholas M. Pajewski, Rowena J. Dolor, Mary Ann Sellers, Letitia H. Purdue, Sheronda R. Peeples, Adam M. Henrie, Nancy Woolard, W. Schuyler Jones, Christine E. Kistler, Daniel E. Forman, L. Kristin Newby, Bradley G. Hammill, Mine S. Cicek, Neely Williams, Mark B. Effron, Rhonda M. Cooper-DeHoff, Mark A. Supiano, Raj C. Shah, Jeffrey C. Whittle, Adrian F. Hernandez, Walter T. Ambrosius, Jeff D. Williamson, Karen P. Alexander. *Acquisition of participants and/or data*: Jacob Joseph, Nicholas M. Pajewski, Rowena J. Dolor, Ariela R. Orkaby, Amanda S. Mixon, Catherine P. Benziger, Jeffrey J. Van Wormer, Michael D. Shapiro, Christine E. Kistler, Tamar S. Polonsky, Ranee Chatterjee, Alana M. Chamberlain, Daniel E. Forman, Kirk U. Knowlton, Thomas M. Gill, L. Kristin Newby, Jake E. Decker, Jiafu Ou, Jack Rubinstein, Gaurav Choudhary, Raúl J. Gazmuri, Kenneth E. Schmader, Christianne L. Roumie, Camille Vaughan, Mark B. Effron, Mark A. Supiano, Raj C. Shah, Jeffrey C. Whittle. *Analysis and interpretation of data*: Jacob Joseph, Nicholas M. Pajewski, Rowena J. Dolor, W. Schuyler Jones, Adrian F. Hernandez, Walter T. Ambrosius, Jeff D. Williamson, Karen P. Alexander. *Preparation of manuscript*: All authors.

AFFILIATIONS

[1]VA Providence Healthcare System, Providence, Rhode Island, USA
[2]Wake Forest University School of Medicine, Winston-Salem, North Carolina, USA

[3]Duke Clinical Research Institute, Duke University School of Medicine, Durham, North Carolina, USA
[4]VA Boston Healthcare System, Boston, Massachusetts, USA
[5]Cooperative Studies Program Clinical Research Pharmacy Coordinating Center, Office of Research and Development, Department of Veterans Affairs, Albuquerque, New Mexico, USA
[6]Essentia Health, Duluth, Minnesota, USA
[7]New England Geriatric Research, Education, and Clinical Center (GRECC), VA Boston Healthcare System, and Division of Aging, Brigham & Women's Hospital, Harvard Medical School, Boston, Massachusetts, USA
[8]Vanderbilt University Medical Center and Geriatric Research Education and Clinical Center (GRECC), VA Tennessee Valley Healthcare System, Nashville, Tennessee, USA
[9]Marshfield Clinical Research Institute, Marshfield, Wisconsin, USA
[10]Department of Family Medicine, School of Medicine, University of North Carolina at Chapel Hill, North Carolina, USA
[11]University of Chicago Medicine, Chicago, Illinois, USA
[12]Mayo Clinic, Rochester, Minnesota, USA
[13]Department of Medicine, Sections of Geriatrics and Cardiology, University of Pittsburgh, Pittsburgh GRECC, VA Pittsburgh Healthcare System, Pittsburgh, Pennsylvania, USA
[14]Intermountain Healthcare, Salt Lake City, Utah, USA
[15]Yale School of Medicine, New Haven, Connecticut, USA
[16]TN CEAL, Nashville, Tennessee, USA
[17]Section of Primary Care Medicine, Medical College of Wisconsin, Milwaukee, Wisconsin, USA
[18]Cardiology Division, John Cochran VA Medical Center and Cardiology Division, Washington University School of Medicine, St. Louis, Missouri, USA
[19]Division of Cardiology, Cincinnati VAMC and Division of Cardiovascular Diseases, Department of Internal Medicine, College of Medicine, University of Cincinnati, Cincinnati, Ohio, USA
[20]Providence VA Medical Center, and Lifespan Cardiovascular Institute, Alpert Medical School of Brown University, Providence, Rhode Island, USA
[21]Captain James A. Lovell Federal Health Care Center, Rosalind Franklin University of Medicine and Science, Chicago, Illinois, USA
[22]Duke University and GRECC, Durham VA Medical Center, Durham, North Carolina, USA
[23]Birmingham/Atlanta Geriatric Research Education and Clinical Center (GRECC), Department of Veterans Affairs, and Division of Geriatrics & Gerontology, Department of Medicine, Emory University, Atlanta, Georgia, USA
[24]John Ochsner Heart and Vascular Institute, The University of Queensland Ochsner Clinical School, New Orleans, Louisiana, USA
[25]University of Florida, College of Pharmacy and College of Medicine, Gainesville, Florida, USA
[26]The University of Utah, Salt Lake, Utah, USA
[27]Family & Preventive Medicine and the Rush Alzheimer's Disease Center, Rush University, Chicago, Illinois, USA
[28]Clement J Zablocki VA Medical Center, Milwaukee, Wisconsin, USA

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ORCID

Nicholas M. Pajewski https://orcid.org/0000-0002-4447-6196
Nancy Woolard https://orcid.org/0000-0003-3900-6410
Catherine P. Benziger https://orcid.org/0000-0002-8992-6197
Michael D. Shapiro https://orcid.org/0000-0002-9071-3287
Christine E. Kistler https://orcid.org/0000-0003-0566-5741
Thomas M. Gill https://orcid.org/0000-0002-6450-0368
L. Kristin Newby https://orcid.org/0000-0002-6394-8187
Mine S. Cicek https://orcid.org/0000-0002-5629-2159
Jiafu Ou https://orcid.org/0000-0001-8831-9515
Raúl J. Gazmuri https://orcid.org/0000-0002-3848-7227
Camille P. Vaughan https://orcid.org/0000-0001-6713-794X
Mark A. Supiano https://orcid.org/0000-0002-5438-5087
Raj C. Shah https://orcid.org/0000-0001-9706-9730
Karen P. Alexander https://orcid.org/0000-0003-4418-1424

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

Ancillary studies.

Enrolling sites.

Cognitive adjudication in the PREVENTABLE trial.

Supplementary Table 1. Pivotal trials included in FDA label for atorvastatin.

Supplementary Figure 1. PREVENTABLE biospecimen collection.

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