STAREE-Mind Imaging Study: a randomised placebo-controlled trial of atorvastatin for prevention of cerebrovascular decline and neurodegeneration in older individuals

Ian H Harding 1,2, Joanne Ryan,3 Stephane Heritier,3 Simone Spark,3 Zachary Flanagan,3 Richard McIntyre,2 Craig S Anderson 4, Sharon L Naismith,5 Trevor T-J Chong,6 Michael O’Sullivan 7,7 Gary Egan,2 Meng Law,1 Sophia Zoungas,3 STAREE Investigator Group

ABSTRACT

Introduction  Cerebrovascular disease and neurodegeneration are causes of cognitive decline and dementia, for which primary prevention options are currently lacking. Statins are well-tolerated and widely available medications that potentially have neuroprotective effects. The STAREE-Mind Imaging Study is a randomised, double-blind, placebo-controlled clinical trial that will investigate the impact of atorvastatin on markers of neurovascular health and brain atrophy in a healthy, older population using MRI. This is a nested substudy of the ‘Statistics for Reducing Events in the Elderly’ (STAREE) primary prevention trial.

Methods  Participants aged 70 years or older (n=340) will be randomised to atorvastatin or placebo. Comprehensive brain MRI assessment will be undertaken at baseline and up to 4 years follow-up, including structural, diffusion, perfusion and susceptibility imaging. The primary outcome measures will be change in brain free water fraction (a composite marker of vascular leakage, neuroinflammation and neurodegeneration) and white matter hyperintensity volume (small vessel disease). Secondary outcomes will include change in perivascular space volume (glymphatic drainage), cortical thickness, hippocampal volume, microbleeds and lacunae, prefrontal cerebral perfusion and white matter microstructure.

Ethics and dissemination  Academic publications from this work will address the current uncertainty regarding the impact of statins on brain structure and vascular integrity. This study will inform the utility of repurposing these well-tolerated, inexpensive and widely available drugs for primary prevention of neurological outcomes in older individuals. Ethics approval was given by Monash University Human Research Ethics Committee, Protocol 12206.

Trial registration number  ClinicalTrials.gov identifier: NCT05586750.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Statins are well-established treatments for cerebrovascular disease, and may have additional neuroprotective properties.
⇒ Cerebrovascular damage is a core feature of neurodegenerative disease and a primary target for intervention.

WHAT THIS STUDY ADDS

⇒ Class I evidence regarding the impact of atorvastatin on brain health.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Guidance regarding the use of statins for primary prevention of neurological decline.

INTRODUCTION

Statins are a cornerstone to the treatment and secondary prevention of cerebral ischaemia, small vessel disease and cerebrovascular events including stroke.1 Emerging evidence has suggested that statins have the potential to reduce cognitive decline and neurodegeneration.2–4 Vascular risk factors and neurovascular damage are well-established predictors of neurodegeneration, defining features of Alzheimer’s disease (AD) and vascular dementia, and clear targets for intervention.5 6 Statins offer a well-tolerated and efficacious treatment or prophylactic option for maintaining brain health in older people.7 8 However, high-quality randomised clinical trials that have examined the effects of statins on contemporary imaging markers of neurovascular and neuroanatomical health are limited.

The primary mechanism of action of statins involves lowering the level of circulating low-density serum lipoprotein cholesterol levels.9 The beneficial effects of statins on the vasculature include reduction of atheroma burden, induction of angiogenesis, antithrombotic
actions and direct vascular benefits, statins also attenuate neuroinflammation—an early, enduring and detrimental feature of neurodegenerative diseases—through potent suppression of microglial activation and inhibition of cytokine production. Statins may also mitigate the aggregation of beta amyloid, a key factor in the development of AD, and inhibit production of oxygen-free radicals. Statins have thus emerged as potential disease-modifying drugs for age-related neurological disorders.

Magnetic resonance imaging (MRI) markers of neurovascular health and brain structure represent compelling potential surrogate endpoints of these effects. This may be particularly relevant early or prior to the manifestation of frank cognitive decline when imaging markers are likely more sensitive to clinically relevant change than behavioural measures. Previous imaging studies of statin effects in healthy older people have primarily focused on conventional markers of severe small vessel disease, namely white matter hyperintensities (WMHs), with mixed results. The PROSPER trial reported no effect on WMH volume (n=425). Recent meta-analyses indicate similar equivocal evidence of statin effects on white matter lesions. Oligoclonal evidence of statin effects on WMHs, with mixed results. The PROSPER trial reported no effect on WMH volume (n=425). Recent meta-analyses indicate similar equivocal evidence of statin effects on white matter lesions.

These findings were supported by subgroup analysis of a randomised controlled trial in 668 hypertensive patients aged 60 years and older, which indicated slowing of WMH growth over 5 years with rosuvastatin. On the other hand, post-hoc analysis of data from the SPRINT-MIND study reported that statin users (various treatments) were more likely to have WMH volume increases over time (n=425). Recent meta-analyses indicate similar equivocal evidence of statin effects on white matter lesions. These complex pathological markers may therefore be less sensitive to the impact of statin therapies relative to more subtle or earlier markers of neurovascular pathology.

Differing blood–brain permeability between the participants (ie, with hypertension, or cerebral small vessel disease or community sample) may account for the mixed findings. WMHs are also late-stage products of small vessel disease, formed by a constellation of robust oedema, gliosis, demyelination and axonal degeneration. These complex pathological markers may therefore be less sensitive to the impact of statin therapies relative to more subtle or earlier markers of neurovascular pathology.

Recent developments in imaging have identified sensitive MRI markers of subtle brain changes that may be specifically relevant to statin effects on vascular brain health. Specifically, local extracellular fluid changes in the brain, resulting from neuroinflammation, cerebral small vessel disease and/or neurodegeneration, can be readily quantified using diffusion-weighted imaging. These diffusivity or ‘brain free water’ (BFW) measures have been shown to be more sensitive to white matter damage, and more strongly correlated with cognition and levels of disability in cerebral small vessel disease than WMHs. In older people, changes in BFW precede the presentation of overt WMHs, predict the rate of subsequent cognitive decline, and correlate with functional outcomes with greater sensitivity than WMHs.

BFW is thus an early and potentially reversible marker of vascular pathology that can be readily quantified using diffusion-weighted imaging. Directly related to pathological increases in fluid diffusivity is the clearance of fluid from the brain via the perivascular spaces (PVSs)-glymphatic system. The PVS-glymphatic system is dedicated to draining away soluble waste proteins and toxic metabolic products such as Aβ protein and tau oligomers. A wider distribution and higher volume of PVS is a robust radiological feature of common cerebrovascular, neuroinflammatory and neurodegenerative diseases. Early evidence suggests a positive impact of statins on preventing accrual of enlarged PVSs. Cerebral perfusion and silent infarcts, such as cerebral microbleeds and lacunae, provide additional imaging markers of neurovascular health, which may be influenced by statin therapy. MRI markers of cerebral cortical thickness and white matter microstructure (eg, diffusion fractional anisotropy) provide complimentary measures both of primary neurodegenerative processes and the secondary impacts of neurovascular pathology. Robust characterisation and tracking of brain health and statin treatment effects can therefore be strengthened through the use of multi-modal imaging protocols.

The aim of the STAREE-Mind Imaging Study is to determine, in relatively healthy people aged ≥70 years without established cardiovascular disease, diabetes or dementia, the effect of statin therapy (40 mg atorvastatin) versus placebo on: 1. The primary outcomes of BFW fraction (ie, diffusivity) and WMH volume. We hypothesise that statin treatment will slow the rate of age-related increases in these measures. 2. Secondary outcomes of neurovascular measures including perivascular space volume, silent infarcts (microbleeds and lacunae count) and cerebral blood flow; and neurodegeneration measures including cortical thickness, hippocampal volume and white matter fractional anisotropy. We hypothesise that statin treatment will slow the rate of age-related change in these measures.

METHODS AND ANALYSIS
Study design
STAREE-Mind Imaging is a nested substudy of the Statins in Reducing Events in the Elderly (STAREE) double-blind, randomised, placebo-controlled prevention trial (ClinicalTrials.gov Identifier: NCT02099123). STAREE is investigating whether statins, when used for primary prevention, can reduce the coprimary outcomes of disability-free survival (a composite of all-cause death, dementia and persistent physical disability) and major cardiovascular events (a composite of cardiovascular deaths, non-fatal myocardial infarction or non-fatal stroke). STAREE-Mind Imaging will acquire a suite of brain MRI measures at baseline (prior to medication commencement) and after...
approximately 4 years follow-up to investigate the effect of statins on structural and vascular brain health.

**Participant recruitment and eligibility**

Recruitment of participants to the STAREE Trial is being conducted in partnership with general practices across metropolitan and regional/rural Australia. Participants recruited in the metropolitan cities of Melbourne and Brisbane are invited to participate in the STAREE-Mind Imaging substudy. Full eligibility criteria for STAREE are available elsewhere; participants include men and women 70 years of age and over who are living independently in the community, do not have a history of clinical cardiovascular events, diabetes or dementia, and have a Modified Mini-Mental State Examination Score of at least 78. Exclusion criteria specific to STAREE-Mind Imaging are contraindications to MRI (eg, ferromagnetic implants), known brain abnormalities (eg, congenital malformations; arachnoid cysts with parenchymal displacement) or invasive intracranial interventions (eg, arteriovenous malformation resection, shunt placement) due to past injury or disease.

**Study intervention, randomisation and blinding**

Participants are randomised upon recruitment into the STAREE Trial to receive either daily atorvastatin 40 mg tablets) or placebo (tablets of identical appearance). Dose reduction to one tablet per day (20 mg) is permitted throughout the trial to manage tolerability and adverse events. Participants, their general practitioners and study investigators are all blinded to treatment arm.

**Outcome measures**

The primary outcome measures will be change from baseline to 4 years follow-up in:

1. **BFW fraction in the whole-brain white-matter tissue mask.** BFW will be modelled using diffusion-weighted imaging, quantifying the fraction of extracellular fluid that is able to diffuse without constraint (ie, diffusion equally likely in all directions), relative to intracellular or periaxonal fluid that is constrained in its direction of motion. For example, fluid in lateral ventricles is entirely free, whereas fluid in a healthy corpus callosum is highly constrained. BFW can increase due to vascular leakage, inflammation and/or neurodegeneration. BFW is a continuous measure that can be quantified across the full spectrum of health and disease without floor or ceiling effects.

2. **WMH volume in the whole-brain white-matter tissue mask.** WMHs will be quantified on FLAIR-weighted MRI, and consist of increased extracellular fluid (ie, BFW) with underlying demyelination and axonal degeneration. These are hallmark indicators of late-stage small vessel disease and are associated with cognitive impairment and increased risk of dementia and stroke. WMHs are absent in young and healthy brains, but are progressive in volume on emergence.

Secondary outcomes will include change from baseline to 4 years follow-up in the following additional continuous (quantitative) markers of brain structure and vascular health:

1. **Enlarged perivascular space (ePVS) volume in the in the whole-brain white-matter tissue mask.** PVS encapsulates the small blood vessels throughout the brain, are filled with cerebrospinal fluid and form a major component of the glymphatic system of the brain. The glymphatic system is essential for metabolic waste clearance and fluid homeostasis. PVSs are not typically visible on MRI scans at standard clinical resolutions in healthy individuals, but become enlarged in people with small vessel disease, dementia and other neurological conditions. The enlarged PVS will be detected, labelled and volume-quantified using T1-weighted and T2-weighted structural MRI.

2. **Cortical thickness in the frontal, temporal, parietal and occipital lobes.** Cortical thickness provides a proxy of the number, size and density of neurons, glia and neuropil in the cerebral cortex. Decreases in cortical thickness are a primary marker of neurodegeneration in accelerated ageing and dementia, and are sensitive to the progression of neuropathology and cognitive decline. Cortical thickness will be quantified as the distance between the outer brain surface (pial surface) and the boundary between the grey and white matter using T1-weighted MRI.

3. **Hippocampus volume.** Hippocampal atrophy is a defining feature of Alzheimer’s dementia and directly linked to memory impairments. The volume of the hippocampus will be quantified using T1-weighted MRI.

4. **Number of microbleeds and lacunae in the whole-brain white-matter tissue mask.** Cerebral microbleeds and white matter lacunae are markers of cerebral small vessel disease and common correlates of dementia and ageing, reflecting spatially constrained (<1.5 mm diameter) haemorrhages or ischaemic infarcts. These vascular features will be quantified using susceptibility-weighted imaging/quantitative susceptibility mapping and T1-weighted and/or T2-weighted structural MRI.

5. **Cerebral blood flow in the prefrontal cortex.** Lower cerebral blood flow, particularly in the frontal lobe, is associated with reduced cognitive performance, accelerated cognitive decline, increased dementia risk and greater dementia severity. The causes of reduced cerebral blood flow in ageing and neurodegeneration are likely multifactorial, and may reflect reduced metabolic demands due to neuronal dysfunction and death, abnormalities in neurovascular coupling and/or cerebrovascular disease. Cerebral blood flow will be measured using pseudo-continuous arterial spin labelling.

6. **White matter fractional anisotropy in the whole-brain white-matter tissue mask.** Fractional anisotropy will be derived using diffusion tensor imaging, quantifying the relative directionality of fluid diffusion at every point in the brain. Reduced fractional anisotropy putatively reflects axonal degeneration and/or demyelination. Reduced
Table 1: STAREE-Mind Imaging MRI protocol

<table>
<thead>
<tr>
<th>Data</th>
<th>Sequence</th>
<th>Resolution</th>
<th>Key parameters</th>
<th>Acq. time</th>
</tr>
</thead>
<tbody>
<tr>
<td>T1-weighted</td>
<td>3D MPRAGE</td>
<td>0.9 mm isotropic Sagittal FOV=235 mm, 208 slices</td>
<td>TR/TE/T1=2300/2.12/900 ms, flip=9°, phase accel (iPAT) ×2</td>
<td>5'30&quot;</td>
</tr>
<tr>
<td>T2-weighted</td>
<td>3D SPACE</td>
<td>0.9 mm isotropic Sagittal FOV=235 mm, 192 slices</td>
<td>TR/TE=3200/450 ms, phase accel (iPAT) ×2</td>
<td>4'08&quot;</td>
</tr>
<tr>
<td>Fluid-inverted</td>
<td>T2-weighted</td>
<td>3D FLAIR 0.9 mm isotropic Sagittal FOV=235 mm, 192 slices</td>
<td>TR/TE/Tl=5000/399/1800 ms, phase accel (iPAT) ×2</td>
<td>6'27&quot;</td>
</tr>
<tr>
<td>Diffusion-weighted</td>
<td>2D EPI (multiband, multishell)</td>
<td>2.0 mm isotropic Transverse FOV=210 mm, 72 slices</td>
<td>PRISMA (P): TR/TE=3300/77 ms SKYRA (S): TR/TE=3800 ms/106 ms, Slice acceleration (multiband) ×3</td>
<td>P: 4'18&quot; + 17&quot;**</td>
</tr>
<tr>
<td>Susceptibility-weighted</td>
<td>3D GRE</td>
<td>0.9 mm isotropic Transverse FOV=230 mm, 160 slices</td>
<td>TE1/TE2/TE3/TE4=6.5/12.1/17.7/23.3 ms, TR 28 ms, flip=15°, bandwidth=280 Hz/Px, phase accel (iPAT) ×2</td>
<td>7'03&quot;</td>
</tr>
<tr>
<td>Perfusion-Weighted</td>
<td>3D pCASL (multidelay)</td>
<td>3.5 mm isotropic Transverse FOV=224 mm, 40 slices (one slab)</td>
<td>TR/TE=4100/37.42 ms Bolus duration=700 ms Inversion time=1800 ms</td>
<td>7'11&quot;</td>
</tr>
<tr>
<td>Carotid flow</td>
<td>2D Phase-Contrast</td>
<td>0.6 x 0.6 x 6.0 mm 40 phases (cardiac gated)</td>
<td>TR/TE=21.1/6.4 ms, velocity=120 cm/s, phase accel (iPAT) ×2 Cardiac Gated: ~3'00&quot;</td>
<td></td>
</tr>
</tbody>
</table>

*Main DWI sequence acquired with anterior-to-posterior (A>P) phase encoding; one b0 image is also acquired with reverse phase encoding (P>A) for postprocessing distortion correction. FOV= Field of View.

DWI, diffusion-weighted imaging; STAREE, Statins for Reducing Events in the Elderly; TE, echo time; TI, inversion time; TR, repetition time.

Regional and whole-brain white matter fractional anisotropy is a common marker of neurodegeneration and correlates with cognitive function in both health and disease.47 48

All outcome measures will be derived with binding of the rater(s) to study arm using validated, automated image processing algorithms implemented in publicly available software packages including Freesurfer (https://surfer.nmr.mgh.harvard.edu/) and FSL (https://fsl.fmrib.ox.ac.uk/fsl/fslwiki). Software versions and processing pipelines will be designated at the time of data analysis to reflect advances and current best practice in the field.

Brain magnetic resonance imaging

MRI is performed as soon as possible after randomisation of the participant into the trial, and before study medication commences. Follow-up scans take place at 4 years±3 months. MRI acquisitions are undertaken at two study sites using a 3-Tesla Siemens Skyra (Monash Biomedical Imaging, Melbourne, Australia) or 3-Tesla Siemens Prisma (Herston Imaging Research Facility, Brisbane, Australia) scanner. A suite of whole-brain MRI sequences are acquired over approximately 35 min (table 1). Sequence acquisition parameters were harmonised across the two scanning sites, except for the diffusion-weighted sequences which were optimised for each scanner due to their differing gradient capabilities. The ComBat approach for harmonisation of multisite MRI49 will be applied to account for systemic site differences, in addition to inclusion of ‘site’ in statistical models.

Sample size

Inclusion of 340 participants at baseline will allow for a target of 300 participants with data at both baseline and follow-up, allowing for up to 10% loss of participants at follow-up due to attrition, incidental detection of radiological features at baseline that meet exclusion criteria (ie, congenital malformations) or the incidence of an acquired or traumatic brain injury during the treatment period. Previous studies of individuals ≥70 years have reported a change in white matter mean diffusivity (analogous to BFW) of approximately 0.89%/year (SD 0.7%),50 while WMHs volume has been reported to increase at a rate of up to 13% (SD 15%) per year in the 70–79 age group.51 A total of 300 participants (150/arm) will provide 84% power to detect a decrease in mean diffusivity rate of change from 13%/year to 8%/year (ie, less than one-third of SD) between the placebo and statin arms.

Statistical analysis

The primary analyses will be based on the intention to treat principle. Both primary outcomes (BFW and WMH)
will be analysed using ANCOVA. Absolute change in the magnitude of the derived continuous imaging outcomes between baseline and follow-up will be assessed. An adjusted analysis will be provided with the following covariates added to the model: age at baseline, time between scans and site. The Hochberg procedure will be used to account for multiplicity across the two primary endpoints. Secondary continuous endpoints will be analysed in a similar way to the primary outcomes after transformation if deemed appropriate. Additional analyses based on multiple imputation will be carried out if missing data are greater than 5% with these analyses considered more relevant in case of discrepancy.

ETHICS AND DISSEMINATION

Ethics and governance
This study is conducted in accordance with the Declaration of Helsinki 1964 as revised in Edinburgh in 2000 and with the National Health & Medical Research Council (NHMRC) Guidelines on Human Experimentation.

Ethics approval has been granted by the Monash University Human Research Ethics Committee (CF14/1927-201400975 and 12206). Approval has also been given by the Governance Office (SSA) in Royal Brisbane and Women’s Hospital.

All participants provided written informed consent to participate, after been informed of the objectives, benefits, risks and requirements of the STAREE-Mind substudy, as well as the nature of the neuroimaging assessments.

Outcomes dissemination and data sharing
Trial outcomes will be published in academic journals. After publication of the trial outcomes, the deidentified data will be available to approved researchers on reasonable request, through a secure portal.

DISCUSSION

An estimated 55 million people around the world are living with dementia, and these numbers are predicted to rise with the ageing population. Dementia is one of the leading causes of disability and death, and primary prevention is a major public health issue. Statins are inexpensive drugs and a widely used treatment for the prevention and treatment of cardiovascular disease. Given the established vascular contributions to dementia, treatments targeting vascular health may be effective strategies for dementia prevention. Repurposing of this existing therapeutic may provide a cost-effective and readily scalable solution.

The STAREE-Mind Imaging substudy, with brain MRI measured at baseline and up to 4 years later, will determine whether daily statin treatment is effective in reducing small vessel cerebrovascular disease and slowing brain atrophy in older, relatively healthy individuals. It will help inform decisions regarding the use of statins for primary prevention of neurological decline through the provision of high-quality, bespoke imaging markers of treatment effects in a double-blind, randomised, placebo-controlled clinical trial.

Author affiliations
1Department of Neuroscience, Central Clinical School, Monash University, Melbourne, Victoria, Australia
2Monash Biomedical Imaging, Monash University, Melbourne, Victoria, Australia
3School of Public Health and Preventive Medicine, Monash University, Melbourne, Victoria, Australia
4Global Brain Health Program, The George Institute for Global Health, University of New South Wales, Sydney, New South Wales, Australia
5School of Psychology, University of Sydney, Sydney, New South Wales, Australia
6Turner Institute for Brain and Mental Health, School of Psychological Sciences, Monash University, Melbourne, Victoria, Australia
7Institute for Molecular Bioscience, University of Queensland, Brisbane, Queensland, Australia

Twitter Trevor T-J Chong @monashaadcneuro

Acknowledgements
STAREE-Mind imaging is funded by the National Health and Medical Research Council (NHMRC, 2006611). The STAREE trial is sponsored by Monash University and has received funding from the NHMRC (grants 1068146 and 1161503), and a grant from the National Heart Foundation of Australia (HF Stroke Prevention grant). JR is supported by an NHMRC Leadership 1 Investigator Grant (2016438). SN is supported by an NHMRC Leadership 2 Investigator Grant (2008064). The funders have no role in the study design, collection, management, analysis and interpretation of data, nor in the writing of the publications. We acknowledge the contributions of Clare Berry, Lachlan Clyde, Tina Zazachis, Stephen Glenville and Jacqui Amadi to the implementation of these protocols at the research sites.

Collaborators
The STAREE Investigator Group includes the following. Steering Committee: Prof Sophia Zoungas (Chair), Prof Lawrence Beilin, Associate Prof Trevor T-J Chong, Prof Geoffrey C Cloud, Prof John J McNeil, Prof Mark R Nelson, Prof Stephen J Nicholas, Prof Christopher M Reid, Prof Andrew Tonkin, Dr Stephanie A Ward, Prof Anthony S Wierzbicki and Prof Rory Wolfe. Executive Committee: Prof Sophia Zoungas (Chair), Dr Andrea J Curtis, Associate Prof Ingrid Hopper, Dr Alissia Kost, Prof John J McNeil, Prof Mark R Nelson, Professor Christopher M Reid, Associate Prof Joanne Ryan, Dr Simone Spark and Prof Rory Wolfe. Data Safety Monitoring Committee: Prof John Simes (Chair), Prof Graeme Hankey, Prof A Mark Richards, Prof Mark Woodward, Dr Alan Hershclal and Dr Thao Le.

Contributors
IHH, JR, SH and SZ wrote the manuscript. All authors contributed to the conceptual and/or practical development and implementation of the protocol, and critically reviewed the manuscript. The STAREE Investigator Group provides oversight and governance of the study protocol and implementation.

Competing interests
No, there are no competing interests.

Patient consent for publication
Not applicable.

Ethics approval
This study involves human participants and was approved by Monash University Human Research Ethics Committee, Protocol 12206 Participants gave informed consent to participate in the study before taking part.

Provenance and peer review
Not commissioned; internally peer reviewed.

Open access
This is an open access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) licence, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited, appropriate credit is given, any changes made indicated, and the use is non-commercial. See: http://creativecommons.org/licenses/by-nc/4.0/.

ORCID iDs
Ian H Harding http://orcid.org/0000-0002-6843-9592
Craig S Anderson http://orcid.org/0000-0002-7248-4963
Michael O’Sullivan http://orcid.org/0000-0002-2869-4580

REFERENCES
Open access


31 Radua J, Vieta E, Shihora R, et al. Increased power by harmonizing structural MRI site differences with the combat batch adjustment method in ENIGMA. *Neuroimage 2020;218:S1053-8119(20)30442-0.


