



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

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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 'Statins 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.

INTRODUCTION

Statins are a cornerstone to the treatment and secondary prevention of cerebral ischaemia, small vessel disease and cerebrovascular events including stroke.¹ Emerging

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, PRACTISE OR POLICY

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

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 maintenance of the endothelium.¹⁰ In addition to direct vascular benefits, statins also attenuate neuroinflammation—an early, enduring and detrimental feature of neurodegenerative diseases¹¹—through potent suppression of microglial activation and inhibition of cytokine production.^{12–13} Statins may also mitigate the aggregation of beta amyloid,¹⁴ a key factor in the development of AD, and inhibit production of oxygen-free radicals.^{10–15} Statins have thus emerged as potential disease-modifying drugs for age-related neurological disorders.^{7–8}

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.¹⁶ 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 change after 33 months treatment with pravastatin (n=270).¹⁷ The ROCAS study reported a reduced rate of WMH accrual over 2 years treatment with simvastatin (n=208) in a subgroup with high baseline WMH load.¹⁸ 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.¹⁹ 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).²⁰ Recent meta-analyses indicate similar equivocal evidence of statin effects on white matter lesions.^{21–22} Differing blood–brain permeability between the statins and health status of 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.²³ 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)²⁴ 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.^{25–27} 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.^{28–29} 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 A β protein and tau oligomers.³⁰ A wider distribution and higher volume of PVS is a robust radiological feature of common cerebrovascular, neuroinflammatory and neurodegenerative diseases.^{31–32} Early evidence suggests a positive impact of statins on preventing accrual of enlarged PVSs.³³ Cerebral perfusion and silent infarcts, such as cerebral microbleeds and lacunae, provide additional imaging markers of neurovascular health³⁴ which may be influenced by statin therapy.^{22–35} 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).³⁶ 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;³⁶ 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 (2×20 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 mitigate study drop-out. 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.*^{24–29 37} 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.*²³ 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*^{30–32}. 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.^{38–40} 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.⁴¹
3. *Hippocampus volume.* Hippocampal atrophy is a defining feature of Alzheimer's dementia and directly linked to memory impairments.⁴² 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 (<15 mm diameter) haemorrhages or ischaemic infarcts.³⁴ 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.^{43 44} 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.^{45 46} 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

Data	Sequence	Resolution	Key parameters	Acq. time
T1-weighted	3D MPRAGE	0.9 mm isotropic Sagittal FOV=235 mm, 208 slices	TR/TE/TI=2300/2.12/900 ms, flip=9°, phase accel (iPAT) ×2	5'30"
T2-weighted	3D SPACE	0.9 mm isotropic Sagittal FOV=235 mm, 192 slices	TR/TE=3200/450 ms, phase accel (iPAT) ×2	4'08"
Fluid-inverted T2-weighted	3D FLAIR	0.9 mm isotropic Sagittal FOV=235 mm, 192 slices	TR/TE/TI=5000/399/1800 ms, phase accel (iPAT) ×2	6'27"
Diffusion- weighted	2D EPI (multiband, multishell)	2.0 mm isotropic Transverse FOV=210 mm, 72 slices 74 diffusion directions (5×b0, 3×b200, 6×b500, 30×b1000, 30×b2500s/mm ²)	PRISMA (P): TR/TE=3300/77 ms SKYRA (S): TR/TE=3800 ms/106 ms Slice acceleration (multiband) ×3	P: 4'18" S: + 17" + 4'58" + 20"
Susceptibility- weighted	3D GRE	0.9 mm isotropic Transverse FOV=230 mm, 160 slices	TE1/TE2/TE3/TE4=6.5/12.1/17.7/23.3 ms, TR 28 ms, flip=15°, bandwidth=280 Hx/Px, phase accel (iPAT) ×2	7'03"
Perfusion- Weighted	3D pCASL (multidelay)	3.5 mm isotropic Transverse FOV=224 mm, 40 slices (one slab) 13 measurements (1×M0, 2×500 ms, 2×1000 ms, 2×1500 ms, 3×2000 ms, 3×2500 ms)	TR/TE=4100/37.42 ms Bolus duration=700 ms Inversion time=1800 ms	7'11"
Carotid flow	2D Phase- Contrast	0.6×0.6×6.0 mm 40 phases (cardiac gated)	TR/TE=21.1/6.4 ms, velocity=120 cm/s, phase accel (iPAT) ×2	Cardiac Gated: ~3'00"

*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 blinding 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 practise 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 systematic 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 (BFW) from 0.89%/year to 0.65%/year and 82% power to detect a decrease in in WMH volume 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 (CF14/1927-2014000975 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.⁵² Dementia is one of the leading causes of disability and death,⁵³ 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.¹ Given the established vascular contributions to dementia, treatments targeting vascular health may be effective strategies for dementia prevention.^{5 6} 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.

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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.

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