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Studies of small vessel diseases: the mild stroke study 3

Submission date
27/06/2019

Recruitment status
No longer recruiting

Registration date
24/07/2019

Overall study status
Ongoing

Last Edited
27/08/2025

Condition category
Circulatory System

[_] Prospectively registered
[X] Protocol
[_] Statistical analysis plan
[X] Results
[_] Individual participant data

Plain English summary of protocol

Background and study aims
Every year there are about 35,000 people in the United Kingdom who have a type of stroke, called ‘lacunar’ or ‘small vessel’ stroke. Cerebral Small Vessel disease is thought to be a major cause for this kind of stroke and also contributes to at least half of existing cases of dementia. Small vessel disease is caused by damage to the lining of the tiny blood vessels in the brain which stops them from functioning normally and can cause damage to the brain. Though there is no known cure for small vessel disease, it now looks possible that some of this damage may be reversible. These studies will help us understand what goes wrong with the small blood vessels in the brain so that we can find ways to prevent and treat small vessel disease.

Who can participate?
Adults who have had a mild non-disabling stroke and are able to have an MRI scan.

What does the study involve?
This is a clinical study of patients who have had a recent stroke in Edinburgh, United Kingdom. Participants will have a brain scan as part of their usual clinical care at the time of index stroke. They will attend their first study visit within 3 months of their stroke diagnosis. At this visit, symptoms reported by the participant will be assessed in detail and they will be asked questions about their medical history, lifestyle (e.g. smoking) and typical eating, sleeping and exercise habits. They will have detailed tests of their thinking and memory. We will also use a small camera (like those found at some opticians) to take pictures of the blood vessels in the back of the eye and take blood and urine samples for detailed tests and genetic analysis to understand what affects blood vessel function and damages the brain. In some patients we will measure blood pressure (BP) for a 24-hour period using a mobile BP cuff worn on the arm.

During this visit, participants will also have a very detailed magnetic resonance (MRI) brain scan to find out about the function of the small blood vessels in the brain, for example subtle leakiness, or the ability to increase blood flow when more oxygen is needed. For a small part of the scan, the participant will wear a face mask that alternates between normal air and air with a small amount of added carbon dioxide for three minute intervals. For another part of the scan, participants will have a dye injected into a vein in the arm. This dye will circulate to the brain and the scanner measures any dye that may leak from the blood vessels.

Participants will be asked to attend a subsequent visit about 3 months after their first visit, and again 6 and 12 months later, and 3-4 years later. During these visits, the participants will be asked some questions about their symptoms, their recovery and thinking and memory. They will also have a 30-minute magnetic resonance brain scan. We will also measure BP and take pictures of the blood vessels in the back of the eye. At the 3-4 years visit, participants will be invited to provide a venous blood sample for genetic analysis and complete a questionnaire on their concerns and healthcare status. Two substudies will also be offered at this time point.

Where is the study run from?
Centre for Clinical Brain Sciences, Edinburgh (United Kingdom) and the UK Dementia Research Institute at the University of Edinburgh

When is the study starting and how long is it expected to run for?
August 2018 to August 2027

Who is funding the study?
The Fondation Leducq Network for the Study of Perivascular Spaces in Small Vessel Disease; UK Medical Research Council Dementia Research Institute; Row Fogo Charitable Trust, The Stroke Association, NHS Research Scotland, NHS Lothian Research and Development, University of Edinburgh

Who is the main contact?
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Contact information

Type(s)
Scientific

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Additional identifiers

Clinical Trials Information System (CTIS)

Nil known

Integrated Research Application System (IRAS)
235737

Protocol serial number
1.0, IRAS 235737

Study information

Scientific Title
The longitudinal study of cerebral small vessel disease following mild ischaemic stroke

Acronym
MSS-3

Study objectives
1. Small vessel dysfunctions (blood brain barrier leak, cerebrovascular reactivity, cerebral blood flow) will influence SVD lesion progression and regression.
2. One of these small vessel dysfunctions will best differentiate abnormal from normal-appearing brain tissue by stage and severity of SVD
3. There will be inter-relationships between CBF, cerebrovascular reactivity, intracranial pulse propagation, interstitial fluid and its drainage via PVS.
4. Patient-related factors will be associated with lesion progression and regression: (a) index stroke characteristics; (b) vascular risk factors/medications; (c) self-reported neuropsychiatric, cognitive and physical symptoms; (d) informant-reported neuropsychiatric and cognitive symptoms; (e) cognitive decline; (f) functional recovery; (g) vascular physiological measures (blood pressure and pulse wave velocity); (h) life course factors (education, socioeconomic status and estimated peak intelligence); and (i) lifestyle factors (dietary and sleep).
5. There will be a relationship between retinal nerve fibre layer characteristics, retinal vessel morphology, retinopathy and SVD burden, brain white matter integrity and fluid content.
6. There will be a relationship between serum and urine markers of inflammation and SVD lesion progression or regression.

Ethics approval required
Ethics approval required

Ethics approval(s)
approved 31/05/2018, South East Scotland Research Ethics Committee 01 (Waverley Gate, 2-4 Waterloo Place, Edinburgh, EH1 3EG, United Kingdom; +44 131 536 9000; Sandra.Wyllie@nhslothian.scot.nhs.uk), ref: 18/SS/0044

Study design
Single-centre longitudinal cohort study

Primary study design
Observational

Study type(s)
Diagnostic

Health condition(s) or problem(s) studied
Cerebral small vessel disease

Interventions
Current interventions as of 27/08/2025:
Baseline visit (visit 1)
Participants will have their baseline visit within a maximum of three months following index stroke. During this visit, informed consent will be obtained. All participants will be asked to provide details on their medical history focusing on recent stroke and non-stroke symptoms, mood, neurological and vascular health (including cardiac health, smoking, and prescribed medications). The neurological assessment will include the National Institute of Health Stroke Scale (NIHSS) score, evaluation of gait (Timed Up and Go [TUG]) and manual dexterity (9-hole peg test). Information on occupation, family history (health and childhood socioeconomic measures) and educational level will be obtained and cognitive tests of current and peak adult cognitive ability will be performed. Information will be sought from a relative or close friend about the participant's mood and cognition in questionnaire format (Informant Questionnaire for Cognitive Decline in the Elderly [IQCODE], Neuropsychiatric Inventory Questionnaire [NPI-Q] and the Apathy Evaluation Scale – Informant Version [AES-I]). Participants will bring completed questionnaires to the first visit including the Fatigue Severity Scale (FSS), Generalized Anxiety Disorder 7 (GAD-7), Center for Epidemiologic Studies Depression Scale (CES-D), an adapted version of the Pittsburgh Sleep Quality Questionnaire (PSQI) and the EPIC Norfolk Food Frequency Questionnaire.

Participants will have retinal imaging of both eyes using a Heidelberg Spectralis retinal and Optical Coherence Tomography (OCT) imaging system. They will also have three measures of brachial blood pressure during the visit and measurement of arterial velocities through pulse wave velocity (PWV) and pulse wave analysis (PWA). These are measured by means of a tonometric device (SphygmoCor®) held over the carotid and radial pulses while the participant is lying on a couch. The retinal imaging, blood pressure, PWV and ultrasound equipment are all in the MRI suite. As many participants as possible will be issued with an automated ambulatory BP monitoring device (Model 90207, SpaceLabs Medical Inc.) and instructions on how to use it to monitor their BP over 24 hours.
A venous blood sample will be taken for inflammatory and endothelial function markers and a sample stored for genetic analysis, where possible drawn via the cannula inserted for the detailed brain imaging. Patients will be provided with a universal container for a mid-stream urine sample; 5ml will be analysed for Albumin Creatinine Ratio (ACR) and 20ml will be stored for analysis of inflammatory markers.

All participants will have core structural brain MRI sequences: quantitative T1, T2, Fluid Attenuated Inversion Recovery (FLAIR), Susceptibility Weighted Imaging (SWI), and Diffusion Tensor Imaging (DTI), which provide details on the index stroke, background SVD features and brain tissue integrity.

Most participants will have brain MRI to measure blood brain barrier (BBB) permeability, cerebrovascular reactivity (CVR), cerebral blood flow (CBF) and intracranial vascular pulsatility (ICP).

BBB permeability will be assessed by using dynamic contrast enhanced (DCE) MRI and injection of Gadolinium contrast agent. Participants with renal impairment (eGFR<30) will not have BBB imaging. CVR will be assessed by using a BOLD MRI sequence combined with breathing air with 6% CO_2 through a tight-fitting facemask. Arterial and CSF pulsatility (CSFp) will be measured

using phase contrast MRI sequences. Cerebral blood flow (CBF) will be measured using arterial spin labelling (ASL) and where feasible, using the phase contrast flow measures from the major arteries obtained during the pulsatility measurements.

CVR, CSFp and BBB imaging are well established in Edinburgh. The time to acquire structural MRI sequences at the follow-up visits is around 30 minutes. The total time to acquire all MRI sequences at the baseline visit is around two and a half hours.

Visit 2
As many participants as possible will be invited to attend an interim visit, starting four weeks after the baseline assessment and up until the ninth month of follow-up. During this visit the participants will answer brief questions about their recovery from the index stroke, any recent stroke or non-stroke symptoms, a short (diagnostic) brain MRI, BP measurement, a neurological assessment (NIHSS), a brief cognitive assessment and retinal imaging.

Visit 3
All participants will return at six months after the baseline assessment for evaluation of any recent stroke or non-stroke symptoms, recurrent vascular events, cognition, repeat diagnostic MRI brain imaging, retinal imaging, National Institute of Health Stroke Scale (NIHSS), modified Rankin Scale (mRS) and BP measurement. Functional status will be assessed using the Stroke Impact Scale questionnaire (SIS) version 3.0.

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All participants will return at twelve months after the baseline assessment for evaluation of any recent stroke or non-stroke symptoms, recurrent vascular events, cognition, repeat diagnostic brain MRI, retinal imaging, NIHSS, mRS, BP measurement and Timed Up and Go. Information will be sought again from the patients' partner, relative or carer on behavioural and psychological symptoms (IQCODE, AES, NPI-Q).

Annually thereafter up to four years after index stroke: Participants will be invited to continue in long-term annual post or phone follow-up with the option of another MRI at 3–4 years. The follow-up questionnaire will cover functional status, cognition, and recurrent vascular events. An additional questionnaire will seek information from the participants' concerns and potential gaps in their clinical management, their experience while participating in the MSS3 study, and their current health status (EuroQol [EQ-5D]). The 3-4 year in-person visit: will be similar to Visit4 and will include a physical examination including NIHSS, TUG, 9-HPT, BP, cognitive tests, and structural/DTI brain imaging. In addition, participants will be invited to provide a venous blood sample for genetic analysis. Two substudies will also be offered at this time point.

Follow-up to 3-4 years has been completed, including repeat brain MRI where feasible.

Two substudies are ongoing in a subset of participants:
1. Retinal vascular reactivity to 6% CO2 and flickering light versus brain vascular reactivity to 6% CO2, change from baseline and long-term brain lesion change
2. Fluoresceine retinal angiography and relation to brain blood-brain barrier leakage and long-term brain lesion change.

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Previous interventions as of 30/12/2024:
Baseline visit (visit 1)
Participants will have their baseline visit within a maximum of three months following index

stroke. During this visit, informed consent will be obtained. All participants will be asked to provide details on their medical history focusing on recent stroke and non-stroke symptoms, mood, neurological and vascular health (including cardiac health, smoking, and prescribed medications). The neurological assessment will include the National Institute of Health Stroke Scale (NIHSS) score, evaluation of gait (Timed Up and Go [TUG]) and manual dexterity (9-hole peg test). Information on occupation, family history (health and childhood socioeconomic measures) and educational level will be obtained and cognitive tests of current and peak adult cognitive ability will be performed. Information will be sought from a relative or close friend about the participant's mood and cognition in questionnaire format (Informant Questionnaire for Cognitive Decline in the Elderly [IQCODE], Neuropsychiatric Inventory Questionnaire [NPI-Q] and the Apathy Evaluation Scale – Informant Version [AES-I]). Participants will bring completed questionnaires to the first visit including the Fatigue Severity Scale (FSS), Generalized Anxiety Disorder 7 (GAD-7), Center for Epidemiologic Studies Depression Scale (CES-D), an adapted version of the Pittsburgh Sleep Quality Questionnaire (PSQI) and the EPIC Norfolk Food Frequency Questionnaire.

Participants will have retinal imaging of both eyes using a Heidelberg Spectralis retinal and Optical Coherence Tomography (OCT) imaging system. They will also have three measures of brachial blood pressure during the visit and measurement of arterial velocities through pulse wave velocity (PWV) and pulse wave analysis (PWA). These are measured by means of a tonometric device (SphygmoCor®) held over the carotid and radial pulses while the participant is lying on a couch. The retinal imaging, blood pressure, PWV and ultrasound equipment are all in the MRI suite. As many participants as possible will be issued with an automated ambulatory BP monitoring device (Model 90207, SpaceLabs Medical Inc.) and instructions on how to use it to monitor their BP over 24 hours.
A venous blood sample will be taken for inflammatory and endothelial function markers and a sample stored for genetic analysis, where possible drawn via the cannula inserted for the detailed brain imaging. Patients will be provided with a universal container for a mid-stream urine sample; 5ml will be analysed for Albumin Creatinine Ratio (ACR) and 20ml will be stored for analysis of inflammatory markers.

All participants will have core structural brain MRI sequences: quantitative T1, T2, Fluid Attenuated Inversion Recovery (FLAIR), Susceptibility Weighted Imaging (SWI), and Diffusion Tensor Imaging (DTI), which provide details on the index stroke, background SVD features and brain tissue integrity.

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BBB permeability will be assessed by using dynamic contrast enhanced (DCE) MRI and injection of Gadolinium contrast agent. Participants with renal impairment (eGFR<30) will not have BBB imaging. CVR will be assessed by using a BOLD MRI sequence combined with breathing air with 6% CO2 through a tight-fitting facemask. Arterial and CSF pulsatility (CSFp) will be measured using phase contrast MRI sequences. Cerebral blood flow (CBF) will be measured using arterial spin labelling (ASL) and where feasible, using the phase contrast flow measures from the major arteries obtained during the pulsatility measurements.

CVR, CSFp and BBB imaging are well established in Edinburgh. The time to acquire structural MRI sequences at the follow-up visits is around 30 minutes. The total time to acquire all MRI sequences at the baseline visit is around two and a half hours.

Visit 2
As many participants as possible will be invited to attend an interim visit, starting four weeks after the baseline assessment and up until the ninth month of follow-up. During this visit the participants will answer brief questions about their recovery from the index stroke, any recent stroke or non-stroke symptoms, a short (diagnostic) brain MRI, BP measurement, a neurological assessment (NIHSS), a brief cognitive assessment and retinal imaging.

Visit 3
All participants will return at six months after the baseline assessment for evaluation of any recent stroke or non-stroke symptoms, recurrent vascular events, cognition, repeat diagnostic MRI brain imaging, retinal imaging, National Institute of Health Stroke Scale (NIHSS), modified Rankin Scale (mRS) and BP measurement. Functional status will be assessed using the Stroke Impact Scale questionnaire (SIS) version 3.0.

Visit 4
All participants will return at twelve months after the baseline assessment for evaluation of any recent stroke or non-stroke symptoms, recurrent vascular events, cognition, repeat diagnostic brain MRI, retinal imaging, NIHSS, mRS, BP measurement and Timed Up and Go. Information will be sought again from the patients' partner, relative or carer on behavioural and psychological symptoms (IQCODE, AES, NPI-Q).

Annually thereafter up to four years after index stroke: Participants will be invited to continue in long-term annual post or phone follow-up with the option of another MRI at 3–4 years. The follow-up questionnaire will cover functional status, cognition, and recurrent vascular events. An additional questionnaire will seek information from the participants' concerns and potential gaps in their clinical management, their experience while participating in the MSS3 study, and their current health status (EuroQol [EQ-5D]). The 3-4 year in-person visit: will be similar to Visit4 and will include a physical examination including NIHSS, TUG, 9-HPT, BP, cognitive tests, and structural/DTI brain imaging. In addition, participants will be invited to provide a venous blood sample for genetic analysis. Two substudies will also be offered at this time point.

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Current interventions as of 15/07/2022:
Baseline visit (visit 1)
Participants will have their baseline visit within a maximum of three months following index stroke. During this visit, informed consent will be obtained. All participants will be asked to provide details on their medical history focusing on recent stroke and non-stroke symptoms, mood, neurological and vascular health (including cardiac health, smoking, and prescribed medications). The neurological assessment will include the National Institute of Health Stroke Scale (NIHSS) score, evaluation of gait (Timed Up and Go [TUG]) and manual dexterity (9-hole peg test). Information on occupation, family history (health and childhood socioeconomic measures) and educational level will be obtained and cognitive tests of current and peak adult cognitive ability will be performed. Information will be sought from a relative or close friend about the participant's mood and cognition in questionnaire format (Informant Questionnaire for Cognitive Decline in the Elderly [IQCODE], Neuropsychiatric Inventory Questionnaire [NPI-Q] and the Apathy Evaluation Scale – Informant Version [AES-I]). Participants will bring completed questionnaires to the first visit including Fatigue Severity Scale (FSS), Generalized Anxiety Disorder 7 (GAD-7), Center for Epidemiologic Studies Depression Scale (CES-D), an adapted version of the Pittsburgh Sleep Quality Questionnaire (PSQI) and the EPIC Norfolk Food Frequency Questionnaire.

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A venous blood sample will be taken for inflammatory and endothelial function markers and a sample stored for genetic analysis, where possible drawn via the cannula inserted for the detailed brain imaging. Patients will be provided with a universal container for a mid-stream urine sample; 5ml will be analysed for Albumin Creatinine Ratio (ACR) and 20ml will be stored for analysis of inflammatory markers.

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Visit 2
As many participants as possible will be invited to attend an interim visit, starting four weeks after the baseline assessment and up until the ninth month of follow-up. During this visit the participants will answer brief questions about their recovery from the index stroke, any recent stroke or non-stroke symptoms, a short (diagnostic) brain MRI, BP measurement, a neurological assessment (NIHSS), a brief cognitive assessment and retinal imaging.

Visit 3
All participants will return at six months after the baseline assessment for evaluation of any recent stroke or non-stroke symptoms, recurrent vascular events, cognition, repeat diagnostic MRI brain imaging, retinal imaging, National Institute of Health Stroke Scale (NIHSS), modified Rankin Scale (mRS) and BP measurement. Functional status will be assessed using the Stroke Impact Scale questionnaire (SIS) version 3.0.

Visit 4
All participants will return at twelve months after the baseline assessment for evaluation of any

recent stroke or non-stroke symptoms, recurrent vascular events, cognition, repeat diagnostic brain MRI, retinal imaging, NIHSS, mRS, BP measurement and Timed Up and Go. Information will be sought again from the patients' partner, relative or carer on behavioural and psychological symptoms (IQCODE, AES, NPI-Q).

Annually thereafter and up to four years after the index stroke, participants will be invited to continue in long-term annual post or phone follow-up with the option of another MRI at the 3-year mark. The follow-up questionnaire will cover functional status, cognition, and recurrent vascular events.

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Baseline visit (visit 1)
Participants will have their baseline visit within a maximum of three months following index stroke. During this visit, informed consent will be obtained. All participants will be asked to provide details on their medical history focusing on recent stroke and non-stroke symptoms, mood, neurological and vascular health (including cardiac health, smoking, and prescribed medications). The neurological assessment will include the National Institute of Health Stroke Scale (NIHSS) score, evaluation of gait (Timed Up and Go [TUG]) and manual dexterity (9-hole peg test). Information on occupation, family history (health and childhood socioeconomic measures) and educational level will be obtained and cognitive tests of current and peak adult cognitive ability will be performed. Information will be sought from a relative or close friend about the participant's mood and cognition in questionnaire format (Informant Questionnaire for Cognitive Decline in the Elderly [IQCODE], Neuropsychiatric Inventory Questionnaire [NPI-Q] and the Apathy Evaluation Scale – Informant Version [AES-I]). Participants will bring completed questionnaires to the first visit including Fatigue Severity Scale (FSS), Generalized Anxiety Disorder 7 (GAD-7), Center for Epidemiologic Studies Depression Scale (CES-D), an adapted version of the Pittsburgh Sleep Quality Questionnaire (PSQI) and the EPIC Norfolk Food Frequency Questionnaire.

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BBB permeability will be assessed by using dynamic contrast enhanced (DCE) MRI and injection of Gadolinium contrast agent. Participants with renal impairment (eGFR<30) will not have BBB imaging. CVR will be assessed by using a BOLD MRI sequence combined with breathing air with 6% CO2 through a tight-fitting facemask. Arterial and CSF pulsatility (CSFp) will be measured using phase contrast MRI sequences. Cerebral blood flow (CBF) will be measured using arterial spin labelling (ASL) and where feasible, using the phase contrast flow measures from the major arteries obtained during the pulsatility measurements.

CVR, CSFp and BBB imaging are well established in Edinburgh. The time to acquire structural MRI sequences at the follow-up visits is around 30 minutes. The total time to acquire all MRI sequences at the baseline visit is around two and a half hours.

Visit 2
As many participants as possible will be invited to attend an interim visit 2-3 months after the baseline assessment. During this visit the participants will answer brief questions about their recovery from the index stroke, any recent stroke or non-stroke symptoms, a short (diagnostic) brain MRI, BP measurement, a neurological assessment (NIHSS), a brief cognitive assessment and retinal imaging.

Visit 3
All participants will return at six months after the baseline assessment for evaluation of any recent stroke or non-stroke symptoms, recurrent vascular events, cognition, repeat diagnostic MRI brain imaging, retinal imaging, National Institute of Health Stroke Scale (NIHSS), modified Rankin Scale (mRS) and BP measurement. Functional status will be assessed using the Stroke Impact Scale questionnaire (SIS) version 3.0.

Visit 4
All participants will return at twelve months after the baseline assessment for evaluation of any recent stroke or non-stroke symptoms, recurrent vascular events, cognition, repeat diagnostic brain MRI, retinal imaging, NIHSS, mRS, BP measurement and Timed Up and Go. Information will be sought again from the patients' partner, relative or carer on behavioural and psychological symptoms (IQCODE, AES, NPI-Q).

Annually thereafter and up to four years after the index stroke, participants will be invited to continue in long-term annual post or phone follow-up with the option of another MRI at the 3-year mark. The follow-up questionnaire will cover functional status, cognition, and recurrent vascular events.

Intervention Type
Other

Primary outcome(s)
The proportion of SVD lesions that regress, progress or appear de novo in the year after stroke

Key secondary outcome(s))
Current secondary outcome measures as of 27/08/2025:
1. BBB integrity as assessed using DCE-MRI brain scan at baseline visit.

2. CVR as determined by BOLD MRI brain scan response to hypercapnic challenge at baseline visit.
3. Intracranial vascular/CSF pulsatility as an index of rate of passage of pulse waves through the brain (stiffness) at baseline visit.
4. The incidence of recurrent stroke or transient ischaemic attack (TIA) and cardiac events.
5. Cognition including executive function, memory and visuospatial reasoning assessed using the MoCA at baseline and 3, 6 and 12 months. Incidence of mild cognitive impairment (MCI) and dementia
6. Neuropsychiatric and cognitive symptoms including apathy, fatigue, anxiety, depression, cognitive changes, informant-reported behavioural and cognitive change at baseline, 3, 6, and 12 months.
7. Change in function including strength, hand function, mobility, activities of daily living, emotion, memory, communication, social participation (Stroke Impact Scale measured at 6 and 12 months), manual dexterity assessment (9 Hole Peg Test measured at baseline) and gait assessment (Timed Up and Go measured at baseline and 12 months).
8. WMH, PVS, lacunes and microbleeds assessed individually and by SVD score using validated visual and computational methods at baseline, 3, 6, and 12 months.
9. White matter structural integrity measured with diffusion tensor parameters, water content (T1) and myelin (magnetisation transfer saturated) imaging methods at baseline, 6 and 12 months.
10. Life course factors including demographic, occupational and educational background measured at baseline.
11. Lifestyle factors including diet, sleep and smoking status assessed at baseline.
12. Brachial blood pressure at baseline, 3, 6, and 12 months and 24 hour Ambulatory Blood Pressure Monitoring (peak systolic, mean, diastolic arterial pressures pulse pressures, and variability) at baseline, 3 or 6 months in as many participants as possible.
13. Systemic measures of vascular stiffness (PWV) at baseline and 12 months.
14. Retinal vascular, pathic and nerve fibre layer measures using the Heidelberg Spectralis retinal camera at baseline and 3, 6 and 12 months.
15. Genetic analysis and plasma markers of inflammation, neuron and glial injury, and cerebral endothelial function in blood samples at baseline.
16. Retinal vascular reactivity to 6% CO2 and to flickering light measured using retinal fluoresceine angiography

Previous secondary outcome measures:
1. BBB integrity as assessed using DCE-MRI brain scan at baseline visit.
2. CVR as determined by BOLD MRI brain scan response to hypercapnic challenge at baseline visit.
3. Intracranial vascular/CSF pulsatility as an index of rate of passage of pulse waves through the brain (stiffness) at baseline visit.
4. The incidence of recurrent stroke or transient ischaemic attack (TIA) and cardiac events.
5. Cognition including executive function, memory and visuospatial reasoning assessed using the MoCA at baseline and 3, 6 and 12 months. Incidence of mild cognitive impairment (MCI) and dementia
6. Neuropsychiatric and cognitive symptoms including apathy, fatigue, anxiety, depression, cognitive changes, informant-reported behavioural and cognitive change at baseline, 3, 6, and 12 months.
7. Change in function including strength, hand function, mobility, activities of daily living, emotion, memory, communication, social participation (Stroke Impact Scale measured at 6 and 12 months), manual dexterity assessment (9 Hole Peg Test measured at baseline) and gait assessment (Timed Up and Go measured at baseline and 12 months).
8. WMH, PVS, lacunes and microbleeds assessed individually and by SVD score using validated

visual and computational methods at baseline, 3, 6, and 12 months.
9. White matter structural integrity measured with diffusion tensor parameters, water content (T1) and myelin (magnetisation transfer saturated) imaging methods at baseline, 6 and 12 months.
10. Life course factors including demographic, occupational and educational background measured at baseline.
11. Lifestyle factors including diet, sleep and smoking status assessed at baseline.
12. Brachial blood pressure at baseline, 3, 6, and 12 months and 24 hour Ambulatory Blood Pressure Monitoring (peak systolic, mean, diastolic arterial pressures pulse pressures, and variability) at baseline, 3 or 6 months in as many participants as possible.
13. Systemic measures of vascular stiffness (PWV) at baseline and 12 months.
14. Retinal vascular, pathic and nerve fibre layer measures using the Heidelberg Spectralis retinal camera at baseline and 3, 6 and 12 months.
15. Genetic analysis and plasma markers of inflammation, neuron and glial injury, and cerebral endothelial function in blood samples at baseline.

Completion date
31/08/2027

Eligibility

Key inclusion criteria
1. History compatible with clinical lacunar stroke syndrome (LACS) and a recent, small subcortical infarct visible on diffusion MRI scan (+/- other sequences) or CT scan compatible with the clinical syndrome or if no subcortical infarct is visible and there is no other lesion present to explain the stroke symptoms.
1.1. Or a history of non-lacunar, minor (i.e. non-disabling) ischaemic stroke syndrome (PACS or POCS) and either a small cortical or striatocapsular or cerebellar +/- brainstem infarct visible on diffusion MRI (+/- other sequences) or if no acute infarct is visible and there is no other lesion to account for the symptoms. Participants with non-lacunar stroke will form the control group.
2. Age 18 years or older.
3. Ability to undergo MRI.
4. Capacity to give written informed consent.
5. Independent in activities of daily living (Modified Rankin score <3).

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Adult

Lower age limit
18 years

Sex
All

Total final enrolment

230

Key exclusion criteria
1. Pregnant or breastfeeding women, women of childbearing age not taking contraception Acceptable contraception in women of childbearing age is a “highly effective” contraceptive measure as defined by the Clinical Trials Facilitation Group (http://www.hma.eu/fileadmin /dateien/Human_Medicines/01-About_HMA/Working_Groups/CTFG /2014_09_HMA_CTFG_Contraception.pdf) and includes combined (oestrogen and progesterone containing) or progesterone-only contraception associated with inhibition of ovulation, or intrauterine device or bilateral tubal occlusion
2. Contraindications to gadolinium contrast agent used for DCE MRI (e.g. renal impairment (eGFR <30 ml/min) – though patients may still participate in other parts of the study.
3. Other major neurological or psychiatric conditions affecting the brain and interfering with the study design (e.g. multiple sclerosis).
4. Other stroke risk factors requiring immediate intervention that would preclude involvement in the study (e.g. tight symptomatic carotid stenosis).
5. Severe cardiac (including symptomatic heart failure) or respiratory disease.

Date of first enrolment
22/08/2018

Date of final enrolment
02/12/2021

Locations

Countries of recruitment
United Kingdom

Scotland

Study participating centre
Centre for Clinical Brain Sciences and the UK Dementia Research Institute at the University of Edinburgh
Chancellors Building Little France Crescent
Edinburgh
United Kingdom
EH16 4SB

Sponsor information

Organisation
University of Edinburgh & NHS Lothian Academic and Clinical Central Office for Research and Development (ACCORD)

ROR

https://ror.org/03q82t418

Funder(s)

Funder type
Government

Funder Name
Fondation Leducq

Alternative Name(s)
Leducq Foundation

Funding Body Type
Private sector organisation

Funding Body Subtype
Trusts, charities, foundations (both public and private)

Location
France

Funder Name
UK Dementia Research Institute

Funder Name
Mrs Gladys Row Fogo Charitable Trust

Alternative Name(s)
Row Fogo Charitable Trust

Funding Body Type
Private sector organisation

Funding Body Subtype
Trusts, charities, foundations (both public and private)

Location
United Kingdom

Funder Name

Chief Scientist Office, Scottish Government Health and Social Care Directorate

Alternative Name(s)
Chief Scientist Office, Scottish Government Health Directorate CSO, Chief Scientist Office, Scottish Government Health Directorates, Chief Scientist Office of the Scottish Government Health Directorates, Scottish Government Health and Social Care Directorate of the Chief Scientist Office, Scottish Government Health Directorate Chief Scientist Office, The Chief Scientist Office, CSO

Funding Body Type
Government organisation

Funding Body Subtype
National government

Location
United Kingdom

Funder Name
Stroke Association

Alternative Name(s)
TheStrokeAssociation, TheStrokeAssoc

Funding Body Type
Private sector organisation

Funding Body Subtype
Associations and societies (private and public)

Location
United Kingdom

Funder Name
NHS Research Scotland

Funder Name
NHS Lothian Research and Development Office

Results and Publications

Individual participant data (IPD) sharing plan

The datasets generated during and/or analysed during the current study are/will be available upon request from Prof Joanna Wardlaw, Joanna.wardlaw@ed.ac.uk on completion of the study and after publication of the primary results paper. This will include imaging, demographic, cognitive, vascular parameters etc. Consent is being obtained from all study participants to store and share anonymised data for future research.

IPD sharing plan summary

Available on request

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Results article		10/10/2023	11/10/2023	Yes	No
Results article		10/12/2024	06/11/2024	Yes	No
Protocol article		01/03/2021	06/04/2021	Yes	No
HRA research summary			28/06/2023	No	No
Interim results article	Secondary outcome results abstract European Stroke Organisation Conference 2021	03/09/2021	29/03/2023	Yes	No
Study website	Study website	11/11/2025	11/11/2025	No	Yes