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SOLVE: Sodium valproate to prevent stroke

Submission date 28/01/2021	**Recruitment status** No longer recruiting	[X] Prospectively registered [_] Protocol
Registration date 02/02/2021	**Overall study status** Ongoing	[_] Statistical analysis plan [_] Results
Last Edited 15/01/2025	**Condition category** Circulatory System	[_] Individual participant data [_] Record updated in last year

Plain English summary of protocol

Background and study aims
A stroke is a serious life-threatening medical condition that happens when the blood supply to part of the brain is cut off.
In a very large study involving stroke patients from throughout the world, we have identified a new gene (called HDAC9) which increases the risk that someone will have stroke caused by narrowing of the blood vessels supplying the brain. This type of stroke is called large artery stroke and accounts for a quarter of all strokes. If the HDAC9 gene becomes 'overactive' it increases stroke risk. This raises the exciting possibility that if we could inhibit HDAC9 we could reduce stroke risk. A commonly used antiepileptic drug called sodium valproate inhibits the activity of HDAC9. Analysis of stroke registers involving thousands of patients has suggested that patients who take sodium valproate may have a lower risk of recurrent strokes. This suggests sodium valproate might prevent large artery stroke.
We now plan to test whether sodium valproate does indeed reduce stroke risk in a clinical study. If this study confirms that sodium valproate reduces narrowing of the arteries to the brain it may then offer an exciting treatment to prevent stroke. An advantage is that as a widely used drug that has been around for decades, sodium valproate has well understood side effects, and is not under patent so is cheap.

Who can participate?
Patients who have suffered a stroke or transient ischaemic attack (TIA) due to narrowing of the arteries to the brain.

What does the study involve?
Participants will be randomised (allocated) between either sodium valproate or no treatment (control group). We will perform imaging of the blood vessels to the brain using CT angiography, PET/CT, and carotid MRI at the beginning of the study, after three months and after two years. We will then see whether patients on sodium valproate have reduced progression of narrowing of the arteries to the brain compared with patients taking no drug.

What are the possible benefits and risks of participating?
Benefits: Any results that may be useful in making decisions about your care will be passed on to the doctors looking after you. There may be no direct benefit for you in taking part, but the results of this study will help our understanding of the processes involved in stroke and may help to improve the treatment of the disease in the future.

Risks: If you take part in this study you will have some FDG PET/CT scans and CT carotid angiograms. All of these will be extra to those that you would have if you did not take part. These procedures use ionising radiation to form images of your body.
Sodium valproate is an anti-convulsant or anti-epileptic agent medication used in routine clinical care, with long-term safety data. However, like any drug it may cause side-effects.

Where is the study run from?
Addenbrooke's Hospital (UK)

When is the study starting and how long is it expected to run for?
November 2019 to March 2027

Who is funding the study?
British Heart Foundation (UK)

Who is the main contact?
Prof Hugh Markus (scientific), hsm32@medschl.cam.ac.uk
Mrs Laurence Loubiere (public), lhl31@medschl.cam.ac.uk

Contact information

Type(s)
Public

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Additional identifiers

Clinical Trials Information System (CTIS)
Nil known

Integrated Research Application System (IRAS)
289372

ClinicalTrials.gov (NCT)
Nil known

Protocol serial number
CPMS 47601, IRAS 289372

Study information

Scientific Title
Inhibiting HDAC9 as a novel treatment for large artery atherosclerotic stroke: a pilot study

Acronym
SOLVE

Study objectives
Sodium valproate will be associated with a reduced progression of atherosclerosis in patients with symptomatic large artery stroke as measured by:
1. CT angiographic (CTA) imaging to assess degree of carotid stenosis and carotid plaque volume
2. Plaque MRI to assess plaque structure and volume.
3. 18Fluoride-fluorodeoxyglucose Positron Emission Tomography/Computed Tomography (FDG-PET) to assess plaque inflammation
This may then lead to a reduced level of disease progression

Ethics approval required
Old ethics approval format

Ethics approval(s)
Approved 01/03/2021, London - City & East Research Ethics Committee (St Bartholomew's Hospital, North Wing, London, EC1A 7BE, UK; +44 (0)207 104 8284; cityandeast.rec@hra.nhs.uk), ref: 21/LO/0037

Study design
Interventional randomized controlled trial

Primary study design

Interventional

Study type(s)
Treatment

Health condition(s) or problem(s) studied
Stroke

Interventions
Subjects with symptomatic carotid stenosis causing stroke or TIA are split equally into two groups: the sodium valproate group and the control group (no treatment). Study participants randomly allocated to the treatment group will take Sodium valproate 200 mg twice a day for the first 2 weeks and then 400 mg twice a day for the remaining 2 years. Study participants randomly allocated to the control group will not take sodium valproate.

At baseline and at 3 months, subjects will undergo clinical assessment, neurological and cardiovascular examination, CT angiogram, PET/CT of the carotids, and an MR of the carotids. In addition, at 2 years subjects will undergo clinical assessment, neurological and cardiovascular examination, and CT angiogram.

Screening (Baseline visit only). During routine clinical care consultations, patients will be approached by their clinical team if they are felt to be appropriate for the project. The suitability of participants will be assessed against the inclusion and exclusion criteria. Those who are eligible will be provided with a participant information sheet (PIS) and the study will be explained by a trained researcher. The participant will then be asked to consent to participate in the study by completing a consent form. They will be given a copy of the consent and PIS to take away.

Blood collection. All participants who have not had their renal function measured will have a blood sample taken to calculate their renal function. If this is below an acceptable level (an eGFR =<30 ml/min/1.73m²) they will not be able to be a part of the study. Creatinine and liver function tests will also be performed if not done in the last three months.

All subjects who are eligible and who have consented will be contacted to book a baseline visit.

Randomisation: Prior to, or on the day of, the baseline visit, participants will be randomly allocated (1:1) to the treatment group or to the control group using a web-based randomisation system. Participants will be notified of their group allocation at the baseline visit.

Clinical assessment, neurological and cardiovascular examination: All subjects who are eligible and who have consented will be asked to attend the clinic at Addenbrooke's for clinical assessment. This will include collection of demographic data as well as cardiovascular risk factors and medical history including medication history. Those assessment will be repeated at the three months and 2 years visit.

Imaging assessments:
1. 18Fluoride-fluorodeoxyglucose Positron Emission Tomography/Computed Tomography (FDG-PET/CT). This will be performed in the PET/CT department of Cambridge University Hospitals NHS Foundation Trust using protocols Dr Evans has established as part of the ICARUSS study. This will involve the insertion of a cannula to allow the administration of the radioactive tracer. Participants are injected intravenously with a radioactive tracer (FDG), followed by a 90-minute uptake time. Participants will be asked to fast for 6 hours before injection. A finger-prick blood

test for glucose will be performed at the time of each PET/CT scan to confirm that the blood glucose concentration is ≤7.0 mmol/L before injection. Participants with diabetes mellitus who are on oral antidiabetic medications will be advised to take it as usual but insulin will be omitted within 4 hours before imaging, in line with previously published methodology.
2. A carotid CT angiogram (CTA) will be completed concurrently with the PET/CT. A radiocontrast agent (Niopam 300) will be injected using the cannula. Individuals taking metformin will be advised to omit this medication for 48 hours after the CTA.
3. Carotid MR: This will be performed using a 3-tesla MRI located in either in the Wolfson Brain Imaging Centre (University of Cambridge) or the Magnetic Resonance Imaging and Spectroscopy Unit (MRIS, Cambridge University Hospitals). The MRI protocol will include conventional MRI sequences as well as contrast-enhanced MRI. This will involve the insertion of a cannula to allow the administration of the contrast agent during the MRI scan.
The PET/CT scans and carotid MRI will be performed within a week of each other depending on patient availability.

Visit Blood collection. A blood samples will be taken for high-sensitivity, C-reactive protein(hs-CRP) as a marker of inflammation at baseline, three month and 2 years visits.

Study medications: For participants allocated to the treatment group, study medications will be dispensed to participants after the last baseline imaging is performed. Sodium valproate will be taken orally twice daily for 2 years. Participants will be asked to record missing doses and to return any untaken medications at their next study visit.

Follow-up assessments: Face-to-face clinical assessments will be repeated in all subjects at three months, twelve months and two years. Phone follow-up calls will be performed at 6, 9, 15, 18 and 21 months to check for adverse effects. Participants will be given a contact card with the contact details of the research.

Intervention Type
Drug

Phase
Not Applicable

Drug/device/biological/vaccine name(s)
Sodium valproate

Primary outcome(s)
Measured at baseline, 3 months and 2 years:
1. Carotid plaque volume will be assessed using CTA
2. Carotid plaque inflammation will be assessed by 18Fluoride-fluorodeoxyglucose Positron Emission Tomography/Computed Tomography (FDG-PET/CT)

Key secondary outcome(s))
Measured at baseline, 3 months and 2 years:
1. Carotid plaque morphology will be assessed using CTA
2. Cognitive assessment score (MoCA)

Completion date
01/03/2027

Eligibility

Key inclusion criteria
Current participant inclusion criteria as of 15/06/2021:
1. Have given written informed consent to participate
2. Be aged 50 years and over
3. Have had a recent (less than 6 months) symptomatic carotid atherosclerotic stroke or transient ischaemic attack (TIA) with carotid stenosis of 30-99%. This will be determined from clinical imaging such as US Duplex/ultrasound, CT Angiogram or MR Angiogram. The percentage of stenosis will be measured using NASCET criteria*

*Patients with tight carotid stenosis (> 70%) will usually be offered carotid endarterectomy and therefore would not be suitable for the study. However many patients present with moderate carotid stenosis (30–70%) and do not receive carotid endarterectomy. Therefore we would anticipate that the majority of our patients will have this degree of stenosis (30-70%). In a recent observational study of PET in acute symptomatic carotid stenosis (ICARUSS, co-ordinated by Dr Nick Evans) approximately two thirds of all patients with carotid stenosis did not progress to endarterectomy and therefore we feel it is feasible to recruit this number of patients.

Previous participant inclusion criteria:
1. Have given written informed consent to participate
2. Be aged 50 years and over
3. Have had a recent (less than one month) symptomatic carotid atherosclerotic stroke or transient ischaemic attack (TIA) with carotid stenosis of 30-99%. This will be determined from clinical imaging such as US Duplex/ultrasound, CT Angiogram or MR Angiogram. The percentage of stenosis will be measured using NASCET criteria*

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Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Adult

Lower age limit
50 years

Sex
All

Key exclusion criteria

1. Unable/unwilling to consent
2. Contraindications to taking part in MRI study as assessed by the local MRI safety questionnaire, e.g., pacemaker
3. Women of childbearing potential*
4. Contraindications to sodium valproate including hepatic dysfunction
5. Atrial fibrillation
6. Known chronic kidney disease that would preclude contrast use: i.e Estimated glomerular filtration rate (eGFR) < 30 ml/min/1.73m2
7. Planned endarterectomy
8. Taking medication contra-indicated to sodium valproate
9. Known hypersensitivity to sodium valproate or its excipients
10 Another diagnosed chronic neurological condition (e.g. Alzheimer's, Parkinson's disease, motor neurone disease, multiple sclerosis).
11. Limited life expectancy due to another illness or chronic condition making the 2 year treatment difficult (e.g. widespread malignancy).

*A woman is considered of childbearing potential following menarche and until becoming post-menopausal unless permanently sterile. Women in childbearing potential who underwent permanent sterilisation which include hysterectomy, bilateral salpingectomy and bilateral oophorectomy will be eligible.

Date of first enrolment
01/03/2021

Date of final enrolment
01/03/2025

Locations

Countries of recruitment
United Kingdom

England

Study participating centre
Addenbrooke's Hospital
Stroke Research group
Dept of Clinical Neurosciences
Cambridge
United Kingdom
CB2 0QQ

Sponsor information

Organisation
Cambridge University Hospitals NHS Foundation Trust

ROR
https://ror.org/04v54gj93

Funder(s)

Funder type
Charity

Funder Name
British Heart Foundation; Grant Codes: RE/18/1/34212

Alternative Name(s)
the_bhf, The British Heart Foundation, BHF

Funding Body Type
Private sector organisation

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

Location
United Kingdom

Results and Publications

Individual participant data (IPD) sharing plan
The datasets generated during and/or analysed during the current study are not expected to be made available

IPD sharing plan summary
Not expected to be made available

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
HRA research summary			28/06/2023	No	No
Participant information sheet	Participant information sheet	11/11/2025	11/11/2025	No	Yes