ISRCTN14911850 https://doi.org/10.1186/ISRCTN14911850

In patients with a "small vessel" stroke, can the risk of further strokes and problems with thinking, memory or mobility be reduced?

Submission date
02/10/2017

Recruitment status
No longer recruiting

Registration date
09/10/2017

Overall study status
Completed

Last Edited
05/11/2024

Condition category
Circulatory System

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

Plain English summary of protocol

Current plain English summary as of 14/02/2020:
Background and study aims
About 35,000 people each year in the UK have a type of stroke, called ‘lacunar’ or ‘small vessel’ stroke, which is different to other common types of stroke and for which there is no proven treatment. Small vessel stroke may be caused by damage to the lining of the tiny blood vessels deep inside the brain that stops them functioning normally. This not only causes stroke but, perhaps more importantly, causes problems with thinking and walking, possibly causing up to 45% of all dementias either on its own, or mixed with Alzheimer’s disease (about 350,000 patients in the UK). Some drugs that are commonly used in other blood vessel diseases may help improve small vessel function and prevent worsening of brain damage. One drug (cilostazol) has been tested in patients with stroke in the Asia Pacific countries but not on dementia; the other drug (isosorbide mononitrate) is widely used in the UK for heart disease but not stroke. The aim of this study is to test if the study methods are practical so that patients and trial centres can follow the procedures, and to confirm how many patients have more stroke-like symptoms or experience worsening of their thinking skills. This information is needed to be sure that a very large clinical trial to find out if these drugs can prevent worsening of small vessel disease will be possible.

Who can participate?
Adults aged 30 and older who have had a small vessel stroke.

What does the study involve?
Participants are randomly allocated to one of four groups. Those in the first group receive cilostazol by mouth twice a day. Those in the second group receive the isosorbide mononitrate by mouth 20 mg twice a day or 50 mg once a day if the extended release formulation used. Those in the third group receive both medications in the same doses and ways above. Those in the last group do not receive any treatment. The treatment lasts one year. Participants are followed up around one to two weeks and three to four weeks by phone as well as six and 12 months by a phone or face to face meeting to assess the tolerability and safety of the medication. The last follow up visit includes a brain scan.

What are the possible benefits and risks of participating?
There are no direct benefits with participation, although some patients find the regular check-ups reassuring and the MRI Brain scan may give more details to your doctors about their stroke. There are no foreseeable risks however there is a chance that you may experience side effects from the Trial drugs. Both drugs have been used for many years to treat other conditions so the side effects are well known. If any of these occur, they are usually noticed when first starting the tablets.

Where is the study run from?
1. Royal Infirmary of Edinburgh (UK)
2. Nottingham City Hospital (UK)
3. NHS Fife, Victoria Hospital (UK)
4. Queen Elizabeth University Hospital Glasgow (UK)
5. Bradford Royal Infirmary (UK)
6. Aberdeen Royal Infirmary (UK)
7. Leeds General Infirmary (UK)
8. Royal Derby Hospital Centre (UK)
9. Raigmore Hospital Inverness (UK)
10. St George's Hospital London (UK)
11. King's College Hospital London (UK)
12. Broomfield Hospital Essex (UK)
13. University Hospital of North Tees (UK)
14. Royal Hallamshire Hospital (UK)
15. Sandwell General Hospital (UK)
16. Royal Hampshire County Hospital (UK)
17. University College London (UK)
18. Northwick Park Hospital (UK)
19. Luton and Dunstable NHSFT University Hospital (UK)
20. Doncaster Royal Infirmary (UK)
21. New Cross Hospital Wolverhampton (UK)
22. Calderdale Royal Hospital (UK)
23. Musgrove Park Hospital (UK)
24. Southampton General Hospital (UK)
25. Homerton University Hospital (UK)
26. Royal Devon and Exeter Hospital (UK)

When is the study starting and how long is it expected to run for?
May 2017 to May 2022 (Updated 08/08/2022, previously August 2022. Updated 18/11/2020, previously: December 2022)

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

Who is the main contact?
Professor Joanna Wardlaw
Joanna.Wardlaw@ed.ac.uk

Previous plain English summary as of 11/09/2019:
Background and study aims
About 35,000 people each year in the UK have a type of stroke, called ‘lacunar’ or ‘small vessel’ stroke, which is different to other common types of stroke and for which there is no proven

treatment. Small vessel stroke may be caused by damage to the lining of the tiny blood vessels deep inside the brain that stops them functioning normally. This not only causes stroke but, perhaps more importantly, causes problems with thinking and walking, possibly causing up to 45% of all dementias either on its own, or mixed with Alzheimer's disease (about 350,000 patients in the UK). Some drugs that are commonly used in other blood vessel diseases may help improve small vessel function and prevent worsening of brain damage. One drug (cilostazol) has been tested in patients with stroke in the Asia Pacific countries but not on dementia; the other drug (isosorbide mononitrate) is widely used in the UK for heart disease but not stroke. The aim of this study is to test if the study methods are practical so that patients and trial centres can follow the procedures, and to confirm how many patients have more stroke-like symptoms or experience worsening of their thinking skills. This information is needed to be sure that a very large clinical trial to find out if these drugs can prevent worsening of small vessel disease will be possible.

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Where is the study run from?
1. Royal Infirmary of Edinburgh (UK)
2. Nottingham City Hospital (UK)

When is the study starting and how long is it expected to run for?
May 2017 to November 2020

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

Who is the main contact?
1. Dr Anna Heye
anna.heye@ed.ac.uk
2. Professor Joanna Wardlaw
Joanna.Wardlaw@ed.ac.uk

Previous plain English summary:
Background and study aims
About 35,000 people each year in the UK have a type of stroke, called ‘lacunar’ or ‘small vessel’ stroke, which is different to other common types of stroke and for which there is no proven treatment. Small vessel stroke may be caused by damage to the lining of the tiny blood vessels deep inside the brain that stops them functioning normally. This not only causes stroke but, perhaps more importantly, causes problems with thinking and walking, possibly causing up to 45% of all dementias either on its own, or mixed with Alzheimer’s disease (about 350,000 patients in the UK). Some drugs that are commonly used in other blood vessel diseases may help improve small vessel function and prevent worsening of brain damage. One drug (cilostazol) has been tested in patients with stroke in the Asia Pacific countries but not on dementia; the other drug (isosorbide mononitrate) is widely used in the UK for heart disease but not stroke. The aim of this study is to test if the study methods are practical so that patients and trial centres can follow the procedures, and to confirm how many patients have more stroke-like symptoms or experience worsening of their thinking skills. This information is needed to be sure that a very large clinical trial to find out if these drugs can prevent worsening of small vessel disease will be possible.

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1. Royal Infirmary of Edinburgh (UK)
2. Nottingham City Hospital (UK)

When is the study starting and how long is it expected to run for?
May 2017 to November 2020

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

Who is the main contact?
1. Dr Julia Boyd
julia.boyd@ed.ac.uk

2. Professor Joanna Wardlaw
Joanna.Wardlaw@ed.ac.uk

Study website
https://stroke.nottingham.ac.uk/laci-2/

Contact information

Type(s)
Scientific

Contact name
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Type(s)
Public

Contact name
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Joanna.Wardlaw@ed.ac.uk

Additional identifiers

EudraCT/CTIS number

2016-002277-35

IRAS number

ClinicalTrials.gov number
NCT03451591

Secondary identifying numbers
CPMS 36168

Study information

Scientific Title
LACunar Intervention (LACI-2) Trial-2: Assessment of safety and efficacy of cilostazol and isosorbide mononitrate to prevent recurrent lacunar stroke and progression of cerebral small vessel disease

Acronym
LACI-2

Study objectives
The trial hypothesis is to test whether a much larger scale study testing the effects of Cilostazol and ISMN on preventing brain damage from small vessel disease will be feasible. We will assess how easy is it to identify suitable patients, how many of them are willing to take part in the study and how many stay on the study for the full 12 months. Feedback from participants on study procedures/burden will also inform any future studies. We will also collect information on how many patients have another stroke, experience difficulties in independent daily living or in thinking skills, and on drug safety such as bleeding.

Ethics approval required
Old ethics approval format

Ethics approval(s)
East Midlands - Nottingham 2 REC, 10/05/2017, ref: 17/EM/0077

Study design
Randomized; Interventional; Design type: Treatment, Drug

Primary study design
Interventional

Secondary study design
Randomised controlled trial

Study setting(s)
Hospital

Study type(s)
Treatment

Participant information sheet
Not available in web format, please use the contact details to request a patient information sheet

Health condition(s) or problem(s) studied
Prevention of stroke

Interventions
Randomisation involves minimisation on a number of key prognostic factors. An electronic randomisation system is used to allocate participants to one of four groups as detailed below. All patients receive best medical therapy for stroke prevention in addition to their randomly allocated trial treatment. Trial treatment period is 54 weeks.
1. Cilostazol: oral, 100 mg twice a day
2. Isosorbide mononitrate (ISMN): oral, 20 mg twice a day or 50 mg once a day if extended release formulation used
3. Cilostazol + ISMN - same doses as above
4. No trial treatment

There are 4 follow-up time points:
1. One-two week follow-up by phone
2. Three-four week follow-up by phone
3. Six month follow-up by phone or face to face
4. 12 month follow-up by phone or face to face

At the end of the 12 months they will stop their allocated treatment, have their final visit which includes a brain scan.

Intervention Type
Drug

Phase
Phase II

Drug/device/biological/vaccine name(s)
Cilostazol, Isosorbide mononitrate

Primary outcome measure
Feasibility of a future Phase III trial is the primary outcome and is measured at 36 months. This will be attained if the feasibility target sample size of 400 patients are recruited in 24 months in the UK and >95% retained in follow-up at one year.

Secondary outcome measures
1. Assessment of drug tolerability are measured using questionnaires and reviewing patient notes at one-two weeks, three-four weeks, six months and 12 months
2. Safety is measured using questionnaires and reviewing patient notes at one-two weeks, three-four weeks, six months and 12 months
3. Event is measured using questionnaires and reviewing patient notes at one-two weeks, three-four weeks, six months and 12 months
4. Recruitment rates are measured using questionnaires and reviewing patient notes at one-two

weeks, three-four weeks, six months and 12 months. Questionnaires include a study specific structured questionnaire to record symptoms, medication history and IMP adherence and a vascular event questionnaire.

Overall study start date
01/11/2017

Completion date
31/05/2022

Eligibility

Key inclusion criteria
1. Clinical lacunar stroke syndrome.
2. Brain scanning* with MR including diffusion imaging wherever possible, and obtained soon after the presentation with stroke, shows either:
2.1. A recent, relevant (in time and location) acute lacunar infarct on diffusion MR imaging1,
2.2. Or, if no visible acute lacunar infarct on diffusion MR imaging2 then there is no competing pathology as a cause for stroke (e.g. no acute cortical infarct, no acute intra-cerebral haemorrhage, no stroke mimic such as tumour, subdural haematoma);
2.3. If only a CT brain scan is available as in section 3 above, then there is a small relevant (in age and location) subcortical infarct, or if no infarct then there is no competing pathology as a cause for stroke (e.g. no acute cortical infarct, no acute intra-cerebral haemorrhage, no stroke mimic such as tumour, subdural haematoma). Note that if there is no acute lacunar infarct on MR diffusion imaging but there is a recent-appearing lacunar infarct on FLAIR, T2, or T1 (i.e. no cavitation or ex-vacuo effect; may be slightly swollen, ill-defined edges; or scan in the few weeks before the stroke does not show a lesion but there is an acute lacunar infarct on MR T2, FLAIR, T1 scanning after the stroke in an appropriate area of the brain for symptoms), then the T2, FLAIR, T1 lesion may be counted as the acute lacunar infarct in the absence of a diffusion lesion. Similarly, on CT2 a recent relevant small subcortical infarct would not show cavitation or shrinkage/ex vacuo effect. Note that about a third of patients with a clinically definite lacunar syndrome do not have a corresponding recent infarct visible on MRI but should still be classed as ‘lacunar stroke’ if no other explanation can be found for the symptoms. The presence of a recent cortical infarct on FLAIR, T2, T1, the recent timing being indicated by the characteristics above, would count as a competing pathology. Note that the complete absence of any abnormality on MR or CT brain imaging (no acute subcortical infarct or pre-existing SVD such as white matter hyperintensities, lacunes, etc.) while occasionally seen in lacunar stroke is unusual and should question the diagnosis of lacunar ischaemic stroke.
3. Age >30 years
4. Independent in activities of daily living (modified Rankin ≤2)
5. Capacity to give consent themselves

Participant type(s)
Patient

Age group
Adult

Lower age limit
30 Years

Sex
Both

Target number of participants
Planned Sample Size: 400; UK Sample Size: 400

Total final enrolment
363

Key exclusion criteria
1. Other significant active neurological illness present since suffering stroke (e.g. recurrent seizures, multiple sclerosis, brain tumour). Well-controlled epilepsy present prior to the stroke, a single seizure at onset of the stroke or provoked seizure is not an exclusion.
2. Requiring assistance with activities of daily living (Modified Rankin ≥3)
3. Has been diagnosed as having dementia on formal clinical assessment
4. Active cardiac disease (atrial fibrillation, myocardial infarction in past 6 months, active angina, symptomatic cardiac failure)
5. Diagnosis of hypotension, defined as sitting systolic blood pressure less than 100mmHg
6. Definite indication for (i.e. already prescribed) either trial medication, or definite contraindication to a trial drug as per SmPCSPCs - lactose intolerance is a contraindication to ISMN preparations which contain lactose monohydrate - (indication for or contraindication to one of the trial drugs still allows randomisation to the other trial drug)
7. Unable to swallow tablets
8. Bleeding tendency (e.g. known platelets<100, active peptic ulcer, history of intracranial haemorrhage such as subdural haematoma, subarachnoid haemorrhage, intracerebral haemorrhage, but not asymptomatic haemorrhagic transformation of infarction or a few microbleeds, taking anticoagulant medication)
9. Unlikely to comply with trial medication based on knowledge of past history, lifestyle
10. Planned surgery during the trial period including carotid endarterectomy. Note prior and apparently successful carotid endarterectomy (or other surgery) is not an exclusion criterion and patients who would otherwise be eligible but require endarterectomy first may be randomised after recovery from successful endarterectomy.
11. Other concurrent life threatening illness
12. Unlikely to be available for follow-up (eg moving outside or visitor to the area)
13. History of drug overdose or attempted suicide or significant active mental illness
14. 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. Contraception must be continued for up to 30 days after the end of the IMP dosing
schedule.
15. Prohibited medications to either trial drug (see sections 4.5 of the appended SmPCSPCs and protocol section 6.6.3, plus no anticoagulant drugs); (prohibited medications to one of the trial drugs still allows randomisation to the other trial drug)
16. Renal impairment (creatinine clearance <25 ml/min)
17. Hepatic impairment
18. Current enrolment in another Clinical Trial of Investigational Medicinal Product (CTIMP); still in extended follow-up beyond the CTIMP primary outcome and no longer taking that trial’s IMP

is not an exclusion to enrolment in LACI-2
19. Unable to tolerate MRI or contraindication to MRI (Claustrophobia, Pacemaker)

Date of first enrolment
08/01/2018

Date of final enrolment
31/05/2021

Locations

Countries of recruitment
England

Scotland

United Kingdom

Study participating centre
Royal Infirmary of Edinburgh (Lead centre)
Royal Infirmary of Edinburgh
51 Little France Drive
Edinburgh
United Kingdom
EH16 4SA

Study participating centre
Nottingham City Hospital
Hucknall Road
Nottingham
United Kingdom
NG5 1PB

Study participating centre
NHS Fife, Victoria Hospital
Hayfield Road
Kirkcaldy
United Kingdom
KY2 5AH

Study participating centre
Queen Elizabeth University Hospital Glasgow
1345 Govan Rd

Glasgow
United Kingdom
G51 4TF

Study participating centre
Bradford Royal Infirmary
Duckworth Lane
Bradford
United Kingdom
BD9 6RJ

Study participating centre
Aberdeen Royal Infirmary
Foresterhill
Aberdeen
United Kingdom
AB25 2ZN

Study participating centre
Leeds General Infirmary
Martin Wing
Great George Street
Leeds
United Kingdom
LS1 3EX

Study participating centre
Royal Derby Hospital Centre
Uttoxeter Road
Derby
United Kingdom
DE22 3DT

Study participating centre
Raigmore Hospital Inverness
Old Perth Road
Inverness
United Kingdom
IV2 3UJ

Study participating centre
St George's Hospital
Blackshaw Road
London
United Kingdom
SW17 0QT

Study participating centre
King's College Hospital London
Denmark Hill
London
United Kingdom
SE5 9RS

Study participating centre
Broomfield Hospital Essex
Court Road
Chelmsford
United Kingdom
CM1 7ET

Study participating centre
University Hospital of North Tees
Stroke Unit
Ward 41
Stockton on Tees
United Kingdom
TS19 8PE

Study participating centre
Royal Hallamshire Hospital
Glossop Road
Sheffield
United Kingdom
S10 2JF

Study participating centre
Sandwell General Hospital
Lyndon
West Bromwich

United Kingdom
B71 4HJ

Study participating centre
Royal Hampshire County Hospital
Romsey Road
Winchester
United Kingdom
SO22 5DG

Study participating centre
University College London
London
United Kingdom
WC1N 3BG

Study participating centre
Northwick Park Hospital
Watford Road
Harrow
United Kingdom
HA1 3UJ

Study participating centre
Luton and Dunstable NHSFT University Hospital
Lewsey Road
Luton
United Kingdom
LU4 0DZ

Study participating centre
Doncaster Royal Infirmary
Doncaster
United Kingdom
DN2 5LT

Study participating centre
New Cross Hospital Wolverhampton
Wolverhampton Road

Wolverhampton
United Kingdom
WV10 0QP

Study participating centre
Calderdale Royal Hospital
Salterhebble
Halifax
United Kingdom
HX3 0PW

Study participating centre
Musgrove Park Hospital
Taunton
United Kingdom
TA1 5DA

Study participating centre
Southampton General Hospital
Tremona Road
Southampton
United Kingdom
SO16 6YD

Study participating centre
Homerton University Hospital
Homerton Row
London
United Kingdom
E9 6SR

Study participating centre
Royal Devon and Exeter Hospital
Barrack Road
Exeter
United Kingdom
EX2 5DW

Sponsor information

Organisation
University of Edinburgh and NHS Lothian - co-sponsors (UK)

Sponsor details
ACCORD Office
The Queen's Medical Research Institute
47 Little France Crescent
Edinburgh
Scotland
United Kingdom
EH16 4TJ

Sponsor type
University/education

ROR
https://ror.org/03q82t418

Funder(s)

Funder type
Government

Funder Name
British Heart Foundation (BHF)

Results and Publications

Publication and dissemination plan
Current publication and dissemination plan as of 14/02/2020:
We are going to publish the study protocol in a peer-reviewed journal before the end of recruitment.

A Statistical Analysis Plan will be published prior to database lock and will describe analysis procedures and procedures for missing, unused or spurious data, and definitions of populations analyzed.

On completion of the study, a clinical study report will be prepared for publication in a peer-reviewed journal in accordance with ICH guidelines. A report will also be submitted to the funder (British Heart Foundation). Papers describing secondary analysis will also be published.

The clinical study report will be used for publication and presentation at scientific meetings on stroke and dementia such as UK Stroke Forum, European Stroke Organisation Conference,

International Stroke Conference, the World Stroke Congress, and conferences on Alzheimer's disease and dementia. Investigators have the right to publish orally or in writing the results of the study. Reporting will be in compliance with CONSORT.

Summaries of results will also be made available to all Investigators for dissemination within their clinics (where appropriate and according to their discretion).

A newsletter will be sent to the participants informing them of the results and of other information relevant to small vessel disease and general information about maintaining a healthy lifestyle.

Intention to publish date
31/08/2023

Individual participant data (IPD) sharing plan
Current IPD sharing plan as of 29/06/2023:
The datasets generated during and/or analyzed during the current study are available upon request from Professor Joanna Wardlaw (Joanna.Wardlaw@ed.ac.uk); these data are available in a non-publically available repository.

Previous IPD sharing plan:
The datasets generated during and/or analyzed during the current study are/will be available upon request from Ms Kat Oatey (laci-2@ed.ac.uk) or Professor Joanna Wardlaw (Joanna. Wardlaw@ed.ac.uk).

Previous IPD sharing plan:
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IPD sharing statement:
The datasets generated during and/or analysed during the current study are/will be available upon request from Dr Julia Boyd julia.boyd@ed.ac.uk or Professor Joanna Wardlaw Joanna. Wardlaw@ed.ac.uk

IPD sharing plan summary
Stored in non-publicly available repository, Available on request

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
	protocol		20/10		

Protocol article		01/09/2020	/2020	Yes	No
Statistical Analysis Plan	baseline data and statistical analysis plan	02/09/2022	12/10 /2022	Yes	No
Results article	results	24/05/2023	16/06 /2023	Yes	No
HRA research summary			28/06 /2023	No	No
Abstract results		22/05/2019	05/11 /2024	No	No
Abstract results		24/05/2023	05/11 /2024	No	No
Abstract results		01/09/2021	05/11 /2024	No	No
Abstract results		26/05/2023	05/11 /2024	No	No