

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

<b>Submission date</b> 02/10/2017	<b>Recruitment status</b> No longer recruiting	<input checked="" type="checkbox"/> Prospectively registered <input checked="" type="checkbox"/> Protocol
<b>Registration date</b> 09/10/2017	<b>Overall study status</b> Completed	<input checked="" type="checkbox"/> Statistical analysis plan <input checked="" type="checkbox"/> Results
<b>Last Edited</b> 05/11/2024	<b>Condition category</b> Circulatory System	<input type="checkbox"/> 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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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.hey@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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### 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

## Contact information

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Scientific

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Public

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Joanna.Wardlaw@ed.ac.uk

## Additional identifiers

**Clinical Trials Information System (CTIS)**  
2016-002277-35

**ClinicalTrials.gov (NCT)**

NCT03451591

**Protocol serial number**

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**

Intentional

**Study type(s)**

Treatment

**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(s)**

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.

## **Key secondary outcome(s)**

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.

## **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 imaging<sup>1</sup>,
  - 2.2. Or, if no visible acute lacunar infarct on diffusion MR imaging<sup>2</sup> 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  $\leq 2$ )

5. Capacity to give consent themselves

### **Participant type(s)**

Patient

### **Healthy volunteers allowed**

No

### **Age group**

Adult

### **Lower age limit**

30 years

### **Sex**

All

### **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  $\geq 3$ )
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](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**

United Kingdom

England

Scotland

**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

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United Kingdom  
AB25 2ZN

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

**Study participating centre**  
**Royal Derby Hospital Centre**  
Uttoxeter Road  
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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  
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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  
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**Study participating centre**

**University College London**  
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**Study participating centre**  
**Northwick Park Hospital**  
Watford Road  
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**Study participating centre**  
**Doncaster Royal Infirmary**  
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**New Cross Hospital Wolverhampton**  
Wolverhampton Road  
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**Study participating centre**  
**Calderdale Royal Hospital**  
Salterhebble  
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**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)

**ROR**

<https://ror.org/03q82t418>

## Funder(s)

**Funder type**

Government

## Funder Name

British Heart Foundation (BHF)

# Results and Publications

## 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-publicly 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:

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.

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?
<a href="#">Results article</a>	results	24/05/2023	16/06/2023	Yes	No
<a href="#">Protocol article</a>	protocol	01/09/2020	20/10/2020	Yes	No
<a href="#">Abstract results</a>		22/05/2019	05/11/2024	No	No

<a href="#">Abstract results</a>		24/05/2023	05/11/2024	No	No
<a href="#">Abstract results</a>		01/09/2021	05/11/2024	No	No
<a href="#">Abstract results</a>		26/05/2023	05/11/2024	No	No
<a href="#">HRA research summary</a>			28/06/2023	No	No
<a href="#">Statistical Analysis Plan</a>	baseline data and statistical analysis plan	02/09/2022	12/10/2022	Yes	No
<a href="#">Study website</a>	Study website	11/11/2025	11/11/2025	No	Yes