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A study of the anti-inflammatory medication colchicine for people with blocked arteries of the legs

Submission date
09/07/2024

Recruitment status
Recruiting

Registration date
07/08/2024

Overall study status
Ongoing

Last Edited
10/11/2026

Condition category
Circulatory System

[ ] Prospectively registered
[ ] Protocol
[ ] Statistical analysis plan
[ ] Results
[ ] Individual participant data
[X] Record updated in last year

Plain English summary of protocol

Background and study aims
Atherosclerosis is a disease that causes narrowing of the arteries including those in the heart, brain and legs. It is caused by chronic inflammation and may lead to heart attack, stroke and removal of the leg (amputation). Atherosclerosis in the legs is called peripheral arterial disease (PAD). The main treatment for people with PAD is to try to reduce further damage to the arteries throughout the body, thereby preventing artery complications such as stroke, heart attack and amputation. These treatments include living a healthier lifestyle, statin medication, aspirin and blood pressure medication. Unfortunately, despite these treatments, people with PAD still have a high risk of developing further artery complications. Because people with atherosclerosis have chronic inflammation of the arteries, researchers think that a commonly used medication called colchicine that reduces inflammation (an anti-inflammatory) may prevent further artery damage and artery complications. Research conducted on individuals with atherosclerosis in the heart's arteries has shown that colchicine can lower the incidence of artery-related complications by approximately 20%. This is a large study to find out whether colchicine can be taken by people with PAD and whether it will prevent further artery damage and complications. If colchicine was shown to be effective in preventing artery complications, it could be a really important treatment to offer people with PAD. The study is part of an international project being led by a team of researchers at Hamilton Health Sciences and McMaster University in Canada. The study will be conducted in other countries including Canada, Australia and the Netherlands. The project as a whole aims to enrol 6,150 adults with PAD. Around 1,500 of these participants will be from the UK. Half of the participants will receive tablets containing the study medication colchicine and half will receive tablets containing a placebo (inactive medicine).

Who can participate?
Patients aged 18 years old and over with symptomatic atherosclerotic lower extremity PAD

What does the study involve?
Patients referred to vascular department clinics or hospitalised with PAD will be eligible for the study. Participants who consent will be given colchicine for 2-3 weeks to make sure they can

tolerate it and don’t experience unwelcome side effects. Participants who tolerate colchicine will then be randomly assigned to colchicine or a dummy pill (placebo). People in the study will not know which type of pill they are taking. Participants will take the tablets daily and have follow-up visits or phone calls with the clinical team, every 6 months for up to 4 years. Information about hospital admissions, blood tests and PAD symptoms will be collected at the follow-up visits. Participants will be asked to complete quality-of-life questionnaires annually. Where blood test results are unavailable for full blood count these may be requested annually.

What are the possible benefits and risks of participating?
Colchicine is a well-tested drug with a long and safe history. It has been extensively used at a larger dose for the treatment of gout. Its safety has been well described in these patients, with the most common side effect being tummy upset (diarrhoea, nausea, vomiting). Colchicine at a lower dose than is being used in this study, has been studied in trials of more than 10,000 people with heart disease. At this dose, there was no difference in the rates of tummy upset in those receiving colchicine compared with those taking a dummy medication (placebo). The study protocol includes a 2-3 week run-in phase during which patients will receive colchicine to ensure that they can tolerate it. Patients will be given a prescription for 20 tablets for the run-in phase. Patients who take a minimum of 11 tablets, who are happy to continue with the trial and whose study doctor assesses them as tolerating colchicine will be randomised. People who have PAD frequently come to the hospital for a variety of assessments and procedures. The number of follow-up visits in the trial has been kept to a minimum; enough to ensure safety without placing excess burden on the participants. Some of the follow-up may be delivered in the form of questionnaires or phone calls that can be completed at home without the need for travelling.

Where is the study run from?
The University of Bristol, UK
Hamilton Health Sciences, Canada

When is the study starting and how long is it expected to run for?
May 2021 to October 2028

Who is funding the study?
In the UK, the study is funded by the British Heart Foundation

Who is the main contact?
In the UK, the main contact is Miss Lucy Ellis, leaderpad-trial@bristol.ac.uk

Contact information

Type(s)
Scientific, Principal investigator

Contact name
Prof Robert Hinchliffe

Contact details
Department of Vascular Surgery, 2nd Floor, Learning and Research Building, Southmead Hospital
Bristol
United Kingdom

BS10 5NB
None provided
robert.hinchliffe@bristol.ac.uk

Type(s)
Public

Contact name
Miss Lucy Ellis

Contact details
Bristol Trials Centre, 1-5 Whiteladies Road
Bristol
United Kingdom
BS8 1NU
None provided
leaderpad-trial@bristol.ac.uk

Additional identifiers

ClinicalTrials.gov (NCT)
NCT04774159

Integrated Research Application System (IRAS)
1009217

Central Portfolio Management System (CPMS)
61099

Protocol serial number
2023-2851

Study information

Scientific Title
Low dose colchicine in patients with peripheral artery disease to address residual vascular risk: a randomized trial (LEADER-PAD)

Acronym
LEADER-PAD

Study objectives
The overall objective is to examine the efficacy and safety of colchicine 0.5 mg daily in reducing the incidence of cardiovascular death, myocardial infarction, stroke or severe limb ischemia requiring an intervention including major vascular amputation in patients with peripheral artery disease.

In addition to the primary objective, outcome data will be collected and analysed:
• To examine the effects of colchicine 0.5 mg/daily on quality of life in PAD patients (assessed via patient questionnaires).
• To examine side effects of colchicine 0.5 mg/daily in PAD patients.

Ethics approval required
Ethics approval required

Ethics approval(s)
1. Approved 07/05/2021, Hamilton Integrated Research Ethics Board (237 Barton Street East, Hamilton ON, L8L 2X2, Canada; -; fspence@mcmaster.ca), ref: CTO Project ID: 3520

2. Approved 25/09/2024, North West - Greater Manchester South Research Ethics Committee (3 Piccadilly Place, Manchester, M1 3BN, United Kingdom; +44 (0)207 104 8014, 207 104 8065, 208 104 8051; gmsouth.rec@hra.nhs.uk), ref: 24/NW/0235

Primary study design
Interventional

Study design
Randomized placebo-controlled double-blind parallel-group study

Study type(s)
Efficacy, Safety

Health condition(s) or problem(s) studied
Peripheral artery disease

Interventions
Eligible participants who consent to take part in the study will undergo a 2-3 week test period when they will take colchicine 0.5 mg daily. Participants who tolerate colchicine (are not sensitive to medication side effects) and have taken at least 11 tablets will then be randomised to either colchicine or a placebo tablet in a 1:1 ratio. Randomisation will be carried out using an online system.

Group 1: Colchicine 0.5 mg daily
Participants will take a colchicine tablet by mouth daily for the duration of study participation. Study medication will be dispensed every year.

Group 2: Placebo
Participants will take a placebo tablet by mouth daily for the duration of the study participation. Study medication will be dispensed every year.

Colchicine drug and placebo are of the same appearance and are indistinguishable. All investigators, study personnel and participants will be blinded to drug treatment assignment.

Participants in each group will be followed up every 6 months for evaluation of clinical outcomes, including major cardiovascular and limb adverse events or hospitalisation for vascular complications or revascularisation. Participants will be asked to complete quality-of-life questionnaires annually. In the first year, participants will be contacted at months 3 and 9 to

discuss any challenges in taking study drugs, and as needed, they will be re-contacted to address adherence issues.

Intervention Type
Drug

Phase
Phase III

Drug/device/biological/vaccine name(s)
Colchicine

Primary outcome(s)
The rate of major adverse cardiovascular and limb events (MACE or MALE). This composite outcome consists of cardiovascular deaths, myocardial infarction, stroke, and severe limb ischemia that requires a vascular intervention (i.e., pharmacological reperfusion, endovascular or surgical revascularisation) or a major vascular amputation (defined as ankle/transtibial amputation or higher). Details of these events will be collected at 6 monthly follow-up visits for the duration of participation via participant reports and using information in participant medical records. The trial is event-driven with the final analysis planned once 731 primary events have occurred.

Key secondary outcome(s)
Major adverse cardiovascular events, major adverse limb events (MALE), extended MALE, cardiovascular deaths, myocardial infarction, stroke, hospitalisation, acute or chronic limb-threatening ischemia, all revascularisation (defined as coronary or cerebrovascular or lower limb or other peripheral revascularisation), total vascular amputation, overall mortality, all thrombosis or thromboembolism (arterial and venous), Fontaine Stage. Details of these events will be collected at 6 monthly follow-up visits using for the duration of participation via participant reports and using information in participant medical records.

EQ-5D-5L, VascuQOL-6 and Standard Assessment of Global Everyday Activities (SAGEA) will be completed by participants at randomisation, and every 12 months for the duration of participation.

Completion date
31/10/2028

Eligibility

Key inclusion criteria
Patients need to meet the following criteria for inclusion:
1. Age > 18 years old
2. Symptomatic atherosclerotic LE PAD fulfilling at least one of the following:
2.1. Intermittent claudication with ankle/arm blood pressure ratio* (ABI ≤ 0.90) or artery stenosis ≥ 50% plus one of
2.1.1. >1 vascular bed affected by atherosclerosis.
2.1.2. Diabetes
2.1.3. Heart failure
2.1.4. Chronic kidney disease (eGFR < 60 mL/min/1.73 m2)
2.2. Rest pain (mostly in the foot) OR necrosis of limb OR gangrene of limb (corresponding to

either Fontaine stages 3 or 4 OR Rutherford Classification categories 4 to 6). All must have an ankle/arm blood pressure ratio* (ABI ≤ 0.90) OR artery stenosis ≥ 50%.
*In cases of incompressible ankle arteries, the presence of toe pressure ≤ 60 mm Hg or toe-brachial index ≤ 0.70 is acceptable
2.3. Revascularization, defined as limb bypass surgery or endovascular revascularization procedures (irrespective of the specific device used), including percutaneous transluminal angioplasty/stent of iliac or infra-inguinal arteries or extra-anatomical bypass surgery.
2.4. Leg or foot amputation for arterial vascular indications
3. Written or verbal informed consent from the patient

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Mixed

Lower age limit
18 Years

Upper age limit
100 Years

Sex
All

Total final enrolment
0

Key exclusion criteria
1. Contraindication to colchicine
2. Long-term requirement for colchicine for another clinical indication
3. Active diarrhoea
4. eGFR < 30 mL/min/1.73 m2 (based on the local method for estimating eGFR)
5. Cirrhosis or severe chronic liver disease
6. Woman who is pregnant, breast-feeding or of child-bearing potential not protected by reliable contraception or is planning conception during the study
7. Current or planned long-term use of cyclosporine, verapamil, HIV protease inhibitors, azole antifungals, or macrolide antibiotics (except azithromycin). Added 31/03/2026: In the UK patients on current or planned long-term use of azithromycin are also excluded.
8. Patients who are deemed unlikely to return for follow-up
9. Patients with life expectancy < 1 year

Date of first enrolment
07/05/2021

Date of final enrolment
01/04/2028

Locations

Countries of recruitment
United Kingdom

England

Australia

Belgium

Brazil

Canada

Ecuador

Germany

Netherlands

Switzerland

United States of America

Study participating centre
Addenbrookes Hospital
Hills Road
Cambridge
England
CB2 0QQ

Study participating centre
Royal Infirmary of Edinburgh at Little France
51 Little France Crescent
Old Dalkeith Road
Edinburgh
Lothian
Scotland
EH16 4SA

Study participating centre
Glenfield Hospital
Groby Road
Leicester

England
LE3 9QP

Study participating centre
Leeds General Infirmary
Great George Street
Leeds
England
LS1 3EX

Study participating centre
Bradford Royal Infirmary
Duckworth Lane
Bradford
England
BD9 6RJ

Study participating centre
Southampton General Hospital
Tremona Road
Southampton
England
SO16 6YD

Study participating centre
Southmead Hospital
Southmead Road
Westbury-on-trym
Bristol
England
BS10 5NB

Study participating centre
Northern General Hospital
Northern General Hospital NHS Trust
C Floor, Huntsmnan Building
Herries Road
Sheffield
England
S5 7AU

Study participating centre
Royal Sussex County Hospital
Eastern Road
Brighton
England
BN2 5BE

Study participating centre
St Georges Hospital
Blackshaw Road
London
England
SW17 0QT

Study participating centre
Norfolk and Norwich University Hospital
Colney Lane
Colney
Norwich
England
NR4 7UY

Study participating centre
Kent and Canterbury Hospital
Ethelbert Road
Canterbury
England
CT1 3NG

Study participating centre
Manchester Royal Infirmary
Cobbett House
Oxford Road
Manchester
England
M13 9WL

Study participating centre

St Thomas' Hospital
Westminster Bridge Road
London
England
SE1 7EH

Study participating centre
Derriford Hospital
Derriford Road
Plymouth
England
PL6 8DH

Study participating centre
Hull Royal Infirmary
Anlaby Road
Hull
England
HU3 2JZ

Study participating centre
Pinderfields Hospital
Aberford Road
Wakefield
England
WF1 4DG

Study participating centre
Royal Free Hospital
Pond Street
London
England
NW3 2QG

Study participating centre
Royal Cornwall Hospital
Treliske
Truro
England
TR1 3LJ

Study participating centre
Cumberland Infirmary
Newtown Road
Carlisle
England
CA2 7HY

Sponsor information

Organisation
University of Bristol

ROR
https://ror.org/0524sp257

Organisation
Hamilton Health Sciences

Funder(s)

Funder type
Charity

Funder Name
British Heart Foundation

Alternative Name(s)
The British Heart Foundation, the_bhf, 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 will be stored in a non-publicly available repository.

12 months after the main LEADER-PAD trial publications, UK anonymised trial data will be made available for sharing with academic researchers subject to the secondary research protocol being approved by a UK REC or other similar, approved ethics review body. Requests for sharing can be made by emailing the UK Chief Investigator Professor Robert Hinchliffe, robert.hinchliffe@bristol.ac.uk.

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