

# Allopurinol as a possible oxygen sparing agent during exercise in peripheral arterial disease

<b>Submission date</b> 02/09/2010	<b>Recruitment status</b> No longer recruiting	<input checked="" type="checkbox"/> Prospectively registered <input type="checkbox"/> Protocol
<b>Registration date</b> 25/10/2010	<b>Overall study status</b> Completed	<input type="checkbox"/> Statistical analysis plan <input checked="" type="checkbox"/> Results
<b>Last Edited</b> 24/03/2016	<b>Condition category</b> Circulatory System	<input type="checkbox"/> Individual participant data

## Plain English summary of protocol

### Background and study aims

Peripheral arterial disease refers to narrowing in the arteries supplying blood to the limbs. It is most commonly experienced by patients as a cramping pain in the legs that comes on whilst walking and rapidly settles when resting. Blood carries oxygen round the body and because of the narrowings in the arteries this means that the leg muscles do not get as much oxygen as they need, causing the cramping pain. It has recently been found that a medication called allopurinol – a safe drug that has been used to treat gout for many years – has helped with another condition where oxygen demand outstrips oxygen supply, namely angina. Our theory is that this same medication may also help patients with peripheral arterial disease, by enabling them to walk further.

### Who can participate?

Men and women aged 35-85 suffering from peripheral arterial disease.

### What does the study involve?

To make sure you are suitable for the study we first ask you to undertake two exercise treadmill tests a week apart to ensure that your symptoms are stable. This test involves you walking on a treadmill. We are trying to find out how far you can walk before you experience leg pain. You will also be asked to walk for six minutes along a level corridor at your own pace to assess your overall exercise ability. We'll also take some blood tests. With your agreement we would also like to store the blood samples we take for a period of 5 years so we can use it to test any new blood markers that become available in the near future. You will be randomly allocated to take either a tablet which contains the medication we are testing (called allopurinol) or an inactive tablet (called a placebo). We will then follow you up regularly, with six hospital visits over six months and several telephone calls. We will use some questionnaires to ask you questions about your normal life and also your walking ability. At three of your visits we will measure blood vessel stiffness in your arm. A blood pressure cuff will be placed below your elbow. We will then take an ultrasound measurement of the artery above the elbow (this involves placing an ultrasound probe and some jelly gently on the skin above the elbow). We will then inflate the blood pressure cuff to block the circulation to the forearm for a period of five minutes. After

five minutes we will then release the cuff and take another scan to measure the artery above the elbow. We will then repeat this process this time before and after giving you a spray of GTN under the tongue (a drug that is also used to treat angina).

What are the possible benefits and risks of participating?

You will be monitored closely during the study and will be seen by a heart specialist at each of your study visits. Besides having tests that have already been mentioned, your medication will be reviewed on a regular basis. The tests will give us information about the function of your heart, kidneys and blood circulation. If any of these investigations reveal any new abnormality we will either discuss this with your GP or refer you to a specialist clinic at Ninewells Hospital (whichever seems most appropriate). The study may not immediately benefit you, but if the results of the study are positive this may change the practice of managing patients with peripheral arterial disease like you and potentially will have a great impact on thousands or even millions of patients in the future. If so, you may gain eventually from our discovering a new treatment for your condition. Allopurinol has been used for about 50 years, mainly for the treatment of gout. It has a good safety record and is generally well tolerated. However, like most medicines, allopurinol occasionally causes side effects. The most common side effect is nausea and some abdominal discomfort which affects less than one in ten of patients on allopurinol. This can be minimised by taking the tablets with food. Allopurinol causes a skin rash in one in a hundred or less of patients. This may be associated with fever, swollen glands, joint pains, unusual blistering or bleeding. Reports of other side effects of allopurinol are very rare (less than 1 in 10,000 people) and it is not always clear if they are truly related to the treatment. These include headache, stomach upset, drowsiness and anaemia. Having blood samples taken can cause some mild bruising. The GTN spray can cause a slight headache but this usually quickly passes. When the blood pressure cuff is inflated there can be some mild discomfort that goes away quickly once it is deflated.

Where is the study run from?

Ninewells Hospital & Medical School (UK).

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

From October 2010 to August 2012.

Who is funding the study?

British Heart Foundation (UK).

Who is the main contact?

Prof Allan Struthers

## Contact information

### Type(s)

Scientific

### Contact name

Prof Allan Struthers

### Contact details

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## Additional identifiers

**ClinicalTrials.gov (NCT)**  
NCT01147705

**Clinical Trials Information System (CTIS)**  
2010-020662-23

**Protocol serial number**  
2009CV16

## Study information

### Scientific Title

Allopurinol as a possible oxygen sparing agent during exercise in peripheral arterial disease: a double-blind, placebo-controlled, parallel group study

### Acronym

APOSA-PAD

### Study objectives

Peripheral arterial disease (PAD) is a common condition that arises due to the build up of atheroma in the arteries supplying blood to the peripheral muscles and other tissues. This imbalance between oxygen supply and demand becomes particularly apparent when patients with the condition are walking. The pain and weakness they experience (mainly in the calf but less commonly in the thigh) is known as intermittent claudication and resolves upon cessation of exercise.

It is an important disease to study as it is (i) common (est. prevalence of symptomatic intermittent claudication in Scotland of 4.5%) and (ii) those with it have a 1.6 times higher relative risk of ischaemic heart disease. These patients also have a significantly higher mortality than age-matched controls at around 12% per year.

There are two main aims of therapy -

1. To reduce the risk of cardiovascular events by way of standard secondary prevention measures (smoking cessation, anti-platelet, anti-hypertensive and cholesterol-lowering therapy, diabetic control)
2. To treat symptoms

Supervised exercise therapy has been shown to be beneficial in improving walking time and distance in selected patients with leg pain from intermittent claudication with an overall increase in walking distance of approximately 150 metres at three months.

There are numerous drug treatments available for consideration in PAD patients (mainly cilostazol in the UK), but many of these have either undesirable side effects or no clear evidence of benefit. The range of increase in walking distance on cilostazol was reported to be a 50-76%

increase over three months compared to 20% with placebo with some significant improvements in Quality of Life (QOL) indicators, although with a significant number of adverse effects (16% vs 8% on placebo) limiting therapy. The current cost (March 2010) is £35.31/month.

Other options for therapy include angioplasty and bypass surgery. At present these are only recommended for patients who fail to respond to medical therapy and have severely disabling symptoms (in the absence of significant exercise-limiting comorbidities).

### **Ethics approval required**

Old ethics approval format

### **Ethics approval(s)**

Scotland A Research Ethics Committee, 19/07/2010, ref: 10/MRE00/51

### **Primary study design**

Interventional

### **Study design**

Single-centre double-blind placebo-controlled parallel-group study

### **Study type(s)**

Treatment

### **Health condition(s) or problem(s) studied**

Peripheral arterial disease

### **Interventions**

Allopurinol vs placebo

### **Intervention Type**

Drug

### **Phase**

Not Applicable

### **Drug/device/biological/vaccine name(s)**

Allopurinol

### **Primary outcome(s)**

The distance to onset of claudication pain at 24 weeks but we will also measure total exercise distance.

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

1. To see if allopurinol improves quality of life in participants with PAD
2. To investigate the anti-oxidant effects of allopurinol of participants with PAD

### **Completion date**

01/08/2012

## **Eligibility**

## **Key inclusion criteria**

1. Men and women age 35-85 years suffering from PAD. PAD will be defined as:
  - 1.1. Claudication defined as leg pain on walking and disappearing within 10 minutes on standing and of presumed atherosclerotic origin
  - 1.2. An ankle brachial pressure index (ABPI) of <0.90 on the worst leg at rest
2. Stable disease demonstrated by having a reproducible pain free walking distance on 2 consecutive treadmill tests, i.e. less than 25% variance. The reason for termination of the test must be claudication pain only. All treadmill tests will be done at a speed of 3.2 km/h (= 2 mph), as is standard practice in PAD trials. The incline will begin at 0% and increase in grade of 2% every 2 minutes. This is the standard Skinner-Gardner protocol (Angiology 1992, 43(8): 661-671).

## **Participant type(s)**

Patient

## **Healthy volunteers allowed**

No

## **Age group**

Adult

## **Sex**

All

## **Key exclusion criteria**

1. Rest pain
2. Childbearing potential
3. Heart failure
4. Any other exercise limiting cardiac disease
5. BP >180/100 mmHg
6. eGFR <60 ml/min
7. Liver disease
8. Malignancy
9. Already on allopurinol or had an adverse reaction to it.
10. Participants who have had a recent marked change in symptoms or recent (in the last six months) intervention for PAD
11. Participants receiving treatment which is contraindicated with the study treatment
  - 11.1. 6-mercaptopurine
  - 11.2. Azathioprine
  - 11.3. Warfarin
  - 11.4. Theophylline

## **Date of first enrolment**

14/01/2011

## **Date of final enrolment**

13/01/2012

## **Locations**

### **Countries of recruitment**

United Kingdom

Scotland

**Study participating centre**  
**Ninewells Hospital & Medical School**  
Dundee  
United Kingdom  
DD1 9SY

## Sponsor information

**Organisation**  
University of Dundee (UK)

**ROR**  
<https://ror.org/03h2bxq36>

## Funder(s)

**Funder type**  
Charity

**Funder Name**  
British Heart Foundation (UK) - Research Fellowship (ref: FS/10/014/28079)

**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

### IPD sharing plan summary

Available on request

### Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
<a href="#">Results article</a>	results	01/02/2016		Yes	No
<a href="#">HRA research summary</a>			28/06/2023	No	No