

# Cardiovascular events and mortality in systemic sclerosis (SSc): a study of the effect of iloprost on these and on disease progression

<b>Submission date</b> 13/07/2005	<b>Recruitment status</b> No longer recruiting	<input type="checkbox"/> Prospectively registered <input type="checkbox"/> Protocol
<b>Registration date</b> 07/09/2005	<b>Overall study status</b> Completed	<input type="checkbox"/> Statistical analysis plan <input checked="" type="checkbox"/> Results
<b>Last Edited</b> 30/04/2020	<b>Condition category</b> Musculoskeletal Diseases	<input type="checkbox"/> Individual participant data

## Plain English summary of protocol

### Background and study aims

Systemic sclerosis is a long-term condition that causes thickening and hardening of the skin and can also affect the internal organs. Death from cardiovascular (heart) disease is a significant problem for patients with systemic sclerosis, accounting for one third of all deaths in this population. The drug iloprost, delivered into a vein (intravenous), will be a familiar treatment to many patients with systemic sclerosis. It is used as a prophylactic (preventative) treatment for Raynaud's phenomenon (spasm of the small blood vessels in the fingers and toes). However, its effect as a blood vessel dilator may also prevent patients with systemic sclerosis from developing cardiovascular disease. The aim of this study is to find out whether oral iloprost treatment is effective at reducing systemic sclerosis disease progression.

### Who can participate?

Patients over 40 years of age with systemic sclerosis

### What does the study involve?

Participants take a placebo (dummy drug) for one month to ensure that they are compliant with the study medication in that period. Following this phase, all participants are reviewed first at three months (to ensure stability on treatment and absence of serious side effects); at six months; and then six monthly until their final visit at the end of the study. Participants are randomly allocated to take either iloprost or placebo as one tablet (50mcg) daily for one week. This is then increased to one tablet twice daily for a further week, then one tablet three times daily for a further week and, if tolerated, then increased to the maximum desired dose of 200mcg daily (100mcg twice daily) and kept at that dose for the duration of the study. Participants are then followed up to assess disease progression for a period of 4 to 7 years based on when they joined the study.

### What are the possible benefits and risks of participating?

This study is important as it takes a medication known to be of use for some aspects of systemic sclerosis and investigates whether it may prevent cardiovascular disease which may result in death. This study involves the collaboration of medical, nursing and other staff with expertise in

this area throughout the UK and Eire. It also provides a further opportunity to follow up patients for over 4 years to look at other important aspects of this disease, namely heart, lung and kidney function, to find out whether this treatment is protective of other organs as well. There may be risks involved with participation in this study related to possible side effects of the drug iloprost, which may include flushing, light-headedness, dizziness, faintness or low blood pressure, nausea, and headache. Although iloprost has been used and tested before, side effects may occur which have not been seen previously.

Where is the study run from?

1. Ninewells Hospital (UK)
2. Foresterhill Hospital (UK)
3. Woolmanhill Hospital (UK)
4. Western General Hospital (UK)
5. St John's Hospital (UK)
6. Glasgow Royal Infirmary (UK)
7. Freeman Hospital (UK)
8. Chapel Allerton Hospital (UK)
9. Royal St James Hospital (UK)
10. Northampton General (UK)
11. Royal Free Hospital (UK)
12. St Vincent's Hospital (Ireland)

When is the study starting and how long is it expected to run for?  
February 2002 to December 2008

Who is funding the study?

Raynaud's and Scleroderma Association (UK)

Who is the main contact?

1. Prof. Jill Belch  
J.J.F.Belch@dundee.ac.uk
2. Dr Stephen McSwiggan  
s.j.mcswiggan@dundee.ac.uk

## Contact information

### Type(s)

Scientific

### Contact name

Prof Jill Belch

### Contact details

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**Type(s)**

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**Contact name**

Dr Stephen McSwiggan

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**Additional identifiers**

EudraCT/CTIS number

IRAS number

ClinicalTrials.gov number

Secondary identifying numbers

N/A

**Study information****Scientific Title**

Cardiovascular events and mortality in systemic sclerosis (SSc): a study of the effect of iloprost on these and on disease progression

**Acronym**

SSTEP: Systemic Sclerosis Trial of Events and Progression

**Study objectives**

That oral iloprost therapy is more effective than placebo in reducing SSc disease progression, and coronary and cerebrovascular events in patients with SSc.

**Ethics approval required**

Old ethics approval format

**Ethics approval(s)**

Scotland 'A' REC, 08/11/2001, ref: MREC 01/0/70

**Study design**

Randomised placebo-controlled parallel-group trial

**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

Systemic sclerosis (SSc)

## Interventions

Oral iloprost or placebo

Added 11/08/2017:

The study was a randomised, placebo-controlled clinical trial with a one month placebo run in to ensure patients were compliant with study medication in that period. Following this placebo run in phase, all patients enrolled in the study were reviewed first at three months (to ensure stability on treatment and absence of serious side effects); at six months; and then six monthly until their final visit at the end of the study period. Block randomisation was done for each site in blocks of six (three active versus three placebo) to ensure even distribution, where possible, of active and placebo allocation at each site. Investigators and participants were blinded to treatment. Study drugs and placebo were in small identical capsules of 50 mcg doses. Participants were advised to continue on one tablet (50mcg) daily for one week. This was then increased to one tablet twice daily for a further week, then one tablet three times daily for a further week and, if tolerated, then titrated to the maximum desired dose of 200mcg daily (100mcg bd) and maintained at that dose for the duration of the trial. Participants were then followed up for a period of 4 to 7 years dependent on time of enrolment.

## Iloprost and placebo composition

Active ingredient in the Iloprost capsules was 0.38 mg Iloprost  $\beta$ -cyclodextrin clathrate (50 $\mu$ g Iloprost and 0.33mg  $\beta$ -cyclodextrin) with the following inactive ingredients:

1. Lactose monohydrate
  2. Microcrystalline cellulose
  3. Methacrylic acid copolymer (Eudragit NE 30D)
  4. Magnesium stearate
  5. Titanium dioxide
  6. Polyethylene glycol 6000
  7. Polysorbate 80
  8. Silicon dioxide
  9. Hard gelatin capsule (containing titanium dioxide, iron oxide (red) and gelatin)
- The matched placebo was identical to the Iloprost capsule but lacked the active ingredient, Iloprost  $\beta$ -cyclodextrin clathrate.

## Intervention Type

Drug

**Phase**

Not Applicable

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

Iloprost

**Primary outcome measure**

A composite primary endpoint is sought for this study.

1. Fatal coronary and stroke events plus non fatal myocardial infarction and stroke
2. Vascular disease death
3. SSc disease progression to include:
  - 3.1. Deteriorating renal function as measured by 24-hour urine and blood sampling for creatinine clearance
  - 3.2. Deteriorating lung function as measured by changes in DLCO total lung capacity
  - 3.3. Increase in pulmonary artery pressure measured in millimetres in mercury by echocardiogram
  - 3.4. Skin score assessed using the modified Rodnan Skin Score

These will be monitored and percentage change from baseline calculated. If deterioration is indicated by an increasing figure then 30% change will be required. If deterioration is based on a decreasing number then 20% change from baseline will be required. Additionally the Medsger categories will be evaluated. A final decision regarding the primary endpoints will be carried out by the Data and Safety Monitoring Committee approximately 8 months into the study. The definition of the above cardiovascular (CV) events will be made according to the World Health Organisation (WHO) Criteria for the diagnosis of coronary events and stroke (fatal and non-fatal).

**Secondary outcome measures**

The main secondary endpoints are:

1. All cause mortality
2. Non-fatal myocardial infarction and stroke
3. Occurrence of other vascular events including requirement of coronary or peripheral arterial bypass surgery and/or angioplasty, development of angina, claudication or development of critical limb ischaemia
4. Severity of Raynaud's Phenomenon

**Overall study start date**

07/02/2002

**Completion date**

31/12/2008

**Eligibility****Key inclusion criteria**

Subjects will be patients with both limited and diffuse SSc, as our pilot work has shown atherosclerotic vascular disease to occur in both groups. The patients considered for this study will be as follows:

1. Any patient fulfilling Arthritis Research Campaign (ARC) criteria for SSc
2. Any patient with Raynauds Phenomenon and at least 3 other features of limited SSc
3. Any patient with Raynauds Phenomenon and the presence of an SSc-related autoantibody (e. g. anticentromere, antitopo1 [scleroderma 70], anti-U1RNP, anti-ThRNP, anti-U3RNP, anti-PmScl)

All will be >40 years of age. These patients will be recruited from Connective Tissue Disease clinics throughout Tayside, Fife, Strathclyde, Lothian, Grampian, Yorkshire, Bath, Northamptonshire and Ireland. Patients with SSc will be invited to attend the clinics to have their vascular risk factors assessed. Volunteers will then be asked to give informed consent and if that consent is given, enter the screening phase of the study

**Participant type(s)**

Patient

**Age group**

Adult

**Sex**

Both

**Target number of participants**

215

**Key exclusion criteria**

1. Suspected serious physical illness such as cancer which may be expected to curtail life expectancy
2. Psychiatric illness (reported by GP)
3. Congenital heart disease
4. Any patient who is pregnant or who wishes to become pregnant within the time course of the study

**Date of first enrolment**

07/02/2002

**Date of final enrolment**

28/02/2005

**Locations****Countries of recruitment**

England

Ireland

Scotland

United Kingdom

**Study participating centre**

Ninewells Hospital

Dundee

United Kingdom

DD1 9SY

**Study participating centre**  
**Foresterhill Hospital**  
United Kingdom  
AB25 2ZG

**Study participating centre**  
**Woolmanhill Hospital**  
United Kingdom  
AB25 1LD

**Study participating centre**  
**Western General Hospital**  
United Kingdom  
EH4 2XU

**Study participating centre**  
**St John's Hospital**  
United Kingdom  
EH54 6PP

**Study participating centre**  
**Glasgow Royal Infirmary**  
United Kingdom  
G4 0SF

**Study participating centre**  
**Freeman Hospital**  
United Kingdom  
NE7 7DN

**Study participating centre**  
**Chapel Allerton Hospital**  
United Kingdom  
LS7 4SA

**Study participating centre**  
**Royal St James Hospital**  
United Kingdom  
LS9 7TF

**Study participating centre**  
**Northampton General Hospital**  
United Kingdom  
NN1 5BD

**Study participating centre**  
**Royal Free Hospital**  
United Kingdom  
NW3 2QG

**Study participating centre**  
**St Vincent's Hospital**  
United Kingdom  
D04 Y8V0

## **Sponsor information**

### **Organisation**

University of Dundee (UK)

### **Sponsor details**

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### **Sponsor type**

University/education

### **Website**

<http://www.dundee.ac.uk>



ROR

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

## Funder(s)

### Funder type

Charity

### Funder Name

Raynaud's and Scleroderma Association

### Alternative Name(s)

RSA

### Funding Body Type

Private sector organisation

### Funding Body Subtype

Associations and societies (private and public)

### Location

United Kingdom

## Results and Publications

### Publication and dissemination plan

Protocol and statistical plan are available direct on request. The trialists plan to publish the protocol if possible. Planned publication in a high-impact peer reviewed journal of 10-year follow-up data.

### Intention to publish date

31/12/2019

### 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 - the local Safe Haven, the Tayside Health Informatics Centre: <https://www.dundee.ac.uk/hic>.

### IPD sharing plan summary

Stored in repository

### Study outputs

Output type Details

[Basic](#)

Date created	Date added	Peer reviewed?	Patient-facing?
09/08	24/08		

<a href="#">results</a>		/2017	/2017	No	No
<a href="#">Results</a>	results	01/01	17/01		
<a href="#">article</a>		/2019	/2019	Yes	No
<a href="#">Results</a>	results	01/11	17/01		
<a href="#">article</a>		/2016	/2019	Yes	No
<a href="#">Results</a>	results of a parenting program among women who began childbearing as adolescents and young adults	01/11	17/01		
<a href="#">article</a>		/2017	/2019	Yes	No
<a href="#">Results</a>	results of promoting child development through group-based parent support within a cash transfer program	01/02	17/01		
<a href="#">article</a>		/2017	/2019	Yes	No
<a href="#">Results</a>	results of stimulating parenting practices in indigenous and non-indigenous Mexican communities	25/12	17/01		
<a href="#">article</a>		/2017	/2019	Yes	No