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# Study to determine the pharmacokinetic profile, safety and tolerability of Sildenafil in cardiac surgery

**Submission date**
24/06/2013

**Recruitment status**
No longer recruiting

**Registration date**
24/06/2013

**Overall study status**
Completed

**Last Edited**
04/01/2019

**Condition category**
Circulatory System

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

## Plain English summary of protocol

Background and study aims
Acute kidney injury (AKI) occurs in up to one third of all patients after heart surgery. It causes rapid loss of kidney function, increases complications and risk of death after surgery. Our understanding of the underlying processes is poor and recent research have concluded that there is no effective treatment. Injecting the drug Sildenafil through the vein, prevents AKI in our research with animal model. This means that Sildenafil is suitable for further development as a potential prevention for AKI that occurs after heart surgery. We intend to first establish a dose of Sildenafil that is tolerated by the patients and compare that to our previous research with the animal model. We therefore propose to find out how safe is Sildenafil and how well it is tolerated by patients undergoing heart surgery.

Who can participate?
Adult patients, who are undergoing heart surgery, who have high risk of developing AKI after surgery, can participate in this study.

What does the study involve?
During hospital stay:
Patients, before their heart operation, will be allocated into one of six different groups, depending on how many patients have already entered the study before them. Patients will be told which group you have been allocated to, after their operation. A single dose of Sildenafil will be given at the start of the operation. The dose given will be based on the group to which patients have been allocated. The maximum dosage being given in this study is 12.5 mg, which represents a small increase over the normal dose of Sildenafil given for the treatment of pulmonary hypertension (increased blood pressure in the blood vessels of the lungs). Apart from the dose of the drug, everything else about the operation, and medical care after the operation, will happen in the usual way, whichever group patients are assigned to. Patients taking part will also be asked to give blood and urine samples. These samples will be tested to the levels of Sildenafil over time to determine how fast the drug is removed from the body. The samples will also be tested for several chemicals that will give us an idea of how well different organs, e.g. the brain, heart and kidneys, work during and after heart surgery.

After hospital stay:
Patients will be asked to complete a short questionnaire about their general health, during their routine hospital follow-up visit, about six weeks after the operation. If participants are unable to attend this visit, we would contact them by telephone to obtain this information about their health.

What are the possible benefits and risks of participating?
Benefits: It is possible that giving Sildenafil may protect the kidneys during the operation. The information that we get from this research may help us to better understand how Sildenafil works and therefore improve treatments for patients having heart surgery in the future.
Risks: There is a risk that patients receiving lower dosage may still experience higher rate of kidney complications, but this risk is no different to that currently experienced by the patients undergoing heart surgery on a day-to-day basis. Conversely, it is possible that patients receiving higher dosage are at greater risks of side effects from the drug. The most common side effects in adults (seen in more than 1 in 10 patients) are low blood pressure, headache, flushing (reddening of the skin), heartburn, diarrhoea and limb (arm or leg) pain. It is possible that other unknown side effects may be experienced when taking Sildenafil. Sildenafil must not be taken by patients with severe liver problems, very low blood pressure, or certain rare inherited eye diseases because Sildenafil has not been studied in these patient groups. Patients are advised to tell the study doctor if they have one of these illnesses or if they have a history of loss of vision in one or eyes.

Where is the study run from?
The research is being organised and run by the Cardiac Surgery Trials support team at Glenfield Hospital, University Hospitals of Leicester NHS Trust, UK.

When is the study starting and how long is it expected to run for?
The study is starting in July 2013 and will last for approximately 12 months.

Who is funding the study?
The research is funded by the British Heart Foundation, UK.

Who is the main contact?
Ms Veerle Verheyden
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# Contact information

### Type(s)
Scientific

### Contact name
Ms Veerle Verheyden

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# Additional identifiers

**EudraCT/CTIS number**
2012-005345-21

**IRAS number**

**ClinicalTrials.gov number**
NCT02136329

**Secondary identifying numbers**
14246

# Study information

**Scientific Title**
A phase I study to determine the pharmacokinetic profile, safety and tolerability of Sildenafil (REVATIO®) in cardiac surgery

**Acronym**
REVAKI-001, REVAKI-1

**Study objectives**
The aim of this study is to evaluate the pharmacokinetic profile, safety and tolerability of sildenafil an its effect on postoperative kidney function in patients undergoing cardiac surgery who are at increased risk of developing acute kidney injury, in an open label, dose escalation study.

**Ethics approval required**
Old ethics approval format

**Ethics approval(s)**
19/03/2013, ref : 13/SC/0131

**Study design**
Non-randomised; Interventional; Design type: Not specified, Prevention

**Primary study design**
Interventional

**Secondary study design**
Non randomised study

**Study setting(s)**
Not specified

**Study type(s)**
Prevention

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

## Health condition(s) or problem(s) studied
Topic: Cardiovascular, Renal and Urogenital; Subtopic: Cardiovascular (all Subtopics), Renal and Urogenital (all Subtopics); Disease: Renal, Cardiac Surgery

## Interventions
Administration of REVATIO, Patients will be screened by the investigators to assess eligibility for entry into the study. Eligible patients undergoing cardiac surgery with CPB who consent to participate will be consecutively allocated, in a 6:6:6:6:6:6 sequence to:
1. Treatment group 1: Sildenafil 2.5 mg bolus IV over 10 minutes (3.125 mL)
2. Treatment group 2: Sildenafil 2.5 mg bolus IV over 10 minutes + Sildenafil 2.5 mg as a 2hrs continuous infusion (6.250 mL)
3. Treatment group 3: Sildenafil 5.0 mg bolus IV over 10 minutes
4. Treatment group 4: Sildenafil 5.0 mg bolus IV over 10 minutes + Sildenafil 2.5 mg as a 2hrs continuous infusion (6.250 mL)
5. Treatment group 5: Sildenafil 10.0 mg bolus IV over 10 minutes
6. Treatment group 6: Sildenafil 10.0 mg bolus IV over 10 minutes + Sildenafil 2.5 mg as a 2hrs continuous infusion (6.250 mL)

Follow Up Length: 2 month(s); Study Entry : Registration only

## Intervention Type
Drug

## Phase
Phase I

## Drug/device/biological/vaccine name(s)
Sildenafil (REVATIO®)

## Primary outcome measure
Plasma levels of Sildenafil; Timepoint(s): Blood samples for pharmacokinetic analysis at the time points outlined below:
1. Prior to the start of the bolus infusion (0 min)
2. End of bolus Sildenafil infusion (10 min)
3.15 minutes, 30 minutes and 45 minutes post bolus infusion (25 min, 40 min and 55 min)
4. 2hrs post bolus infusion or end of cardiopulmonary bypass, whichever is the latest (2 hrs 10 min)
5. Return to CICU (4 hrs 10 min)
6. 6 hrs post bolus infusion (6 hrs 10 min)
7. 12 hrs post infusion (12 hrs 10 min)
8. Day 1 (24 hrs post infusion)
9. Day 2 (48 hrs post-infusion)

## Secondary outcome measures
Not provided at time of registration

## Overall study start date

09/07/2013

### Completion date
09/04/2014

# Eligibility

### Key inclusion criteria
1. Adult cardiac surgery patients (>18 years and <80 years) undergoing cardiac surgery with moderately hypothermic CPB (32-34° C) and blood cardioplegia.
2. Identified as representing a high risk group for acute kidney injury using a modified risk score.
3. Female subjects of childbearing potential are not to be pregnant (to be confirmed by urine human chorionic gonadotropin pregnancy test). Women are considered not to be of childbearing potential if they have been surgically sterilised (eg, tubal ligation, oophorectomy or hysterectomy) or are postmenopausal (defined as serum follicle-stimulating hormone level of =30 IU/mL) in the absence of hormone replacement therapy and complete absence of menses for at least 24 consecutive months.
Target Gender: Male & Female; Upper Age Limit 80 years ; Lower Age Limit 18 years

### Participant type(s)
Patient

### Age group
Adult

### Lower age limit
18 Years

### Sex
Both

### Target number of participants
Planned Sample Size: 36; UK Sample Size: 36

### Key exclusion criteria
1. Emergency or salvage procedure
2. Ejection fraction <30%
3. CKD Stage 5, defined as eGFR<15ml/min or renal replacement therapy

4. Administration of potent CYP 3A4 inhibitors within 1 month prior to study participation.

5. Administration of nitrate medicines (e.g. glyceryl trinitrate within 24 hours of surgery.

6. Any ongoing malignancy, or prior malignancy that currently requires treatment.

7. Patients allergic to any other PDE-5 Inhibitor.

8. Patients who are participating in another interventional clinical study."

### Date of first enrolment

09/07/2013

**Date of final enrolment**
09/04/2014

# Locations

**Countries of recruitment**
England

United Kingdom

**Study participating centre**
**Glenfield Hospital**
Groby Road
Leicester
United Kingdom
LE3 9QP

# Sponsor information

**Organisation**
University of Leicester (UK)

**Sponsor details**
Department of Genetics
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**Sponsor type**
University/education

**ROR**
https://ror.org/04h699437

# Funder(s)

**Funder type**
Charity

**Funder Name**
British Heart Foundation (BHF) (UK); Grant Codes: RG/13/6/29947

**Alternative Name(s)**
the_bhf, The British Heart Foundation, BHF

**Funding Body Type**
Private sector organisation

**Funding Body Subtype**
Trusts, charities, foundations (both public and private)

**Location**
United Kingdom

# Results and Publications

**Publication and dissemination plan**
Not provided at time of registration

**Intention to publish date**

**Individual participant data (IPD) sharing plan**

**IPD sharing plan summary**
Not provided at time of registration

**Study outputs**

| Output type | Details | Date created | Date added | Peer reviewed? | Patient-facing? |
|---|---|---|---|---|---|
| Results article | results | 01/04/2017 | | Yes | No |
| HRA research summary | | | 28/06/2023 | No | No |