ISRCTN92249277 https://doi.org/10.1186/ISRCTN92249277

New biomarkers of endothelial dysfunction

Submission date 18/02/2018	**Recruitment status** No longer recruiting	[_] Prospectively registered [_] Protocol
Registration date 25/02/2018	**Overall study status** Completed	[_] Statistical analysis plan [_] Results
Last Edited 23/02/2018	**Condition category** Circulatory System	[_] Individual participant data [_] Record updated in last year

Plain English summary of protocol

Background and study aims
Pulmonary arterial hypertension (PAH) occurs when the walls of the pulmonary arteries become thick and stiff, increasing blood pressure. TSP-1 has been recently proposed as a marker for PAH by a couple of studies that have reported higher blood levels of TSP-1 in patients with PAH. The aim of this study is to measure blood TSP-1 levels in hypertensive patients with endothelial (blood vessel lining) dysfunction before and after one year of treatment with perindopril, an antihypertensive drug with vascular (blood vessel) protective effects.

Who can participate?
Patients aged over 18 with primary arterial hypertension

What does the study involve?
All patients underwent a thorough screening and, if their previous antihypertensive treatment did not manage to properly control their blood pressure, the patient had some side effects or presented other risk factors under the previous treatment, their treatment was changed to either perindopril 5mg or 10mg, based on their blood pressure level. Participants are monitored every 3 months, and a complete investigation is done at the beginning of the treatment and after one year of treatment. Blood samples are collected to measure levels of TSP-1 and other markers. Blood pressure and endothelial dysfunction are also measured.

What are the possible benefits and risks of participating?
Participants may benefit from normalization of blood pressure, stabilization of vascular damage and reversing the degree of endothelial dysfunction (although the period of treatment is short). There are few risks for participants, mainly due to the side effects to the drug used: hypotension (low blood pressure), hypersensitization, dry cough, and dizziness.

Where is the study run from?
Cardiology Clinic of Timisoara City Hospital (Romania)

When is the study starting and how long is it expected to run for?
January 2015 to June 2016

Who is funding the study?
"Victor Babes" University of Medicine and Pharmacy (Romania)

Who is the main contact?
Valentina Buda
buda.valentina.oana@gmail.com

Contact information

Type(s)
Scientific

Contact name
Mrs Valentina Buda

Contact details
str. eneas nr.80
Timisoara
Romania
400477
+40 (0)755100408
buda.valentina.oana@gmail.com

Additional identifiers

EudraCT/CTIS number
2018-000467-88

IRAS number

ClinicalTrials.gov number

Secondary identifying numbers
7/2016

Study information

Scientific Title
The influence of perindopril on TSP-1 and PTX3 plasma levels at the beginning and after one year on treatment, in hypertensive patients with endothelial dysfunction

Study objectives
TSP-1 has been recently proposed as a prognostic marker for pulmonary arterial hypertension (PAH) by a couple of studies that have reported high plasma levels of TSP-1 in patients with PAH compared with their controls. The aim of this study is to quantify TSP-1 plasma levels in hypertensive patients with endothelial dysfunction before and after one year of treatment with perindopril (an antihypertensive drug with vascular protective effects).

Ethics approval required
Old ethics approval format

Ethics approval(s)

Ethical Committee of the “Victor Babes” University of Medicine and Pharmacy, Timisoara, Romania, 29/06/2016, no. 7/2016

Study design
Single-center Phase IV observational study

Primary study design
Observational

Secondary study design
Cohort study

Study setting(s)
Hospital

Study type(s)
Prevention

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
Essential arterial hypertension, endothelial dysfunction

Interventions
All recruited patients completed the informed consent form and underwent a thorough screening including the disease and other associated medical conditions, a family medical history, and laboratory/paraclinical investigations. After the clinic-biological evaluation, if the previous antihypertensive treatment did not manage to properly control blood pressure, the patient had some side effects or presented other risk factors under the previous regimen of treatment, the antihypertensive treatment was changed to Perindopril 5mg or 10mg, based on each patient’s blood pressure level. All patients were evaluated at the initial moment To (under treatment with other antihypertensive drugs, period: 01/01/2015 – 30/06/2015) and after one year of treatment (T1, period: 01/01/2016 – 30/06/2016) with Perindopril.

Laboratory analysis
Venous blood samples were collected in the morning (8:30AM), a jeun, in a temperature controlled room (22-24ºC) of the hospital, after at least 8 hours from their last consumption of food, sweet fluids, coffee, cigarettes and during that time no physical effort was made. The standard biochemical tests (e.g. complete blood count, total cholesterol, creatinine, hepatic transaminase) were completed in the hospital, following the normal procedures. The plasma levels of TSP-1, PTX3 (pentraxin-3) and hs-CRP (high-selectivity C reactive protein) were assessed by the Bioclinica SA Laboratory from Timisoara. The plasma concentrations of TSP-1 and PTX3 were assessed through the ELISA method, the kits being provided by R&D Systems. The plasma levels of hs-CRP were assessed through the high sensitive immunoturbidimetric method, the kits being provided by Abbott Diagnostic Company. All these methods are standardized. The normal range of TSP-1 plasma levels given by the laboratory was: 8794 – 28335 ng/dl.

Arterial pressure
The blood pressure was measured after 30 minutes of rest, in a supine position, at the right

brachial artery, in the same temperature controlled room. The final value of the arterial pressure is calculated as follows: the arithmetic mean of 3 consecutive measurements at five minute intervals.

The flow mediated dilation assessment (FMD)
The presence/absence of endothelial dysfunction was assessed through flow mediated dilation measurement dependent of the endothelium (FMD) - a functional assessment, and also by assessing the intimal-medial thickness (IMT) - a structural assessment.

The procedure was performed after the patient fasted for a minimum of 8 hours, during that time he was not allowed to consume any type of foods, coffee, tea, vitamins, no physical effort was allowed, he did not smoke and did not take any vasoactive drugs. After 10 minutes of rest in a supine position, in a soundproof room, the brachial arterial diameter was measured with a high resolution ultrasonography system, a General Electric medical system VIVID S5, equipped with a linear transducer of 9MHz. The longitudinal scans of the brachial artery were performed approximately 5cm proximal of the antecubital fossa. The diameter measurements of the vessel were marked down at the initial moment and after 5 minutes of reactive hyperaemia, induced by the deflation of the blood pressure cuff, previously inflated to 50mmHg above the patient's systolic blood pressure point. The FMDs being calculated as follows:
%FMD = [(reactive hyperaemia diameter – standard diameter)/standard diameter] x100

The trialists concluded (based on the literature) that FMD is:
1. "Normal" – if the brachial artery was dilated with 20% more than the initial standard diameter
2. "Impaired – "endothelial dysfunction" – if the brachial artery did not dilate with 20% more than the initial standard diameter

Three measurements were performed for each patient and the arithmetic mean was noted.

The intima-media thickness assessment (IMT)
The IMT, as agreed in the Mannheim Consensus, was assessed at the baseline of the common carotid artery, bilateral, 2 cm under the branch level of the internal and external carotid. A high-resolution ultrasonography system was used for this, a General Electric medical system VIVID S5, in B mode, equipped with 9MHz linear transducer. The patients were examined in a supine position and the IMT value was given online by the built-in software of the medical system. The following were taken into consideration: values smaller than or equal to 0.9mm were considered normal and values over 1.2mm were considered high (values that clearly shows the atherosclerosis presence and the high risk of cardiovascular diseases).

Echocardiography
An echography was performed using a high-resolution ultrasonography General Electric medical system VIVID S5, to assess the effects of hypertension on the structures and functions of the heart. The patients with low ejection fraction (<40%) were excluded from the study. The evaluated parameters included: the diameter of the left atrium (DLA), the dimensions of the interventricular septum (IVS) of the posterior wall, the end diastolic diameter of the left ventricle diameter (EDLV) and the ejection fraction (EF).

All the measurements that were done during the study were performed by the same certified cardiologist.

Drugs used:
Prestarium 5mg or 10mg – the main pharmaceutical form used
Perindopril Actavis 5mg or 10mg

Perindopril Tosilat Teva TEVA 5mg or 10mg
Frequency of adm: 1tb/day
Total duration of the treatment: 1 year
Follow up: after 1 year of treatment

During the study, the patients came to visits and were monitored every 3 months, the complete investigation being done at the beginning of the treatment and after one year of treatment for each patients in function of the date of entry in the study.

Intervention Type
Drug

Phase
Phase IV

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

Primary outcome measure
1. Arterial pressure was measured after 30 minutes of rest, in a supine position, at the right brachial artery
2. The presence/absence of endothelial dysfunction was assessed using flow mediated dilation (FMD) and intimal-medial thickness (IMT)
3. Plasma levels of TSP-1, PTX3 (pentraxin-3) and hs-CRP (high-selectivity C reactive protein) measured using the ELISA method (TSP-1, PTX3) and the high sensitive immunoturbidimetric method (hs-CRP)
All outcomes measured at baseline and after one year of treatment

Secondary outcome measures
1. Cardiovascular morbidity and mortality were measured using clinical examination of patients, electrocardiography, blood pressure measurements every time the patients visited the doctor
2. Incidence of strokes, myocardial infarction, and heart failure were measured using electrocardiography, echocardiography by determining the specific parameters in every visit and also by evaluating the presence of clinical symptoms
All outcomes measured at baseline and after one year of treatment

Overall study start date
01/01/2015

Completion date
30/06/2016

Eligibility

Key inclusion criteria
1. Age >18 years
2. Established diagnosis of primary arterial hypertension

Participant type(s)
Patient

Age group
Adult

Lower age limit
18 Years

Sex
Both

Target number of participants
112

Key exclusion criteria
1. Atherosclerotic disease
2. Coronary artery disease
3. Heart failure
4. Diabetes
5. Renal and hepatic pathologies
6. Asthma
7. Acute and chronic inflammatory diseases

Date of first enrolment
01/01/2015

Date of final enrolment
30/06/2015

Locations

Countries of recruitment
Romania

Study participating centre
Cardiology Clinic of Timisoara City Hospital
12, Revolutiei Boulevard
Romania
300041

Sponsor information

Organisation
"Victor Babes" University of Medicine and Pharmacy

Sponsor details

2nd Eftimie Murgu Street
Timisoara
Romania
300041

Sponsor type
University/education

ROR
https://ror.org/00afdp487

Funder(s)

Funder type
University/education

Funder Name
"Victor Babes" University of Medicine and Pharmacy

Results and Publications

Publication and dissemination plan
Planned publication in Scientific Reports.

Intention to publish date
01/03/2018

Individual participant data (IPD) sharing plan
The datasets generated during and/or analysed during the current study are/will be available upon request from M.D. Andor Minodora (cardiologist) (andorminodora@gmail.com) and Pharm. Valentina Buda (clinical pharmacist) (buda.valentina.oana@gmail.com). All the data will be available after publication.

IPD sharing plan summary
Available on request