A randomized, placebo-controlled, double blind, 4-period, cross-over trial, to study the effects of aliskiren, hydrochlorothiazide and moxonidine on endothelial dysfunction in obesity related hypertension

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Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Vascular hypertensive disorders
Study type	Interventional

Summary

ID

NL-OMON34298

Source
ToetsingOnline

Brief title
Treatment of Adiposity Related hypErTension (TARGET)

Condition

- Vascular hypertensive disorders

Synonym
Hypertension, increased blood pressure

Research involving

Human

Sponsors and support

Primary sponsor: Universitair Medisch Centrum Utrecht
Source(s) of monetary or material Support: Ministerie van OC&W,Novartis

Intervention

Keyword: Abdominal obesity, Hypertension, Metabolic syndrome

Outcome measures

Primary outcome

Mean intrapersonal changes in endothelial function (FMD).

Secondary outcome

Mean intrapersonal changes in serum adipokine concentrations, serum lipid concentrations, HOMA, mean 24-hour SBP/DBP, mean day/night time SBP/DBP, central blood pressure (PWA), serum and urine concentrations of markers of oxidative stress, serum concentrations of markers of systemic inflammation, arterial stiffness (PWV, PWA), RAS-hormone concentrations, MSNA, HRV, fractional sodium excretion.

Study description

Background summary

Treatment of obestiy related hypertension is challenging and has become an important global health problem. According to guidelines, most classes of antihypertensives are equally effective for the treatment of hypertension. However, these guidelines are mainly based on evidence from studies in patients with essential hypertension, but without obesity. There is an increasing body of evidence about the complex pathophysiological mechanisms of obesity related hypertension. Adipose tissue dysfunction is commonly regarded as a common soil that eventually causes up regulation of the sympathetic nervous system (SNS) and the renin-angiotensin-system (RAS). Moreover, development of obesity

related hypertension is closely related to development of endothelial dysfunction, dyslipidemia and disorders of glucose metabolism. We hypothesise that treatment with antihypertensives that are directed at down regulation of the SNS (moxonidine) and the RAS (aliskiren) will result in more beneficial effects than treatment with a diuretic (hydrochlorothiazide), because the latter reduces blood pressure by inhibition of sodium resorption, without influencing the underlying causal mechanism.

Study objective

Primary objective: to compare changes in endothelial function in patients with obesity related hypertension after 8 weeks of treatment with aliskiren, moxonidine and HCTZ. Secondary objectives: to compare changes in the following parameters in patients with obeisty related hypertension after 8 weeks of treatment with aliskiren, moxonidine and HCTZ: adipose tissue function, lipid metabolism, insulin sensitivity, blood pressure, oxidative stress, systemic inflammation, arterial stiffness, RAS-activity, SNS-activity and renal sodium handling.

Study design

A randomized, placebo-controlled, double blind, 4-period, cross-over trial.

Intervention

Once daily doses of aliskiren (300 mg), moxonidine (0,4 mg), HCTZ (25 mg) and placebo following standardised 8-week treatment schedules. The dubbel-dummy method will be applied to achieve optimal blinding. Participants receive all four interventions in a randomized and blinded order.

Study burden and risks

The current guideline for cardiovascular risk management states that persons who fit the eligibility criteria of the TARGET-study do not have a strong indication for pharmacologic treatment of hypertension, but that it can still be considered. Patients who have a strong indication for pharmacologic hypertension treatment (SBP > 180 mmHg, DBP > 110 mmHg, therapy resistant hypertension, SCORE mortality risk > 10%, history of cardiovascular disease or type 2 diabetes mellitus) are excluded from participation. All study medication is registered for the treatment of hypertension in this patient category. Subjects are thus not withheld from any indicated treatment, but are not over-treated as well. Participants are asked to pay a total of 10 study visits (6 for measurements (visit 1 to 6) and 4 for returning the ambulatory blood pressure meter) to the UMC Utrecht. Prior to 5 visits, patients need to have fasted for 13 hours. Most measurements are non invasive, but also some venous blood samples (11 mL during the first visit and 43 mL during each of the visits

3-6) will be drawn and in a sub sample of patients the SNS-activity will be determined by means of MSNA. Participants do not directly benefit from study participation. The scientific value, however, is considerable. After the study is ended (last participant, last measurement), participants can choose to receive an overview of some of their metabolic parameters, in order to optimise their future risk management of cardiovascular disease.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

Patient is a male or post-menopausal female of 30-70 years of age on the day of signing informed consent. Post menopausal status is assumed if a woman has not experienced a menstrual bleed for a minimum of 12 months, assuming that she still has a uterus, and is not pregnant or lactating. In women without a uterus, menopause or postmenopause is defined

by a very high FSH level. All patients should fulfil the diagnostic criterion of abdominal adiposity: waist circumference > 102 cm (men) or > 88cm (women). The waist circumference is measured halfway between the lower rib and iliac crest in standing position. All patients should fulfil the following diagnostic criterium for hypertension: - SBP >/= 130 mmHg and/or DBP >/= 85 mmHg during both visits. Blood pressure is assessed by office readings in accordance with current guidelines for hypertension diagnosis. The patient needs to be seated some minutes before and during the measurement. The cuff size should be adjusted to the patients* arm circumference and needs to be on the same height level as the patients* sternum during the measurements. Blood pressure is determined to a 2 mmHg accuracy-level. Blood pressure is measured on both arms during the first visit. In both measurements differ more than 10 mmHg, the highest value is taken. After at least 15 seconds, the measurement is repeated during the same visit. The highest mean of the two measurements on the same arm is considered as the actual blood pressure value. Patients should fulfil one or more of the following criteria to meet the definition of the metabolic syndrome: - Hypertriglyceridemia (serum triglycerides >/= 1.7 mmol/L); - Low High-density lipoprotein (HDL)-cholesterol (serum HDL-cholesterol < 1.04 mmol/L (men) or < 1.29 mmol/L (women)); - High fasting glucose (fasting serum glucose > 5.6 mmol/L). Patient understands the study procedures, alternative treatments available, and risks involved with the study and voluntarily agrees to participate by giving written informed consent.

Exclusion criteria

SBP > 180 mmHg and/or DBP > 110 mmHg during one or more screening measurements and/or use of more than one type of antihypertensive medication. Ten year cardiovascular mortality risk according to the SCORE-risk model > 10% BMI > 35 kg/m2 Current smoking or smoking during the previous 3 months Use of *recreational* or illicit drugs Recent history (within the last year) of alcohol abuse or dependence. History of hypersensitivity reactions or intolerance to any (components of) medication used in this trial. Current / recent participation (within 30 days of signing informed consent) in a study with an investigational compound or device. Laboratory values as listed below: - Hemoglobin (Hb) < 8,6 mmol/L (men) or < 7.4 mmol/L (women) - TSH <0.3 mcIU/mL or > 5.0 mcIU/mL - Potassium < 3,8 mmol/L or > 5,0 mmol/L - Sodium < 136 mmol/L or > 146 mmol/L - MDRD < 60 mL/min/1,73m2 Medical conditions as listed below: - Secondary hypertension - Congestive Heart Failure - Atherosclerotic vascular disease. (As per NCEP ATP III and AHA/ACC Guidelines: Established atherosclerotic vascular disease includes history of myocardial infarction, stable angina, coronary artery procedures (angioplasty or bypass surgery) or evidence of clinically significant myocardial ischemia. Other atherosclerotic vascular disease includes clinical manifestations of non-coronary forms of atherosclerotic disease (peripheral arterial disease, cerebrovascular disease, abdominal aortic aneurysm, and carotid artery disease [transient ischemic attacks or stroke of carotid origin or >50% obstruction of a carotid artery]). - Cardiac arrhythmia*s, for example bradycardia, atrial fibrillation, sick-sinus syndrome, sinoatrial block, atriovertricular block or any other arrhythmia. - Obstructive sleep apnea syndrome (OSAS) or a score of 10 or higher on the Epworth Sleepiness Scale questionnaire. - Type 2 diabetes mellitus - Serious liver function disorders (Child-Pugh-Class C). - COPD (GOLD classification of severity 2 or higher) - Celiac disease or other significant intestinal

malabsorption - Malignancy <= 5 years prior to signing informed consent, except for adequately treated basal or squamous cell skin cancer or in situ cervical cancer. - Mental instability or major psychiatric illness - Polyneuropathy or clinical suspicion for autonomic nervous system dysfunction. - Any diseases that would limit or complicate study evaluation or participation. - Any diseases or screening abnormalities that call for treatment that can not be postponed until after the study period without causing harm. Any concomitant medication, particularly antihypertensive co-medication, glucose lowering medication, lipid lowering drugs, systemic corticosteroids, birth control pills and vitamin C or E supplements, but also any other kinds of drugs, including over the counter medication. Exceptions can be made for the following categories of drugs: - paracetamol; - proton-pump inhibitors; - topical creams and unguents that do not lead to uptake of any of the active components into the circulation (in case of steroid creams: class II or lower); - inhalation medication, nasal sprays and eye drops that do not lead to uptake of any of the active components into the circulation.

Study design

Design

Study phase:	4
Study type:	Interventional
Intervention model:	Crossover
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Basic science

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	10-09-2010
Enrollment:	30
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	-
Generic name:	Hydrochlorothiazide

Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	-
Generic name:	Moxonidine
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Rasilez
Generic name:	Aliskiren
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	24-06-2010
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	27-07-2010
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	24-08-2010
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	15-09-2010
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	14-10-2010
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	27-10-2010
Application type:	Amendment

Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	02-11-2010
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
EudraCT	EUCTR2009-015982-29-NL
ClinicalTrials.gov	NCT01138423
CCMO	NL32814.041.10