Renal hemodynamic effects of aliskiren (rasilez) in comparison to ramipril (tritrace) in patients with overweight/obesity and hypertension

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The primary objective of this study is to determine the effects of aliskiren, as compared to ramipril, on renal hemodynamics in overweight/obese and hypertensive patients.

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Other condition
Study type	Interventional

Summary

ID

NL-OMON34045

Source
ToetsingOnline

Brief title
The renal HEALTH-STudY

Condition

- Other condition

Synonym
elevated blood pressure in the kidney, glomerular hypertension

Health condition

systemische en glomerulaire hypertensie

Research involving
Human

Sponsors and support

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

Intervention

Keyword: hypertension, obesity, renal hemodynamics, renin inhibitor

Outcome measures

Primary outcome

- Renal hemodynamics (GFR, ERPF, FF)

- Blood pressure

Secondary outcome

- Volume status (extracellular fluid volume/ECV)

- RAAS parameters (plasma renin activity, plasma renin concentration,

angiotensin II, aldosteron)

- Urine en derum 'kidney injury markers', zoals, maar niet uitsluitend, TGFß,

KIM-1, NGAL en NAG.

Study description

Background summary

The combination of hypertension and obesity is a highly prevalent clustering of cardiovascular risk factors which considerably contributes to over-all morbidity and mortality in the general population. The kidneys play a central role in the interaction between these two risk factors.
Obese or overweight hypertensive patients have increased glomerular pressure, which is considered a driving force for progressive end-organ damage of the kidney, thus contributing to the vicious circle of hypertension and target organ damage. In line, weight excess is an independent risk factor for renal damage that adds to the effect of elevated blood pressure. Accordingly, specific correction of increased glomerular pressure, on top of reduction of systemic blood pressure, has been shown to be renoprotective in experimental

animals and in renal patients. Glomerular pressure is determined by the net balance between the tone of the afferent and efferent glomerular vessels and is mainly regulated by the Renin Angiotensin Aldosterone System (RAAS) that modifies efferent vascular tone. This is particularly relevant given the availability of antihypertensive drugs that specifically interfere in the RAAS, i.e. the ACE-inhibitors (ACEi), the Angiotensin Receptor Blockers (ARB) and specific renin-inhibition. Based on these considerations it is likely that the renal hemodynamic actions of RAAS-blockade will be of specific benefit in overweight or obese hypertensive patients.
Aliskiren represents the new class of direct renin inhibitors, i.e. blockade of the RAAS at its point of activation. Importantly, the effects of aliskiren on glomerular pressure have not been tested so far. A beneficial short term (decrease of glomerular pressure) and long term (prevention of end stage renal disease) renal profile has been proven with the older RAAS blocking drug classes (ACEi, ARB). It seems logical to assume that aliskiren will decrease glomerular pressure as well, in particular because renin-inhibition with older renin-inhibitors was shown to have more potent renal effects than ACEi and ARB. In our hands renin-inhibition with remikiren was shown to reduce glomerular pressure in hypertensive and normotensive volunteers.

Study objective

The primary objective of this study is to determine the effects of aliskiren, as compared to ramipril, on renal hemodynamics in overweight/obese and hypertensive patients.

Study design

The study question will be addressed in a prospective, single-centre, double-blind, double-dummy, cross-over, randomized clinical trial. Before inclusion, patients visit the outpatient nephrology clinic for clinical assessment. Patients treated with antihypertensive medication will enroll in a 6 week wash-out period in which antihypertensive medication is discontinued. In week 3 of the wash-out period, systolic and diastolic blood pressure is measured and must remain lower than 180 and 110 mmHg, respectively. When blood pressure exceeds these values, the patient will be considered a screen failure and prior antihypertensive medication is restarted. A wash-out period is not mandatory in patients with no antihypertensive medication. Consecutively, patients will be randomly assigned to either a 6-week treatment period with aliskiren and ramipril-placebo or a 6-week treatment period with ramipril and aliskiren-placebo, in a cross-over double-dummy design. To safeguard patients, serum potassium and blood pressure is measured 2 weeks after start of each treatment period (see paragraph 7.4.1 for action to be taken when hyperkalemia or hypotension occurs). Between both treatment periods an 8-week wash-out period is present in which systolic and diastolic blood pressure are measured and must remain lower than 180 and 110 mmHg, respectively. When blood pressure

exceeds these values, clonidin is started in an initial dosage of 2 dd 0.075 mg with subsequent increase of dosage (maximal 3 dd 0.15 mg) to reach target blood pressure. Patients visit the outpatient nephrology clinic at start and end of both treatment periods (four times in total) for clinical assessment and renal hemodynamic (GFR, ERPF and FF) and volume status (ECV) measurements. Renal hemodynamics are measured by infusion of radioactive isotopes (GFR by iothalamate; ERPF by hippuran and FF as a ratio of GFR and ERPF) and volume status (ECV) is calculated using the distribution volume of iothalamate. A fasting blood sample for measurement of status of the renin-angiotensin-aldosterone system, including plasma renin activity, plasma renin concentration, angiotensin II and aldosterone, is collected with a venapuncture already performed for measurement of renal hemodynamics. Additional parameters include routine blood and urine chemistry and total blood cell count. Blood pressure is measured by an ambulant device (Spacelab) and 24hr urine is collected at the day prior to the hospital visit.

Intervention

Treatment period 1: aliskiren 1dd 300 mg and placebo ramipril (double-dummy design)
Treatment periode 2: ramipril 1dd 10 mg and placebo aliskiren (double-dummy design)

Treatment period is randomised

Study burden and risks

Patients visit the outpatient nephrology clinic on a more regular base than standard patient care - i.e. at study inclusion and at start and end of each treatment period (5 hospital visits in a total study duration of 26 weeks) - for clinical assessment, renal hemodynamics (GFR, ERPF, FF) volume status (ECV) measurements. Renal hemodynamics are measured by infusion of radioactive isotopes (GFR by iothalamate; ERPF by hippuran and FF as a ratio of GFR and ERPF) and volume status is calculated using the distribution volume of iothalamate. A fasting blood sample is collected with a venapuncture already performed for measurement of renal hemodynamics. Blood pressure is measured by ambulant device (Spacelab) and 24hr urine is collected at the day prior to the hospital visit. The amount of radioactive radiation during renal hemodynamic measurements is comparable to a single X-thorax (less then 5% of the accepted yearly dosage of background radiation). In this hospital, renal hemodynamic measurements are routinely performed for daily patient care and are of minimal risk. No other invasive measurements will be executed. There are no direct benefits for the patients to be included and participation is on a free-will base. Patients receive financial support of 200 euro and restitution of all travel costs. Patients receive no priority in treatment of other diseases in the clinic during this study.

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

- Male caucasian patients
- Age >=18 and <=70 years
- Overweight or obese (BMI >=27 and <=35 kg/m2)
- Essential hypertension according to WHO-criteria (systolic and diastolic blood pressure >=140 or
>=90 mmHg, respectively)
- Normal renal function (creatinine clearance >90 ml/min/1.73m2)
- Normo- or microalbuminuria (albuminuria <=300mg/day)
- Written informed consent

Exclusion criteria

- Inability to meet inclusion criteria
- Previously treated (within 3 months prior to start of study) with aliskiren or ramipril.
- Cardiovascular disease (myocardial infarction, angina pectoris, percutanous transluminal coronary angioplasty, coronary artery bypass grafting, stroke, heart failure (NYHA I-IV), Diabetes
Mellitus
- Active malignancy
- Any medication, surgical or medical condition which might significantly alter the absorption, distribution, metabolism, or excretion of medications including, but not limited to any of the following:
- History of active inflammatory bowel disease within the last six months;
- Major gastrointestinal tract surgery such as gastrectomy, gastroenterostomy, or bowel resection;
- Gastro-intestinal ulcers and/or gastrointestinal or rectal bleeding within last six months;
- Pancreatic injury or pancreatitis within the last six months;
- Evidence of hepatic disease as determined by any one of the following: ALT or AST values exceeding 3x ULN at inclusion visit, a history of hepatic encephalopathy, a history of esophageal varices, or a history of portocaval shunt;
- Evidence of urinary obstruction of difficulty in voiding at inclusion
- History of severe hypersensitivity or contraindications to ramipril or aliskiren
- Hypersensitivity to 125I-iothalamate or 131I-hippuran
- History of angioedema
- History of autonomic dysfunction (e.g. history of fainting or clinically significant orthostatic hypotension)
- Participation in any clinical investigation within 3 months prior to start of the study
- Donation or loss of 400 ml or more of blood within 3 months prior to initial dosing
- History of drug or alcohol abuse within the 12 months prior to dosing, or evidence of such abuse
as indicated by the laboratory assays conducted during the screening.
- History of noncompliance to medical regimens or unwillingness to comply with the study protocol.
- Any surgical or medical condition, which in the opinion of the investigator, may place the patient
at higher risk from his/her participation in the study, or is likely to prevent the patient from complying with the requirements of the study or completing the study.

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Crossover
Masking:	Double blinded (masking used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	15-01-2011
Enrollment:	16
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	ramiril
Generic name:	tritace
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	rasilez
Generic name:	aliskiren
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO

Date:	09-09-2010
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)

Approved WMO

Date:	15-10-2010
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

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

ID: 28302
Source: Nationaal Trial Register
Title:

In other registers

Register	ID
EudraCT	EUCTR2010-021987-13-NL
CCMO	NL33146.042.10
OMON	NL-OMON28302