Bioprofiling response to mineralocorticoid receptor antagonists for the prevention of heart failure. A proof of concept clinical trial within the EU FP 7 *HOMAGE* programme « Heart OMics in AGing

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

Summary

ID

NL-OMON44913

Source
ToetsingOnline

Brief title
HOMAGE

Condition

- Heart failures

Synonym
patients at risk of heart failure

Research involving

Human

Sponsors and support

Primary sponsor: ACS Biomarker
Source(s) of monetary or material Support: EU FP7

Intervention

Keyword: biomarkers, prevention of heart failure

Outcome measures

Primary outcome

Changes in serum concentrations of PIIINP (RI assay, central lab) from baseline to nine months. Nine months is thought to be a period sufficient to influence cardiac fibrosis for which PIIINP is a widely accepted marker. Serum PIIINP concentration is reduced by MRAs; reduction in serum PIIINP is associated with more favourable clinical outcomes.

Secondary outcome

Changes in serum or plasma levels of biomarkers of extracellular matrix turnover: PICP (synthesis) and ICTP (degradation), from baseline to 9 months (RIA, central Lab).

Cardiac remodelling, assessed by echocardiography, including left atrial volume, left ventricular mass and Doppler measures of right and left ventricular function and NT-proBNP (ELISA, central Lab), from baseline to 9 months (Certified centers and central readings).

Distance walked on a shuttle walk-test with assessment of peak heart and respiratory rate.

Vascular function assessed by non-invasive technologies

Rate of the clinical composite of development of heart failure or atrial fibrillation, non-fatal myocardial infarction or stroke or CV death from baseline to 9 months. The HOMAGE blinded clinical event committee will adjudicate all serious adverse events.

Safety endpoints: Investigator reported adverse events (AEs) will be collected using the ad hoc reporting system. In addition, pre-specified expected AEs will be monitored:

4.1. Worsening renal function (decline in eGFR >20%)

4.2. Hyperkalemia (rise of serum potassium to >5.5 mmol/L)

4.3. Rate of gynaecomastia and/or breast pain

4.4 Changes in serum potassium and eGFR will be assessed at day 7, Month 1, 3, 6 and 9.

4.5 Hypotension, falls and fractures

Study description

Background summary

Despite advances in care, prognosis remains poor once overt Heart Failure (HF) has developed. Prevention is most efficient when directed toward patients at risk and when mechanistically targeted to patients most likely to respond. An increase in myocardial and possibly vascular collagen content (fibrosis) may be a major determinant of the transition to HF. In patients with hypertension and diabetes, two important risk-factors for HF, changes in blood markers of fibrosis occur before clinically overt HF develops. These markers are also related to prognosis.

In the general population, Galectin-3 (Gal-3), a potential marker of fibrosis, is associated with cardiovascular (CV) risk factors, and predicts development of HF. In animal models, Gal-3 is a key mediator of aldosterone-induced CV and renal fibrosis and dysfunction.

We hypothesize that the mineralocorticoid receptor antagonist (MRA), spironolactone, may prevent HF by acting on extracellular matrix remodelling, especially in patients with active fibrogenesis, identified by high Gal-3 levels. The benefit/risk ratio of spironolactone might be superior in patients with a higher compared to lower plasma concentrations of Gal-3.

Study objective

Main objective: To investigate whether spironolactone can favourably alter extra-cellular matrix remodelling, assessed by changes in the fibrosis biomarker Procollagen Type III N-Terminal Peptide (PIIINP), in patients at increased risk of developing heart failure and whether this effect is greater in patients with increased plasma concentrations of Gal-3.

Secondary objective: To investigate the interaction between spironolactone and plasma concentration of Gal-3:
On cardiac remodelling, assessed by echocardiography. This includes left atrial volume, left ventricular mass and Doppler measures of left and right ventricular function,
On cardiorespiratory performance during exercise
On vascular function assessed using pain-free, non-invasive technologies
On N-terminal pro-B-type natriuretic peptide (NT-proBNP), a measure of haemodynamic stress.
On a clinical composite of development of heart failure or atrial fibrillation, non-fatal myocardial infarction or stroke or CV death.

To describe the interaction between changes in PIIINP, Procollagen Type 1 C terminal peptide (PICP), 1-Collagen Telopeptide (ICTP) and baseline levels of Gal-3, and of other biomarkers involved in the aldosterone-related fibrosis process, including:
- Cardiotrophin-1
- Serum soluble interleukin-1 receptor family member (ST-2)
- Neutrophil gelatinase-associated lipocalin (NGAL)
- Other omics-based biomarkers, including genomic, currently at the clinical evaluation stage in other HOMAGE work-packages.

Study design

PROBE - Open Randomized clinical trial with Blinded Evaluation (Phase II)

Intervention

Experimental group - Spironolactone, titrated from 25 mg/day (or every other day in some cases) to 50 mg/day, adapted (decreased / stopped / reinitiated) according to a pre-specified algorithm depending on occurrence/resolution of hyperkalemia and/or worsening renal function.

Control group - Background treatment only - no additional treatment.

Background therapy may include any agent other than loop diuretics or potassium saving diuretics including mineralo-corticoid antagonists (eg:- angiotensin converting enzyme inhibitors, angiotensin receptor blocker inhibitors, beta blockers and thiazide or thiazide-like diuretics).

Study burden and risks

Benefits: In patients at risk for HF, a mechanism-driven, targeted therapeutic intervention could delay the progression of CV disease and the occurrence of HF / CV events compared to current usual care. Our trial will act as a catalyst for the development of biomarkers/ biotargets that identify specific biological pathways that may help deliver personalised therapy.
Personalised medicine should improve clinical outcomes, by avoiding therapy in patients identified as having a low likelihood of therapeutic response or a high likelihood of adverse events. Such tailored therapies also improve cost-effectiveness. Targeting specific agents at those patients most likely to benefit is still an unmet need in cardiovascular medicine, as opposed to the field of oncology where personalized therapies are increasingly common and successful.
Risks: Spironolactone has been used to treat patients since 1959. Its side effects are well known, reversible and, using the doses and monitoring regimen we intend, infrequent. Risks include hyperkalemia, worsening renal function and breast pain/gynaecomastia. Patients will be monitored for adverse effects at follow-up visits at day 7, Month 1, 3, 6, and 9 (final visit), with clinical assessment and evaluation of serum potassium and eGFR. Venepuncture may cause bruising. There are no other invasive procedures.

Contacts

Public
ACS Biomarker

Meibergdreef 39
Amsterdam 1105 AZ
NL
Scientific
ACS Biomarker

Meibergdreef 39
Amsterdam 1105 AZ
NL

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

1.Written informed consent will be obtained prior to any study procedure;
2. Age > 60years
3. Clinical risk factors for developing heart failure, either:
Coronary artery disease (h/o myocardial infarction, angioplasty or coronary artery bypass);Or
B. At least two of the following:
• Diabetes Mellitus requiring Hypoglycaemic Pharmacotherapy
• Receiving pharmacological treatment for Hypertension;• Microalbuminuria, defined as creatinin >30mg/g whatever the gender
• Abnormal ECG (left ventricular hypertrophy, QRS >120msec,
abnormal Q-waves)
4. Biological risk: NT-pro-BNP values between 125 and 1,000 ng/L or BNP values between 35 and 280 pg/ml (consistent with ESC guidelines indicating risk of HF but helping to rule out prevalent HF or atrial fibrillation which are associated with marked increases in NT-proBNP/BNP and should be investigated)

Exclusion criteria

1. Recent wound healing/inflammation:
• Surgical procedure, coronary, cerebral or peripheral vascular events or infection in the prior 3 months
• Cancer (life limiting or less than 2 yours in remission)
• Autoimmune disease
• Hepatic Disease
2. Pre-existing diagnosis of clinical HF
3. Moderate/severe LV systolic ventricular dysfunction, i.e. LVEF <45%
4. Moderate or severe valve disease (investigators opinion)
5. Corrected eGFR< 30ml/min/ 1,73 m2, using the MDRD four variable equation

6. Serum potassium > 5.0 mmol/L and serum sodium ,125 mmol/l (whether or not associated with hepatic cirrhosis)
7. Treatment with an MRA or a loop diuretic (furosemide, bumetanide, ethacrynic acid or torasemide) in the previous three months
8. Potassium supplements or potassium-sparing diuretic at time of enrolment.
9. Atrial fibrillation within one month prior to inclusion (AF lasting < 60 seconds on ambulatory ECG monitoring is permitted)
10. History of hypersensitivity to spironolactone or to any of its excipients.
11.Patients who require treatment with prohibited medication according to the summary of product characteristics with the exception of ACE inhibitors or angiotensin receptor blockers - although not their combination (a list is provided in the appendix)
12. Patients unable to give written informed consent.
13. Participation in another interventional trial in the preceding month
14. Ability to walk is, in the investigators opinion, clearly limited by joint disease or other locomotor problems or lung disease rather than by cardiorespiratory fitness

Study design

Design

Study phase:	2
Study type:	Interventional
Intervention model:	Other
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Prevention

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	30-03-2016
Enrollment:	80
Type:	Actual

Medical products/devices used

Product type:	Medicine

Brand name:	Spironolocatone Sandoz
Generic name:	Spironolactone
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	19-05-2015
Application type:	First submission
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	30-12-2015
Application type:	First submission
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	10-10-2016
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	17-10-2016
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	20-04-2017
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	10-05-2017
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)

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	EUCTR2015-000413-48-NL
ClinicalTrials.gov	NCT02556450
CCMO	NL52729.068.15