cGMP Enhancing Therapeutic Strategy for HFpEF: The cGETS Study;An interventional, single blind, multicentre study.

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

Summary

ID

NL-OMON39169

Source
ToetsingOnline

Brief title
cGETS

Condition

- Heart failures

Synonym
Diastolic Heart Failure; Heart Failure with normal Ejection Fraction

Research involving
Human

Sponsors and support

Primary sponsor: Vrije Universiteit Medisch Centrum

Source(s) of monetary or material Support: FP7-MEDIA

Intervention

Keyword: cGMP, HFpEF, Treatment

Outcome measures

Primary outcome

1) Hemodynamics during low dose dobutamine stress testing

2) Extent of diastolic dysfunction determined by echocardiography

3) Magitude of LV hypertrophy

Secondary outcome

1) Plasma levels of cGMP

Study description

Background summary

Most trials testing modern heart failure therapy in patients with heart failure and preserved ejection fraction (HFpEF) had a neutral outcome in contrast to the positive outcome observed with similar pharmacotherapy in patients with heart failure and reduced ejection fraction (HFrEF). The main reason for this discrepancy is failure of modern heart failure therapy to sufficiently address pathophysiological mechanisms driving left ventricular (LV) remodeling in HFpEF. LV remodeling substantially differs between HFpEF and HFrEF. In HFpEF, the left ventricle is concentrically remodeled with normal LV cavity size, increased wall thickness and increased LV mass/volume ratio whereas in HFrEF, the left ventricle is eccentrically remodeled with LV dilatation, normal or decreased wall thickness and low LV mass/volume ratio. Similar findings are also observed at the microscopic and ultrastructural level with enlarged, stiff cardiomyocytes in HFpEF and small, more compliant cardiomyocytes in HFrEF. A recent study identified important differences of myocardial cyclic guanosine monophosphate (cGMP) - protein kinase G (PKG) signaling between HFpEF and HFrEF phenotypes. In HFpEF patients, myocardial PKG activity and cGMP level were respectively two and eight times lower than in HFrEF patients. The lack of cGMP in HFpEF resulted from high nitrosative/oxidative stress and low natriuretic peptide level respectively related to obesity and low LV wall stress because of concentric LV remodeling. Low myocardial PKG activity had previously been shown

to favour maladaptive concentric LV remodeling and to increase cardiomyocyte stiffness. Furthermore, the increased stiffness of HFpEF cardiomyocytes was corrected in-vitro by administration of PKG.

Study objective

The present study protocol proposes a novel cGMP Enhancing Therapeutic Strategy (cGETS) to 1) enhance plasma levels of cGMP, 2) to increase cGMP-related control of the myocardial response to low dose dobutamine stress testing, 3) to improve diastolic LV dysfunction, 4) to regress myocardial hypertrophy and 5) to improve symptoms in HFpEF patients. cGETS intends to raise myocardial cGMP level through concerted upregulation of cGMP production by soluble (s) and particulate (p) guanylate cyclase (sGC and pGC respectively) and downregulation of cGMP breakdown by phospodiesterase 5A (PDE5A).

Study design

Upregulation of cGMP production in HFpEF patients will be achieved through simultaneous administration of angiotensin converting enzyme inhibitors (ACEi) and statins. In case patients concomitantly suffer of type 2 diabetes mellitus, which is either untreated or solely treated with metformin, sitagliptin is also started. Downregulation of cGMP breakdown will be achieved through administration of the PDE5A inhibitor sildenafil. Through concerted upregulation of cGMP production and downregulation of cGMP breakdown, cGETS hopes to substantially raise myocardial cGMP level, which is eight times lower in HFpEF. This is expected to result in a modified myocardial response to low dose dobutamine stress testing, in less diastolic LV dysfunction through destiffening of cardiomyocytes, in regression of hypertrophy and in improvement of exercise tolerance.

Intervention

HFpEF patients will be recruited from out-patient clinics. The diagnosis of HFpEF will be established in accordance to the recommendations of the European Society of Cardiology. Patients have to be overweight or obese (BMI >25 kg/m2) with evidence of systemic (RR > 140/90 mmHg or use of antihypertensive medications) and pulmonary hypertension (pulmonary artery systolic pressure (PASP) > 35 mmHg), clinically justifying the combined treatment strategy in cGETS. The echocardiogram used to establish the diagnosis of HFpEF will be regarded as the recruitment visit echocardiogram (recruitment visit echocardiography). Included patients will be started on ACEi/sartan or will drugs dosages be optimized in patients already treated with ACEi/sartan. Patients not yet receiving ACEi will be started on 4 mg perindopril daily. Patients already using 4 mg perindopril will be uptitrated to 8 mg perindopril. Patients using lisinopril will be uptitrated to 40 mg (SID) if tolerated. Patients using ramipril will be uptitrated to 10 mg (SID). Patients using

enalapril or captopril will be switched to perindopril because of the more convenient dosage schedule of perindopril (SID) compared to enalapril (BID) or captopril (TID). Patients who cannot tolerate an ACEi will be treated with candesartan.
At baseline, an echocardiogram will be performed. Additional baseline investigations (blood sampling, low dose dobutamine stress testing and cardiac MRI) will also be performed. In addition, hemodynamic measurements obtained with a Nexfin device will be recorded during the echocardiography. During this baseline visit, the patient will receive a single, oral dose of sildenafil (100mg) as a safety control of drug tolerance. 1 hour after intake, the echocardiography will be repeated to observe potential differences in diastolic function.
In addition to ACEi or ARB treatment, the cyclic GMP enhancing strategy will consist of the following interventions:
1) Initiation or uptitration of statin therapy: Patients not yet on statin therapy will be started on atorvastatine 40 mg (SID). Patients on rosuvastatine will be uptitrated to a dose of 20 mg. Patients on simvastatine will be uptitrated to 80 mg. Pravastatine will be switched to atorvastatine 40 mg.
2) Initiation of sitagliptin in case of untreated DMII or DMII solely treated with metformin. Sitagliptin eligible patients will be treated with sitagliptin 100 mg once daily.
After a month, during the second visit, the non-invasive imagaging and blood sample are repeated and the patient again will receive a single, oral dose of 100mg of sildenafil as a safety control of drug tolerance. After 1 hour, the echocardiography is repeated. If sildenafil improves diastolic distensibility at the second challenge and the drug is well tolerated, the patient enters the chronic treatment phase of the study, which will take 1 month and consists of additional treatment with sildenafil 3x50mg/day. After this phase, the aforementioned procedureds will be repeated.

Study burden and risks

The nature and extent of the burden and risk are limited and related to the non-invasive nature of investigations. There is a small risk of a local hematoma after venapuncture. During low-dose stress echocardiography, no harmful effects of dobutamine are expected.
The cyclic GMP enhancing therapies can have side-effects, of which the most common are:

- Sildenafil (1-10% of patients): headache, hypotension, blushing, dizziness, nausea, palpitations.
- Atorvastatine (1-10%): headache, muscular of articular pain, nausea, obstipation, diarrea, dyspepsia.
- Sitagliptine (1-10%): hypoglycaemia, nausea.

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

HFpEF patients over 18 years old and concomitant arterial hypertension, overweight or obesity and pulmonary hypertension will be recruited from the outpatient clinic.

Exclusion criteria

* A history of acute coronary syndrome, coronary revascularization, evidence of reversible ischaemia or stroke within the previous 6 months.;* Valvular disease (more than moderate mitral or aortic regurgitation or greater than mild aortic or mitral stenosis).;* Hypertrophic, or infiltrative or inflammatory myocardial disease (e.g., amyloid, sarcoid).;* Pericardial disease, cor pulmonale or primary pulmonary arteriopathy.;* Use of nitrates or anticipated future need for nitrate therapy.;* Previous statin-induced myopathy or hypersensitivity reaction to statins

or PDE5 inhibitors.;* Neuromuscular, orthopedic, or other non-cardiac condition that prevents the individual from exercise testing on a bicycle ergometer or from walking in a hallway.;* Non-cardiac condition that limits life expectancy to less than 1 year at the time of study entry, based on the judgment of the physician.;* History of reduced ejection fraction (less than 50%).;* Implanted metallic device that will interfere with MRI examination (in people without atrial fibrillation).;* Severe kidney dysfunction (estimated glomerular filtration rate [GFR] less than 20 ml/min/1.73m2 by modified modification of diet in renal disease [MDRD] equation).;* Pregnant or not using an effective form of contraception.;* Hemoglobin level of less than 10 g/dL (=6.2 mmol/l).;* Taking alpha antagonists or cytochrome P450 3A4 inhibitors (e.g., ketoconazole, itraconazole, erythromycin, saquinavir, cimetidine, or serum protease inhibitors for HIV).;* Retinitis pigmentosa, previous diagnosis of nonischemic optic neuropathy, untreated proliferative retinopathy, or unexplained visual disturbance.;* Sickle cell anemia, multiple myeloma, leukemia, or penile deformities that increase the risk for priapism (e.g., angulation, cavernosal fibrosis, Peyronie's disease).;* Severe liver disease (aspartate aminotransferase [AST] level greater than three times the normal limit, alkaline phosphatase or bilirubin greater than two times the normal limit).;* In being consistent with American College of Cardiology (ACC)/American Heart Association (AHA) guidelines, people with dyspnea and risk factors for coronary artery disease should have had a stress test and those people with a clinically indicated stress test demonstrating significant ischemia in the 1 year before study entry will be excluded.;* Previous or planned heart transplantation.;* Chronic muscle disease or an unexplained creatine kinase level of more than 2.5 times of the normal range.

Study design

Design

Study phase:	2
Study type:	Interventional
Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Pending
Start date (anticipated):	01-01-2014
Enrollment:	35
Type:	Anticipated

Medical products/devices used

Product type:	Medicine
Brand name:	Atacand
Generic name:	Candesartan
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Coversyl
Generic name:	Perindopril
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Lipitor
Generic name:	Atorvastatine
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Tritace
Generic name:	Ramipril
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Zestril
Generic name:	Lisinopril
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	11-11-2013
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	28-02-2018
Application type:	First submission
Review commission:	METC Amsterdam UMC

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	EUCTR2012-002877-71-NL
CCMO	NL40842.029.12