Discovery and validation of diagnostic biomarkers for left ventricular diastolic dysfunction and HEart faiLure with Preserved ejection Fraction

Published: 18-08-2016
Last updated: 31-12-2024

To obtain sex-specific biomarkers, based on pathogenesis of microvascular disease, that improve the early diagnosis of diastolic dysfunction and HFPEF. These biomarkers come from innovative sources such as circulating endothelial cells,...

Ethical review	Approved WMO
Status	Completed
Health condition type	Heart failures
Study type	Observational invasive

Summary

ID

NL-OMON50536

Source
ToetsingOnline

Brief title
HELPFul study

Condition

- Heart failures

Synonym
Diastolic Heart Failure, Heart failure with preserved ejection fraction

Research involving
Human

Sponsors and support

Primary sponsor: Universitair Medisch Centrum Utrecht

Source(s) of monetary or material Support: Ministerie van OC&W,CVON

Intervention

Keyword: Biomarker, Ejection, Fraction, Preserved

Outcome measures

Primary outcome

Our primary aim is to improve the (early) diagnosis of diastolic dysfunction and HFPEF with the discovery and validation of new biomarkers. Since HFPEF is more prevalent in females, we will focus on discovery of sex-specific biomarkers..

Endpoint: diagnosis of grade of diastolic dysfunction (LVDD) confirmed by E/e* values or HFpEF

Additioneel ARGUS:

To describe the prevalence of CAD and coronary microvascular disease (CMD) in a population of patients from the general population who are referred to the Cardiology Center Netherlands, location Utrecht or the Diakonessenhuis by their general practitioner and present with chest pain as the main symptom.

Secondary outcome

1. As a secondary objective, we aim to get a better understanding of the aetiology of diastolic dysfunction and HFPEF. Discovery of causal biomarkers may serve as lead targets for treatment of diastolic dysfunction and HFPEF.

2. To assess the prognostic ability of discovered biomarkers to predict

hospitalization for heart failure or death within 5 years.

3. To investigate the underlying genetics contribution to the development of diastolic dysfunction and HFPEF.

Power will be limited to detect genetic associations with small effects and HELPFUL will therefore join a genetic consortium that aims to perform a genome-wide association study on diastolic dysfunction and HFPEF.

Addititional ARGUS:

To examine whether there are any blood (cell-based) biomarkers that predict either a positive or a negative CAD and CMD imaging outcome.

To evaluate whether more extensive phenotyping of individuals who present with chest pain complaints will improve long-term outcomes (time to) hospitalisation for heart failure and all-cause mortality using linkage studies.

Study description

Background summary

Heart failure is a severe syndrome formed by two entities, systolic heart failure and diastolic heart failure. Currently the term *heart failure with reduced ejection fraction (HFREF)* is used for systolic heart failure and *heart failure with preserved ejection fraction (HFPEF)* for diastolic heart failure. Until recently it was thought that diastolic heart failure had a better prognosis because the pump function of the heart was maintained. Most research has therefore been in the area of systolic heart failure resulting in good biomarkers, such as BNP, and better treatment options. Recent literature has pointed out the severity of diastolic heart failure, for which current biomarkers are not optimal and treatment options remain inadequate. New

medicine for diastolic heart failure is in phase II clinical trial setting, which brings hope for better treatment options. To treat the correct type of patient good diagnostic modalities are necessary. For diastolic heart failure echocardiography is the golden standard, though there is much debate concerning the cutoff value for the ejection fraction (a value for the pomp function of the heart) and which combination of echocardiographic abnormalities should classify diastolic dysfunction or heart failure. Wall motions of the left ventricle, together with the volume of the left atrium, are viewed as the most important parameters. The addition of a biomarker to this echo for improvement of the diagnosis would be of great value. This is the goal of HELPFul, to discover and validate a biomarker in the diagnosis of diastolic dysfunction and HFPEF.

Recent data shows that the causes of HFPEF are different from HFREF. HFPEF mostly affects women, with persistent high blood pressure and diabetes. These risk factors appear to damage the endothelium (lining of the vascular wall) in the small blood vessels of the heart (microvasculature). As a result these small vessels will collaps, causing regional oxygen deficiency and thereby thickening and stiffening of the heart. Another hypothese is that micro-embolia (small clots) let go of artery sclerosis (erosion) and cause the small vessels to get clogged. This could also result in thickening and stiffening of the heart.

For the biomarker discovery we will aim for these two hypothese which centre around the endothelium and the coagulation. We will study the transcriptoma (information) of cells released from the smalls vessels of the heart for information on the presence of diastolic dysfunction or HFPEF. Furthermore we will study the blood for information suggestion the presence of micro-embolia. Our biomarker discovery is mostly aimed at the endothelium and blood coagulation. Promising biomarkers will be validated.

Additionally ARGUS:

Chest pain is a common symptom in the general practitioner*s office, affecting between 20 and 40% of the general population during their lifetime. Chest pain may be a symptom of underlying coronary artery disease (CAD), which is a potentially life-threatening condition. Therefore, exclusion of CAD is the first priority in patients with chest pain.

However, not only obstructive CAD, which affects the coronary arteries, but also non-obstructive CAD with microvascular obstruction is associated with a poor prognosis. Despite angiographical lack of macrovascular obstruction, ischemia induced by coronary microvascular disease (CMD) can give rise to symptoms as well.

Approximately two-thirds of all patients with chest pain and non-obstructive

CAD have some form of coronary microvascular dysfunction.

Current algorithms and scores have been developed and validated for the exclusion of obstructive CAD only, but not for CMD. This may lead to unintentional false reassurance and discharge of CMD patients with a poor prognosis and potentially fatal result.

The aim of this proposal therefore is to develop an algorithm that can be used by the general
practitioner that identifies individuals who do not have any coronary ischemia either from obstructive CAD or CMD, and whose referral to a screening center or a cardiologist is unnecessary, based on information derived from a drop of blood.

To this end, we perform extensive cardiac and coronary imaging in individuals referred to screening centers for chest pain. In addition we draw blood. Advances in CCTA together with CMR imaging allows for quantified measures of the macro- and microvascular disease of the heart. Based on imaging outcome, we can identify two groups: 1) CAD and/or CMD and 2) no ischemia at all, not requiring further additional testing.

ARGUS will result in an algorithm based on clinical information and extensive blood-based information for the exclusion diagnosis of myocardial ischemia. This algorithm will be validated in hospitalized and outpatient clinics individuals in a cross-sectional manner, also using follow-up information on hospitalizations and mortality. In the new era of predictive modeling and machine learning, ARGUS will uncover nuances and patterns that yet remained hidden within the wealth of medical data to improve clinical care and outcome.

Study objective

To obtain sex-specific biomarkers, based on pathogenesis of microvascular disease, that improve the early diagnosis of diastolic dysfunction and HFPEF. These biomarkers come from innovative sources such as circulating endothelial cells, extracellular vesicles and endothelial micropartcicles

Endpoint: diagnosis of grade of diastolic dysfunction (LVDD) confirmed by E/e* values or HFpEF.

Additioneel ARGUS:
To develop an algorithm based on clinical information and blood-based information that
accurately excludes coronary vascular disease.

Study design

Case cohort study.

Study burden and risks

There is a small risk to the patient of getting bruises after venapuncture. But this is the same risk as venapuncture within healthcare.

Additioneel ARGUS:

As part of the ARGUS study, participants will be invited for a cardiac CT scan (using x-rays and intravenous (IV) infusion of an iodine contrast agent) and a cardiac MRI scan (using IV adenosine and gadolinium contrast). Nine tubes of venous blood (each 5-10cc) will be drawn from the patient at the day of consultation for the CT scan. For these investigations the risk is the same risk as during a regular care CT or MR-scan.

Contacts

Public
Universitair Medisch Centrum Utrecht

Heidelberglaan 100
Utrecht 3584 CX
NL
Scientific
Universitair Medisch Centrum Utrecht

Heidelberglaan 100
Utrecht 3584 CX
NL

Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age

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

Inclusion criteria

- Patients in the cardiology outpatient clinic of Cardiology Centre Netherlands, Diakonessenhuis Utrecht or HeartLife Klinieken Utrecht who receive cardial screening, including an echocardiography, because of general practitioner*s request
- Age 45 year and older
- Patient is willing and able to provide written informed consent for participation in this study
- The inclusion criteria match the criteria for diagnosis of diastolic dysfunction or HFpEF., Additional ARGUS, Inclusion criteria ARGUS
In order to be eligible to participate in the ARGUS study, a subject must meet the additional following criterium:
• Chest pain as main symptom

Exclusion criteria

• Patients from whom no informed consent is obtained
• Incapacitated adults: language barriers or other obstacles for full understanding of the study objectives
• Patients with former cardiac procedures.
• Patients with congenital heart disease,

Additional ARGUS:
A potential subject who meets any of the mentioned criteria or any of the following will be excluded from participation in the ARGUS study:
• Patients for whom (a part of) the cardiac CT study protocol is contra indicated prior to inclusion (if CT is contra indicated after completion of MRI-scan patient will not be excluded but collected data will be used in study)
• Patients for whom (a part of) the cardiac MRI study protocol is contra indicated prior to inclusion (if MRI is contra indicated after completion of CT-scan patient will not be excluded but collected data will be used in study)
• Participants who are referred for an intervention immediately after completing the cardiac CT scan

Study design

Design

Study type:	Observational invasive
Intervention model:	Other
Allocation:	Non-randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Basic science

Recruitment

NL

Recruitment status:	Completed
Start date (anticipated):	19-09-2016
Enrollment:	1000
Type:	Actual

Ethics review

Approved WMO Date:	18-08-2016
Application type:	First submission
Review commission:	METC NedMec
Approved WMO Date:	21-09-2016
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	03-05-2017
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	13-10-2017
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	18-05-2018

Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	12-09-2018
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	05-09-2019
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	24-02-2020
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	19-05-2020
Application type:	Amendment
Review commission:	METC NedMec

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: 21717
Source: Nationaal Trial Register
Title:

In other registers

Register	ID
CCMO	NL57077.041.16

Study results

Date completed:	05-12-2023
Results posted:	19-01-2024
Actual enrolment:	977

First publication
01-01-1900