The role of nutritional deficiencies in chronic heart failure

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Primary Objective:• To investigate the relationship between ID, VB12D or FD and outcome (HF hospitalization and all-cause mortality) in patients with chronic HF. Secondary Objectives:• To investigate the prevalence of ID, VB12D or FD in chronic HF...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Heart failures
Study type	Observational non invasive

Summary

ID

NL-OMON37469

Source
ToetsingOnline

Brief title
Nutritional deficiencies in heart failure

Condition

- Heart failures

Synonym
Heart failure and iron deficiency

Research involving
Human

Sponsors and support

Primary sponsor: Van Buchem Stichting
Source(s) of monetary or material Support: van Buchem stichting

Intervention

Keyword: Folate deficiency, Heart failure, Iron deficiency, Vitamin B12 deficiency

Outcome measures

Primary outcome

Primary study parametes/endpoint:

Prognosis of ID, VB12D and FD in patients with chronic HF. Data on all cause mortality, HF hospitalization or the combined endpoint of both will be collected from the BENEFICIAL database. We will only collect data that were obtained during participation in the BENEFICIAL trial. Follow-up information after this trial will not be taken into consideration.

Secondary outcome

Secondary study parameters/endpoints:

Data will be collected from the BENEFICIAL database to investigate possible relationships between chronic HF patients with/without ID, VB12D or FD, or markers of these deficiencies, on:

- Exercise capacity (peak oxygen consumption)
- Blood markers (e.g. hemoglobin, markers of inflammation, NT-proBNP, renal function)
- Echocardiographic parameters (systolic/diastolic function)
- Non-invasive cardiac index (Nexfin)

Study description

Background summary

Despite improvements in chronic heart failure (HF) treatment, mortality and morbidity rates remain high. Also, daily activities of many patients stay behind. Exercise intolerance is a cardinal feature of HF, and is related to a poor quality of life and an heightened risk of morbidity and mortality. In addition, comorbidities, such as anemia are common in chronic HF and might further contribute to impaired exercise capacity. Despite the focus on anemia as a target for therapy in HF, the cause of anemia in chronic HF patients is a matter of ongoing debate. Similarly, the mechanism by which the presence of anemia contributes to an adverse outcome in these patients, is often complex and multifactorial.

In regard to the etiology of anemia in chronic HF, there is growing evidence that nutritional deficiencies, in particular iron deficiency (ID), play a role in chronic HF. Iron deficiency is the most common nutritional disorder, affecting more than one-third of the general population. Traditionally, ID has been considered to have clinical consequences only in the presence of anemia. Alternatively, a reduced hemoglobin level can be viewed as the end result of a process beginning with the gradual depletion of iron stores. Even if patients are not anemic, ID may already be common in HF.

In the past few years, it has been recognized that chronic HF patients are prone to develop ID or other nutritional deficiencies. For ID, this may result from either an absolute deficiency of iron, due to the result of a gradual depletion of iron stores (absolute ID), causing iron deficiency anemia. Alternatively, ID may be *relative* or *functional*, the result of inflammatory process and the sustained elevation of pro-inflammatory cytokines, including interleukin 6 (IL-6) and tumor necrosis factor alpha (TNFα). An increase in these cytokines causes a decrease in erythropoietin (EPO) production and a reduced erythropoietic response of the bone marrow to increased EPO levels. Also, IL-6 increases the synthesis of hepcidin, a liver derived protein. Hepcidin, in return, causes reduced iron absorption and dysregulation of iron homeostasis and accumulation of iron in cells of the reticuloendothelial system, which is a characteristic feature of anemia of chronic disease.

However, not much is known about the prevalence of ID and other nutritional deficiencies (e.g. vitamin B12, folate) in chronic HF. Also, they relationship between these nutritional deficiencies and exercise capacity or outcome has not been fully explored. For that reason, we want to investigate the prevalence of ID, vitamin B12 deficiency (VB12D) and folate deficiency (FD) and examine their relation with exercise capacity and outcome.

Study objective

Primary Objective:
• To investigate the relationship between ID, VB12D or FD and outcome (HF hospitalization and all-cause mortality) in patients with chronic HF.

Secondary Objectives:
• To investigate the prevalence of ID, VB12D or FD in chronic HF.
• To investigate the relationship between ID, VB12D or FD and exercise capacity in chronic HF patients.
• To investigate possible differences in blood markers (e.g. NTproBNP, renal function, inflammatory markers) between chronic HF patients with/without ID, VB12D or FD.
• To describe differences in chronic HF patients with/without ID, VB12D or FD regarding echocardiographic parameters and non-invasive cardiac index (Nexfin).

Study design

This protocol concerns a non-interventional study, in which previous stored blood samples from all patients, who participated in the BENFICIAL (A double-Blind, placEbo-coNtrolled, randomized trial Evaluating the efFICacy and safety of ALagebrium (ALT-711) in patients with chronic heart failure) trial, will be analyzed. All assessments will be done at the University Medical Center Groningen (UMCG) in Groningen, the Netherlands.

In 2010 the BENEFICIAL trial ended. This prospective, randomized, double-blind, placebo-controlled, phase II trial studied the effects of the advanced glycation end-product (AGE) breaker Alagebrium (ALT-711) on the severity of chronic HF. 15,16 102 patients with stable chronic HF and a reduced left systolic function (left ventricular ejection fraction < 45%) were included in this study. One of the main conclusions of this study was that adding Alagebrium to the treatment of chronic HF patients did not improve exercise capacity (measured by 2 cardiopulmonary aerobic capacity tests). During this study, blood samples from all patients were frozen and stored (for a period of 15 years) to perform additional analysis on in the future.

Rationale for choosing patients from the BENEFICIAL trial
Nutritional deficiencies, in particular ID, have been associated with chronic systolic HF. It has also been suggested that ID also predicts impaired exercise capacity in these patients.9,11 To further investigate these findings, we will use stored blood and data from patients, who participated in the BENEFICIAL trial. This trial included only patients with a reduced left systolic function and who performed two cardiopulmonary aerobic capacity tests during this study to objectify the exercise capacity of these patients.

Blood sample analysis:
Once written informed consent has been obtained by the principal investigator, blood sample analysis will take place. Approximately 5 mL aliquots of the stored blood samples will be taken. Validated methods will be used to analyze multiple blood markers by the laboratory of the University Medical Center Groningen, the Netherlands. Hematological blood markers that will be assessed include (but are not limited to): vitamin B12 and folate. Markers that reflect iron status that will be assessed include (but are not limited to): ferritin, serum iron, total iron binding capacity, transferrin and soluble transferrin receptor. Contributors of ID (IL-6, TNFα, hepcidin and growth differentiation factor 15) will be assessed. Blood samples that are not used will stay frozen and stored for the remaining period of the 15 years (which started when patients participated in the BENFICIAL trial). Patients will have to give their informed consent again to enable possible future analyses on their blood.

ID will be defined as ferritin < 100 µg/L or 100-299 µg/L in combination with a transferrin saturation of < 20%.
VB12D will be defined as a vitamin B12 level < 142 pmol/L.
FD will be defined as a folate level < 13.6 nmol/L when supplemented and as a folate level < 6.8 nmol/L when not supplemented.

Study burden and risks

There are no burdens or risks associated with this study. Only frozen and stored blood samples from all patients, who participated in the BENEFICIAL trial (NL16287.042.07), will be used for analysis.

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

This study encloses additional analyses on already frozen and stored blood samples of patients from an earlier judged study (NL16287.042.07). No inclusion criteria will be necessary for this study. For inclusion criteria, see protocol from study NL16287.042.07

Exclusion criteria

This study encloses additional analyses on already frozen and stored blood samples of patients from an earlier judged study (NL16287.042.07). No exclusion criteria will be necessary for this study. For exclusion criteria, see protocol from study NL16287.042.07

Study design

Design

Study type: Observational non invasive

Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Basic science

Recruitment

NL

Recruitment status:	Recruitment stopped

Start date (anticipated):	27-04-2012
Enrollment:	0
Type:	Actual

Ethics review

Approved WMO Date:	27-04-2012
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

No registrations found.

In other registers

Register	ID
CCMO	NL39695.042.12