The HF-AF ENERGY Trial: Attenuate atrial fibrillation with nicotinamide riboside (niagen)

Published: 08-04-2022
Last updated: 04-04-2024

Primary objective: Our primary objective is to investigate whether niagen normalizes blood-based energy metabolites, mitochondrial levels and proteostasis levels. Secondary objective: To examine whether niagen reduces AF burden in patients with...

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Cardiac arrhythmias
Study type	Interventional

Summary

ID

NL-OMON52394

Source
ToetsingOnline

Brief title
The HF-AF ENERGY Trial

Condition

- Cardiac arrhythmias

Synonym
Atrial fibrillation

Research involving
Human

Sponsors and support

Primary sponsor: Erasmus MC, Universitair Medisch Centrum Rotterdam
Source(s) of monetary or material Support: Ministerie van OC&W,Chromadex, voor het leveren van het voedingssupplement niagen

Intervention

Keyword: Atrial fibrillation, Heart failure, Niagen, Nicotinamide Riboside

Outcome measures

Primary outcome

Our primary objective is to investigate whether niagen normalizes blood-based

energy metabolites, mitochondrial levels, and proteostasis levels.

Secondary outcome

To examine whether niagen reduces AF burden in patients with ischemic and/or

non-ischemic heart disease.

Study description

Background summary

Zie protocol page 8 & 9.

Atrial fibrillation (AF) and heart failure (HF) are the two dominant cardiovascular diseases of this century. Failure rates of AF therapy in HF patients are high, particularly when AF becomes more persistent. Therefore, the need for novel, less-invasive therapy is higher than ever. We recently observed that AF causes a significant reduction in nicotinamide adenine dinucleotide (NAD+) levels and consequently deteriorate the mitochondrial function due to DNA damage-induced activation of the DNA repair protein ADP-ribose-polymerase 1 (PARP1) in atrial tissue of patients with AF. In line, we showed that supplementation with NAD+ or nutraceutical treatment with nicotinamide conserves the energy metabolisms and protects against electrophysiological dysfunction and AF in experimental model systems for AF. Nicotinamide is the building block of NAD+ and mainly present in the mitochondria. NAD+ plays a key role in the energy metabolism in cells, especially cells which are metabolic very active such as cardiomyocytes. Nicotinamide riboside (NR) is a registered form of vitamin B3 and a potent inducer of NAD+ levels in humans without causing serious side effects.

Experimental and human studies have shown that supplementation with NR raises NAD+ levels, which protect against dilated cardiomyopathy, ischemic heart disease and heart failure. Although experimental studies revealed important

evidence for nicotinamide to protect against heart diseases by conserving the NAD+ levels, it is unknown whether nicotinamide riboside can restore NAD+ metabolism in ischemic and/or non-ischemic heart failure patients with AF and subsequent prevent AF onset and progression. Therefore, the main objective of the current proposal is to reveal the impact of nicotinamide riboside (Tru Niagen® ChromaDex) on blood-based energy metabolites and proteostasis levels (including NAD+/NADH) in ischemic and/or non-ischemic heart disease patients with paroxysmal or persistent AF. Furthermore, it is examined whether niagen reduces the AF burden (sum of the duration of all episodes divided by the duration of observation periods). This is determined by utilizing rhythm monitoring software of implantable cardiac devices (ICD) enabling monitoring detection of the cardiac rhythm.

Positive outcomes of this first therapeutic study aimed at protection from cardiomyocyte damage and subsequently reduction of AF burden in HF patients will be a major breakthrough in the therapy of AF. In addition, it will provide, for the first time, novel therapeutic options for AF in patients with ischemic and/or non-ischemic heart disease.

Study objective

Primary objective: Our primary objective is to investigate whether niagen normalizes blood-based energy metabolites, mitochondrial levels and proteostasis levels.

Secondary objective: To examine whether niagen reduces AF burden in patients with ischemic and/or non-ischemic heart disease.

Study design

Patients that come to the outpatient clinic of Cardiology will be screened for fitting the inclusion criteria. Patients will be informed about the HF-AF ENERGY trial and asked for informed consent. Laboratory tests will be performed for testing mitochondrial biomarkers, energy metabolite levels, and various proteostasis markers in the blood. Echocardiography will be done for baseline measurement, if patients did not have an echocardiography in the previous 3 months. Furthermore, clinical history of the patient, including start date/year of AF, diagnosis date, symptoms, AF incidence and prior AF therapy/treatments is evaluated. A start date of oral intake of the niagen supplement will be chosen with the patient. The patient will receive the niagen capsules (enough for 4 months). The patient starts with 500 mg (2 capsules) per day, move up to 1000 mg (4 capsules) per day, then take 1500 mg (6 capsules), and eventually take 2000 mg (8 capsules) per day, with a duration of one week for each incremental increase. After 4 weeks, patients have reached the maximum dose (1000 mg, twice daily) and will continue on this dose until the end of the study (Week 16). The study will stop 4 months after the start date. The

supplements (TRU NIAGEN® ChromaDex 250 mg) will be taken twice a day: for the first week: 1 capsule in the morning, 1 capsule in the evening. Week 2: 2 capsules in the morning, and 2 capsules in the evening. Week 3: 3 capsules in the morning, and 3 capsules in the evening. The patient have reached the final dose in week 4: 4 capsules in the morning and 4 capsules in the evening. This patient continue on this dose until the end of the study (Week 16). If, at any step, a dose increase is not tolerated, the maximum previously-tolerated dose will be continued through to week 16. Patients will be asked to fill in a diary where they keep track of their supplement intake and potential side-effects. After 4 months, patients are evaluated at our outpatient clinic of Cardiology, which will be the endpoint. This evaluation will consist of history taking, as well as blood sampling and echocardiographic examination. AF therapy, AF symptoms, HF symptoms and possible side effects of niagen are evaluated. The answers will be filled in on a questionnaire. Finally, the patient diary is checked together with the patient for compound intake, plus the remaining pills will be collected.

Study design
The HF-AF ENERGY trial is an intervention study with a planned duration of 36 months to test whether niagen has a positive effect on AF burden, metabolite, proteostasis and energy levels. For the study we want to include 20 patients. This is based on a calculation that niagen increases NAD+ levels by 35%.

Research Product: nicotinamide riboside (Tru Niagen® ChromaDex®)
- Dosage: 2 x 1000 mg per day. The initial dose will be 1 capsule twice daily, followed by weekly up-titration by 1 capsule/dose to a final dose of 4 capsules (1000mg) twice daily at the end of Week 4. Participants will be continued on the final dose up to the final follow up visit (week 16).
- Total duration study: 36 months **Allow us to include patients at different time points**
- Observation period: 4 months (determine AF burden and baseline metabolite, proteostasis and energy levels)
- Supplementation period: 4 months
- End point: after 4 months niagen treatment (determine effect of niagen on AF burden, metabolite, proteostasis and energy levels)

Part 1 (0-36 months):
1. Inclusion 20 patients
2. Determination baseline blood sample values
3. Determination AF burden
4. Niagen supplementation (4 months)

Visit 1 - start of the observation period
- Discuss AF- and clinical history with the patient (previous therapy, incidence AF, symptoms)
- Blood samples (venipuncture) max. 4 tubes of blood (4x7ml) (tests proteostasis, mitochondrial biomarkers and energy markers, including NAD+/NADH)

- Determine the starting date of niagen intake
- Informing about a supplement diary for niagen intake, AF episodes, AF symptoms, side effects
- Echocardiographic examination (evaluation of Left Ventricle function and atrial size)

Visit 2 - 4 months after taking niagen supplement = endpoint
- Clinical evaluation
- Blood samples (venipuncture) max. 4 tubes of blood (4x7ml) (tests proteostasis biomarkers and energy markers, including NAD+/NADH) (difference pre- and post-supplementation)
- Echocardiographic examination
- Calculate AF burden (difference pre- and post-supplementation)
- Review patient food diary, check niagen intake
- Collecting the remaining niagen supplements

Intervention

Patients will be taking the commercially available dietary supplement nicotinamide riboside (Tru Niagen® ChromaDex®), a form of vitamin B3. In earlier studies, this compound was shown to enhance NAD+ levels, a coenzyme which is present in reduced levels in patients with AF. The initial dose will be 1 capsule twice daily, followed by weekly up-titration by 1 capsule/dose to a final dose of 4 capsules (1000mg) twice daily at the end of Week 4. Participants will be continued on the final dose up to the final follow up visit (week 16). If, at any step, a dose increase is not tolerated, the maximum previously-tolerated dose will be continued through to week 16.

Study burden and risks

Neither the patient, nor the investigators are in any way compensated for their participation with regards to this study. For participants of this study Participants may experience less AF which will be associated with less complications and symptoms. Niagen did not cause any serious side-effects in clinical studies. In addition, this study may provide more insight into the mechanism of AF by investigating the presence and extent of metabolic and electrical changes. Knowledge is important as it may benefit future preventive or curative AF therapies.

The risk of niagen supplementation is considered to be very low, since studies have shown no serious adverse effects for using niagen. To date, studies have reported minimal side effects from clinical studies with niagen. The minimal observed side effects are: changes in glucose and insulin sensitivity but these values are within the normal range, mild nausea, mild sleeping problems, mild headache symptoms. However, niagen has not been extensively studies in heart failure patients. Therefore, we will closely monitor all subjects for adverse

events during the study period. The extra tests for this study (blood draw, echocardiography) also have minimal risks. Therefore, the risks associated with participation in the HF-AF ENERGY trial study are low. The burden associated with participation in this study is estimated to be minimal. The intake of supplements takes a maximum of 5 minutes per day.

Contacts

Public
Erasmus MC, Universitair Medisch Centrum Rotterdam

Dr. Molewaterplein 40
Rotterdam 3015 GD
NL
Scientific
Erasmus MC, Universitair Medisch Centrum Rotterdam

Dr. Molewaterplein 40
Rotterdam 3015 GD
NL

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

- Patients diagnosed with paroxysmal or persistent AF
- Left ventricle function <=40%
- Implantable cardiac device (ICD) equipped with rhythm monitoring software
- Ischemic and/or non-ischemic cardiomyopathy

• Aged between 18-90 years

Exclusion criteria

• Permanent AF
• Hemodynamic instability
• Absence of atrial sensing
• Malabsorption diseases
• Metabolic diseases
• Inflammatory disease

Study design

Design

Study type:	Interventional
Intervention model:	Other
Allocation:	Non-randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	13-05-2022
Enrollment:	20
Type:	Actual

Ethics review

Approved WMO

Date:	08-04-2022
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam

	(Rotterdam)
Approved WMO Date:	19-12-2022
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

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	NL70369.078.21