Quantitative-imaging in cardiac transthyretin amyloidosis (I-CARE)

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This study has been transitioned to CTIS with ID 2024-513310-36-01 check the CTIS register for the current data. Primairy objectives 1. To determine the presence and extent of myocardial microcalcification and myocardial denervation in ATTR-CM;2. To...

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Myocardial disorders
Study type	Observational invasive

Summary

ID

NL-OMON55211

Source
ToetsingOnline

Brief title
i-CARE

Condition

- Myocardial disorders

Synonym
cardiac amyloidosis, hart amyloidstapeling

Research involving
Human

Sponsors and support

Primary sponsor: Universitair Medisch Centrum Groningen
Source(s) of monetary or material Support: Nederlandse Hartstichting

Intervention

Keyword: [123I]MIBG, 18F-NaF, Cardiac amyloidosis, PET

Outcome measures

Primary outcome

Primary Endpoints

• Quantification of myocardial microcalcification on 18F-sodiumfluoride PET/CT;

• Mean difference in [123I]MIBG uptake between early and progressive ATTR-CM at baseline and after one years on tafamidis.

Secondary outcome

Secondary Endpoints

• Change in myocardial microcalcification activity on 18F-sodiumfluoride PET/CT;

• Cardiac indices on magnetic resonance imaging, such as left ventricular ejection fraction, left ventricular mass, extracellular volume and global longitudinal strain;

• Cardiac biomarkers including NT-ProBNP and high-sensitivity cardiac troponin I;

• Clinical measures such as 6-minute walk test (6MWT), Kansas City Cardiomyopathy Questionnaire - Overall Summary (KCCQ-OS) score, and Norfolk Quality of Life-Diabetic Neuropathy questionnaire total score (Norfolk QOL*DN);

Study description

Background summary

Systemic amyloidosis represents a spectrum of conditions characterised by disordered protein folding and formation. The two predominant forms affecting

the heart are amyloid light-chain (AL) and amyloidosis transthyretin (ATTR). Transthyretin amyloidosis cardiomyopathy (ATTR-CM) is gradually progressive and is ultimately fatal if left untreated. It is characterised by deposition of amyloid fibrils from liver-derived transthyretin (TTR) in the myocardial extracellular space. Microcalcification has been described in association with these deposits. ATTR-CM can be classified as sporadic, associated with the deposition of wild-type transthyretin (ATTRwt), or hereditary, associated with genetic variants of TTR (ATTRv). Historically, there has been a mismatch between the number of clinical diagnoses of ATTR-CM and autopsy findings where cardiac ATTR amyloid deposits have been observed in up to a quarter of elderly individuals. In recent years, greater awareness of ATTR-CM as an underrecognized cause of heart failure, coupled with an ageing population and advances in diagnostic techniques have resulted in a dramatic increase in new clinical diagnoses of ATTR-CM. For example, the prevalence of ATTR-CM is currently estimated at ~1 in 7 patients with heart failure with preserved ejection fraction (HFpEF) and 1 in 6 with severe aortic stenosis (AS) requiring transcatheter aortic valve replacement. Based upon these statistics and the growing population of elderly people in Europe (100 million), the prevalence of ATTR-CM in Europe can be estimated at up to a million patients. We aim to investigate myocardial microcalcification in TTR amyloid using 18F-sodium fluoride PET/CT, a tracer with high affinity for developing cardiovascular microcalcification. In particular, we seek to establish that bone tracers bind to microcalcification in the myocardium, and then establish whether the degree of microcalcification is associated with ATTR-CM burden and whether changes in microcalcification can be tracked with disease progression and in response to therapy in ATTRCM. We will use 18F-SodiumFluoride because it is a cheap, well established and widely available PET bone tracer with exciting potential in patients with ATTR-CM [25]. Similar to the SPECT bone tracers, we have also demonstrated in a small pilot study that 18F-fluoride PET demonstrates increased uptake in ATTR-CM, again likely due to the underlying myocardial microcalcification. However, a key added advantage of using PET rather than SPECT to image ATTR-CM, is that PET provides sensitive and fully quantitative measurements of microcalcification both within the heart and in extra-cardiac structures (also commonly affected in ATTR). We are here to make use of this quantitative ability of PET to fully investigate the relationship between myocardial microcalcification and ATTR-CM.

Furthermore, ATTR-CM poses a risk on arrhythmia due to amyloid infiltration of the cardiac conduction system and the myocardial tissue. Iodine-123 labelled metaiodobenzylguanidine ([123I]MIBG) imaging can determine the damage to the cardiac sympathetic innervation in ATTR-CM. In ATTR variant (ATTRv) patients [123I]MIBG scintigraphy can detect myocardial denervation before signs of amyloidosis are even evident on echocardiography. The value of [123I]MIBG scintigraphy in wild type ATTR (ATTRwt) -CM has not yet been studied in detail. Based on a small pilot study (unpublished data), [123I]MIBG scintigraphy is abnormal in patients with ATTRwt and harbours prognostic value in these patients, as in ATTRv-CM. [123I]MIBG imaging provides us with the opportunity

to evaluate the effect of treatment with tafamidis on myocardial denervation in ATTR-CM. This will help to identify responders and non-responders to treatment with tafamidis at an early stage, therewith improving treatment strategy options for patients with until now still a limited prognosis. Finally I-CARE will be able, for the first time to our knowledge, compare 18F-NaF and [123I]MIBG in ATTR-CM patients using tafamidis.

Study objective

This study has been transitioned to CTIS with ID 2024-513310-36-01 check the CTIS register for the current data.

Primairy objectives
1. To determine the presence and extent of myocardial microcalcification and myocardial denervation in ATTR-CM;
2. To quantify the burden of myocardial microcalcification and myocardial denervation in ATTR-CM;
3. To assess whether myocardial microcalcification and myocardial denervation is reduced is improved following treatment for ATTR-CM.

Secondary objectives
1. To determine whether there is a threshold of myocardial microcalcification or myocardial denervation associated with the presence of ATTR-CM;
2. To determine whether myocardial microcalcification and myocardial denervation correlates with disease progression or treatment regression in patients with ATTR-CM.

Study design

In this international study, we will investigate the role of myocardial microcalcification in ATTR-CM within 4 work packages (WP). The MIBG scan will be researched in the UMCG as single-center.

Study burden and risks

Burden/risk: a cumulative radiation burden of 15.40mSv for the first 5-15 ATTR-CM patients and 14.34mSv for the later ATTR-CM patients and 4.27mSv for the control group. Allergy to gadolinium.
Benefit: insight in imaging technique (18F-NaF) for early and accurate detection of cardiac amyloidosis and the effect of clinical therapy.

Contacts

Public

Universitair Medisch Centrum Groningen

Hanzeplein 1
Groningen 9713CZ
NL
Scientific
Universitair Medisch Centrum Groningen

Hanzeplein 1
Groningen 9713CZ
NL

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

• Completion of informed consent • Age > 18 years • ATTR cardiac amyloid according to Expert Consensus Recommendations • AL amyloidosis according to Expert Consensus Recommendations • Hypertrophic cardiomyopathy according to European Society of Cardiology guidelines

Exclusion criteria

• Inability or unwilling to give informed consent
• Women who are pregnant, breastfeeding or of child-bearing potential (women who have
experienced menarche, are pre-menopausal and have not been sterilised) will not be enrolled
into the trial.
• Renal dysfunction (eGFR <=30 mL/min/1.73m2)
• NYHA Class IV heart failure

• Patients with atrial fibrillation and poor rate control.
• Contraindications to MR
• Previous history of contrast allergy of adverse reactions (gadolinium)
• Contraindications to Tafamidis therapy

With regards to patient exclusion for solely 1[23I]MIBG scan:
• Tricyclic antidepressants (TCA) usage (most importantly amitriptyline, clomipramine, imipramine, nortriptyline, chlorpromazine or perphenazine);
• Parkinson*s disease as mentioned in patients* medical history;
• Insulin dependent diabetes mellitus as shown in patients* actual medication list.

Study design

Design

Study type:	Observational invasive
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Diagnostic

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	25-08-2022
Enrollment:	70
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	[123I] metaiodobenzylguanidine
Generic name:	[123I]MIBG
Product type:	Medicine
Brand name:	[18F]SodiumFluoride

Generic name:	[18F]NaF

Ethics review

Approved WMO Date:	25-02-2021
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	12-07-2021
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	16-11-2021
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	03-07-2024
Application type:	Amendment
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
EU-CTR	CTIS2024-513310-36-01

Register	ID
EudraCT	EUCTR2020-003350-72-NL
CCMO	NL74564.042.20