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Protocol of the follow-up of patients with transthyretin amyloid cardiomyopathy by multimodality imaging (FAITH) study: a prospective observational study in patients with ATTR-CM undergoing treatment with tafamidis

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ABSTRACT

Introduction This prospective observational study of patients with transthyretin amyloid cardiomyopathy (ATTR-CM) undergoing treatment with tafamidis aims at identifying quantitative image markers and comparing imaging modalities regarding the follow-up and prognostication of these patients, with the goal of providing a multiparametric score to predict treatment response.

Methods and analysis Patients with a board-approved decision to receive tafamidis will undergo, in addition to standard of care, baseline and follow-up cardiovascular magnetic resonance (CMR) scans at 9 and 18 months. In total, the study plans to recruit and scan 60 patients. A blinded read will take place in a CMR research core laboratory. The final statistical analysis will be based on developing a multiparametric score for the prediction of treatment response. The study will be managed through the Amyloidosis Center Charité Berlin, a clinical unit formed from the three clinical campus sites of the Charité in Berlin, using the Berlin Research Network for CMR.

Ethics and dissemination The study was approved by the Charité—Universitätsmedizin Berlin ethics committee EA1/262/23. The results of the study will be disseminated through international peer-reviewed publications and congress presentations.

Trial registration number Approved WHO primary register: German Clinical Trials Register: https://www.drks.de/DRKS00033884. WHO International Clinical Registry Platform: https://trialsearch.who.int/?TrialID=DRKS00033884. Recruitment started on 1 July 2024.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ The follow-up of patients with transthyretin amyloid cardiomyopathy by multi-modality imaging (FAITH) study uses a multiparametric approach with its main focus on imaging led by cardiovascular magnetic resonance (CMR) to develop a score detecting patients with transthyretin amyloidosis not responding to therapy with tafamidis.
⇒ CMR scans will be carried out in an established scanner research network, guaranteeing equivalence across all sites.
⇒ Research sequences, such as four-dimensional (4D) flow CMR, will help to understand haemodynamic interactions and changes in patients with transthyretin amyloidosis undergoing targeted therapies.
⇒ The small sample size might reduce the generalisability of the findings in addition to potential confounding factors, such as the high prevalence of concomitant disorders in the older population.
⇒ Patient dropouts might be significant during follow-up scans given the high frequency of atrial fibrillation requiring restoration of sinus rhythm before the scan.

INTRODUCTION

Amyloidosis refers to a variety of different diseases caused by extracellular tissue deposits of various misfolded proteins.[1] Given the wide array of potential protein deposition, the term amyloidosis refers to a heterogenic group of clinical presentations.[1] The three major forms encountered in clinical practice are immunoglobulin light chain amyloidosis (AL), transthyretin amyloidosis (ATTR) and apolipoprotein deposition amyloidosis.[2] From a cardiological standpoint, ATTR and AL are of specific importance, as they are

frequently associated with the development of cardiomyopathies such as transthyretin amyloid cardiomyopathy (ATTR-CM) and AL cardiomyopathy (AL-CM) and are responsible for approximately 95% of cardiac amyloidosis cases,[3 4] often affecting prognosis. ATTR can be further subdivided into a more common wild-type ATTR (wtATTR) and a less frequent hereditary-type ATTR (hATTR). Recent evidence suggests that wtATTR is highly prevalent in patients aged over 60 years, with heart failure and preserved ejection fraction.[5] Some studies suggest that wtATTR might be the underlying cause in up to 13% of these patients, with many still being underdiagnosed.[6] Cardiomyopathies due to hATTR and AL also occur but are less common than wtATTR. However, in patients with AL, cardiac involvement is the most important determinant of prognosis.

Diagnosis of cardiac amyloidosis

Since the introduction of targeted therapies, awareness of amyloidosis has increased significantly, yet the most important step in the diagnosis of cardiac amyloidosis still remains for it to be suspected in the first place. Therefore, current guidelines of the European Society of Cardiology (ESC) and the American Heart Association/American College of Cardiology for heart failure recommend primarily focusing on 'red-flags' based on history, physical examination, ECG, laboratory tests and imaging, especially with the use of echocardiography and cardiovascular magnetic resonance (CMR).[7 8] Transthoracic echocardiography (TTE) can detect high-risk features of cardiac amyloidosis such as left ventricular hypertrophy, reduced stroke volume index, reduced global longitudinal strain with apical sparing, a sparkling myocardium and reduced diastolic function.[9] However, all these findings are unspecific and can occur in other disease entities as well.[10] A definitive diagnosis is established by scintigraphy and/or biopsy with the concomitant exclusion of AL by serum and urine laboratory testing. CMR plays an essential role in scenarios where nuclear scintigraphy is inconclusive independent of haematological test results, as the array of parameters provided, such as T1 and T2 mapping, extracellular volume (ECV) and late gadolinium enhancement (LGE), can help in the diagnosis of cardiac amyloidosis. Other guidelines recommend that CMR be used upstream in the diagnostic cascade on the same level as TTE.[8] In the recent ESC guidelines covering cardio-oncology from 2022, CMR is recommended as a mandatory test for the basic assessment of cardiac amyloidosis,[11] with the ESC guidelines on cardiomyopathies from 2023 providing a class IB recommendation for the initial assessment and a class IIaC recommendation for serial follow-ups by CMR for cardiomyopathies, including amyloidosis.[12]

Treatment of cardiac amyloidosis

Treatment of ATTR-CM has changed with the introduction of therapies aiming at different targets. In general, therapy can be divided into subgroups of drugs targeting the suppression of transthyretin synthesis, transthyretin stabilisers and molecules enhancing the degradation and absorption of the fibrils.[13] Tafamidis, a transthyretin binding site stabiliser, has not only changed therapy overall but also the prognosis for patients with ATTR-CM. Studies investigating tafamidis have shown a significant reduction in all-cause mortality as well as cardiovascular-related hospitalisations.[14 15] It is especially important to consider that patients with mild to moderate symptoms and an accompanying functional New York Heart Association (NYHA) class of I–II benefit most from the treatment, emphasising the importance of an early and precise diagnosis. Additionally, two other forms of genetic silencer therapies by the names of patisiran and vutrisiran, both messenger ribonucleic acid (mRNA)-interfering molecules and inotersen, an antisense oligonucleotide, might potentially play a role in the therapy of ATTR-CM in the future.[7 16] Recently, a novel recombinant human anti-ATTR antibody has been developed with the aim of providing the removal of ATTR depositions in the myocardium.[17] CMR analysis of patients included in this Phase 1 trial showed a reduction in ECV, potentially signifying a positive recovery effect on the myocardium.[17]

Follow-up during treatment for cardiac amyloidosis

Except for the ESC cardiomyopathy guidelines from 2023, no definitive recommendations regarding the follow-up of patients with ATTR-CM undergoing targeted treatment are available. In general practice, a combination of functional assessments, for example, NYHA class, exercise testing and most often TTE imaging are applied.[18 19] Initial studies reported that certain CMR parameters, like ECV, native T1 and left ventricular mass, or even strain, might be potential markers to monitor the effect of tafamidis on the heart.[20–23] T2 mapping may also emerge as a possible predictor of prognosis; however, data in ATTR-CM is lacking.[24 25] A change in any of these parameters might help to detect non-responders to therapy.[26] In contrast to the lack of evidence regarding the optimal follow-up of patients, the prognosis of patients was previously thoroughly investigated using imaging parameters. This mainly included imaging parameters derived from TTE, like global longitudinal strain, mitral and tricuspid annular plane systolic excursion, and from CMR ECV, native T1, and pattern of LGE, all of which carry a negative prognosis.[26] However, no imaging parameters have been incorporated into a score for the assessment of prognosis and treatment response.[27] Due to the future availability of different therapeutic approaches, an objective assessment of the treatment response will be essential for determining a change or extension of treatment.

MATERIALS AND ANALYSIS

Study aims

This prospective, observational study of patients with ATTR-CM undergoing treatment with tafamidis aims to identify a set of relevant quantitative image markers and

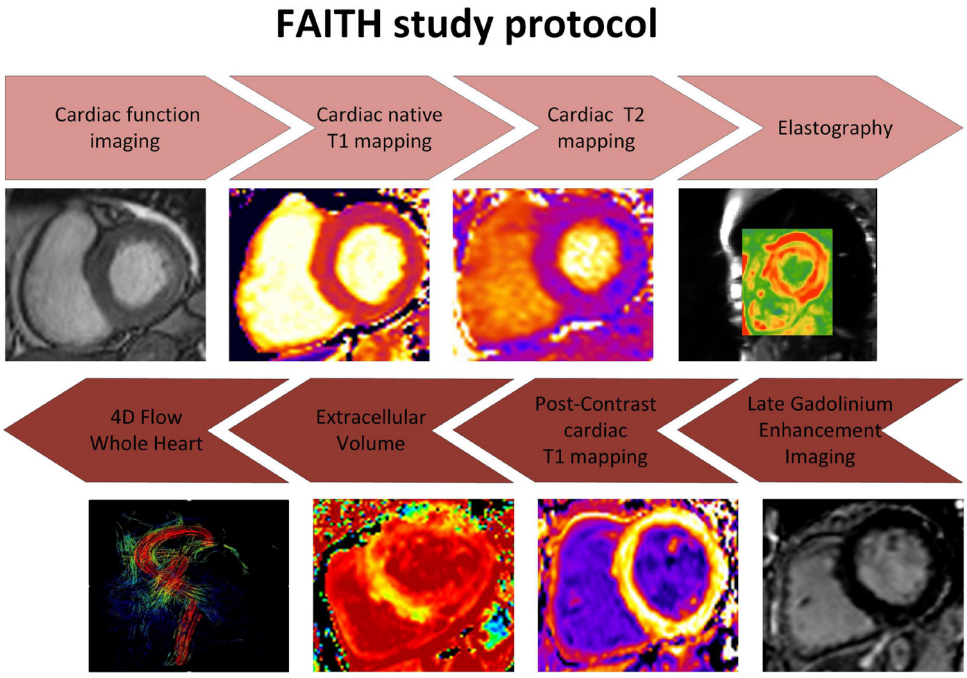

Figure 1 CMR study protocol for the FAITH study. CMR, cardiovascular magnetic resonance; FAITH, follow-up of patients with transthyretin amyloid cardiomyopathy by multi-modality imaging study; 4D, four dimensional.

compare imaging modalities for prognostication. The main focus of the proposed study is to generate data to assess the ability to integrate deep phenotyping of the myocardium by CMR into an overall clinical algorithm. The planned sample size of 60 patients is regarded as sufficient to explore the value of imaging markers and to identify further areas of potential research. It also allows for the generation of initial data as a basis for adequately powered studies. The addition of CMR to the routine follow-up assessment of patients with ATTR-CM undergoing targeted therapy with tafamidis aims to assess the importance of quantitative imaging parameters, which will facilitate and aid in the early detection of a clinical response to the targeted therapy in the light of established clinical and imaging parameters. In addition, the utilisation of CMR will help to precisely assess the involvement of the right ventricle (RV) and the atria in patients with ATTR-CM and potential effects of the treatment with tafamidis.

Standard of care in the setting of the Amyloidosis Center Charité Berlin

The prospective recruitment of treatment-naïve patients with ATTR-CM will be managed through the Amyloidosis Center Charité Berlin (ACCB), a clinical unit formed from the three clinical campus sites of the Charité: Charité Campus Mitte, Campus Virchow Clinic and Campus Benjamin Franklin. The working group for CMR at the Charité Campus Berlin Buch will manage the CMR imaging part.

In addition to being a multicampus unit, the ACCB also runs interdisciplinary board meetings where each patient is individually discussed in-depth regarding further work-up and therapy. The disciplines taking part in the ACCB include the departments of neurology, cardiology, haematology, nephrology, gastroenterology and rheumatology, as well as nuclear medicine and radiology. An interdisciplinary conference is held weekly to evaluate the diagnostic findings, use them to make a diagnosis and then determine the treatment with targeted therapies. On average, six to eight patients are discussed weekly in this way. Patients will undergo routine assessments, including multidisciplinary visits, laboratory panel assessment, ECG, TTE, 3,3-diphosphono-1,2-propanodicarboxylic acid (DPD)-nuclear scintigraphy and potentially biopsy if other tests are inconclusive.

DPD scintigraphy is assessed visually based on the Perugini grades and semiquantitatively based on the heart-to-contralateral ratio, where a threshold of ≥1.6 at 3 hours postinjection is considered diagnostic for ATTR-CM.

For endomyocardial biopsy, at least five samples are taken from the left ventricle and sent for analysis in a core laboratory. Samples are fixed in 4% formaldehyde and embedded in paraffin. Staining methods applied are Masson, Trichrome, H&E, Giemsa and Congo red. Amyloidosis is diagnosed if there are clear Congo red-positive areas in the interstitium or the vessel walls. For the subtyping of amyloidosis by immunohistochemistry, six different antibodies are used. If immunohistochemistry does not provide a definite subtype, mass spectrometry is applied.

Genetic testing for transthyretin mutations will be performed using Next-Generation Sequencing (Centogene GmbH, Rostock, Germany).[28]

CMR protocol for the FAITH study

The FAITH study will be nested in the Berlin Research Network for CMR (BER-CMR).[29] A multisite CMR

Table 1 Inclusion and exclusion criteria

Inclusion criteria	Exclusion criteria
1. Diagnosed ATTR-CM according to current standards (TTE, DPD-scintigraphy and/or biopsy). 2. Age >18 years. 3. Eligible to receive treatment with tafamidis. 4. Informed consent. 5. Agrees to receive a note about incidental findings. 6. Valid health insurance.	1. Non-ATTR-CM. 2. Severe cardiovascular comorbidities including: a. Myocardial infarction within the last 6 months. b. After coronary stenting within the last 6 month. c. After coronary artery bypass graft (CABG). d. Permanent atrial fibrillation. 3. Absolute contraindications for CMR. 4. Allergy against gadolinium-containing contrast agent. 5. Chronic kidney insufficiency with a GFR<30 mL/min. 6. Pregnancy/breastfeeding. 7. No consent to study.

ATTR-CM, transthyretin amyloid cardiomyopathy; CABG, coronary artery bypass graft; CMR, cardiovascular magnetic resonance; DPD, 3,3-diphosphono-1,2-propanodicarboxylic acid; GFR, glomerular filtration rate; TTE, transthoracic echocardiography.

network spanning across all sites of the Charité, including three 3 Tesla scanners, all from the same vendor (Siemens Healthineers, Erlangen, Germany). A cohort of travelling volunteers has provided reference ranges and demonstrated equivalences for T1 and T2 mapping analysis across all sites.[29] The setup and protocol of the FAITH study will be built on the existing infrastructure, making it the second multisite study running in the BER-CMR. The planned CMR study protocol can be found in figure 1. Cine imaging for the assessment of cardiac function will be carried out using balanced steady-state free-precession sequences in four long-axis (4-chamber, 2-chamber, 3-chamber and RV-view) as well as a short-axis (SAX) stack covering the entire left ventricle and RV without a gap. Parametric mapping will be acquired in 3 SAX slices (basal, midventricular and apical) and a 4-chamber view. T1 mapping will be based on a motion-corrected modified Look-Locker inversion recovery sequence in a 5-3-3 scheme and T2 mapping, based on a motion-corrected fast low-angle shot sequence. After administration of gadobutrol at the clinically approved dose, LGE imaging in three long-axis (4-chamber, 2-chamber and 3-chamber views), as well as SAX stack, will be acquired. The SAX LGE stack will be without gaps. Postcontrast, T1 mapping will be carried out in the same location and sequence as the precontrast T1 mapping in order to postprocess the images for ECV assessment (using the routinely acquired haematocrit). The protocol is finished with a 4D flow whole-heart acquisition to assess blood flow over time.[30] This technique will allow us to not only quantify flow volume and peak velocities but also to grade flow by the assessment of vortices and helices, as well as wall shear stress in the aorta.[31]

The FAITH study will integrate elastography sequences for the detection of viscoelastic properties of the liver and the heart.[32] Elastography will be performed using both magnetic resonance elastography (MRE) and ultrasound-based time-harmonic elastography (THE) on the same day. For MRE, we will use the Copenhagen protocol, in which three consecutive mechanical vibration frequencies of 80, 90 and 100 Hz will be acquired by spin-echo echo planar imaging (EPI)-MRE during three separate breath-holds.[33] Four image slices will be acquired in a short-axis view of the heart with a field view of 218×206 mm^2 and a voxel size of 1.5×1.5×8 mm^3. THE will be applied in a similar frequency range of 60–70 Hz in a clinical ultrasound scanner equipped with a 2 MHz phased array transducer (GAMPT, Merseburg, Germany).[34] After phase-based line-by-line motion estimation and Fourier decomposition, the diastolic wave images are converted into frequency-compounded stiffness maps using the kMDEV inversion method, which is also used for MRE data processing.[35]

To ensure consistent quality assurance across the participating sites in the BER-CMR, regular phantom measurements are carried out to provide reproducible and precise quantitative values.[36]

CMR image readings will be carried out in a core laboratory blinded to the patient information, baseline result and follow-up scan. All reads will be carried out according to standard operating procedures adhering to current recommendations of the society.[37 38] A dedicated software (CVI42) will be used for all reads. Any incidental findings on CMR will be disclosed in the final report. In the case of significant incidental findings, the participant will receive detailed information and assistance for further work-up. In case of indications for cardiological or interventional therapy, continuous long-term support and treatment will be offered. Additionally, participants can agree for the report to be sent to their dedicated primary care physician. It should be noted that no change in the targeted therapy on analysis of CMR results will take place.

Patient selection

The prospective recruitment of treatment-naïve patients with ATTR-CM will be managed through the ACCB. Inclusion and exclusion criteria are summarised in table 1. Of note, it should be that only permanent atrial fibrillation is an exclusion criterion, as other forms of atrial fibrillation

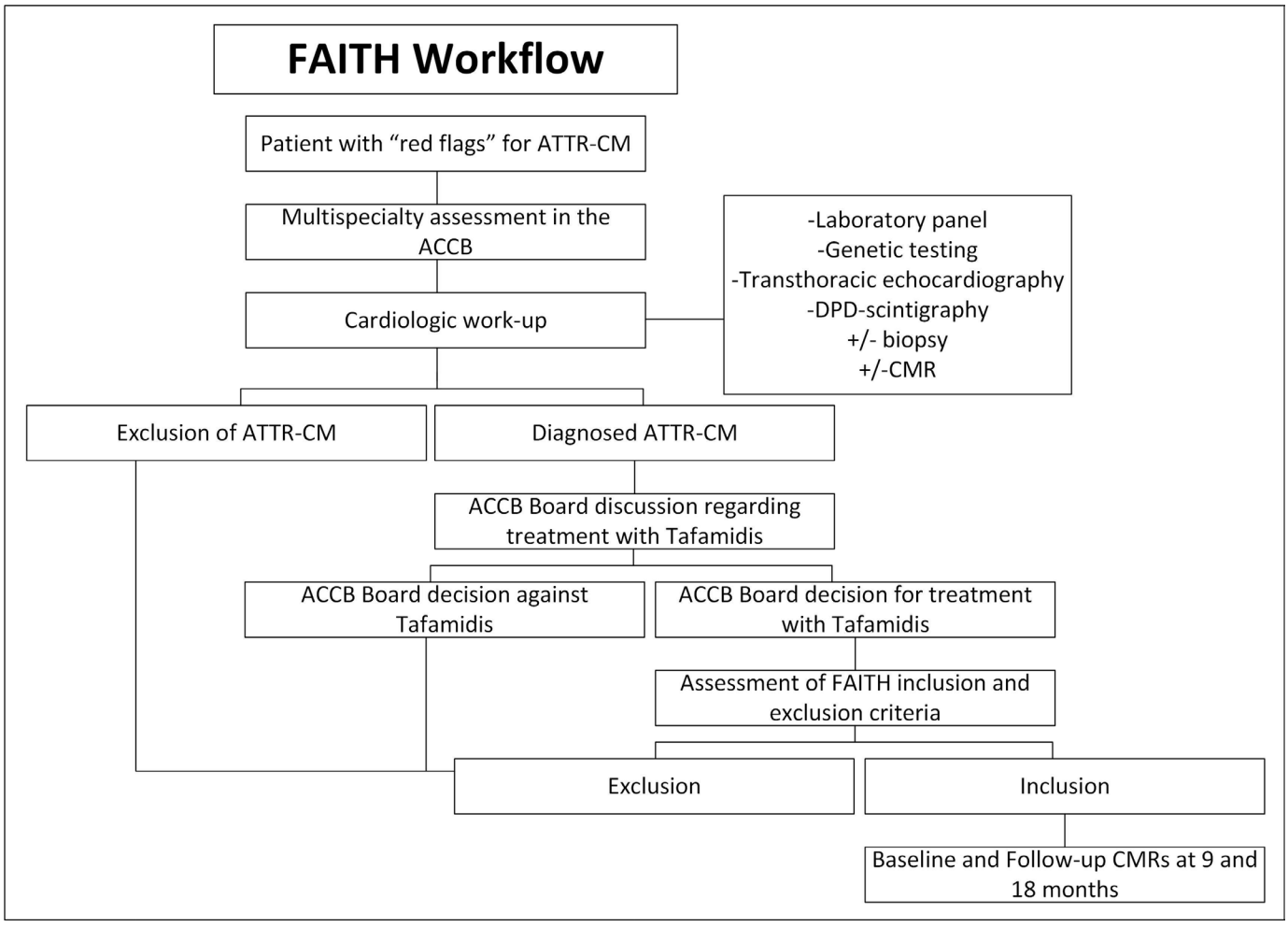

Figure 2 Workflow of the FAITH study. ACCB, Amyloidosis Center Charité Berlin; ATTR-CM, transthyretin amyloidosis cardiomyopathy; CMR, cardiovascular magnetic resonance; DPD, 3,3-diphosphono-1,2-propanodicarboxylic acid; FAITH, follow-up of patients with transthyretin amyloid cardiomyopathy by multi-modality imaging study.

might be directed to rhythm therapy before the CMR examination, increasing image quality.

Workflow

Patients with a suspicion of ATTR-CM will be evaluated in the ACCB. After the board decides to begin treatment, patients will receive a baseline CMR scan. Afterwards, patients will begin treatment with tafamidis. In addition to routine follow-up visits, patients will receive a follow-up CMR scan at 9 months and 18 months after inclusion. These time points were chosen as the survival curves of the cohorts of the Tafamidis in Transthyretin Cardiomyopathy Clinical Trial (ATTR-ACT) split in this timeframe.[14] Current routine follow-up includes assessment of symptoms, physical examination, laboratory analysis and TTE. TTE will be carried out based on a local research protocol on a Vivid E95 (GE Healthcare), which includes an assessment of biventricular and biatrial function and strain, as well as an analysis of the valvular apparatus. Patients who develop absolute contraindications to CMR or exhibit exclusion criteria to the study will be discounted from further CMR assessment; however, they will remain within the ACCB registry.

Data management and ethics

All collected data will be dealt with according to good clinical practice guidelines according to the clinical trials office rules of the Charité. Data will only be transmitted in a pseudonymised form with restricted access to the database. Ethical approval has been granted by the local ethical committee (EA1/262/23).

Time frame and clinical endpoints

This study aims to include 60 patients with ATTR-CM to prospectively undergo baseline and follow-up CMR scans at time points of 9 and 18 months. CMR baseline scans will be scheduled as quickly as possible after diagnosis to not delay the initiation of therapy. Primary analyses are expected 3 months after the final follow-up scan with an interim analysis after 6 months of recruitment to assess for planned versus achieved inclusion. A workflow is provided in figure 2. Given the demonstrated efficacy and prognostic impact of tafamidis, no comparative group without targeted therapy will be available for analysis due to ethical concerns.

Based on a recent ESC consensus document, which introduced consensus criteria defining progression

Table 2 Parameters for the multiparametric score to predict treatment response

Parameter	Unit	Comment
Clinical parameters		
Age	Years	
Gender	Males/females	
Body mass index	kg/m^2	
NYHA class	I–IV	
KCCQ	0–100	
6-minute walking test	Distance in metres	
Modified NIS+7	Points	
12-lead ECG		Standard ECG interpretation and arrhythmias
Laboratory parameters		
GFR based on CKD-EPI	mL/min/1.73 m^2	
NT-pro-BNP	ng/L	
High-sensitivity troponin	ng/L	
Neurofilament light chain	pg/mL	
Imaging parameters—TTE		
Interventricular septal thickness	mm	
Global longitudinal strain	(%)	
Imaging parameters— DPD-scintigraphy		
Perugini grade	0–3	
Imaging parameters—CMR		
Left ventricular ejection fraction	%	Based on the SAX
Left ventricular end-diastolic volume	mL and mL/body are (m^2)	Based on the SAX
Left ventricular mass	g and g/body are (m^2)	Based on the SAX
Right ventricular ejection fraction	%	Based on the SAX
Right ventricular end-diastolic volume	mL and mL/body are (m^2)	Based on the SAX
Native T1 time	ms	Global/septal
T2 times	ms	Global septal
ECV	%	Global/septal

CKD-EPI, Chronic Kidney Disease - Epidemiology Collaboration; CMR, cardiovascular magnetic resonance; ECV, extracellular volume; GFR, glomerular filtration rate ; KCCQ, Kansas City Cardiomyopathy Questionnaire; NIS, neuropathy impairment score; NT-pro-BNP, N-terminal prohormone of brain natriuretic peptide; NYHA, New York Heart Association; SAX, short axis; TTE, transthoracic echocardiography.

based on three domains, we will adopt these to define responders as patients with a change in less than three domains and non-responders as those with a change in all three domains.[39] Non-response to tafamidis will be the primary endpoint, with secondary endpoints including all-cause death and cardiovascular death, new onset, progression or hospitalisation due to heart failure and new onset of arrhythmias (including supraventricular and ventricular episodes) or stroke.

Statistical analysis

This exploratory observational study aims to collect initial data on potential parameters to develop a multiparametric score to predict treatment response. The score will be developed using regression methodology with backward selection in a training set of 50 patients. Fivefold cross-validation will be used to validate the outcome using 40 patients from the training set to select the parameters and 10 patients to assess the performance. With the final model, the validation set of the remaining 10 patients will be used to get a first glance at the performance of the score in an independent set of patients. The parameters assessed are grouped into clinical, laboratory and imaging parameters.

Table 2 provides a summary of these parameters. Analysis of covariance will be used to identify relevant parameters to develop a total score. F-tests will be used to select the relevant parameters by backward selection. Depending on the feasibility, elastography parameters will be incorporated into the score. The following subgroups were prospectively planned for analysis with the primary

objective: stage of cardiac amyloidosis,[27] hATTR versus wtATTR, age ≥80 years and <80 years, glomerular filtration rate ≥60 mL/m^2 and <60 mL/m^2 and ECV<30% and ≥30%.[40] In the case of dropouts or missing data, a new proband will be recruited until the final inclusion number of 60 is reached.

Patient and public involvement

None.

DISCUSSION

With the advances in targeted therapies, ATTR has not only become treatable but also the prognosis and survival have been greatly enhanced. Currently, different therapies are available targeting the misfolded protein in the tissues, such as stabilisers (eg, tafamidis), silencers or degraders.[41] With more drugs becoming available, patient selection and detection of non-responders are of crucial importance. To properly guide therapy and provide adequate patient selection, a multimodality approach is needed. The current standard of care relies on surrogate parameters such as subjective clinical scales (eg, NYHA assessment) or laboratory assessment[42] in order to detect non-responders.

A recent statement from an expert panel recommended follow-up CMR scans if new or worsening symptoms are present.[43] A standardised approach regarding multimodality imaging is lacking. Therefore, in the expert consensus by Garcia-Pavia *et al*, the authors called for future studies, including a multiparametric assessment to detect progression in ATTR-CM.[39] The FAITH study aims to tackle this lack of prospective, longitudinal multiparametric follow-up using non-invasive diagnostic methods without radiation.

Retrospective analysis of follow-up CMR in patients receiving tafamidis showed stable ECV values over a time from 9 to 12 months after baseline scans.[20 21 42] In contrast, case reports analysing different gene variants provided data that tafamidis might potentially reverse amyloid burden.[44] Therefore, the question remains whether different types of mutations might react more intensively to a specific therapy. As the ACCB database provides routine genetic testing panels, the FAITH study will shed light regarding this subpoint, trying to provide evidence for a personalised approach.

Ethics and dissemination

The FAITH study has been approved by the responsible local Ethics Committee of the Charité University Medicine (EA1/262/23, decision of February 26, 2024). For any changes to the study protocol, we will seek approval by the ethics committee before implementation. The study is conducted in accordance with the Declaration of Helsinki in its current version, Good Epidemiological Practice and the applicable German laws. Where applicable, guidelines of the International Conference on Harmonisation of Good Clinical Practice are adhered to.

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Contributors JG developed the study design and grant application, applied for ethical approval and drafted the manuscript with input from GB, JZ, EB, KH, IS, ERD, PvD, BH, JS-M, CS and SS. GB applied for ethical approval and was involved in manuscript writing. EB assisted with the design of the study and was involved in manuscript writing. KH assisted with the design of the study and was involved in manuscript writing. JZ, IS, ERD, PvD and BH assisted with the study design and manuscript writing. JS-M helped design the study, supervised manuscript writing and provided continuous guidance. SS developed the study design, supported the grant application, applied with JG for ethical approval and supervised manuscript writing. All authors read and approved the final manuscript. SS is the guarantor of the study.

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Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, conduct, reporting or dissemination plans of this research.

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