Diagnostic value of cardiac magnetic resonance imaging vs coronary angiography as primary diagnostic strategy in heart failure with reduced ejection fraction – the randomized CMR first/CATH first study

CMR-first vs Cath-first in HFrEF

(MRT-HF DIAGNOSTIK STUDIE)

National Coordinator

Prof. Dr. S. Störk

Deutsches Zentrum für Herzinsuffizienz
Universität Würzburg
Am Schwarzenberg 15
97078 Würzburg

Biometry

Prof. Dr. Dr. G. Gelbrich

Institut für Klinische Epidemiologie und Biometrie
Universität Würzburg
Josef-Schneider-Str. 2 / D7
97080 Würzburg

Site Coordinator Würzburg

Prof. Dr. G. Güder

Medizinische Klinik und Poliklinik I
Universität Würzburg
Oberdürrbacherstr. 6
97080 Würzburg

Date of Version: 14.01.2021

TABLE OF CONTENTS

1 GENERAL INFORMATION

1.1 Study Team

Financial Sponsor	German Society of Cardiology (Deutsche Gesellschaft für Kardiologie e.V.)
National Coordinator	Prof. Dr. S. Störk, Deutsches Zentrum für Herzinsuffizienz, Am Schwarzenberg 15, 97078 Würzburg Tel.: 0931-201 46266 Email: Stoerk_S@ukw.de
Site Coordinator Würzburg	Prof. Dr. G. Güder, Medizinische Klinik und Poliklinik I, Universität Würzburg, Oberdürrbacherstr. 6, 97080 Würzburg Tel.: 0931-201 39989 Fax.: 0931-201 36075 Email: Gueder_G@ukw.de Prof. Dr. W. Bauer, Medizinische Klinik und Poliklinik der Universität Würzburg, Oberdürrbacherstr. 6, 97080 Würzburg Tel.: 0931-201 39901 Email: Bauer_W@ukw.de
Data management	http://www.zksw.ukw.de/ together with Clinical Research Unit of the Comprehensive Heart Failure Center, Würzburg
Biometry	Study protocol and supervision: Prof. Dr. Dr. G. Gelbrich, Institut für Klinische Epidemiologie und Biometrie, Josef-Schneider-Str. 2 / D7, 97080 Würzburg Tel.: 0931-201 47312 E-Mail: Gelbrich_G@ukw.de Study conduct: Dr. U. Malzahn, Zentrale für Klinische Studien, Josef-Schneider-Str. 2 / D7, 97080 Würzburg Tel.: 0931-201 47306 E-Mail: Malzahn_U@ukw.de
MRI Core Lab	Prof. Dr. Dr. Wolfgang Bauer
Scientific endpoint committee	To be announced
Participating study centers	**Prof. Dr. med Gerd Hasenfuß** Universitätsklinikum Göttingen Klinik für Kardiologie und Pneumologie

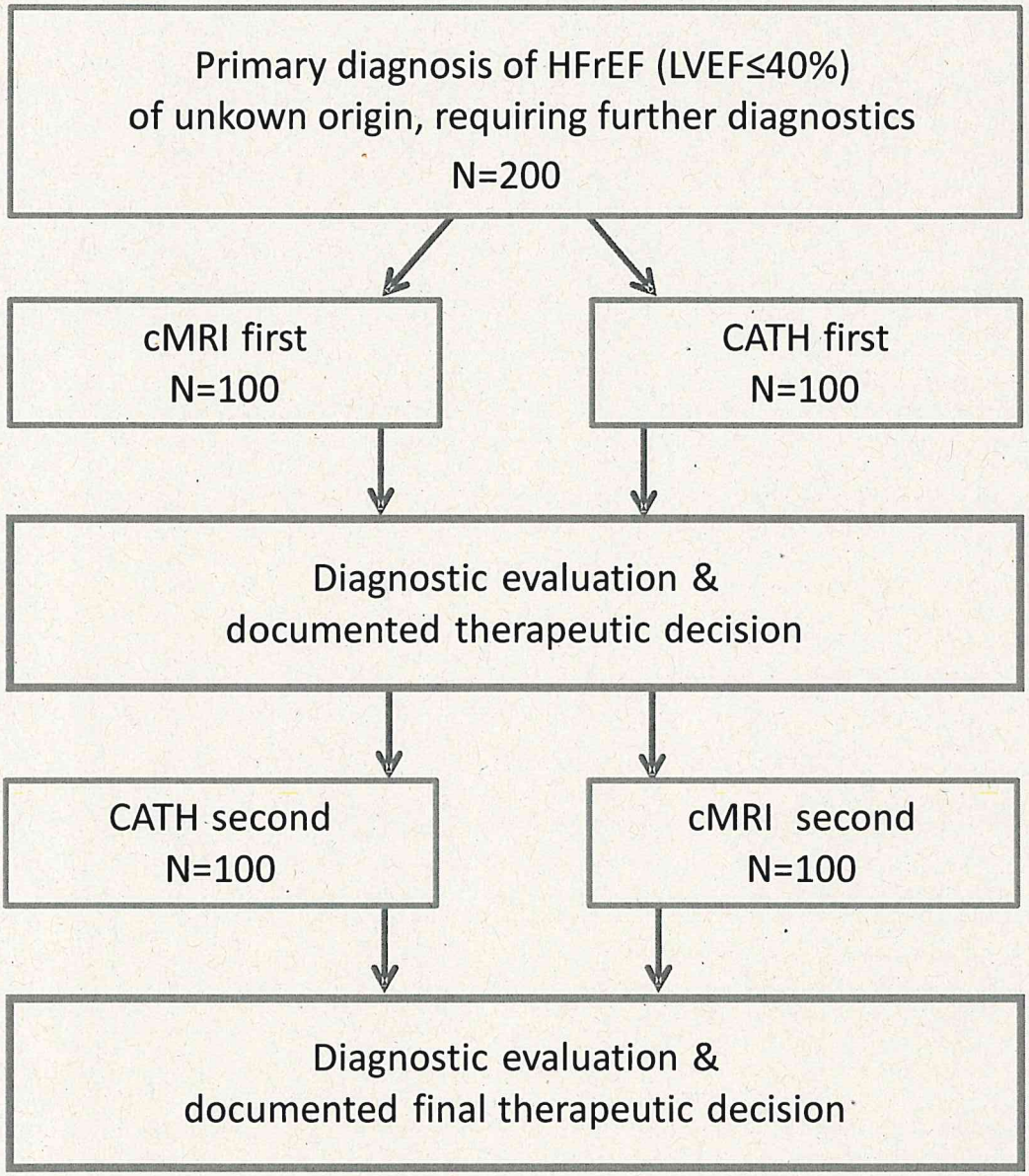
	Robert-Koch-Str. 40 37075 Göttingen Email: rfaber@med.uni-goettingen.de **Prof. Dr. med. Matthias Pauschinger** Universitätsklinik der Paracelsus Medizinischen Privatuniversität Breslauer Straße 201 90471 Nürnberg E-mail: Matthias.Pauschinger@klinikum-nuernberg.de

1.2 Synopsis

Title of the study	Diagnostic value of cardiac magnetic resonance imaging vs coronary angiography as primary diagnostic strategy in de novo heart failure with a reduced ejection fraction – The randomized CMR vs CATH study
Short title	CMR vs CATH first in HFrEF
Indication	Newly diagnosed HFrEF without previous history for coronary artery disease
Objectives	To examine which diagnostic sequence is superior in regard of minimizing the number of diagnostic procedures needed.
Primary endpoint	In brief: "First diagnostic modality is sufficient to definitively establish an ischemic cause of heart failure: yes or no". The primary objective is to compare the two diagnostic strategies CATH-first vs CMR-first. Thus, the primary null hypothesis is: Obtaining sufficient diagnostic information already from the first diagnostic procedure to satisfactorily establish or exclude ischemic origin of heart failure: "yes or no", rendering the second diagnostic procedure redundant
Secondary endpoints	Secondary endpoints: 1. The major secondary objective is to estimate the number of catheter procedures that could be avoided when applying the diagnostic CMR-first strategy. Further secondary endpoints are to examine, 2. how often the second diagnostic modality adds clinical relevant diagnostic information to the first. 3. which diagnostic items are not satisfactorily provided by either diagnostic procedure. 4. whether therapeutic concepts will be changed by the second diagnostic procedure. 4. whether costs will be lower in CMR-first vs. CATH-first. 5. whether the safety profile will be more favorable in CMR first vs. CATH first.
Study design	Prospective randomized, controlled, 2-armed, parallel group study CMR-CATH vs CATH-CMR
Eligibility – inclusion	• Age ≥ 18 years • Physical and mental ability to give informed consent

	• Written informed consent for study participation • Indication for coronary angiography and signed copies of patient information forms for coronary angiography and CMR • Heart failure with reduced ejection fraction and a left ventricular ejection fraction ≤40% in echocardiography (or comparable imaging modality) within the preceding three months after best possible cardiac recompensation. • Cause of heart failure not yet determined • Indication by treating physician for cardiac catheterization after best possible cardiac recompensation.
Eligibility – exclusion	• Pregnancy • End-stage renal disease (glomerular filtration rate < 30 ml/min/m² MDRD and/or dialysis-dependency) • Acute coronary syndrome • History of coronary artery disease or myocardial infarction • Acute heart failure (NYHA IV) • Chronic Heart failure stage NYHA IV • Valvular stenosis (any) ≥ grade II • Standard exclusion criteria for cardiac MRI (e.g., incompatible metal implants or devices, known, claustrophobia, allergy against gadolinium-based contrast-agents, bodily dimension incompatible with scanner)
Number of patients	200 patients
Intervention	CMR-CATH vs CATH-CMR
Planned interim analyses	N=60, 100, and 140
Type I and II error rates	Type I error rate (significance level): 0.05 (2-sided) Power: at least 0.84 if the primary endpoint is "yes" in 61% vs. 39% of the patients undergoing the two diagnostic sequences
Time schedule	24 months

1.3 Study Flow Chart



2 RATIONALE AND OBJECTIVE

2.1 Background

Heart failure is one of the most common causes of dyspnea and describes the inability of the heart to sufficiently pump blood through the cardiovascular system.[1, 2] It is a clinical syndrome that originates from different cardiovascular disease entities as coronary artery disease, hypertension, diabetes, valvular heart disease and a vast amount of other diseases subsumed under the category of dilated cardiomyopathy.[1, 3]

In Germany heart failure is a major health cost burden and the most common disease necessitating hospitalization.[4-6] More than 2 million patients in Germany may currently suffer on heart failure and approximatively 3.2 billion Euros have been spent on this clinical syndrome in 2009 (http://www.gbe-bund.de). Despite of relevant improvements in therapy and prognosis in the last two decades, mortality is still high and the prevalence of heart failure and subsequently public health care spending is increasing.[7, 8] Thus strategies that may improve diagnostic work-up and aim for cost-reduction are urgently needed.

According to the European Society of Cardiology guidelines the diagnostic evaluation of heart failure origin is essential as further therapy primarily depends on the type (heart failure with reduced or preserved ejection fraction, HFrEF or HFpEF) and origin of heart failure (valvular, rhythm-associated, ischemic, non-ischemic).[1, 3] Transthoracic echocardiography is recommended in all patients suspected of having heart failure to further evaluate cardiac structure and function.[1] However, the information derived from echocardiography is limited, and cardiac catheterization and MRI may add substantial or even essential diagnostic information including a variety of etiologies. Thus, further evaluation may be required for comprehensive diagnostics and specific therapy. Besides the standard medical and device treatment, a revascularization strategy may be offered to patients with HFrEF of ischemic origin. Additional recommendation for further diagnostic workup is however inconclusive in the guidelines.[3, 9]

Coronary angiography in patients with a primary diagnosis of HFrEF is recommended in patients with angina pectoris symptoms or pathological stress-testing.[1] As exertional dyspnea is an angina pectoris equivalent[9] and the leading syndrome in heart failure[1], coronary angiography may be justified in most patients with newly diagnosed HFrEF.

Approximatively 60% of all cases of HFrEF can be attributed to coronary artery disease.[1, 2] In the majority of these cases HFrEF progresses from long-standing coronary artery disease (CAD) or after myocardial infarction, thus the ischemic etiology of HFrEF in these patients can be easily anticipated and coronary angiography may be clearly indicated to exclude progression of the established disease. The prevalence of an ischemic origin in patients with

new-onset HFrEF without a history of CAD may be however much lower (10-40%).[10-12] Up to 70% of patients diagnosed with new-onset HFrEF and without typical angina admitted for coronary angiography had for instance no evidence of CAD.[13]

2.2 Coronary angiography ("CATH")

Coronary angiography (CATH) is the Gold standard to diagnose CAD with and without left ventricular dysfunction.[14] It is a diagnostic procedure that uses contrast agents and x-rays to visualize coronary arteries and thus coronary arteriosclerotic obstruction. For this purpose, a catheter is passed through the radial or femoral artery into place, contrast agent is injected through the catheter and coronary arteries are visualized with fluoroscopy.[15, 16] Thus, diagnostic coronary angiography is an invasive technique with potentially life-threatening risks and complications at any step of the procedure. Besides an increased bleeding risk, contrast agent reactions, acute renal failure due to contrast exposition, rhythm disturbances, vascular and cardiac injury, myocardial infarction, thromboembolism, air embolism and death are of concern.[17]

Any alternative method that excludes CAD non-invasively with high accuracy may thus spare affected individuals potential harm and suffering.

2.3 Cardiac magnetic resonance imaging ("CMR")

Cardiac magnetic resonance imaging (CMR), by contrast, is non-invasive with a very low risk burden that produces resting and moving pictures of the heart and vessels using magnetic waves.[18] The patient is lying in a tube and receives a special contrast dye (gadolinium) with a low side-effects profile. CMR has a high accuracy to predict the ischemic origin of HFrEF, and hence, the existence of coronary artery disease. It enables the accurate measurement of cardiac chamber volumes and of left and right ventricular function.[19] It enables characterization of myocardial tissue and assessment of myocardial fibrosis using late gadolinium enhancement (LGE) and thus helps understanding the etiology of LV dysfunction. The new European guidelines of heart failure, emphasize its' discriminative power to differentiate ischaemic from non-ischaemic HF, and highlights its' ability to further specify the origin of non-ischaemic heart failure for myocarditis, amyloidosis, sarcoidosis, Chagas disease, Fabry disease non-compaction cardiomyopathy and haemochromatosis with high accuracy.[3, 20]

2.4 CATH or CMR as first diagnostic modality?

CMR has been suggested to replace coronary angiography as further diagnostic tool in

patients with HFrEF already a decade ago.[19] Although multiple observational studies followed that confirmed the high accuracy of excluding an ischemic origin in HFrEF by CMR and thus proved good reliability, the reluctance to skip coronary angiography is still high under clinicians, as false-negative test results may deprive the patient from a potential life-saving revascularization strategy.[13, 14] However once CAD is excluded in coronary angiography, the origin of HFrEF may still be unclear and CMR helpful for further evaluation of heart failure origin and prognosis in this situation. Additionally CMR is able to identify scar and thus viability in HFrEF patients with an ischemic etiology and thus may help to improve or adapt interventional and operative strategies when performed beforehand.[21]

2.5 The quandary of CMR in HFrEF

Although European and American guidelines for heart failure appreciate the vast amount of diagnostic advantages of CMR over coronary angiography in patients with left ventricular dysfunction, there is no official recommendation to perform CMR as first diagnostic strategy once HFrEF is established.[3, 22] To date no study evaluated the utility of performing cMRT before coronary angiography in patients with new-onset HFrEF in a randomized controlled trial, thus formally the level of evidence is rather low and originates from observational studies only.

The current study compares the diagnostic value of performing CMR before coronary angiography and vice versa in a randomized controlled trial. The aim of the current study is to examine the superior diagnostic sequence in regard of minimizing the number of diagnostic procedures needed. The trial has the potential to implement a so far non-existing diagnostic work-flow in patients with new-onset HFrEF.

2.6 Primary objectives and study hypothesis

The primary objective is to compare the two diagnostic strategies CATH-first and CMR-first. The primary null hypothesis is: "Obtaining sufficient diagnostic information already from the first diagnostic procedure to satisfactorily establish or exclude an ischemic causeof heart failure therapy: "yes" or "no".

2.7 Secondary objectives:

1. The major secondary objective is to estimate the number of catheter procedures that could be avoided when applying the diagnostic CMR-first strategy.

Further secondary goals are:

2. To examine how often the second procedure adds useful diagnostic information.

3. To examine which diagnostic items are not satisfactorily provided by the diagnostic procedures.

4. To examine whether therapeutic concepts will be changed by the second diagnostic procedure

6. To examine whether costs will be lower in CMR-first vs. CATH-first.

7. To examine whether the safety profile will be more favorable in CMR first vs. CATH first.

3 STUDY DESCRIPTION

3.1 Study design and number of patients

Multi-centric, two-armed, randomized, controlled, unblinded, parallel-group study with N=200 patients. Patients are randomized either to the "CMR-first" or the "CATH-first" arm. Both diagnostic procedures (CMR and coronary angiography) are performed in each patient consecutively and results are presented to a joint panel committee after each diagnostic modality. The panel will elaborate the need of the other diagnostic modality and decide, whether diagnosis would be conclusive with the first procedure.

3.2 Participating centers and number of patients

The trial is a multicenter study with the University Hospital Wuerzburg (N=134) as main study center and the following centers that have agreed to participate: the University Hospital Goettingen (N=33) and the University Hospital Nuremberg (N=33) as participating centers. Each study site should host a high-volume CMR lab with >100 CMR scans per year and a high-volume CATH lab with >500 coronary angiographies per year.

3.3 Adjudication and Endpoint Panels

Dedicated panels will be composed that will judge on image quality and the conclusions that can be drawn from images based on otherwise provided patient information. Specific panel charters (incl. information on image blinding etc.) will be agreed prior to the start of the evaluation process.

3.4 Expected study duration

The expected study duration is 24 months.

4 STUDYPOPULATION

4.1 Inclusion criteria

Patients must meet all of the following criteria:

- Age ≥ 18 years
- Physical and mental ability to give informed consent
- Written informed consent for study participation
- Indication for coronary angiography and signed copies of patient information forms for coronary angiography and CMR
- Heart failure with reduced ejection fraction and a left ventricular ejection fraction ≤40% in echocardiography (or comparable imaging modality) within the preceding three months
- Cause of heart failure not yet determined
- Hospital admission for coronary angiography for further evaluation of heart failure origin or in case of primary in-hospital diagnosis of HFrEF, clinical indication for coronary angiography after best possible cardiac recompensation.

4.2 Exclusion criteria

None of the following criteria should apply to the patient

- Pregnancy
- End-stage renal disease (glomerular filtration rate < 30 ml/min/m² (MDRD) and/or dialysis-dependency)
- Acute coronary syndrome
- History of coronary artery disease or myocardial infarction
- Acutely decompensated heart failure or heart failure stage NYHA IV
- Valvular stenosis (any) ≥grade II
- Standard exclusion criteria for cardiac MRI (e.g., incompatible metallic implants or devices, known, claustrophobia, allergy against gadolinium-based contrast-agents, bodily dimensions incompatible with scanner)

5 INDIVIDUAL TRIAL PROCEDURES

5.1 Screening

All patients with newly diagnosed HFrEF admitted for diagnostic coronary angiography are screened for the inclusion and exclusion criteria by the study physician. Eligible patients are offered to participate into the study. Patients admitted for dyspnea to the emergency department, who are diagnosed with new-onset HFrEF and a LVEF of ≤ 40% during hospitalization are also eligible for the study after cardiac recompensation.

5.2 Patient Information and Informed Consent

Written *Informed Consent* will be sought by a standard statement written in a patient-friendly, non-technical language. The content of the Informed Consent is explained to the participant by the study physician. The participant will read the statement and reconsider the decision before signing and dating the document. No patient will be able to enter the study before the written Informed Consent has been obtained. The signed Informed Consent form will be copied and one version will be given to the participant and one will be filed at the trial site. The patient will be informed explicitly on the purpose and extent of the assessment and the use of his/her personal data and that choosing not to participate or to withdraw the consent will not affect the further medical treatment.

5.3 Withdrawal of informed consent

Patients will be informed that they may withdraw their consent to participate at any time of the trial without giving any reason for it. The patient will be asked for the reason of the premature termination but is not obliged to respond. Date of enrolment, date of withdrawal and reason for withdrawal will be documented. The patient´s data will by anonymized after withdrawal. If the patient is unable to undergo one of the study procedures and aborts the investigation, data collected up to the termination of the study may be evaluated, whenever sufficient for the respective analyses. Additional patients will be recruited for patients not available for the primary analysis.

5.3.1 Retrospective observation of non-eligibility

If it is noticed after inclusion that a patient does not match the eligibility criteria, then

- the patient is excluded from the study if non-eligibility results from a legal reason.

- the patient is excluded from the study after confirmation by the steering committee if the patient does not belong to the target population.
- the patient's participation is stopped if non-eligibility results from a safety issue; if the patient has already provided sufficient data, these data will be included into analysis.
- the patient's data will be included into analysis if non-eligibility resulted from purely technical criteria, but the patient underwent the study procedures per protocol.

Regardless of their use in analyses, data of both in- and excluded patients will be stored for a period of 15 years, unless legal requirements imply deletion.

5.4 Enrolment and Randomization

Once eligibility of the study participants is confirmed, a patient-ID will be assigned to the participant and the patient will be randomized to one of the two study arms on the basis of severity of left ventricular dysfunction (left ventricular ejection fraction ≤25% vs >25% of qualifying echocardiography). This randomization will become effective only if a written informed consent has been obtained after a study doctor has informed the patient about the conduct of the study.

5.5 Study Procedures

During the study visit, the following procedures will be performed and information captured by the study team (nurse or study physician):

- Vital signs (blood pressure, heart rate, body weight and length)
- Medication
- 12-lead ECG
- Laboratory parameters (including renal function, natriuretic peptides)
- Echocardiography
- Quality of life
- Angina pectoris symptoms
- Cardiovascular risk factors and comorbidities

5.6 Description of the Intervention

This RCT will be two-armed: "CMR first" vs "CATH first". **In all patients both diagnostic procedures will be performed.** The operational sequence will however be different.

CMR first arm:

Patients in the "CMR first" arm will have a CMR before CATH. The results of the CMR will be provided to a joint panel committee who will decide whether coronary angiography is useful for further diagnostic or therapeutic work-up (in case of evidence for CAD) or not (no signs for CAD or extensive scar formation). The MRI results will also be provided to the consulting cardiologist of the patient at the study site, who will be asked the same questions as the expert panel after CMR but has full eligibility to clinical information.

CATH first arm

Patients in the "coronary angiography first" arm will have a coronary angiography before CMR. The results of the coronary angiography will be provided to a joint panel committee who will decide whether further CMR is useful (in case of exclusion of CAD or for viability assessment in patients with multi-vessels disease). The consulting cardiologist of the patient at study site will be asked the same questions as the expert panel after CATH but has full eligibility to clinical data.

5.6.1.1 Definitions

Definition of coronary artery disease

Diagnosis of coronary artery disease is established if the patient has coronary artery obstruction of >= 50% in the left main coronary artery or ≥70% in one or several first order arteries.[9]

Definition of ischemic cardiomyopathy

Diagnosis of ischemic cardiomyopathy is established if the extent of coronary artery disease explains the left ventricular dysfunction sufficiently.

5.6.1.2 Protocol for CMR

A manual will be provided prior to study start specifying technical/methodological requirements. In brief, CMR will be performed on dedicated cardiovascular 1,5 or 3 Tesla scanners using a 32 channel coil and Multitransmit technology. The MRI protocol will be include the following steps:

1. Survey (clinical routine)

2. Pre-scans for planning (clinical routine)
3. Imaging acquisition for morphology and function (short axis stack, 4 long axes images (4Ch, 2Ch, 3Ch), cine loops with Balanced Turbo Field Echo (bTFE, clinical routine)
4. Application of extracellular MR contrast agent (e.g. Gadobutrol). Details see recommendations of the Societey of Cardiovascular Magnetic Resonance Imaging (SCMR, Schulz-Menger et al, 2013)[23] (meanwhile clinical routine)
5. Look Locker inversion recovery Sequence and Late enhancement for detection of scars, focal fibrosis and microvascular obstruction, T1 TFE sequence (clinical routine)
6. Image analyis: This is also done according to the recommendations of the Society of Cardiovascular Magnetic Resonanz imaging (SCMR).[23] Evaluated are: left ventricular volumes, ejection fraction and scars in the left ventricular myocardium. The latter are differentiated into scars which are typical as residuals of an ischemic event (endocardial localization) and the rest. As the trial aims to resemble the real world scenario, no further assignment of the scars to myocardial segments is claimed. Also the statement whether the extend or morphology of the scar is related to "heart failure" is not demanded on the base of quantitative parameters, however it is open to the MR-investigators discretion.

5.6.1.3 Protocol for coronary angiography and cardiac catheterization

A manual will be provided prior to study start specifying technical/methodological requirements. In brief, coronary angiography will be performed by an experienced cardiologist according to standard procedures. Whenever possible, ventriculography will be performed additionally. The results of CMR will not be available to the clinician, but can be made available at the special request of the interventional cardiologist after coronary angiography for viability assessment.

6 BIOMETRICAL ASPECTS

6.1 Randomization

Randomization will be performed centrally and electronically, 1:1 for either CMR first or CATH first. Stratification will be done by LVEF (≤25% / >25% of qualifying echocardiography).

6.2 Endpoints

The primary objective is to compare the two diagnostic strategies CATH first vs CMR first. Thus, the primary null hypothesis is: Obtaining sufficient diagnostic information already from the first diagnostic procedure to satisfactorily establish or exclude ischemic origin of heart failure: "yes or no", rendering the second diagnostic procedure redundant.

Secondary endpoints:

1. The major secondary objective is to estimate the number of catheter procedures that could be avoided when applying the diagnostic CMR-first strategy.

Further secondary endpoints are to examine,

2. how often the second diagnostic modality adds clinical relevant diagnostic information to the first.
3. which diagnostic items are not satisfactorily provided by either diagnostic procedure
4. whether therapeutic concepts will be changed by the second diagnostic procedure.
4. whether costs will be lower in CMR-first vs. CATH-first.
5. whether the safety profile will be more favorable in CMR first vs. CATH first.

6.3 Methods of statistical analysis

The primary null hypothesis states equal rates of "yes" in the primary endpoint in CMR-first and CATH-first. The primary hypothesis test will be carried out by Fisher's exact test for two frequencies.

The major secondary goal, estimation of the number of catheter procedures that can be avoided by applying the CMR-first scheme, will be answered by an exact 95% confidence interval for the "yes" rate in the primary endpoint in the CMR-first arm.

Descriptive analyses will be carried out for the diagnostic items responsible for "no" in the primary endpoint, of information added by the second diagnostic procedure, and adverse

events.

Exploratory analyses of clinical correlates and the diagnostic success of the procedures will be carried out. If considered useful, multiple regression analyses may be added, again, at an exploratory level.

Cost analysis will use fixed rates for diagnostic and other procedures but will incorporate actual frequencies of procedures and treatment of procedure-related adverse events. Costs will be calculated for the scenario that the second diagnostic procedure would not have been performed if the first provided sufficient diagnostic information.

6.4 Prespecified interim analyses

Interim analyses for the primary endpoint will be carried out according to the following scheme, using type I error levels according to O'Brien-Fleming:

Analysis	n	Type I error level
Interim 1	60	0.000085
Interim 2	100	0.003
Interim 3	140	0.012
Final	200	0.035

In case of significance at the interim level, the steering committee may decide to stop randomization and continue recruitment only for the CMR-first scheme until 100 patients in this arm are reached.

6.5 Sample size considerations

Global type I error level is set at 0.05 (2-sided). The power should be 0.80 or more in reasonable scenarios for the "yes" rates in the primary endpoint in the two diagnostic schemes. The following table displays the power reached in different scenarios after each of the scheduled analyses, using the type I error levels listed in the preceding section:

Rates "yes"	**Cumulative probability of significant result after each analysis**			
(1° endpoint)	Interim 1	Interim 2	Interim 3	Final
80% vs. 20%	0.74	>0.99		
75% vs. 25%	0.45	0.97	>0.99	
70% vs. 30%	0.19	0.83	0.99	>0.99
65% vs. 35%	0.05	0.48	0.84	0.98
62% vs. 38%	0.02	0.25	0.61	0.90
61% vs. 39%	0.01	0.20	0.52	0.84
60% vs. 40%	<0.01	0.15	0.42	0.76

We conclude that a maximum total sample size of 200 patients evaluable for the primary endpoint is a reasonable choice. In addition, to provide a 95% confidence estimate for the "yes" rate in the CMR group with a precision of ±10% or better, 100 patients are needed in this arm.

7 ETHICAL, LEGAL AND ADMINISTRATIVE ASPECTS

All trial participants consider conducting the study in accordance with the Declaration of Helsinki and its amendments, local laws and, as far as applicable to this non-drug study, the ICH guideline for Good Clinical Practice (GCP) issued in July 2002 and CPMP/ICH/135/95 from September 1997.[24, 25]

Submission to the Ethics Committee

The study may be started only after approval of the protocol by the central Ethics Committee at the University of Würzburg. At each trial site, additional approval of the responsible local Ethics Committee is required before initiation of the site.

Changes to the study protocol should be made in written amendments. Ethical approval for an amendment before the changes become effective is required if the amendment implies a revision of the anticipated risk for the trial subjects of a revision of the informed consent.

8 DATA HANDLING AND RECORD KEEPING

Source data

The following materials are considered to be source data in the sense of the ICH-GCP guideline:

- the electronic recordings of CMR and catheter procedures
- the patient files at the trials sites for clinical and history data entered into these files
- the CRF for other information not recorded in the patient files
- the forms for reporting endpoint information filled out by the endpoint adjudication committee

Case report forms (CRF)

The CRF will be provided by the Clinical Trial Center Würzburg in electronic form. Investigators will connect to the SecuTrial user interface via internet and enter data directly into the database.

In case the internet connection fails or the database is out of service, a paper version is available of CRF pages that require immediate data capture. Data may be provisionally captured there. They should be entered into the database as soon as possible.

Data Management

The set-up of the database and the data handling process (including data entry, data checks, query management and recall for owing documentation) will follow the respective Standard Operating Procedures (SOPs) of the Clinical Trial Center Würzburg. Handling guidelines with information on the procedures that apply to this trial will be provided to the trial sites.

The data flow concerning the Endpoint Adjudication Committee will be described in the charter for endpoint adjudication.

Note that rapid delivery of documentation and adjudication by the endpoint committee is required when the sample size for an interim analysis is expected to be reached. The Clinical Trial Center Würzburg will, therefore, establish a reminder procedure to speed up the collection of the information needed for interim analyses.

Archival Storage

All data entered into the SecuTrial database are considered to represent primary research data in the sense of the Charter on Good Scientific Practice by the Deutsche Forschungsgemeinschaft (DFG). The coordinating investigator will establish a procedure to retain this information for at 15 years after the publication of the study results. In case secondary analyses from the data will be published, the storage period will be prolonged accordingly.

9 DATA PROTECTION

Within this study personal data of the trial subjects (name, data of birth, address) and data regarding the diagnostic work-up and the course of disease (medical results, medication) will be collected: The trial subject will be informed that all data will be stored electronically and handled strictly confidential. Subjects will be identified throughout documentation and evaluation by the individual patient key (pseudonym) that is used within the study only. Subject names and all other identifying information and the link between it and the pseudonym (patient identification list) will be kept secret by the site investigator.

All study data and information will be handled confidential and will be only used by the persons involved in the trial conduct. Study material or information collected in this trial will not be available to third parties, except for regulatory authorities.

Data will be processed in the Clinical Trial Center Würzburg, according to the written safety concept of this institution. Access to the data will be strictly limited to authorized persons. Loss of data is excluded due to extensive back-up procedures. All legal requirements concerning data protection and confidentiality will be respected. All authorized persons are sworn to secrecy.

In the case of withdrawal of consent the stored data relevant for analysis will be kept in anonymous form unless deletion is implied by legal requirements.

Declaration to data protection

During data entry, handling and analysis, all requirements of the data protection act will be take into account. Access to the data is strictly limited to authorized persons. Data are protected against unauthorized access.

10 ADMINISTRATIVE AGREEMENTS

Funding and Insurance

The sources of funding of this study are the following:

Study specific grant by the

Deutsche Gesellschaft für Kardiologie – Herz- und Kreislaufforschung e.V.

German Cardiac Society, Grafenberger Allee 100, 40237 Düsseldorf

Tel.: + 49 211 600692-0, Fax: + 49 211 600692-10, info@dgk.org

11 PUBLICATION POLICY

The results of the study will be submitted for publication within one year after finishing the study in national and international peer-reviewed journals. The principle investigators of each study site will judge about the authorships. All authors must approve the manuscript before submission.

12 REFERENCES

1. McMurray JJ, Adamopoulos S, Anker SD, Auricchio A, Bohm M, Dickstein K, Falk V, Filippatos G, Fonseca C, Gomez-Sanchez MA, Jaarsma T, Kober L, Lip GY, Maggioni AP, Parkhomenko A, Pieske BM, Popescu BA, Ronnevik PK, Rutten FH, Schwitter J, Seferovic P, Stepinska J, Trindade PT, Voors AA, Zannad F, Zeiher A. Esc guidelines for the diagnosis and treatment of acute and chronic heart failure 2012: The task force for the diagnosis and treatment of acute and chronic heart failure 2012 of the european society of cardiology. Developed in collaboration with the heart failure association (hfa) of the esc. *Eur Heart J*. 2012;33:1787-1847
2. Mosterd A, Hoes AW. Clinical epidemiology of heart failure. *Heart*. 2007;93:1137-1146
3. Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JG, Coats AJ, Falk V, Gonzalez-Juanatey JR, Harjola VP, Jankowska EA, Jessup M, Linde C, Nihoyannopoulos P, Parissis JT, Pieske B, Riley JP, Rosano GM, Ruilope LM, Ruschitzka F, Rutten FH, van der Meer P. 2016 esc guidelines for the diagnosis and treatment of acute and chronic heart failure: The task force for the diagnosis and treatment of acute and chronic heart failure of the european society of cardiology (esc)developed with the special contribution of the heart failure association (hfa) of the esc. *Eur Heart J*. 2016
4. Zugck C, Muller A, Helms TM, Wildau HJ, Becks T, Hacker J, Haag S, Goldhagen K, Schwab JO. [health economic impact of heart failure: An analysis of the nationwide german database]. *Dtsch Med Wochenschr*. 2010;135:633-638
5. Vogt V, Koller D, Sundmacher L. Continuity of care in the ambulatory sector and hospital admissions among patients with heart failure in germany. *European journal of public health*. 2016
6. Neumann T, Biermann J, Erbel R, Neumann A, Wasem J, Ertl G, Dietz R. Heart failure: The commonest reason for hospital admission in germany: Medical and economic perspectives. *Dtsch Arztebl Int*. 2009;106:269-275
7. Ohlmeier C, Mikolajczyk R, Frick J, Prutz F, Haverkamp W, Garbe E. Incidence, prevalence and 1-year all-cause mortality of heart failure in germany: A study based on electronic healthcare data of more than six million persons. *Clinical research in cardiology : official journal of the German Cardiac Society*. 2015;104:688-696
8. Schmidt S, Hendricks V, Griebenow R, Riedel R. Demographic change and its impact on the health-care budget for heart failure inpatients in germany during 1995-2025. *Herz*. 2013;38:862-867
9. Montalescot G, Sechtem U, Achenbach S, Andreotti F, Arden C, Budaj A, Bugiardini R, Crea F, Cuisset T, Di Mario C, Ferreira JR, Gersh BJ, Gitt AK, Hulot JS, Marx N, Opie LH, Pfisterer M, Prescott E, Ruschitzka F, Sabate M, Senior R, Taggart DP, van der Wall EE, Vrints CJ, Zamorano JL, Baumgartner H, Bax JJ, Bueno H, Dean V, Deaton C, Erol C, Fagard R, Ferrari R, Hasdai D, Hoes AW, Kirchhof P, Knuuti J, Kolh P, Lancellotti P, Linhart A, Nihoyannopoulos P, Piepoli MF, Ponikowski P, Sirnes PA, Tamargo JL, Tendera M, Torbicki A, Wijns W, Windecker S, Valgimigli M, Claeys MJ, Donner-Banzhoff N, Frank H, Funck-Brentano C, Gaemperli O, Gonzalez-Juanatey JR, Hamilos M, Husted S, James SK, Kervinen K, Kristensen SD, Maggioni AP, Pries AR, Romeo F, Ryden L, Simoons ML, Steg PG, Timmis A, Yildirir A. 2013 esc guidelines on the management of stable coronary artery disease: The task force on the management of stable coronary artery disease of the european society of cardiology. *Eur Heart J*. 2013;34:2949-3003
10. Melo RM, Melo EF, Biselli B, Souza GE, Bocchi EA. Clinical usefulness of coronary angiography in patients with left ventricular dysfunction. *Arquivos brasileiros de cardiologia*. 2012;98:437-441
11. Soriano CJ, Ridocci F, Estornell J, Jimenez J, Martinez V, De Velasco JA. Noninvasive diagnosis of coronary artery disease in patients with heart failure and systolic dysfunction of uncertain etiology, using late gadolinium-enhanced cardiovascular magnetic resonance. *Journal of the American College of Cardiology*. 2005;45:743-748
12. Won E, Donnino R, Srichai MB, Sedlis SP, Feit F, Rolnitzky L, Miller LH, Iqbal SN, Axel L, Nguyen B, Slater J, Shah B. Diagnostic accuracy of cardiac magnetic resonance imaging in the

evaluation of newly diagnosed heart failure with reduced left ventricular ejection fraction. *The American journal of cardiology*. 2015;116:1082-1087

13. Silva F, Borges T, Ribeiro A, Mesquita R, Laszczynska O, Magalhaes D, Silva JC, Azevedo A, Bettencourt P. Heart failure with reduced ejection fraction: Should we submit patients without angina to coronary angiography? *International journal of cardiology*. 2015;190:131-132

14. Lim MJ, White CJ. Coronary angiography is the gold standard for patients with significant left ventricular dysfunction. *Progress in cardiovascular diseases*. 2013;55:504-508

15. Judkins MP. Selective coronary arteriography. I. A percutaneous transfemoral technic. *Radiology*. 1967;89:815-824

16. Lotan C, Hasin Y, Mosseri M, Rozenman Y, Admon D, Nassar H, Gotsman MS. Transradial approach for coronary angiography and angioplasty. *The American journal of cardiology*. 1995;76:164-167

17. Tavakol M, Ashraf S, Brener SJ. Risks and complications of coronary angiography: A comprehensive review. *Global journal of health science*. 2012;4:65-93

18. Rangamani S, Varghese J, Li L, Harvey L, Hammel JM, Fletcher SE, Duncan KF, Danford DA, Kutty S. Safety of cardiac magnetic resonance and contrast angiography for neonates and small infants: A 10-year single-institution experience. *Pediatric radiology*. 2012;42:1339-1346

19. McCrohon JA, Moon JC, Prasad SK, McKenna WJ, Lorenz CH, Coats AJ, Pennell DJ. Differentiation of heart failure related to dilated cardiomyopathy and coronary artery disease using gadolinium-enhanced cardiovascular magnetic resonance. *Circulation*. 2003;108:54-59

20. Pennell DJ, Sechtem UP, Higgins CB, Manning WJ, Pohost GM, Rademakers FE, van Rossum AC, Shaw LJ, Yucel EK. Clinical indications for cardiovascular magnetic resonance (cmr): Consensus panel report. *Eur Heart J*. 2004;25:1940-1965

21. Morton G, Schuster A, Perera D, Nagel E. Cardiac magnetic resonance imaging to guide complex revascularization in stable coronary artery disease. *Eur Heart J*. 2010;31:2209-2215

22. Yancy CW, Jessup M, Bozkurt B, Butler J, Casey DE, Jr., Drazner MH, Fonarow GC, Geraci SA, Horwich T, Januzzi JL, Johnson MR, Kasper EK, Levy WC, Masoudi FA, McBride PE, McMurray JJ, Mitchell JE, Peterson PN, Riegel B, Sam F, Stevenson LW, Tang WH, Tsai EJ, Wilkoff BL. 2013 accf/aha guideline for the management of heart failure: A report of the american college of cardiology foundation/american heart association task force on practice guidelines. *Circulation*. 2013;128:e240-327

23. Schulz-Menger J, Bluemke DA, Bremerich J, Flamm SD, Fogel MA, Friedrich MG, Kim RJ, von Knobelsdorff-Brenkenhoff F, Kramer CM, Pennell DJ, Plein S, Nagel E. Standardized image interpretation and post processing in cardiovascular magnetic resonance: Society for cardiovascular magnetic resonance (scmr) board of trustees task force on standardized post processing. *Journal of cardiovascular magnetic resonance : official journal of the Society for Cardiovascular Magnetic Resonance*. 2013;15:35

24. Recommendations guiding physicians in biomedical research involving human subjects. World medical association declaration of helsinki. *Le Journal medical libanais. The Lebanese medical journal*. 1994;42:88-89

25. Baber N. International conference on harmonisation of technical requirements for registration of pharmaceuticals for human use (ich). *British journal of clinical pharmacology*. 1994;37:401-404