ESC HEART FAILURE
ESC Heart Failure 2017; **4**: 209–215
Published online 14 March 2017 in Wiley Online Library (wileyonlinelibrary.com) **DOI:** 10.1002/ehf2.12145

STUDY DESIGN

TranslatiOnal Registry for CardiomyopatHies (TORCH) – rationale and first results

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Abstract

Aims Non-ischemic cardiomyopathies (CMPs) comprise heart muscle disorders of different causes with high variability in disease phenotypes and clinical progression. The lack of national structures for the efficient recruitment, clinical and molecular classification, and follow-up of patients with non-ischemic CMPs limit the thorough analysis of disease mechanisms and the evaluation of novel diagnostic and therapeutic strategies. This paper describes a national, prospective, multicenter registry for patients with non-ischemic CMPs. The main objective of this registry is to create a central hub for clinical outcome studies, a joint resource for diagnostic and therapeutic trials, a common biomaterial bank, and a resource for detailed molecular analyses utilizing patients' biomaterials.

Methods and results A comprehensive characterization of the register population and patients' subgroups is planned. First analyses will include descriptive methods evaluating the distribution of outcome variables and possible risk factors followed by test statistics in a cross-sectional design. The aim of the current study is to recruit 2300 patients all over Germany. Eligible participants are patients with primary non-ischemic cardiomyopathies, including hereditary and inflammatory dilated CMP (DCM), left-ventricular noncompaction CMP (LVNC), hypertrophic CMP (HCM), arrhythmogenic right-ventricular CMP (ARVC), myocarditis, and amyloidosis. Of already recruited patients 70% are male and 30% female. With 56% of patients included, DCM is most common.

Conclusion/Outcome The primary outcome is all-cause death. Key secondary endpoints are cardiovascular death, adequate ICD shock, survived sudden cardiac death, syncope, documented potentially life-threatening arrhythmia, cardiac transplantation, hospitalization due to worsening of heart failure (HF), and any non-elective cardiovascular hospitalization.

Keywords Cardiomyopathy; Heart failure; Registry; Non-ischemic

Received: 17 November 2016; Revised: 2 January 2017; Accepted: 10 February 2017
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Introduction

Cardiomyopathies (CMPs) are primary heart muscle disorders that account for about 40% of all heart failure (HF) cases and represent the leading cause for heart transplantation in patients below 55 years of age.[1] Although both, gene mutations and chronic inflammatory processes are well accepted disease mechanisms, their relative contribution to specific disease phenotypes and progression of HF are essentially unknown. The clinical care of patients with CMP is challenging since the disease causes and mechanisms in an individual patient are often unknown and even in patients with identified causes the clinical phenotype and disease progression is highly variable. Furthermore, there is little knowledge from large trials on the diagnostic performance of clinical and molecular tools and even less on appropriate and personalized treatment strategies. Considering the poor outcome and the limited knowledge of disease modifiers, there was an unmet need for an integrated research alliance that can refer to a comprehensive

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national registry on patients with CMP, which are carefully phenotyped by clinical variables, state-of-the-art imaging modalities and molecular, genetic and epigenetic investigations.

For HF, there are national registries providing large numbers of patients with advanced phenotypes.[2–4] However, these registries do not focus on primary heart muscle disorders. Thus, the number of suitable patients for CMP research is low and phenotyping in these registries does often not meet the distinct requirements needed. Especially for non-ischemic CMPs, already some studies do exist, however, they focus on specific topics, e.g. the benefit of an ICD implantation,[5,6] statin therapy,[7] or beta blocker therapy.[8] Nevertheless, none of these studies puts special attention on the genetic background or the complex underlying mechanisms of non-ischemic CMP. Moreover, up to now, the lack of national structures for the efficient recruitment, clinical and molecular classification, and follow-up of patients with CMP inhibited the thorough analysis of disease mechanisms and the evaluation of novel diagnostic and therapeutic strategies.

Evidence

The clinical care of patients with CMP including their diagnostic work-up, risk stratification, and treatment is challenging due to marked individual variability in clinical phenotypes and progression. Furthermore, despite the application of drug- and device-related treatment modalities, which are mostly derived from randomized HF trials, a reasonable number of patients with CMP shows progression to end-stage HF or sudden cardiac death. Only a small proportion of familial and sporadic CMPs can be genetically diagnosed by conventional human genetics approaches[9] and even if identified, the clinical impact of a distinct mutation or genetic variant is uncertain even within families carrying the same mutation.[10,11] For inflammatory CMPs, studies indicate the contribution of genetic variants and host–environment interactions. However, the meaning for individual patients is not well defined. This indicates the limited knowledge on possible causative genes, the role of genetic risk variants, epigenetic, inflammatory and autoimmune mechanisms, gene–environment, and gender-related interactions with disease phenotype and outcome.

The need of the project

Up to now, the lack of national structures for the efficient recruitment, clinical and molecular classification, and follow-up of patients with CMP prevented not only the initiation of comprehensive molecular investigations of disease mechanisms in CMP but also the conduction of larger, multicenter studies to investigate diagnostic and therapeutic strategies to improve patient care and outcome. The TranslatiOnal Registry of CardiomyopatHies (TORCH) is the first national, multicenter registry recruiting 2300 patients with non-ischemic CMP according to uniform standard operating procedures (SOPs) developed in cooperation with the German Center for Cardiovascular Research (DZHK). Medical data and biomaterial of TORCH patients will, for the first time, allow us to draw conclusions on a larger scale regarding medical reasons of non-ischemic CMPs and to develop therapeutic strategies for CMP patients. The key objective of TORCH is, apart from data and biomaterial collection, to serve as a central hub for further clinical outcome studies, to build up a joint resource for diagnostic and therapeutic trials, to create a common biomaterial bank of well phenotyped patients as a resource for detailed molecular analyses on patients' biomaterials, and to develop patient-specific model systems.

Based on the expertise of the TORCH nucleus, together with experts from the DZHK, a structured biomedical informatics solution and protocols for secure data exchange were implemented. This includes the harmonization of diagnostic criteria and methodologies used for phenotyping and the application of rules for quality control and protection of personal data. Under these premises all recruited patients will be accessible for sub-studies of distinct phenotypes, for gender- and outcome-related research. All recruiting centers will have access to data and biomaterials and will be able to conduct research program-specific investigations according to standardized DZHK use and access rules. Besides the gain of knowledge on pathomechanisms of inherited and acquired CMPs, this research facilitates the initiation of large further treatment trials due to the harmonized national diagnostic standards (e.g. immune-pathology, molecular biomarkers, genetic screening).

Study design

TORCH is a prospective, national multicenter registry. The main study centre is composed of two partners: the scientific and clinical steering center in Heidelberg and the data and quality center in Greifswald. Thus, Heidelberg is responsible for clinical and scientific aspects and Greifswald is responsible for the data quality management and data monitoring. All patients fulfilling the inclusion criteria and none of the exclusion criteria are eligible for enrolment. At the baseline visit patients are asked to give informed consent. Consecutively biomaterial and clinical data are collected. The clinical data comprise a comprehensive anamnesis including all current and past diagnoses, a thorough cardiomyopathy anamnesis, medication, laboratory values, electrocardiogram, echocardiography and/or MRI, exercise testing, and a chest X-ray. Furthermore, the patient is asked to fill out the Minnesota

Living With Heart Failure questionnaire (MLHFQ, University of Minnesota, USA) to get a reference of the patient's subjective well-being. A follow-up visit is scheduled after 12 months.

Population and setting

TORCH comprises a comprehensive data collection of patients with non-ischemic cardiomyopathies. Currently, there are 36 medical faculties in Germany, of which 19 university medical centres are recruiting for TORCH (including all DZHK centres). These 19 centres are distributed all over Germany (see *Figure 1*). First patient recruitment started in December 2014 and patient inclusion is aimed to be completed at the end of February 2017.

Inclusion criteria

Eligible participants are patients with non-ischemic CMPs including hereditary and inflammatory dilated cardiomyopathy (DCM), left-ventricular non-compaction cardiomyopathy (LVNC), hypertrophic cardiomyopathy (HCM), arrhythmogenic right-ventricular cardiomyopathy (ARVC), myocarditis, and amyloidosis. Participants have to be able to read and write

Figure 1 Currently, 19 centers are actively recruiting TORCH patients all over Germany (red circles).

German language, and to give written informed consent (*Figure 2*).

Exclusion criteria

Exclusion criteria are other pre-existing cardiac diseases such as significant valvular, ischemic, or pericardial disease, uncontrolled arterial hypertension, primary pulmonary arterial hypertension, chronic advanced disorders, treatment history with cardio-toxic agents and chest radiation, as well as drug and alcohol abuse. Patients must be between 18 and 80 years of age and should not have a life expectancy less than 1 year.

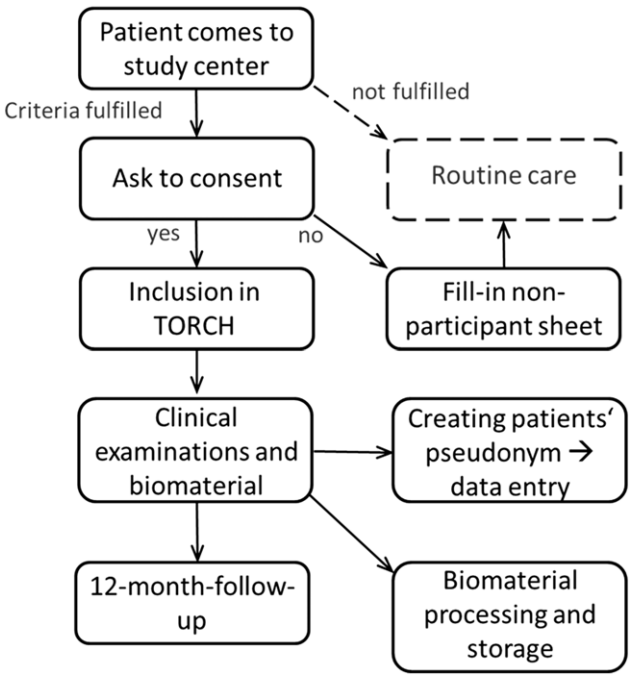
Participant and recruitment procedures

Patients are identified by daily screening in the clinical routine. Potentially eligible patients are asked to participate in the study by a responsible staff member. After written informed consent is given, blood and urine samples are collected and processed and medical data are obtained.

Pre-packed sets for the collection of the biomaterial including a set of sample tubes, rack, standardized 2D-barcode labels, and a biomaterial data sheet were packed by the institute for clinical chemistry and laboratory medicine (IKCL) in Greifswald for each patient.

Blood samples and urine, except for the PAXgene samples and one EDTA-plasma sample, are centrifuged, aliquoted and frozen at −80 °C. All participants' identifying data (IDAT) and their biomaterials are allocated a unique identifying pseudonym after uploading their informed consent to the DZHK independent trusted third party via an encrypted connection. After that procedure biomaterials are stored at the local DZHK centers under these pseudonyms and all medical data are stored in a web-based eCRF system provided by another institution, the data holding center in Göttingen. This system provides high data security and accounts for all relevant issues and regulations of data protection. Non-DZHK centers send their samples for storage to the Cardiobiobank in Heidelberg. More detailed information regarding data holding and management is given in Schwaneberg *et al*. (unpublished data).

Figure 2 Recruiting scheme of TORCH.



Measurements and outcomes

Phenotyping of participants comprises medical history, co-morbidities, family history (including pedigree and family history of cardiac diseases), medication, clinical examination (as age, sex, body weight, height, heart rate, blood pressure, ankle edemas, ascites, pulmonary rales and 3rd heart sound), a 12-lead electrocardiogram, an exercise test (6 minute walk test and/or ergospirometry), chest X-ray, blood sampling (including sodium, potassium, creatinine, HbA1c, hemoglobin, red blood cells, NTproBNP etc.), transthoracic echocardiography, MRI (optional), cardiac catheterization, histopathology (optional) and MLHFQ (*Table 1* baseline). Follow-up is scheduled after one year (± 4 weeks) and includes information on the following outcomes: Cardiac and non-cardiac death as well as survived sudden cardiac death, heart transplantation, adequate ICD therapy, frequency of cardiac and non-cardiac hospitalizations, syncope or documented potentially life-threatening arrhythmia, hospitalization due to worsening of HF and any non-elective cardiovascular hospitalization. The follow-up clinical examinations are repeated after one year: comprehensive anamnesis including medical history, co-morbidities, medication and clinical examination, 12-lead electrocardiogram, exercise testing, chest X-ray, echocardiography, MRI, cardiac catheterization, and MLHFQ (*Table 1* 12-month-follow-up).

Biomaterial storage

The following biomaterials are collected for the TORCH trial at the baseline visit: serum (10 mL, aliquoted; storage at −80°C); EDTA-plasma (7.5 mL, aliquoted; storage at −80°C); citrate-plasma (6 mL, aliquoted; storage at −80°C); urine (10 mL, aliquoted; storage at −80°C); for the extraction of RNA, two PAXgene tubes of each patient are collected (2.5 mL each, storage at −80°C); for the extraction of genomic DNA EDTA Plasma primary tubes of each patient are collected (7.5 mL, storage at −80°C). Myocardial tissue biopsies are collected according to the center's routine if the patient was undergoing a diagnostic biopsy (optional).

Table 1 Clinical examinations in TORCH with optional and obligate examinations

Clinical examinations	baseline	12-month-follow-up
Anamnesis and clinical diagnoses	obligatory	obligatory
6-minutes-walk-test	optional	optional
Depression screening	if applicable	
Echocardiography	obligatory	obligatory
12-lead electrocardiogram	obligatory	obligatory
Medication	obligatory	obligatory
Cardiomyopathy anamnesis	obligatory	obligatory
Minnesota Living with Heart Failure Questionnaire	optional	optional
X-ray	optional	optional
Ergospirometry	optional	optional
Laboratory testing	obligatory	obligatory
MRI	optional	optional
Cardiac catheterization	optional	optional
Biomaterial	obligatory	not applicable
Vital status	if applicable	

Participant data and study management

To each participant one unique identifying pseudonym for their medical data and another one for their biomaterial are assigned by the DZHK trusted third party at the University Medicine Greifswald. By dividing up the identifying data and the clinical and biomaterial data this system provides high data security and accounts for all relevant issues and regulations of privacy. On this basis, the Greifswald data and quality center implemented a data protection concept, which obtained a positive vote of the working group Data Safety of the TMF e.V. (Technology, Methods, and Infrastructure for Networked Medical Research e.V.). The collection of patient data is done interactively in the study centers using standardized data collection instruments. The central data management (CDM) of the DZHK provides data protection and IT-support for the documentation and management of each investigated patient. Further information about data privacy management and data quality monitoring can be found in Schwaneberg *et al*. (unpublished data). Physicians, study nurses and laboratory staff involved in data and sample collection were trained in on-site sessions to ensure a standardized data and sample collection and processing. Data access is granted by the DZHK use and access committee (for further details see Schwaneberg *et al*., unpublished data).

Preliminary results

In the TORCH registry currently 1052 patients have been included, 111 patients already completed one-year of follow-up.

The first 462 patients who underwent quality monitoring were already analyzed regarding gender and age distribution, NYHA classification and CMP diagnosis. Results are summarized in *Figure 3*. In line with previously published data, 70% of the patients are male and 30% are female. Diagnosis, age, NYHA-class distribution and participation rate are given in *Figure 3A-E*.

Biometric concept / statistical analyses

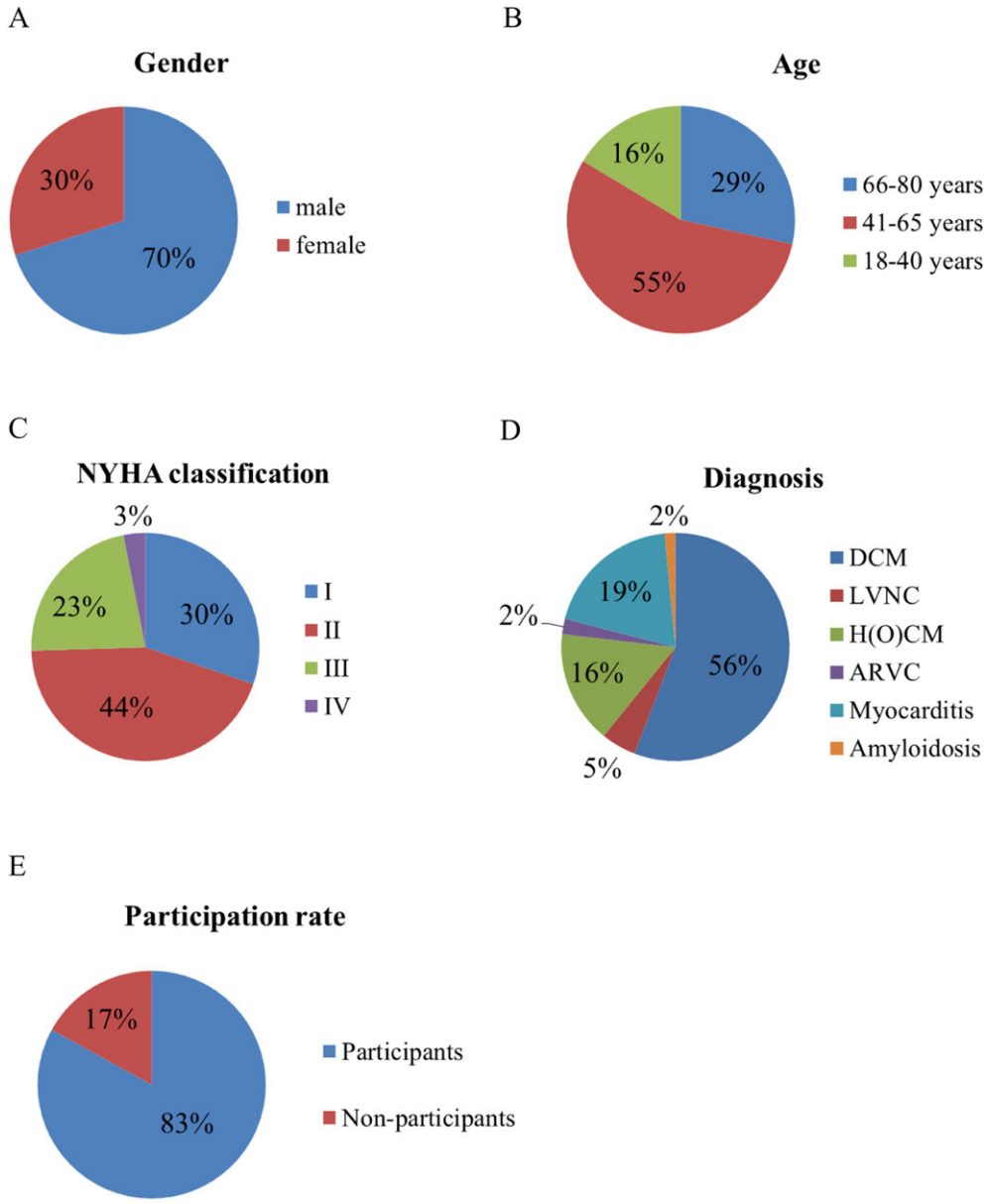
All patients with valid informed consents fulfilling the inclusion criteria and none of the exclusion criteria will be considered eligible for inclusion in the analysis in accordance with the intention to treat analysis principle. Appropriate methods for dealing with missing end point data will be addressed. When data are missing, the reasons will be evaluated, and whenever possible, extracted from patients' records or completed in follow-up. In statistical analyses missing data will be imputed by an appropriate imputation algorithm. Any impact of imputation on the results will be evaluated in sensitivity analyses.

For non-participants (patients who fulfilled the criteria but refused to participate) a short questionnaire will be filled out, including age, sex, diagnosis and the reason for refusal (*Figure 2*). For all data and sample relevant procedures homogeneous standards were defined across centers and documented in SOPs. Samples will be analyzed in a limited number of certified labs using the same jointly agreed upon standards throughout this project. Clinical examinations are performed by trained staff in the participating institutions. To address possible confounders, all analyses will be either stratified (e.g. for age and gender, disease status, comorbidity) or the outcome measurement will be adjusted for possible confounders in multivariate and/or multivariable analyses.

A comprehensive characterization of the register population and patients' subgroups is planned. First analyses will include descriptive methods evaluating the distribution of outcome variables and possible risk factors followed by test statistics in a cross-sectional design. Depending on the outcome measurement, appropriate statistical tests will be chosen: for comparison of categorical/nominal variables (e.g. gender aspects) Chi-Square or Fischer's exact test will be applied, continuous variables (e.g. age) will be compared using a parametric or nonparametric test considering the respective distribution. Multivariate/multivariable methods will be used to analyze the association of one or more independent variable/s (e.g. smoking behaviour) while simultaneously adjusting for possible confounders. The prospective course of outcome parameters will be analyzed using statistical tools for repeated measures in a longitudinal design. Time-to-event models are performed to analyze the impact of possible risk factors on relevant endpoints.

Important gender differences will be addressed by stratifying all analyses according to gender in order to detect possible gender-related interactions with disease phenotype and outcome. Cardiomyopathies can occur at any age.

Figure 3 Distribution of gender, age, NYHA classification, individual CMP diagnosis and participation within the first 462 TORCH patients. DCM = dilated cardiomyopathy, LVNC = left-ventricular noncompaction cardiomyopathy, H(O)CM = hypertrophic (obstructive) cardiomyopathy, ARVC = arrhythmogenic right-ventricular cardiomyopathy.



Therefore, all analysis will be stratified and adjusted according to age groups in order to achieve large scale validity in regards to diagnosis, risk factors and outcome prediction, and specifically to avoid age bias.

Discussion

Today, there is little knowledge from large trials on the diagnostic performance of clinical and molecular tools and even less on appropriate and personalized treatment strategies. Considering the poor outcome and the limited knowledge of disease modifiers, there was an unmet need for a national registry of patients with CMPs. Thus, TORCH represents the first large-scaled registry in Germany focusing on non-ischemic CMPs. In TORCH patients are carefully phenotyped by clinical variables, state-of-the-art imaging modalities and molecular-, genetic- and epigenetic investigations. Information from this trial will enable planning further national and international studies regarding diagnostic tools and therapeutic treatment strategies. It will create a common biomaterial bank thereby enabling detailed molecular analyses on

patients' biomaterials and the development of patient specific model systems. Currently, 1052 patients have been included, 111 patients already completed one-year of follow-up. The first 462 patients who underwent quality monitoring were already analyzed regarding gender and age distribution, NYHA classification and CMP diagnosis. In line with previously published data, 70% of the patients are male and 30% are female. TORCH explicitly welcomes national and international cooperations and multi-center studies. Thus, international collaborators are welcome to submit formal proposals to work with the TORCH team. Research requests can be submitted via a special form on the DZHK homepage to the Use and Access Committee of the DZHK.

Ethics and Trial registration numbers

Ethical approval has been obtained from the leading ethics committee (University of Heidelberg, S-344/2014) and subsequently from all responsible ethics committees of the participating centers involved. ClinicalTrials.gov Identifier: NCT02187263. DRKS-ID (Deutsches Register Klinischer Studien): DRKS00008017.

Acknowledgments

We thank D. Wilhelm and M. Wittek for their excellent assistance.

Conflict of interest

None declared.

Funding

This work was supported by the DZHK (German Centre for Cardiovascular Research, grant number: FKZ 81X1500103) and by the BMBF (German Ministry of Education and Research).

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