Project & Subprojects
Subprojects of the Competence Network Heart Failure

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Goals of the Competence Network Heart Failure

Background
The German Competence Network Heart Failure (CNHF) was established in June 2003 and is funded by the Federal Ministry of Research and Education. Its main purpose is to provide and nurture interdisciplinary cooperation between research and primary, secondary and tertiary health care. Many internationally renowned heart failure researchers and working groups live and work in Germany. Nevertheless, there is insufficient cooperation of the respective working groups and research projects in this area. In order to remain internationally competitive in the heart failure research community, excellent implementation of large scale clinical and genetic trials is indispensable. Further, deficits in the effective presentation and transfer of research findings into clinical practice need to be addressed. An adequate translation of guidelines into practical, tangible instructions can facilitate clinical practice both in primary and tertiary care fundamentally. The need for action to address the research-practice-gap is obvious.

Objectives
1. Augmentation of research efficiency and effectiveness
   Research deficits are to be identified in order to create the basis for new diagnostic and therapeutic strategies
2. Improvement in the quality of health care
   Initially, a review of health care in different locations will be carried out for this purpose. Results of these analyses will provide a rational basis for preventive strategies amongst the German population
3. Influence of the network on the general population
   The aim of the Competence Network Heart Failure is to provide patients and the general public alike with comprehensive information about heart failure and latest research results in this area to form the basis for more effective prevention.

Implementation
There are three main elements which play a key role in the achievement of these objectives: Firstly, the establishment of a capable, high-quality infrastructure for cooperation; secondly, the formation of a centre for clinical trial coordination, management and biometrics; and thirdly the setup of a central biomaterial bank to process and store biomaterial for the whole network. The scientific emphases of the respective working groups and reference centres are integrated into the whole network project in such a way that research findings are only obtainable in cooperation and could not have been delivered by any individual facility. Fast and effective translation of new research findings into clinical practice is to be achieved by facilitating interactions between science and hands-on health care. The various stakeholders to be integrated into specific research projects include all those involved in the provision of health care, for example general practitioners, cardiology specialists, support groups as well as rehabilitation specialists. The German population is to be informed about heart failure, its risk factors and development by means of public relations strategies such as continuous, widespread media attention. Patient information leaflets are to be developed to provide heart failure information and practical advice on how to cope with the illness.
Subproject 1

Central Office

Background
In order to find new ways in prevention, alleviation and healing of the widespread disease congestive heart failure, bundling of the entire scientific expertise is required. Scattered individual “research islands” will be incapable of providing answers for urgent medical questions and at the same time meet the high standards of scientific data. Only long-term research collaborations within a large network can meet these requirements. For this reason, large-scale research projects like the CNHF demand for a central management and controlling.

Objective
The establishment of a central office located at the Charité in Berlin serves the purpose of organizational scientific and strategic coordination of the entire network. Among its duties the following are crucial:
1. supporting the development and expansion of a sustainable scientific infrastructure and creation of an interdisciplinary working culture
2. information of patients, physicians and other interest groups regarding new research results
3. establishment of the CNHF as a quality seal for clinical and experimental research and thereby the assurance of the scientific future as well as economic survival after subsidization by the German Federal Ministry for Research and Education

Implementation
In close cooperation with the scientific advisory board, the central office clears the way for a collaborative culture by selection of appropriate projects. Only those scientific projects will be supported which clearly answer the questions: “Does implementation of the project require assistance of the network?” and “Does the project have specific advantages for the network?” in the affirmative. The best research and health care facilities contribute with their expertise and infrastructure to the network on the basis of relevant previous work. Independence of the networks central office from the other scientific projects within the Competence Network is necessary to ensure good quality assurance and to identify weak points quickly. Beyond that, the central office is responsible for processing ethical and legal inquiries as well as for the management of all other administrative affairs. The Web portal as a contemporary tool for communication between internal and external partners is another important instrument for a collaborative work culture. It offers physicians, scientists, patients and other interested parties the opportunity to obtain general information regarding the syndrome heart failure and also latest research results. The Web portal offers contact to experts and other persons with a general interest in heart failure but also the opportunity for training and continuing education. Support of young scientists by means of prizes and grants is a further task of the central office. Last but not least the central office coordinates the public relations work of the Competence Network Heart Failure at conventions and other public events and also in print media, radio and television.

The central office of the CNHF is responsible for reporting to the project sponsors during the subsidization period. Integration of national and international collaboration partners from the scientific community as well as industry is an aim in order to create the necessary prerequisites for a long term investment. The most important basis for this is the design of the future organizational form of the network after the period of funding by the German Federal Ministry for Education and Research (BMBF).

Contact:
Prof. Dr. Rainer Dietz
Speaker
E-Mail: rainer.dietz@charite.de

PD Dr. Cemil Özcelik
Scientific Director
E-Mail: cemil.oezcelik@charite.de

Ass. jur. Hans-Peter Wabro, Mag.rer.publ.
Administrative Director
E-Mail: hans-peter.wabro@charite.de

Address:
Charité Universitätsmedizin Berlin
Medizinische Klinik mit Schwerpunkt Kardiologie
Charité Campus Virchow-Klinikum
Augustenburger Platz 1
13353 Berlin
Germany
Subproject 2

Study Center, Telematics and Information Services

**Background**
One significant prerequisite for the implementation of high-quality studies in the network is the establishment of a uniform, standardized process quality for project planning, implementation and analysis for all partners as well as for documentation and material flow. Beyond that there is a great need to make information and data available to all partners in an efficient, timely manner. At the same time, electronic storage and transmission of medical data requires great care with regard to data protection and privacy. As an instrument of communication, procurement and increasingly for the publication of specialist information, the Internet has become the most important medium.

**Objective**
With the development of the Center for Study Coordination, Study Management and Biometrics (CSSB), structures for the implementation of large-scale, internationally competitive scientific studies are now available to the Heart Failure Competence Network. The studies are carried out with uniform quality standards at all participating partner institutes and meet the highest biometric, documentary and data protection criteria. The central database structures must be continuously maintained, evaluated and expanded. New requirements for data protection and secure data exchange necessitate ongoing evaluation and adaptation of the implemented concepts.

**Implementation**
In order to achieve uniform process and documentation quality, the CSSB is responsible for the harmonization of the documentation content of all research projects, the formulation of standard operating procedures (SOPs), support in the preparation of study protocols and case report forms (CRFs), the implementation of monitoring processes to ensure quality control and the coordination of data and material flows. To ensure biostatistical quality, the CSSB provides support to all projects during the planning, implementation and analyses of the studies.

The CSSB develops and implements the entire information technology and telematics infrastructure required throughout the network. It installs and operates an online database system for recording all of the study data collected with an integrated three-level monitoring process for quality control of the data capture. A comprehensive plan for data protection and secure data exchange is integrated in the database design. Among other things, this includes encrypted data transmission, a firewall system and pseudonymization of the medical data, during which these are separated from the personal data in clear text. For the operation of the Internet portal, a state-of-the-art content management system (CMS) is used for the generation, structured filing, distribution and targeted retrieval of information. This enables the collaborating partners to publish contents in a timely manner and to classify documents without special programming knowledge. The CSSB also functions as a training center for all partners in the competence network. Various courses on documentation, logistical processes and project-specific data processing systems are held.

**Contact:**
Prof. Dr. Markus Löfler
Koordinierungszentrum für Klinische Studien Leipzig (KKSL)
Härtelstraße 16-18
04107 Leipzig
Germany
E-Mail: loeffler@imise.uni-leipzig.de
Subproject 3

Central Biomaterial Bank

Background
To find new methods of treating heart failure, it is necessary to understand the causes and pathophysiological mechanisms involved in its development. There are numerous laboratory methods available for this purpose, the range of which is expanding year by year. The starting materials for many of these methods are blood (whole blood, plasma and serum) and DNA. Materials for which additional information about the clinical course of the disease or special laboratory parameters exist are extraordinarily valuable. Particularly meaningful results can be achieved from this combination. Until now, these materials were always acquired as part of a single study. For later inquiries or for use in newly established laboratory methods, patients must once again be identified and material collected in laborious, time-consuming processes. This means that it takes a long time until results can be achieved using new methods.

Objective
The goal of this project is the creation of an extensive biomaterials bank. Materials (blood, serum, plasma, DNA) from all patients who participate in studies in the network will be collected for this purpose. The objective is a consistently high quality standard for the processing, storage and management of all samples. The biomaterials bank is an investment in the future by the network. It enables the competence network and the research community in general to acquire new scientific knowledge about the development, progression and prognosis of the different forms of heart failure.

Implementation
Each time a patient is documented in a study in the competence network, blood (EDTA whole blood and serum) is drawn from the patient, sent by post to the central biomaterials bank and processed there in the central incoming sample laboratory according to specified standards. In the first two subsidization periods, a total of 100,000 samples from approximately 10,000 patients was documented and processed (aliquoting, DNA extraction). These samples are stored in climate-controlled rooms used especially for this purpose at the biomaterial bank of the Experimental and Clinical Research Center (ECRC) in Berlin-Buch at temperatures between -20 and -80 °C. Some of these samples are already in use in different subprojects (SP 5, SP 6b, SP 9a, SP 10 and SP 12). Further internal and external projects will follow.

Added value via networking:
As the central infrastructure project for all samples, the biomaterials bank is deeply involved in the networking. There are also intensive collaborations with other competence networks (e.g. the Competence Network for Congenital Heart Defects) and biobanks. The biomaterial bank of the Heart Failure Competence Network also participates in domestic and European pilot projects for networking biomaterial banks (BBMRI, ESFRI, etc.). The goal of these projects is to develop uniform methods for sample processing and use.

Contact:

PD Dr. Cemil Özcelik
Charité – Universitätsmedizin Berlin
Medizinische Klinik mit Schwerpunkt Kardiologie
Charité Campus Virchow-Klinikum
Augustenburger Platz 1
13353 Berlin
Germany
E-Mail: cemil.oezcelik@charite.de

Dr. Maximilian Posch
Charité – Universitätsmedizin Berlin
Experimental and Clinical Research Center
Charité Campus Buch
Lindenberger Weg 80
13125 Berlin
Germany
E-Mail: maximilian.posch@charite.de
Background
Heart failure, including systolic and diastolic dysfunction, has rarely been investigated in epidemiological studies up to now, because expensive echocardiographic tests are required to differentiate the types of cardiac dysfunction. Thus, little was known until now about the prevalence and course of heart failure and the currently predominant determinants of its incidence in the German population.

Objective
The objective of the epidemiology subproject is to collect up-to-date reliable data on the prevalence and incidence of the various forms of heart failure in Germany. The determinants of the development of heart failure in the population are also being investigated. Determinants include gender, body fat distribution, dietary and lifestyle factors, arterial hypertension and left ventricular hypertrophy, as well as their changes over time (increase and decrease).

Implementation
SP 4 is based on the close collaboration of three large population-based prospective studies in Germany: the KORA study in the Augsburg region, the SHIP study in Western Pomerania and the EPIC-Potsdam study. Projects relating specifically to heart failure were incorporated in these ongoing studies. In the KORA ECHO-LVH substudy, over 1,000 people between the ages of 25 and 74 years were again examined with regard to the occurrence of diastolic and systolic dysfunction. In the SHIP study, the 5-year follow-up examination of approximately 3,500 participants between the ages of 20 and 79 years was likewise carried out using echocardiographic methods. Finally, the EPIC-Potsdam study includes an 8-year follow-up for more than 27,000 people, for whom incident fatal and non-fatal cases of symptomatic cardiac insufficiency were recorded.

The analyses of these extensive data bases are currently in progress. The 10-year follow-up of the KORA study focuses on the echocardiographically measured changes in cardiac function. Interesting correlations to prehypertension, changes in weight and prevalent and incident diabetes mellitus were found. The first population-based data on the 5-year incidence of cardiac dysfunction and heart failure in eastern Germany, which generally has a higher rate of cardiovascular disease, will soon be available from the SHIP study, in which the echocardiographic procedures were less complex (no tissue Doppler imaging). Special analyses for the EPIC-Potsdam study, which investigated the influence of exercise, diet and biomarkers on the development of heart failure as part of embedded case control studies, show that diet also appears to play a role in the development of heart failure which has received little attention up to now.

Added value via networking
The enhancement of the collaboration and network formation succeeded thanks to the integration of state-of-the-art echocardiographic examination techniques as well as modern biometric analyses. The coordination of the analytical process among the three cohort studies was accomplished by means of coordination meetings, project conferences and workshops.

The combination of scientific expertise in cardiology and epidemiology in this form is unique in Germany and facilitates new insights into the progression and the determinants of cardiac dysfunction. This work is reinforced by collaboration with SP 7 and SP 15.

Contact:
Prof. Dr. Ulrich Keil
Institut für Epidemiologie und Sozialmedizin
Universität Münster
Domagkstr. 3
48149 Münster
Germany
E-Mail: keil@uni-muenster.de

Prof. Dr. Hans-Werner Hense
Institut für Epidemiologie und Sozialmedizin
Universität Münster
Domagkstr. 3
48149 Münster
Germany
E-Mail: hense@uni-muenster.de
Background
Illnesses originating primarily in cardiac muscle tissue - the cardiomyopathies - are the third most common cause of heart failure in western industrialized nations after coronary artery disease and hypertension. The most common form of cardiomyopathy is dilated cardiomyopathy (DCM), in which the cardiac cavities are enlarged and there is a loss of function. The second most common form is hypertrophic cardiomyopathy (HCM), in which the myocardial tissue thickens abnormally.

The enormous progress in the identification of disease genes have fundamentally changed our understanding of cardiomyopathies. It is well-known that mutations lead to different forms and variations in the progression of the illness. However, genetic examinations have been reserved for scientific research up to now, and thus limited to very few patients and families. For this reason, we do not have enough experience with a sufficient number of precisely genotyped patients in estimating the significance of individual mutations for the highly variable clinical progression of cardiomyopathies.

Objective
SP 5 has two primary goals: on the one hand, cross-linked research should enable us to offer patients with hypertrophic and dilated cardiomyopathy (HCM and DCM) molecular diagnoses. The primary focus here is on the development and validation of a molecular genetic diagnostic procedure that meets the requirements of timely, cost-effective and accurate human genetic examinations. On the other hand, these examinations should be representative and record the frequency of mutations in the known disease genes as well as their correlation to the clinical forms of heart failure.

Implementation
The starting point comprises patients with HCM and DCM nationwide who have been clinically genotyped at leading cardiological centers. For these patients a systematic search for the underlying mutations will be performed using DNA sequencing. In patients with positive genetic findings, a follow-up examination will be carried out, and a family-oriented examination targeted. The data generated as part of the genetic testing will be used for the clinical testing of a microarray for HCM. If this so-called HCM chip is successful, a validated, uniform method for human genetic testing of HCM patients would be available throughout Germany for the first time.

Added value via networking
The networking of leading university and non-university cardiological centers and genetic laboratories facilitated for the first time the comprehensive clinical and genetic characterization of a large group of HCM and DCM patients nationwide. Thus it is possible to generate results regarding the type and frequency of mutations as well as their specific clinical manifestations with a high degree of scientific accuracy. Genetic testing for HCM and DCM are still very labor-intensive and time-consuming and are offered only by a few laboratories according to individual standards. The collaboration of molecular genetic laboratories in subproject 5 facilitates the creation of a range of diagnostic procedures for affected persons according to uniform standards. There is also collaboration with work groups of the German National Genome Research Network (NGFN). The collaboration with other projects of the competence network on the basis of patient recruitment and centralized data and sample recording is crucial to the successful implementation of the project. Afterwards, patient data and samples can be made available to other groups within the network for work on numerous issues.

Contact:
PD Dr. Thomas Scheffold
Institut für Herz-Kreislaufforschung an der Universität
Witten/Herdecke
Heinstück 11
44225 Dortmund
E-Mail: scheffold@herz-kreislaufforschung.de

Prof. Dr. Heribert Schunkert
Medizinische Klinik I I
Universität zu Lübeck
Ratzeburger Allee 160
23538 Lübeck
E-Mail: heribert.schunkert@innere2.uni-luebeck.de
Subproject 6a

New Diagnostic Strategies in Heart Failure - Cardiac Imaging and Biomarkers

Background
Patients with clinical signs and symptoms of heart failure usually present first to their primary care physician (general practitioner, GP). However, the differential diagnosis is often difficult, in particular in the elderly, and a definitive diagnosis can often only be reached by a specialist with more sophisticated diagnostic tools at hands. Several studies revealed a surprisingly low rate of diagnostic accuracy regarding heart failure when only symptoms and clinical signs were used as diagnostic criteria. Usually GPs have no means to visualize and assess cardiac function, such as by a handheld echocardiography device (ECHO). The determination of natriuretic peptides (BNP) as a point-of-care test has become available only recently, and GPs are neither used to the interpretation of the test results nor is information available on the cost-effectiveness and diagnostic value of this test in diagnostically naïve symptomatic patients with suspected heart failure in a primary care setting. Thus, a large randomized trial was set up to clarify feasibility and benefit of these diagnostic methods if applied in primary care.

Objective
The objective of the first study of subproject 6 – the Handheld BNP Study – was to carry out a study aiming to improve the diagnosis of heart failure in the setting of primary care. In cooperation with the University Hospital of Essen, the Coordinating Center for Clinical Trials in Leipzig, 12 cardiologists and 48 GPs the feasibility and diagnostic yield of ECHO and BNP regarding the differential diagnosis of heart failure signs and symptoms in diagnostically naïve primary care patients was tested. In a follow-up study, the prognostic value of the initially obtained data and measurements is currently investigated.

Implementation
Training study: As a first step, a structured program designed to train GPs in the use and interpretation of ECHO and a point-of-care test for BNP was developed and evaluated in a two-center trial also regarding supra-regional reproducibility. The primary end point of this study was the expert time required to enable the GPs to achieve the correct diagnosis (confirmation or exclusion of heart failure) in at least 80% of cases. The study revealed that GPs required at both sites approximately 5 hours theoretical and practical training to reach this goal.

Screening study: A cluster-randomized four-arm design was employed in which each cardiologist co-ordinated with 4 GPs. Patient recruitment was completed in June 2008. A total of 922 patients (63.5% female) were enrolled in the study. Due to 76 dropouts, the data of 846 patients have been entered in the database for further analysis after an extensive data cleaning and query management process. The results of this paper are expected in February 2009.

Follow-up: The first follow-up of the patients is performed 2 years after the inclusion in the diagnostic trial. Further follow-ups are planned in 2-year intervals. Long-term data outcome assessment will allow to also assess the prognostic value of the variables measured at baseline. In addition, novel biomarkers will be tested in blood samples stored in the bank of biomaterials regarding their diagnostic potential in this particular patient population. These results are urgently needed as information on the value of biomarkers in a decompensated state of heart failure are amply available, but data in clinically stable patients with only mild symptoms are scarce.

Added value via networking
The competence network facilitated establishment of a long-term administrative office enabling the generation of ambitious multicentre trials. The local diagnostic networks generated for the purpose of this trial enabled recruitment of the worldwide largest patient sample ever included in a primary care diagnostic heart failure study. This should allow valid statistical analyses and facilitate reliable statements regarding the potential added value of BNP and handheld echo when used in primary care.

Contact:
Prof. Dr. Christiane E. Angermann
Medizinische Poliklinik / Kardiologie der Universität Würzburg
Klinikstr. 6-B
97070 Würzburg
E-Mail: angermann_c@klinik.uni-wuerzburg.de

Prof. Dr. Georg Ertl
Medizinische Klinik der Universität Würzburg
Josef-Schneider Str. 2
97080 Würzburg
E-Mail: ertl_g@klinik.uni-wuerzburg.de
Subproject 6b

Prevalence, Genesis and Prognostic Relevance of Beta1-Adrenoceptor Autoantibodies in Human Myocardial Disease

Background
In heart failure, evidence is growing for a pathogenic significance of functionally active (auto-)antibodies being able to recognize and to stimulate the cardiac beta1-adrenergic receptor (anti-beta1 abs). Anti-beta1 abs are thought to play a key role particularly in the initiation and course of idiopathic dilated cardiomyopathy (DCM), a heart muscle disease of unknown etiology. Patients with chronic heart failure (CHF) often present alterations in humoral and cellular immunity. Therefore, current theories on cardiac tissue injury in DCM focus on abnormal or misled immune responses to infections caused by cardiotropic viruses, bacteria, and/or parasites. As a consequence, a substantial number of CHF-patients develop cross-reacting antibodies and/or autoantibodies to a wide panel of cardiac antigens, including membrane proteins (i.e., cell surface receptors), mitochondrial proteins, and myocyte structural proteins. Irrespective of whether development of DCM is primarily due to chronic myocardial infection or to ab-normalities in the adaptive or innate immune system, cardiac tissue injury is thought to be mediated mainly by cytokines and/or heart-specific autoantibodies. At least for antibodies directed against the human beta1-AR, recently we provided conclusive evidence for a beta1-receptor-directed autoimmune attack as a possible cause of heart failure in a human-analogous rat model. However, in humans

1. the true prevalence of stimulating anti-beta1 abs depending on the nature and severity of the underlying myocardial disease, and
2. the sequence of events leading to the formation of functional receptor autoantibodies have not yet been systematically investigated.

Implementation
Results from a first smaller pilot study clearly indicated that anti-beta1 abs may have an adverse effect on cardiac function in chronic heart failure. Ten years of clinical follow-up of the patients from this pilot study revealed, that anti-beta1 antibody-positive patients had an almost threefold increased cardiovascular mortality risk. In the last few years the basis for a larger prevalence study and thus re-evaluation of the predictive potential of anti-beta1 abs has been formed with the aid of the Competence Network Heart Failure (CNHF) at the Cardiovascular Center in Würzburg. However, the so far available defined CNHF patient groups will be soon expanded by prospective inclusion of patients with acute myocarditis or acute myocardial infarction in the frame of a national multicentre study under the auspices of the CNHF. In the last few years we equally developed a novel highly sensitive method to detect and quantify antibody-induced receptor activation using fluorescence resonance energy transfer (FRET), which reliably identifies stimulating receptor-autoantibodies in humans. Moreover, the FRET methodology will facilitate the sequential analysis of larger patient cohorts. Our planned prospective study on the genesis and time-course of stimulating anti-beta1 abs after acute inflammatory or acute ischemic myocardial damage (ETICS-study) will be funded in the frame of the BMBF-program “molecular diagnostics” and carried out in cooperation with the Center for Study Coordination, Study Management and Biometrics (CSSB) in Leipzig, and, of course, will include more than 10 established CNHF-network partners as well.

Added value via networking
Without the extensive database and bio-material bank of the CNHF and the biometrics at the CSSB the project would not be feasible. Conversely, for the CNHF there is considerable added value from the analysis of the bio-materials obtained in various CNHF-subprojects with a novel, highly sensitive autoantibody detection method contributed by subproject 6b. Our studies across the various projects will serve to acquire substantial knowledge on the development and pathophysiologic significance of autoimmunity in heart failure. In particular, fruitful synergies are to be expected with SP 9a of the CNHF.

Contact:
Prof. Dr. Roland J. Jahns / Prof. Dr. Christiane E. Angermann
Medizinische Poliklinik / Kardiologie der Universität Würzburg
Klinikstr. 6-8
97070 Würzburg
Germany
E-Mail: jahns_r@klinik.uni-wuerzburg.de
E-Mail: angermann_c@klinik.uni-wuerzburg.de
**Background and objective**
The heart functions like a mechanical pump, such as a bellows, for example. Blood is pumped from the left ventricle of the heart into the aorta when the myocardium contracts. This phase is known as systole. Afterwards the myocardium relaxes; during this phase the main chambers fill with blood again. This phase is called diastole. Until a few years ago, it was assumed that dysfunctions (failure) occurred primarily in the systolic phase, we know in the meantime that at least as many people, particularly women in the higher age ranges, suffer from diastolic dysfunction, i.e. a problem with filling the heart.

**Interim results**
Within the Competence Network Heart Failure we have carried out two studies on diastolic heart failure. In a large, nationwide collaborative project in Germany within the Competence Network Heart Failure, we examined nearly 2,000 patients with cardiovascular risk factors (hypertension, diabetes mellitus, hyperlipidemia) or known coronary artery disease with regard to their cardiac function. This study revealed that diastolic dysfunction increased significantly with age (Fig. 1). In patients 80 years of age or older, the prevalence of diastolic dysfunction was over 90%.

An analysis of the severity revealed that the majority of the patients suffered from a mild form of diastolic dysfunction. The proportion of patients with more severe diastolic dysfunction was only approximately 5 percent. However, it is not yet clear what predictive value these findings have for individual patients. Thus the collected data will not only be useful in improving the diagnosis of diastolic dysfunction but will also help in the future to detect heart disease in the early stages and facilitate timely intervention to prevent complications. For this purpose, all of the patients will be monitored for a period of at least 5 years after the study.

As part of a small but very complex study we researched the changes in the pressure/volume ratio in the myocardium using a special cardiac catheter examination. This revealed that the hearts of the patients with diastolic heart failure (in red, Fig. 2) are not able to pump more blood to the organs at a higher heart rate. As we were able to prove, this is due to impaired and incomplete relaxation of the myocardium.

**Contact:**
**Prof. Dr. Burkert Pieske**
Department of Cardiology
Auenbrugger Platz 15
8036 Graz
Austria
E-Mail: burkert.pieske@meduni-graz.at

**Prof. Dr. Gerd Hasenfuss**
Kardiologie und Pneumologie
Herzzentrum der Universität Göttingen
Robert-Koch-Str. 40
37075 Göttingen
Germany
E-Mail: hasenfus@med.uni-goettingen.de

**Dr. Rolf Wachter**
Kardiologie und Pneumologie
Herzzentrum der Universität Göttingen
Robert-Koch-Str. 40
37075 Göttingen
Germany
E-Mail: wachter@med.uni-goettingen.de
Background
We are far from being able to treat the causes of heart failure in patients, let alone heal them. This is primarily because the significance of molecular, pathophysiologically relevant processes has been only inadequately reviewed in experimental models up to now. Our subproject is intended to change this and is working on selected signal cascades and key molecules and their pathophysiologic significance in the regulation of hypertrophy, cell division, survival and function of cardiac muscle cells as the basis for the development of heart failure. In addition, we are working on a series of known and newly-identified secretory factors that are responsible for the communication between the different types of cells in the failing heart.

Objective
The purpose of this subproject is to utilize molecular biological research to develop prerequisites for innovative intervention strategies which can be used as the foundation for innovative treatment approaches for patients with heart failure.

Implementation
The following teams are participating in our subproject: Prof. K. Wollert at Hannover Medical School, Dr. S. Donath at the Charité Hospital of Humboldt University in Berlin, Prof. M. Böhm at the University of the Saarland, Prof. B. Pieske at the University of Goettingen, now relocated to the University of Graz, Dr. C. Zobel at the University of Cologne, and professors S. Engelhardt and J. Bauersachs at the University of Wuerzburg. These groups are currently working on messenger substances of the adrenergic system and their downstream signal molecules, including signal pathways dependent on CA2+, and the mechanisms by which these signal cascades influence the cardiac remodeling processes in heart failure. A further focal point is the functional analysis of the apoptosis repressor with caspase recruitment domain (ARC) signal molecule which regulates the survival of myocardial cells. In addition, we are studying known growth factors such as the insulin-like growth factor 1 and its significance in the development of heart failure. With the aid of gene expression analyses and yeast signal peptide trap screens, we are also searching for previously unknown secretory factors that could be used as treatments and/or biomarkers for patients with heart failure.

Added value via networking
With regard to validity, each individual model has certain limitations. It is therefore useful to examine the pathophysiologic relevance of identified factors and signal molecules not only in one but in several complementary model systems. The consortium of work groups involved in the subproject „Molecular Mechanisms of Heart Failure“ offers outstanding opportunities to do so. Added value should also be achieved by the vertical networking with other clinical subprojects to accelerate the process of integrating knowledge gained from basic research in the design of clinical studies as well as the reverse process of taking knowledge from the clinic into the laboratory.

Contact:
Prof. Dr. Kai C. Wollert
Klinik für Kardiologie und Angiologie
Medizinische Hochschule Hannover
Carl-Neuberg-Str. 1
30625 Hannover
Germany
E-Mail: wollert.kai@mh-hannover.de
Background
Diseases originating primarily from cardiac muscle (the myocardium) – the cardiomyopathies – are the third most common cause of heart failure. The most common form of cardiomyopathy is dilated cardiomyopathy (DCM), in which the cardiac cavities are enlarged and there is a loss of systolic and often also of diastolic function. A multifaceted combination of genetic, autoimmune and viral factors is suspected as the cause of DCM, but the involvement of modifier genes and environmental factors is also under discussion. Familial forms appear to account for DCM in up to 40% of cases. Some of these patients may have an autoimmune disorder or dysregulation or a predisposition for infections. In individuals, this can apparently lead to symptoms of inflammatory DCM, triggered by a particular vulnerability of the myocardium, resulting for example from an infection with cardiotropic viruses or from environmental factors.

Objective
The purpose of this subproject is to improve the understanding of the pathogenesis of DCM by answering the following questions. Therefore a detailed family history, which includes the family tree, will be taken. In the second phase of the project all family members will be included, as far as this is possible. Particular questions include the following:
1. In families with DCM, is there a genetic association with autoimmune diseases or with infections?
2. In addition to a genetic association or predisposition, is there a change in the regulation of the expression of responsible genes?

Implementation
The first milestone of the project was to record as many patients with DCM as possible. This group of DCM patients was checked to find out what proportion of the patients had familial or sporadic DCM. Their etiology was reviewed to find out how many became ill with an idiopathic, inflammatory or virus-induced form of DCM. This was done by using comprehensive diagnostics, analysis of questionnaires and family trees for the family history as well as the examination of endomyocardial biopsies. The second milestone of the project was the molecular biological examination of the blood of patients and family members within the identified families.

Up to now, 323 patients with DCM and 117 family members were enrolled. So far, we identified 65 families (21%) with a minimum of two affected family members. The underlying etiologies were distributed as follows: In total we were able to identify an inflammatory DCM in 21% of the index patients and in 20% of the index patients a viral heart disease. In 54% of all patients’ families we detected a history of autoimmune diseases. Genetic analysis of the patients resulted so far in identification of a lamin A/C mutation in two patients, a new phospholamban mutation and a myopalladin and a N-cadherin mutation in one patient each. The CD45 polymorphism 77C>G probably associated with autoimmune diseases was detected in 5 patients.

Using DNA-based testing methods, new mutations in particular genes such as CARP, lamin A/C or melusin were identified, partially in collaboration with SP 3 and SP 5. With the help of microchip technology, a changed expression of genes involved in the development and regulation of autoimmune reactions as well as polymorphism clusters in HLA class II and CTLA4 genes were found in patients with DCM.

Background
Infection with the HIV virus affects not only the human immune system; organ systems, including the cardiovascular system, are also repeatedly affected. The introduction of new therapeutic concepts for the treatment of HIV infection in recent years made it possible to improve the immunological situation of the majority of HIV-positive patients on a sustained basis. Despite a lack of knowledge of long-term effects, the new treatments are widely used in the western industrialized countries. However, the range of side effects of anti-retroviral therapy is expected to result in an increase in heart disease. It is not clear whether diseases such as dilated cardiomyopathy will play a lifetime-limiting role in this patient group in the coming years. Up to now, there has not been any reliable data available in Germany or internationally on HIV-associated cardiomyopathy and its causes.

Objective
The goal of the subproject „Congestive Heart Failure in HIV-infected Patients“ is the recording of the incidence of dilated cardiomyopathy in patients infected with HIV, taking into account gender, the stage of HIV infection and anti-retroviral therapy. In addition to the incidence of HIV-associated cardiomyopathy, the present research project will collect information about the pathological mechanisms and the course of the disease. From these data, evidence for the incidence and prognosis of HIV-associated cardiomyopathy can be derived which can contribute to early detection and development of preventive measures.

Implementation
A network consisting of specialist cardiology departments, hospital wards and private practices with a focus on HIV. The prerequisites for answering questions about the topic of heart disease in patients infected with HIV were created only by the close collaboration of the project participants with the Competence Network Heart Failure and the previously established HIV & AIDS Competence Network. With the assistance of the network, more than 800 HIV-positive persons were tested for cardiovascular disease in the past two years. The follow-up examinations will take place in the second support phase and currently include over 95% of the target sample size. In addition to information about HIV infection and pre-existing illnesses, the physical stamina and cardiac function of the HIV-positive persons was recorded using a 6-minute walking test and transthoracic echocardiography. Moreover, the status of the HIV infection, blood parameters (CD4 cells, viral load) and anti-retroviral therapy are included in the analysis. The HIV-positive patients will be monitored for three years to record the progress of the dilated cardiomyopathy.

Added value via networking
The objectives of the research project are the comprehensive analysis and exploration of HIV-associated dilated cardiomyopathy. Due to the limited number of HIV-positive people with cardiovascular disease in each individual center and the heterogeneity of the illnesses, data collection that was adequate for performing representative analyses of the type, severity, etiology and progression was made possible only via the network.

Contact:
Prof. Dr. Raimund Erbel
Klinik für Kardiologie
Westf. Herzzentrum Essen
Universität Duisburg-Essen
Hufelandstr. 55
45122 Essen
Germany
E-Mail: erbel@med.uni-essen.de

PD Dr. Till Neumann
Klinik für Kardiologie
Westf. Herzzentrum Essen
Universität Duisburg-Essen
Hufelandstr. 55
45122 Essen
Germany
E-Mail: till.neumann@uni-essen.de
Background
The quality of life of patients with chronic heart failure is severely restricted; co-morbid anxiety and depression aggravate compliance and constitute a risk factor for increased hospitalization and mortality. Reliable information regarding the quality of life and depression throughout the course of the illness depending on age, gender and the health care infrastructure has been lacking. There is hardly any research on approaches to interventions for improving quality of life and adequate diagnosis and treatment of depressive comorbidity.

Objective
For the first time in Germany a nationwide, representative documentation of the quality of life and depression status that covered all patient groups was carried out. The interrelations and changes of quality of life, psycho-social and somatic factors were investigated in selected patient groups. Based on these results, psychotherapeutic interventions for patients with depressive illnesses were developed. To optimize the quality of life for heart failure patients, training and care approaches for primary care practices were designed and evaluated.

Implementation
By the end of the second support phase, 12,000 records of patient quality of life and depression were created by the Competence Network Heart Failure. A cross-sectional study of the network-wide screening data on depression was presented at the spring conference of the German Cardiac Society in Mannheim 2008. We confirmed that the measurable cardiac output is not associated with the presence of depression. The analysis of possible predictive factors for a depression based on process data are in preparation. In addition, we are carrying out studies on gender-specific aspects of quality of life in collaboration with SP 13 and on depression in HIV-positive patients with heart disease in cooperation with SP 9b.

Within the local cardiological research network HELUMA (Heidelberg, Ludwigshafen, Mannheim) in the HELP5 study, we could show that standardized screening for depression and quality of life was a useful and economical complement to the diagnostic procedures for patients with heart failure (Holzapfel & Zugck et al., 2007 Psychosomatics). Moreover, depressed patients with heart failure described their symptoms of depression differently than depressed patients without heart disease, which could be a reason for the low rate of diagnosis of depression (Müller-Tasch et al., 2008 J Card Fail). Every 10th patient with a chronic heart failure also suffers from symptoms of a panic disorder (Müller-Tasch et al., 2008 J Psychosom Res). In the second support phase, a psychotherapeutic intervention was developed for patients with manifest depressive comorbidity, which will be evaluated in a randomized clinical trial. In the train-the-trainer (ttt) study, we evaluated a training program for primary care physicians to improve the quality of life and health care for patients with chronic heart failure. The compliance of the primary care physicians with the guidelines, measured by the prescription rates, was very good; however, with regard to the tapered reduction of ACE inhibitors/ AT1 blockers and beta blockers it was further optimized (Peters-Klimm et al., 2008, Clin Res Cardiol). In the second support phase, practice-based case management was developed as part of the HICMan study and tested on 200 patients with heart failure over a period of 12 months (Peters-Klimm et al., 2008 BMC Cardiovasc Disord). Initial results will be published shortly.

Added value via networking
Maximum horizontal networking was achieved with the implementation of a screening for quality of life and depression in the basic record of the competence network. The aforementioned collaborations provide a solid foundation for future projects. Optimal vertical networking and thus the transfer of specialist expertise into daily practice were achieved by involving the primary care practices in the ttt and HICMan studies.

Contact:
Prof. Dr. Wolfgang Herzog
Universität Heidelberg / Allg. Klinische und Psychosomatische Medizin
Im Neuenheimer Feld 410
69120 Heidelberg
Germany
E-Mail: wolfgang.herzog@med.uni-heidelberg.de

Prof. Dr. Markus Haass
Theresien-Krankenhaus Mannheim / Innere Medizin I
Bassermannstr. 1
68165 Mannheim
Germany
E-Mail: m.haass@theresienkrankenhaus.de

Prof. Dr. Hugo Katus
Medizinische Universitätsklinik Heidelberg / Abt. Innere Medizin III
Im Neuenheimer Feld 410
69120 Heidelberg
Germany
E-Mail: hugo_katus@med.uni-heidelberg.de
Background
Drug treatment for heart failure has undergone a fundamental transformation in the past 20 years. Today, beta blockers are indispensable. Their use is recommended by national and international specialist associations for all patients, regardless of age. Elderly patients are the largest group with heart failure: 90 percent of patients with heart failure are over 65 years of age. However, due to fear of side effects with multiple accompanying medications and comorbidity, this treatment is frequently withheld from elderly patients in particular. The situation is made more difficult by the fact that the average age of study patients has traditionally not reflected the older age of the population under investigation.

Objective
We want to develop an internationally recognized study group – "Multicentric Heart Failure Therapy Studies" – with good organizational structures. The study group should be composed of staff members from the centers collaborating with the competence network and involve experts from all subspecialties in cardiology, cardiovascular surgery, biometrics and statistics. The purpose of this is to substantially improve the quality of clinical therapy studies in the area of heart failure.

Implementation
With our independent CIBIS-ELD study, we compare the tolerability of the beta-blocker treatment in a targeted fashion in older patients with heart failure. This is a prospective, randomized, double-blind study, and thus meets the toughest requirements for study design. More than 1,000 patients, who were treated with a low dosage before the study began, can be enrolled. During a period of twelve weeks, they will be treated with one of the two approved beta blockers bisoprolol or carvedilol. The dosage corresponds to current recommendations and will be adapted to the patient's individual tolerance. At the end of the study we will determine whether one of the two beta blockers was better tolerated or whether varying dosages were achieved. In another part of the study, patients who received a higher dose of beta blockers before the beginning of the study can also be enrolled. We want to establish the current status of heart failure treatment in Germany.

Added value via networking
The expertise in carrying out multicentric treatment studies is offered within the established structures of the Competence Network Heart Failure and outside the network, and used to carry out further studies. The demonstrated professionalism and neutrality in the implementation of the multicentric CIBIS-ELD treatment study will be made known to a professional audience. Collaboration with international work groups is desired. The label „Competence Network Heart Failure“ as the initiator of multicentric treatment studies will be established as a guarantee of a professionally and neutrally conducted study.

Contact:
Dr. Hans-Dirk Düngen
Medizinische Klinik mit Schwerpunkt Kardiologie
Charité Campus Virchow-Klinikum
Augustenburger Platz 1
13353 Berlin
Germany
E-Mail: hans-dirk.duengen@charite.de
Background
SP 13 was initiated and launched based on the results of a large retrospective study at the German Heart Institute Berlin, which revealed significant differences in progress after aortocoronary bypass surgery to the disadvantage of women, whereby no significant gender differences in the influence of numerous clinical parameters were found. This prospective study examines the influence of heart failure, hormone status and psychosocial factors on the result after ACVB surgery. Clinical symptoms of systolic heart failure were more frequent in women in the retrospective analysis. In associated studies of the German Heart Institute Berlin, biopsies taken during surgery revealed indications of gender-specific differences in mechanisms for adaptation to ischemia, which could be the cause of diastolic dysfunction.

Objective
Thus, the primary goals of the subproject, in cooperation with other subprojects, are the investigations of
1. gender-specific factors which have a substantial influence on cardiovascular mortality and morbidity within the first year after ACVB surgery, whereby the influence of systolic and diastolic functional limitations in women play a main role, and
2. the influence of hormonal and psychosocial factors on progress after ACVB surgery.

Fundamental information for the improvement of management of the disease should be gained from this data. Knowledge and targeted monitoring of the risk factors for women as well as men saves resources and facilitates better intervention planning. This applies to the planning of surgical interventions as well as interventions in the hormone status and psychosocial care. Moreover, the following molecular and genetic analyses facilitate the discovery and targeted use of new or existing drug strategies.

Implementation
This is a prospective clinical study of patients with coronary heart disease who underwent ACVB surgery. By the end of May 2006, pre-, intra- and postoperative variables were recorded for 1,050 patients. The data of the 2-month observation period for 900 patients and for the 1-year observation period for 200 patients are available, in which total morbidity and mortality were documented in the course of illness.

Initial results show a tendency toward more frequent clinical signs of heart failure (stress dyspnea) preoperatively with a better left ventricular ejection fraction. Impairment of psychosocial well-being is worse in women both preoperatively as well as in the early postoperative stage (2-month follow-up) than in men.

Added value via networking
The project looks at a large and important patient group with gender-specific manifestations of heart failure and the significance of these with regard to the prognosis, underlying mechanisms, interactions with psychosocial and hormonal components and treatment options. This puts the project at the heart of the network’s focus on interdisciplinarity.

Networking facilitates the optimization of the use of specific data on gender-specific mechanisms and the significance of heart failure before and after ACVB surgery, which improves the treatment management for both women and men.

Contact:
Prof. Dr. Vera Regitz-Zagrosek
Deutsches Herzzentrum Berlin
Institut für Frauen spezifische Gesundheitsforschung mit Schwerpunkt Herz-Kreislaufkrankungen an der Charité Berlin
Augustenburger Platz 1
13353 Berlin
Germany
E-Mail: vrz@dhzb.de
Background
There are hardly any structured care and support programs for patients with chronic heart failure. However, these are urgently needed: the prevalence of heart failure is steadily increasing, due to demographic change and advancements in acute therapy. Treatment of these frequently multimorbid patients is complex, time-consuming and requires innovative strategies that improve continuity between different health care, and interrelate in particular in- and outpatient treatment.

Objective
A randomized, open trial is investigating the impact of a structured disease management program (Network Care (NC)) compared to Usual Care (UC). Network care includes evidence-based medication, enhancement of compliance via specialized nursing staff, patient monitoring by telephone and patient education. In order to document the sustainability of the intervention, an extension of the post-observation from 6 to 18 months and an increase in the number of cases to n=1000 was requested and approved, even before the end of recruitment of the first cohort of n=700. The study clarifies the effect of Network Care compared to Usual Care with regard to 1) death and hospitalization due to any cause (combined primary end point) and 2) components of the primary end point separately, cardiovascular death, quality of life, depression, days alive and out of hospital, guideline-compliant pharmacotherapy according to guidelines, health economy.

Implementation
In this multidisciplinary patient care and support network, 9 internal medicine and cardiological hospitals screen and recruit all patients hospitalized for symptomatic heart failure. Specialist nurses at the study headquarters recruit the patients into the program, if after best possible cardiac recompensation the left ventricular ejection fraction has remained significantly impaired (<40%); all patients receive the INH study pass, in which all consumption of medical resources is to be documented. NC patients receive, in addition, an educational booklet containing relevant information on heart failure and a symptom calendar. After discharge, patients are regularly monitored via telephone by the nurses according to a pre-defined schedule, and receive education about self-empowerment and -monitoring, typical signs of worsening disease, medication, life style aspects including diet and heart-failure-related psychological issues.

Six-month follow-up of the primary cohort (n=700): The average age of the patients was 68 years; 29% were women, and 40% had severe heart failure. In 180 days, 51 patients (14%) died under Usual Care, while 28 patients (8%) died in Network Care (relative risk reduction 43%; p=0.018). While there was an initial increase in the number of days hospitalized among the NC patients, this figure declined from the third month onward, so that days alive and out of hospital gained per patient amounted to 4.6 days after 6 months. In the group of NC patients, the severity of heart failure decreased to a significantly greater extent and the quality of life increased (all p<0.03). After six months, NC patients were treated with higher mean equivalence doses of beta-blockers and ACE inhibitors / ARBs.

Added value via Networking
Broad supraregional implementation of the program should be further investigated within the competence network heart failure to facilitate better estimation of the potential for use in routine care. By means of networking of 9 hospitals, 30 cardiologists in private practice and more than 400 primary care physicians and internists working as primary care physicians, a local high-performance research and health care network was created thus providing a sustainable basis for the processing of scientific issues and the care of patients with heart failure in the future as well. The implementation of the program is documented in detail (HeartNetCare HF Würzburg©), and is currently being tested in a non-university setting under expert supervision. The results could be implemented in the national health care guideline. Furthermore, it is expected that public insurance companies will recognize the importance of this non-pharmacological intervention and will help to facilitate sustainable reimbursement strategies.

Contact:
Prof. Dr. Christiane E. Angermann
Medizinische Poliklinik / Kardiologie der Universität Würzburg
Klinikstr. 6-8
97070 Würzburg
Germany
E-Mail: angermann_c@klinik.uni-wuerzburg.de

Prof. Dr. Georg Ertl
Medizinische Klinik der Universität Würzburg
Josef-Schneider Str. 2
97080 Würzburg
Germany
E-Mail: ertl_g@klinik.uni-wuerzburg.de
Background
Chronic heart failure is one of the most significant illnesses in the western industrialized countries. In addition to its medical aspects, chronic heart failure also has a sustained relevance to health economics. Due to the high prevalence of the illness and its progression, it leads – particularly because of the high costs of repeated hospitalization – to a considerable financial burden on society as a whole.

Objective
The objective of the project is to investigate the economic dimensions of chronic heart failure. The costs and cost-effectiveness of various medical interventions in the treatment of chronic heart failure that are being investigated in other subprojects of the competence network will be evaluated. For this purpose, cost and outcome assessments as well as incremental cost-effectiveness analyses for the observation period will be carried out in the other subprojects. Furthermore, the long-term clinical and economic consequences of the interventions will be determined using decision-analytic modeling.

A generic health economics questionnaire will be developed and adapted to the specific conditions of the various studies in the competence network. Based on the assessed cost and outcome parameters of these studies, cost assessments as well as a health economics-based evaluation (cost-effectiveness analysis) will be carried out for the study period. A decision-analytic Markov model in the context of the German health care system will be developed and clinical and economic data from the INH study will be incorporated in order to determine the long-term effectiveness and the incremental cost/effectiveness ratio of this strategy.

Implementation
The following measures will be determined as part of the research project entitled „Economic Evaluation and Decision-analytic Modeling of Chronic Heart Failure“:
1. an assessment of the costs in subprojects 7 and 9b as well as in the INH study.
2. a description of the costs of the illness based on the data from SP 7 and SP 9b.
3. a cost-effectiveness analysis juxtaposing costs and effects as part of the INH study, including decision-analytic modeling of the long-term clinical and economic consequences.

Added value via networking
The close links between the medical collaborators and the health economists will facilitate the collection of data on the costs of the illness as well as the investigation of the issue of medical results and their cost-effectiveness. The results of this subproject will generate substantial information regarding the costs of the illness, cost-effectiveness in treatment and the management of chronic heart failure. The recommendations derived from these results are intended to support physicians and decision-makers in the health care system in making their decisions and contribute to the efficient allocation of resources in the health care system. Thus, in addition to the scientific aspects, this project is also highly significant for health care policy.

Contact:
Prof. Dr. Uwe Siebert, MPH, MSc
Dept. of Public Health, Medical Decision Making and Health Technology Assessment UMIT
University for Health Sciences, Medical Informatics and Technology Eduard Wallnöfer Zentrum I
A-6060 Hall I.T.
Austria
E-Mail: uwe.siebert@umit.at

Prof. Dr. Jürgen Wasem
Alfried Krupp von Bohlen und Halbach Stiftungslehrstuhl für Medizinmanagement Universität Duisburg-Essen
Universitätsstr. 9
45141 Essen
Germany
E-Mail: juergen.wasem@uni-essen.de

Dr. Dr. Anja Neumann
Alfried Krupp von Bohlen und Halbach Stiftungslehrstuhl für Medizinmanagement Universität Duisburg-Essen
Universitätsstr. 9
45141 Essen
Germany
E-Mail: anja.neumann@uni-essen.de

Dr. Alexander Göhler
MGH - Institute for Technology Assessment
101 Merrimac St, 10th floor
Boston MA 02114
United States
E-Mail: agohler@hsph.harvard.edu
Background
Various medical experts (e.g. cardiologists and surgeons) as well as medical facilities (study centers, university clinics, hospitals) work together to carry out cardiological studies. Participating specialists and facilities collect a multitude of data; however, for the most part this data is not uniformly defined or documented. This can result in inconsistencies in the understanding of medical terms and in the interpretation of medical data. In order to minimize such discrepancies, it is necessary to develop a uniform data dictionary, which gives clear and sound definitions of medical terms.
Up to now, there has never been a medical data dictionary that takes different expert views adequately into account and is suitable for a variety of applications (study protocols, digital documentation sheets (case record form [CRF]), study management software). It is therefore necessary to develop a data dictionary that includes the various expert points of view and offers term definitions that can be used for different systems (paper-based, computer-based).

Objective
The semantically accurate data dictionary will contribute to medical quality assurance. The data contained in the data dictionary should be available to a community of diverse medical experts. Furthermore, it is essential to promote the collaboration of international experts, because only in this way can the data dictionary contribute over the long term to the worldwide standardization of treatment methods in the field of cardiology.

Implementation
The „Onto-Builder“ software developed by the Onto-Med research group (www.onto-med.de) will be used. The requirements for terms and definitions (particularly for the basic record) of the Heart Failure Competence Network will be specified in detail in a corresponding data dictionary model. Likewise, the entry of the basic record generated within the Heart Failure Competence Network in the Onto-Builder as well as quality assurance will be organized and the approval of the terms entered in the data dictionary will be implemented.

Added value via networking
The link between the Heart Failure Competence Network and the data dictionary project is an outstanding one, because numerous specialists with different views of medical issues work together within the competence network. These experts possess specialist medical knowledge (e.g. in cardiology) as well as knowledge of carrying out studies (e.g. biometrics) which is indispensable for the development of a data dictionary for cardiological studies. The data dictionary for cardiological studies provides a uniform basic terminology for the Heart Failure Competence Network that supports the harmonization of study databases and the interaction between study management software and hospital information systems. In addition, the data dictionary facilitates reusability of precise definitions of medical terms in various contexts. This is especially relevant with regard to optimizing the preparation of study protocols and CRFs as well as to the improvement of the comparability of study results. The interactive capability between software systems and improved study comparability are essential prerequisites for vertical and horizontal networking.

Contact:
Prof. Dr. Markus Löffler
Koordnierungszentrum für Klinische Studien Leipzig (KKSL)
Universität Leipzig
Härtelstraße 16-18
04107 Leipzig
E-Mail: loeffler@imise.uni-leipzig.de

Prof. Dr. Heinrich Herre
Institut für Informatik
Abt. Formale Konzepte
Universität Leipzig
Augustusplatz 10/11
04103 Leipzig
E-Mail: herre@informatik.uni-leipzig.de
Background
Patients with severe chronic heart failure have a poor prognosis for survival and high morbidity. The stroke volume and ejection fraction are standard measurements for the degree of reduction in cardiac function. Thus, in patients with chronic heart failure a reduced ejection fraction less than or equal to 35 percent represents a significant risk factor for mortality and the occurrence of a stroke. However, it is still unclear what the optimal treatment strategy for the prevention of a stroke in patients with heart failure and/or a reduced ejection fraction is. Several international studies have compared the effects of the anticoagulant substances warfarin and aspirin in reducing the frequency of strokes and mortality. However, these were not heart failure studies.

The WATCH study (Warfarin and Antiplatelet Therapy in Chronic Heart Failure), the goal of which was to compare the effectiveness of warfarin, aspirin and clopidogrel specifically against the background of cardiac insufficiency, was discontinued without a clear result due to lack of recruitment.

Objective
The study was designed to investigate whether there is a difference between treatment with aspirin and warfarin in patients with a reduced stroke volume and/or a low ejection fraction within three to five years with regard to the occurrence of the combined end point death and/or ischemic stroke and/or intracerebral hemorrhaging.

Implementation
WARCEF is a two-arm, double-blind, randomized, multicentric and international clinical trial with a total of 3,000 patients in over 80 centers in the United States and in more than 80 centers in Europe. Patients with a reduced ejection fraction (LVEF ≤ 35%) receive either warfarin or aspirin after randomization.

Added value via networking
In Germany, Poland and the Netherlands, a total of 850 patients were to be enrolled in the study. After nearly 4 years (December 2004 – September 2008) a total of 450 patients in 10 German, 12 Polish and 9 Dutch centers were enrolled.

The networking in the Competence Network Heart Failure was intended to ensure successful recruitment. The research resources of the National Institutes of Health were to support the German research perspective. As a result of the collaboration among German, Polish and Dutch study centers, an extensive blood database has been established.

Contact:
Prof. Dr. Dr. Stefan Anker
Medizinische Klinik mit Schwerpunkt Kardiologie
Charité Campus Virchow-Klinikum
Augustenburger Platz 1
13353 Berlin
Germany
E-Mail: s.anker@charite.de
Background
Particularly in the case of uncontrolled ventricular rate, the sudden occurrence of supraventricular tachycardia leads to progressive heart failure and morphologically to the enlargement of the ventricles as well as a decline in pumping performance. Patients with pre-existing heart failure are particularly at risk. However, the tachycardia-induced cardiac dysfunction can also appear in patients without systolic or diastolic heart failure. Cardiac dysfunction is most frequently triggered by the initial occurrence of tachycardial atrial fibrillation. Treatment is absolutely necessary and clearly indicated. In addition to a drug-induced lowering of the heart rate (e.g. with beta blockers or class III and class IV antiarrhythmic medications), electrical cardioversion is the most effective method to restore a sinus rhythm with normal frequency. This leads to regression of the clinical and hemodynamic effects of the tachycardia on the heart and improves left ventricular systolic pump function. This regenerative effect on cardiac dysfunction with effective treatment is generally completed after four weeks. Whether the restoration of a sinus rhythm by means of electrical cardioversion improves the contractility of the left ventricle more than drug treatment alone remains to be clarified. Furthermore, the effect of the beta blocker nebivolol on heart frequency and rhythm has been shown only in experimental animal studies.

Objective
The present prospective, randomized, comparative study investigates whether electrical cardioversion with biphasic current is superior to the sole frequency-controlling treatment with nebivolol for the restoration of a normal sinus rhythm. In addition to clinical improvement, improvement in left ventricular pump function based on echocardiographic parameters is to be shown. Furthermore, it is to be documented that after electrical cardioversion a normal sinus rhythm over the long term can be achieved with continuing treatment with the beta blocker nebivolol and that effective heart rate control in the case of atrial fibrillation can be achieved with nebivolol.

Contact:
Prof. Dr. Martin Möckel
Medizinische Klinik mit Schwerpunkt Kardiologie
Charité Campus Virchow-Klinikum
Augustenburger Platz 1
13353 Berlin
Germany
E-Mail: martin.moehckel@charite.de

Dr. Malte Schröder
Medizinische Klinik mit Schwerpunkt Kardiologie
Charité Campus Virchow-Klinikum
Augustenburger Platz 1
13353 Berlin
Germany
E-Mail: malte.schroeder@charite.de
**Background**

Arteriosclerosis is one of the most common diseases of the cardiovascular system in the western industrialized nations. Due to the increasing aging of society, an increased rate of arteriosclerosis is to be expected. In addition, there are widespread risk factors in the population such as disorders of lipid metabolism, smoking, diabetes and hypertension.

The consequence of progressive arteriosclerosis in the coronary vessels is the occlusion of the vessel lumen, which causes a myocardial infarction in the cardiac tissue downstream. This destruction of myocardial cells weakens the heart and can lead to development of chronic heart failure with reduced pumping capacity and enlargement of the heart chambers.

For patients, the reduced pumping capacity is accompanied by reduced physical performance, which in the case of severe heart failure can progress to shortness of breath at rest.

**Objective**

The Heinz-Nixdorf Recall study was a large scientific study of cardiovascular diseases which made it possible for the first time to generate conclusions about arteriosclerosis in the population of the Ruhr region. As part of the Heinz-Nixdorf Recall study, the calcification of the coronary blood vessels was determined using electron beam computer tomography (EBCT). The degree of coronary calcification indicates the degree of arteriosclerosis in the coronary blood vessels. Furthermore, the degree of arteriosclerosis was evaluated using indirect procedures including Doppler tests and stress tests. The information about the extent of the arteriosclerosis was linked to heart failure parameters as part of the research project. This made it possible to clarify the influence of arteriosclerosis in the development of chronic heart failure in Germany within the context of an epidemiological study. The 5-year follow-up was completed in 2008.

**Contact:**

**Prof. Dr. Raimund Erbel**  
Klinik für Kardiologie  
Westf. Herzzentrum Essen  
Universität Duisburg-Essen  
Hufelandstr. 55  
45122 Essen  
Germany  
E-Mail: erbel@med.uni-essen.de

**PD Dr. Till Neumann**  
Klinik für Kardiologie  
Westf. Herzzentrum Essen  
Universität Duisburg-Essen  
Hufelandstr. 55  
45122 Essen  
Germany  
E-Mail: till.neumann@uni-essen.de

**Dr. Stefan Möhlenkamp**  
Uniklinik Duisburg-Essen  
Hufelandstr. 55  
45122 Essen  
Germany  
E-Mail: stefan.moehlenkamp@uni-essen.de
Background
The superiority of specialized care and support of patients with chronic heart failure with regard to inpatient morbidity, cost reduction and health-related quality of life of the patients compared to „conventional care“ has been proven. Telemedical monitoring systems can represent a crucial structural element in new models of care for patients with chronic heart failure. As part of the „nextgenerationmedia“ technology initiative, the German Federal Ministry of Economics and Technology is supporting prototype development and a clinical study of an innovative system for telemedical care and support. The „Partnership for the Heart“ (PfH) project began in 2005 and will run until 2009.

The technical system consists of a mobile sensor platform in the patient’s home, in which measurement devices tailored to the patient’s individual needs can be integrated, and a telemedical center (TMC). This facility complements the primary care and specialist care in a particular region, especially at night and on weekends. The specialists at the TMC make medical decisions based on the vital signs transmitted by the patient and the individual medical history stored in an electronic patient file. The electronic patient file used in the PfH system is compatible with the current stage of development of the telematic infrastructure in the health care system.

The clinical study entitled „Telemedical Interventional Monitoring in Heart Failure“ (TIM-HF) included 600 patients with chronic heart failure (NYHA stages II to III) in a two-arm, open multicentric (n=2), randomized parallel study; the two arms were „conventional guideline-compliant treatment“ and „guideline-compliant treatment plus telemedical monitoring“. The primary end point is the total mortality rate. Secondary end points include the survival period without hospitalization (days alive and not hospitalized due to heart failure), non-elective hospitalization of any type, quality of life, plasma level of NT-proBNP as well as other biomarkers and a cost-efficiency analysis.

Objective
Several goals are being pursued with the PfH project:

- the clinical study TIM-HF tests the concept with regard to medical effectiveness and cost effectiveness to facilitate integration in conventional care over the long term.
- entities in medicine, industry and health care work intersectorally to incorporate it in the relevant daily work routines and in existing health care structures.
- the open system architecture permits cross-manufacturer integration of new measurement devices, new indications and core elements of the telematic infrastructure, reciprocal networking of multiple TMCs and integration in PIS and private practice software programs.

Contact:
Dr. Friedrich Köhler
Medizinische Klinik mit Schwerpunkt Kardiologie, Angiologie, Pneumologie
Charité Campus Mitte
Schumannstr. 20 / 21
10117 Berlin
Germany
E-Mail: friedrich.koehler@charite.de

Dr. Michael Schieber
Robert-Bosch-Krankenhaus
Zentrum für Innere Medizin Kardiologie/Pneumologie
Auerbachstr. 110
70367 Stuttgart
Germany
E-Mail: michael.schieber@rbk.de
Associated Subproject

**Aldosterone Receptor Blockade in Diastolic Heart Failure (ALDO-DHF)**

**Background**
In diastolic heart failure the increased tissue rigidity impairs the filling of the heart chambers, but the ejection fraction during systole is typically normal. Risk factors for diastolic heart failure include arterial hypertension, diabetes mellitus and sleep apnea. However, a number of other diseases can also lead to diastolic heart failure. Unfortunately, the diagnosis of diastolic heart failure has been possible up to now only with complex cardiac catheter techniques. Very recently, however, the use of state-of-the-art imaging procedures (e.g. Doppler echocardiography) and new laboratory markers (BNP, Nt-pro BNP) facilitate definitive diagnosis with non-invasive methods. The use of these new diagnostic techniques has shown that in Germany up to 50% of patients with symptoms of heart failure suffer from isolated diastolic heart failure. However, up to now there has been hardly any data available from prospective, placebo-controlled treatment studies with regard to the treatment of diastolic heart failure.

**Objective**
Thus, the objective of the ALDO-DHF study is to investigate the significance of an aldosterone receptor blockade with spironolactone in the course of diastolic heart failure. For this purpose, a total of 420 patients are to be treated in a placebo-controlled study over a follow-up observation period of one year. The primary end points are physical performance (quantified by spiroergometry) and Doppler-echocardiographic parameters for diastolic dysfunction. The secondary end points include quality of life and morbidity. The ALDO-DHF study is financed as an industry-independent clinical study as part of the „Clinical Studies“ program of the German Federal Ministry for Education and Research (Bundesministerium für Bildung und Forschung (BMBF)). The study uses the infrastructure of the Competence Network Heart Failure, thus enhancing its effectiveness. It was therefore integrated in the Competence Network Heart Failure as an associated subproject.

**Contact:**
Prof. Dr. Burkert Pieske  
Department of Cardiology  
Auenbrugger Platz 15  
8036 Graz  
Austria  
E-Mail: burkert.pieske@meduni-graz.at
Background
Diseases of the rheumatic type are accompanied by an increased risk of the occurrence of arteriosclerosis and an increased cardiovascular mortality rate. Chronic inflammation is an underlying factor in both diseases. The chronic inflammation in rheumatoid diseases may lead to the accelerated development of arteriosclerosis. The role of traditional cardiovascular risk factors in the group of patients with rheumatic diseases and their prognostic value are currently unclear.

Objective
The present project pursues two objectives in particular: First, the prevalence and characteristics of cardiovascular risk factors as well as the (cardiovascular) event rate are to be documented in the follow-up. For this purpose, in accordance with a graduated scheme, 1,000 consecutive patients with inflammatory rheumatic diseases (rheumatoid arthritis, vasculitides, collagenoses, Bechterew’s disease and psoriatic arthritis) will be examined using non-invasive methods and followed up during a 2-year monitoring period. Then the prognostic value of established predictor sets (prognosis scores such as EURO-SCORE, PROCAM score, Framingham score) will be compared with a newly derived predictor set in a patient group. The ease of documentation of the predictor as well as the financial resource consumption will be taken into account in the selection of the predictors.

Implementation
Patients with rheumatic diseases will be prospectively consecutively recruited from two large centers for rheumatic diseases and given cardiovascular screenings. Recruitment was completed at the end of 2006.

Added value via networking
The structure of the project is designed for cross-regional expansion and potentially suited to function as a catalyst for the linkage of two competence networks (rheumatic diseases and heart failure). Thus the newly derived risk score could be externally validated with a large cohort. Furthermore, the project contributes a large number of biomaterials as a basic prerequisite for clarifying pathophysiological connections within the competence network.

Contact:
PD Dr. Stefan Störk
Medizinische Poliklinik / Kardiologie der Universität Würzburg
Klinikstr. 6-8
97070 Würzburg
E-Mail: stoerk_s@klinik.uni-wuerzburg.de

Prof. Dr. Christiane E. Angermann
Medizinische Poliklinik / Kardiologie der Universität Würzburg
Klinikstr. 6-8
97070 Würzburg
E-Mail: angermann_c@klinik.uni-wuerzburg.de
Effects of a Selective Serotonin Reuptake Inhibitor on Morbidity, Mortality and Mood in Patients with Heart Failure and Depression (MOOD-HF Study)

Background
Depression and chronic heart failure play very significant roles both clinically and economically. Between 20 and 40 percent of the 4 million people with heart failure in the Federal Republic of Germany also suffer from depression. Heart failure and depression influence each other, with adverse effects on the quality of life, costs, morbidity and mortality. MOOD-HF is the first randomized, controlled trial to study the long-term effect of treatment with a selective serotonin reuptake inhibitor for clinically relevant comorbid depression in patients with heart failure for “hard” clinical end points. MOOD-HF will thus contribute to the development of evidence-based guidelines.

Objective
The multicentric MOOD-HF study was designed as a two-arm, double-blind and placebo-controlled study to clarify whether treatment with the selective serotonin reuptake inhibitor improves mortality, morbidity, quality of life, psychological well-being and other end points (e.g. health economics, biomarkers, vasoreactivity) in patients with heart failure and clinically relevant comorbid depression, and if so, by what mechanisms. At the same time, the extent to which optimization of the heart failure therapy also leads to improvement in depression will be investigated.

Implementation
Nine German sites are taking part in the study; study management and biometrics are the responsibility of the Coordinating Center for Clinical Trials in Leipzig. The data collection includes the basic record of the Heart Failure Competence Network in a slightly modified form. Seven hundred patients are to be enrolled. The duration of the study for individual patient is a minimum of 12 and a maximum of 24 months. The primary inclusion criterion is a major depression confirmed by a structured clinical interview (SCID). In addition to the study medication, all patients receive optimal treatment for heart failure in accordance with applicable treatment guidelines as well as regular telephone monitoring by nursing staff. The degree of depression, quality of life, anxiety and cognitive functions are monitored throughout the course of the study using standardized and validated psychometric instruments. The follow-up includes meticulous monitoring of patient safety. The study requires close, interdisciplinary cooperation among cardiologists, psychiatrists, psychosomatic specialists and specialized nursing staff and would be impossible without this. A starting event with training and certification of those involved was already held; enrollment of the first patients is scheduled for November 2008.

Added value via networking
A multicenter design is a crucial prerequisite for the implementation of MOOD-HF, as the calculated study power of 700 enrolled patients with heart failure and clinically relevant comorbid depression could not otherwise be achieved within a reasonable period of time. The Heart Failure Competence Network and its affiliated partners offered outstanding conditions for site recruitment. MOOD-HF will enrich the database of the competence network with basic and dynamic process data of patients with systolic heart failure and clinically relevant comorbid depression, thus contributing to the data pool of the network. The data collected here will be made available to network partners for further comparative analyses. Requests can also be sent to the biomaterial bank of the Würzburg study headquarters analogous to the usual procedure in the Heart Failure Competence Network. In addition, the interdisciplinary networking of the study partners provides innovative opportunities for collaboration and new options for improved care of multimorbid patients with heart failure.

Contact:
Prof. Dr. Christiane E. Angermann
Medizinische Poliklinik / Kardiologie der Universität Würzburg
Klinikstr. 6-8
97070 Würzburg
E-Mail: angermann_c@klinik.uni-wuerzburg.de
**Background**

Heart failure is the only cardiovascular disease whose incidence and prevalence are increasing in Germany as well as worldwide. Its course is progressive and medicated inadequately its prognosis resembles malignant diseases. Numerous controlled studies on selected patients have proven that due to a stage-adapted therapy both morbidity and mortality can be reduced considerably and the quality of life can be improved. However, the penetration of these results in the daily clinical routine is insufficient. On the one hand, the currently increasing hospitalization- and mortality rates account primarily to older patients who are underrepresented in the randomized studies. On the other hand, the implementation of evidence based therapy measures on suitable patients is insufficient, at least because of economic constraints. In contrast to other heart diseases as Myocardial Infarction or Atrial Fibrillation, whose epidemiology and supply situation are well examined within the scope of national and regional registers (Berlin Myocardial Infarction Registry), no systematical examinations with representative data exist when it comes to heart failure.

**Objective**

“TOP 40” is the breeding ground of a Berlin Heart Failure Registry which is to determine the supply situation of hospitalized patients with systolic heart failure. Special attention will be given to evidence based heart failure medication and device therapy (ICD, CRT). Results of the pilot project are to serve as basis for concepts for quality assurance and for an optimization of regional supply structures.

**Implementation**

“TOP 40” is a prospective, multi-center study at Berlin hospitals of all health care levels. Included are hospitalized patients with a LV-EF < 40%, NYHA class I-IV, of all etiology and age groups (> 18 years). After a follow up of 12 months, prognostic parameters regarding morbidity and mortality are collected. The study has started on 1. March, 2009.