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Research plan

Integrated, multidisciplinary, person-centered care for patients with complex comorbidities: heart, kidney and diabetes - a randomized trial

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Integrerad, multidisciplinär personcentrerad vård för patienter med komplex multisjuklighet: hjärta, njure, diabetes - en randomiserad prövning

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CareHND

Clinical steering group, Danderyd University Hospital:
Jonas Spaak, Head Physician, HND
Karin Malmqvist, Head, Dept. Cardiology
Joakim Bragd, Head, Dept. Internal Medicine
Björn Samnegård, Head, Dept. Nephrology

HND-centrum
För dig med hjärtsjukdom, njursjukdom, diabetes

Research group:
Jonas Spaak, Docent[1]
Mats Brommels, Professor[2]
Thomas Kahan, Professor[1]
Stefan Jacobson, CEO, Professor[1]
Carl Savage, PhD[2]
Pamela Mazzocato, MSc, PhD[2]
Terese Stenfors Hayes, PhD[2]

1. Department of Clinical Sciences, Danderyds Hospital (KIDS), Karolinska Institutet
2. Medical Management Centre, Department of Learning, Informatics, Management and Ethics (LIME), Karolinska Institutet

Contact information:
Jonas Spaak
Hjärtkliniken, Danderyds sjukhus
182 88 Stockholm
SWEDEN
Email: jonas.spaak@ki.se
Cell/text: +46 (0)76 - 201 4178

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SWEDISH ABSTRACT

Patienter med samtidig hjärt- och kärlsjukdom, njursvikt och diabetes representerar nästan hälften av alla patienter som vårdas vid hjärt-, njur- och diabeteskliniker, och cirka 15% lider av alla tre. Andelen patienter med flera samtidiga kroniska tillstånd ökar markant med åldern. Dessa komplicerade sjukdomar interagerar, och behandling av en påverkar de andra. Trots detta har en ökande subspecialisering medfört att kardiologen "bara" behandlar hjärtat, nefrologen "bara" njurarna och endokrinologen "bara" diabetes. Studier och riktlinjer följer samma mönster. I bästa fall leder detta till att patienterna får besöka flera specialister inom varje fält. I värsta fall till onödigt upprepade undersökningar, underdiagnostik och underbehandling. Ur patientperspektivet finns ett stort behov av samordning och förbättring av vården, inte bara för att minska sjukdomsprogression utan även för att optimera livskvalitet.

Vi avser att studera om behandling och utfall för patienter med samtidig hjärtkärlsjukdom, njursvikt och diabetes kan förbättras genom en ny vårdmodell. Vi har utformat en integrerad klinik som hanterar alla tre förhållandena vid samma besök, med ett personcentrerat teambaserat tillvägagångssätt mellan patienter, sjuksköterskor och läkare, med två terapikonferenser per vecka med dedikerade och utbildade kardiologer, nefrologer och endokrinologer. Vid dessa utvecklas optimerade vårdplaner, och vid återbesök och telefonkontakter implementeras dessa tillsammans med patienten.

Interventionen studeras i en randomiserad kontrollerad studie (CareHND; n = 131) vid HND-centrum, en unik integrerad öppenvårdsklinik i Stockholm och i en matchad långtidskohortuppföljning vid ”The Integrated Care Clinic”, i Vancouver, den första integrerade hjärt-njur-diabetes- kliniken i världen. 62 patienter har randomiserats i pilotstudien.

Vår huvudhypotes är att HND-centra resulterar i bättre vård, från flera aspekter, med ett ur ett helhetsperspektiv lägre resursutnyttjande.

ENGLISH ABSTRACT

Patients with concomitant cardiovascular disease, renal dysfunction and diabetes represent almost half of all patients attending cardiac, kidney and diabetes clinics, and about 15 % suffer all three. This proportion of patients with multiple chronic conditions increase markedly by age. These complicated diseases interact, and treatment of one affect the others. Despite this have a progressive subspecialisation caused cardiologist to treat “only” the heart, nephrologists “only” the kidneys and endocrinologists’ “only” diabetes. Studies and guidelines follow the same pattern. At best this require patients to visit specialists in each field; at worst result in redundant examinations, under-diagnosis and under-treatment of comorbidities. From the patient perspective, there is a great need for coordination and improvement of the care, not only to reduce disease progression but also to optimise quality of life.

We aim to study if the treatment and outcome for patients with concomitant cardiovascular disease, renal dysfunction and diabetes can be improved through a new model to deliver healthcare. We have designed an integrated clinic to handle all three conditions at the same visit, with a person-centered team-based approach between patients, nurses and physicians, with bi-weekly therapy conferences by dedicated and educated cardiologists, nephrologists and endocrinologists. At these, optimised care-plans are developed, and at following team-visits and phone contacts, these are implemented.

The intervention will be studied in a randomised controlled trial (CareHND; n=260) at HND-centrum, a novel integrated outpatient clinic in Stockholm, and a matched long-term cohort follow-up at the Integrated Clinic in Vancouver, the first integrated heart-kidney-diabetes clinic in the world. 62 patients have been randomized in the pilot study.

Our main hypothesis is that HND-centra results in better care, from several aspects, at lower overall burden on the health care system.

Background – co morbidities more common than not

Cardiovascular diseases (CVD) are the leading cause of death both in Sweden and globally, and if not prevented and treated optimally causing increased morbidity, impaired quality of life and premature death [2]. Hyperlipidemia, smoking, hypertension and diabetes are well established as the most powerful modifiable risk factors for CVD. CKD and diabetes share many of the mechanisms causing accelerated vascular aging [3], and in recent years chronic kidney disease (CKD) has emerged as a factor of equal importance [4]. About 20% of the population in developed countries have hypertension, while the prevalence exceeds 50% in those above age 60 years [2]. The prevalence of chronic kidney disease (CKD), defined by reduced glomerular filtration rate (GFR) or albuminuria, is in the range of 10–13% in the general population and about 30% in those above 65 years of age [5]. The prevalence of diagnosed diabetes mellitus in adults ≥65 years is 10-20% in Sweden, compared to 27% in North America, and an additional 50% have pre-diabetes [6]. In addition, data from NHANES 2005–2006 show that 46% of diabetes cases may remain undiagnosed [7]. Thus, with this high prevalence numbers, the risk of having several of these diseases is high. In fact, in patients 65 years or older, it is more common to have two or more chronic conditions, than just one [8]. Patients with multiple chronic conditions receive a remarkable amount of health-care recourses (Fig. 1.). However, in the Swedish health-care system, no one is coordinating these interventions. Least of all, the patient, whom often feel out of control, their daily lives filled with taking pills, injections, checking blood-glucose levels, seeing doctors and nurses, and doing blood works [1].

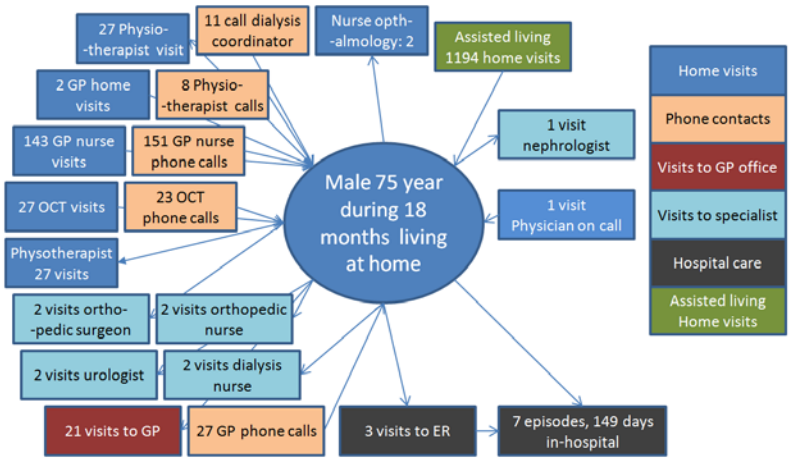

Fig 1. Overview of healthcare consumption during 18 months for a 75 years old man with concomitant cardiovascular disease, CKD and diabetes; a typical "HND-patient". Adapted from "Team for the elderly, vision and reality" [1]. Review shows medical notes on the medical centre taken by 6 different doctors, 20 nurse practitioners, two RN, and regular notes from many more during 149 days of hospitalisation. OC: occupational therapist.

Background – co morbidities and compound risk

The reasons why kidney failure causes heart disease, and vice versa (the cardiorenal syndrome) is still incompletely understood [9]. Patients with concomitant cardiovascular disease, renal dysfunction and diabetes are despite their high risk and high health care consumption often inadequately treated, since an increasingly specialised medical care too often focus on only one part of the disease panorama. Current studies and guidelines follow the same pattern.

In acute coronary syndromes, the single most common cause of death worldwide [2], approximately 40% of the patients have at least moderate kidney dysfunction with an eGFR below 60 mL/min/m^2 [10]. The 1-year-mortality among these is about 25%, compared to 5% in patients with normal renal function [10]. The increased mortality in CKD patients after an acute coronary event is directly related to decreasing kidney function [4]. This may in part be due to the fact that patients with kidney dysfunction are receiving less active treatment, such

as early revascularisation [11], but may also be caused by a range of disturbances in for instance haemostasis and vascular function [3]. The lack of guidelines, which can be attributed to limited clinical data, as the majority of randomised trials in acute coronary syndromes so far have often excluded CKD patients [12].
More than 80% of all cardiovascular deaths can be delayed using changes in life-style and commonly prescribed drugs [13]. Despite this, many patients never receive the full benefits from these interventions because of frequent under-diagnosis, late presentation and consequent under-treatment [14,15]. This is particularly an issue for subjects with complex diseases such as concomitant cardiovascular disease, kidney dysfunction and diabetes.

Background – Multidisciplinary secondary preventive interventions

There exists good evidence for a range of measures that reduce the risk of relapse in patients with established cardiovascular disease [16]. The consensus is that all these interventions should take place simultaneously [16]. An excellent example of how efficient this approach can be when implemented rigorously is the STENO-2 study, where a multifactorial intervention in type 2 diabetes halved the absolute risk of death over 13 years [17]. However the STENO-2 study excluded patients with concomitant heart disease or kidney failure, notwithstanding their higher risk. Despite the high indication for optimal treatment, we have shown that only one in four patients with hypertension reach target blood pressure [14], and that few patients reach a good secondary prevention after myocardial infarction [15]. Traditional health-care models ascribe this to lack of patient compliance; a term implying that the patient and not the physician is at fault.

Background – Person-centered care in chronic disease management

Chronic diseases require a different way of providing care than acute, since almost all the actual care is done by the patient him/herself through changes in lifestyle and actively taking medications. This requires a well-informed and involved patient; informed at a level which the patient can take in. A model that in recent years been shown to produce very positive results also in chronic cardiovascular diseases is person centered care [18-20]. Person-centered care can be described as a partnership between patients and professional caregivers, where the patient is seen as a person with resources and abilities to participate in their own care [18]. The prerequisite for being able to provide person-centered care is that health professionals thoroughly understand not only the patient's illness but also the patient's situation in life. After establishing this relationship, a plan with goals and strategies for implementation and short - and long-term follow-up can be made. Realistic short-term successive goals on life-style improvements are usually an important part.

Background – Integrated care units

HND-centrum is a new way of conducting health care in the form of an integrated care unit [21]. Pilot studies using this approach have shown promising results, for instance the North West London Integrated Care Pilot for elderly patients with diabetes [22]. It is yet not clear how to efficiently design and develop integrated care units [21]. HND-centrum enables studies on how to design these to maximise patient value, in terms of health outcomes, and efficiency. The research aims to increase our knowledge on how health processes are formed within the HND-centrum; how staff integrates their knowledge and develops health care, and how the value of this can be measured by the ratio of outcomes and cost.

Purpose and aims

Patients with concomitant cardiovascular disease, renal dysfunction and diabetes represent a large proportion of all patients in cardiology, nephrology and diabetology. The progressively increased subspecialisation has caused the cardiologist to treat "only" the heart, nephrologists "only" the kidneys and endocrinologists' "only" diabetes. Current studies and guidelines

follow the same pattern. At best, this requires the patient to visit multiple specialists in each field; while at worst, may result in serious under-diagnosis and under-treatment of co-morbidities. From the patient's perspective, there is a great need for coordination and improvement of the care, not only to reduce the rate of disease progression but also to optimise quality of life.
We will use HND-centrum, a new integrated outpatient clinic, which opened in Nov. 2013 as Sweden's first, and the second in the world after Vancouver, Canada. HND-centrum is staffed by experienced specialists from the three specialties, by nurses and paramedics. Already from the start the HND-centrum implements a person-centred healthcare. The clinical part of the project is supported by Danderyd Hospital.
Our main hypothesis is that HND-centrum results in better care, from many aspects, at a lower overall cost to society. This is an application for a grant to show this through a randomised trial (Care-HND).

Project plan

HND-centrum is an outpatient clinic that will replace visits to several doctors and nurses, where instead competence and care are organised and integrated around the patient.
The recently initiated study Care-HND (Fig. 2) will randomise 260 patients to HND-centrum or standard care.
The sample size is based on a power calculation for the combined outcome: death, readmission for heart failure, myocardial infarction, PCI/CABG, end stage renal failure or TIA / stroke with two years follow up.
The same power for quality of care and health care consumption require fewer patients, 131, to be randomized, and followed for 1 year.

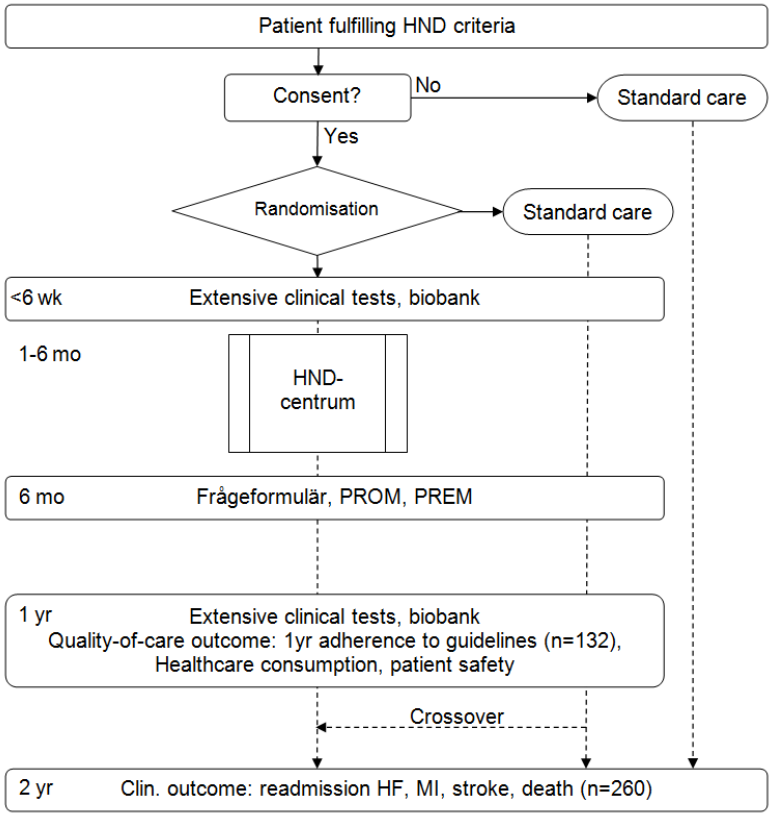

Figure 2. Flowchart for the Care-HND study where 260 patients are randomised to HND-centrum or standard care. After one year's time crossover to the intervention arm is permitted. Intention-to-treat anaysis.

Inclusion criteria – Care-HND:
1 - Established cardiovascular disease (history of myocardial infarction, angina, or heart failure requiring hospitalization. Previous stroke or TIA with certain diagnosis), as well as:
2 - Diabetes mellitus type 1 or 2 (treated diabetes, or new onset diabetes according to WHO criteria or HbA1C > 48, and symptoms, as well as:
3 - Established kidney disease (eGFR <60 mL/min/m^2 calculated with the CKD-EPI formula, or an average of the CKD -EPI and Cystatin-C eGFR, or borderline GFR but concomitant microalbuminuria, or macroalbuminuria, or kidney transplant).

Integration with quality registries

The majority of HND patients will continuously be registered in the national quality registries SWEDEHEART, National Diabetes Register and the Swedish Renal Registry. These in combination with National Welfare records on morbidity and mortality, and the Prescription Registry will be used for analysis of outcomes. Registry data will be used to characterize patients that meet the criteria HND but that are not randomised, in order to understand potential selection bias.

Value-based health care

Value-based health care analyse outcome measures in relation to expenses over the whole course of the disease [23]. The outcome measures are described at three levels: immediate effects, time to recovery, and long-term consequences. Data from hospital management, process mapping and quality registry data will be used to monitor the randomised trial. From cost per patient (CPP), the estimated value for patients and society will be determined.

Interprofessional teams, clinical microsystems and inter-professional learning

HND causes changed work routines for all involved professions, specialties including patients. This can be seen as a clinical microsystem around the patient. Today there are no studies that illustrate how members of such microsystem work together in this type of clinic. We aim to describe and understand this using observations, interviews, and surveys of the personnel.

Sample Collection for bio banking and biochemical analyses

Patients will be tested regularly for clinical routine tests such as electrolytes, CRP, urinary albumin/creatinine ratio, cystatin-C, and PTH. Patients will also give blood / plasma / serum / urine for a biobank for later analysis within:
Transcriptomics: genetics and RNA including mRNA, SNPs and CNVs.
Proteomics: fibrosis markers PICP, C1TP, TIMP1. Inflammatory markers as IL6, IL8, MCP1, CXCL16.
Renal function markers: as NGAL KIM1, NHE3, IL18.
Hemodynamic markers: MR- proADM, copeptin, titin.
Markers of haemostasis: PAI-1 AG, D- dimer, VWF, E- selectin, and OHI. Free RNA and DNA. Microparticles.
Metabolomics: insulin, leptin, GLP-1, PPY, GIP.
A number of patients will give leukocytes.

(Re-)defining health related outcome

From a patients' perspective many more things matter than mortality, and we will develop a combined outcome-model based on the collaborative effort between Karolinska Institutet, Harward Business School, and Boston Consulting; ICHOM (ichom.org).
In 2006, Professor Michael E. Porter wrote the well-known book, Redefining Health Care leading to the work redefining health related outcome. This concept has clear advantages by not selecting a single outcome measure as the only one to focus on, but takes into account all issues that may impact on the patient's life and quality of life. A model has been developed

for a few common diseases, such as Myocardial Infarction (Fig. 3). However, myocardial infarction is a disease with a clear event in time; while HND are chronic conditions. Thus, the model will need some re-development for HND, in collaboration with LIME and ICHOM.

Figure 3. International Consortium for Health Outcomes Measurement (ICHOM) is a non-profit organization founded by Harvard Business School, Karolinska Institutet and Boston Consulting Group with the purpose to improve health care studies worldwide by measuring and reporting patient outcomes in a standardized way.

Primary outcome measures

Disease progression (n=260)
Combined death or readmission due to heart failure, myocardial infarction, PCI/CABG, end stage renal failure, acute renal failure or TIA / stroke.

Patient centered outcome measures (n=131)
Perceived quality of care and patient empowerment
Form based on PROMs (Patient Reported Outcome Measure) and PREMs (Patient Reported Experience Measure).

Quality-of-care outcome measures (n=131)
Achieved target blood pressure, lipids, HbA1c

Secondary outcome measures

Organ damage (n=131)
Decline in eGFR.

System biology (n=260)
Changes in markers of disease progression in transcriptomics, proteomics and metabolomics.

Health care structure and utilization (n=131)
we will study the health care structure and function, involving cost effectiveness, both at HND-centrum and within usual care. Mixed model to describe health care utilization and explain changes in patterns. Number of outpatient and inpatient visits.

Patient safety (n=131)
Using logged patient safety reports.

Interdisciplinary learning:
Qualitative analysis of interdisciplinary learning between personnel.

Methods: Cardiovascular structure and function

Cardiac ultrasound, 24- hour blood pressure monitoring, sleep apnoea registration, thumb-ECG (AF screening) performed in clinical routine with validated equipment and structured interpretation. Arterial Stiffness measured using applanation tonometry and pulse-wave velocity. Endothelial function evaluated by forearm flow -mediated vasodilatation (FMD).

Methods: PROM and PREM

PROM (patient reported outcome Measures) stands for health-related quality of life, patient experience of care outcomes, measured by questionnaires EQ5 -D and RAND-36. PREM (patient- reported experience Measures) means that patients describe their experiences of care and can include measures of quality of life, experience, self-awareness and control. For PREM there are currently no standardised instruments, and we have developed a number of questions about the patient's experience.

Methods: Statistics and Data Management

Data are analyzed with statistics. Differences between groups in the time to outcome analyzed by log-rank test. Survival using Kaplan-Mayer. Hazard ratios with Cox proportional hazard model. Primary outcomes analysed according to the intention-to-treat principle.

Research project organisation

Dr Spaak is medically responsible physician at HND-centrum and PI for the Care-HND study. Dr Spaak participates in and coordinates the following groups:

PostDoc project 1:

Piotr Sobocinski Doliwa, Jonas Spaak, Mårten Rosenqvist
Study 1: Screening for atrial fibrillation in HND patients using thumb-ECG. How high is the prevalence of silent atrial fibrillation in patients with high CHA_2DS_2-VASc score without previous diagnosis?

Project 1: Value-based analysis of integrated clinic - traditional outcome measures

Jonas Spaak, Thomas Kahan, Stefan Jacobson, Pia Lundman, Gun Jörneskog, Mårten Rosenqvist. **Post-doc Peter Doliwa.**
Study 1: Improved prognosis.
Study 2: Increased adherence to evidence- based therapy and secondary prevention goals.
Study 3: Reduced progression of vascular dysfunction.
Study 4-5: Difference in biomarkers in relationship to vascular structure and function.

PhD Project 2: Value-based analysis of integrated clinic - perceived quality of care and patient empowerment

Åsa Franzén Dalin, Susanna Jäghult, Terese Stenfors-Hayes. **PhD student Gudrun Evén.**
Study 1: Can Care-HND improve the patient's health-related quality of life?
Study 2: Can a multidisciplinary approach lead to a more involved patient?
Study 3: Can Care-HND fewer health care contacts in a patient safely?

PhD Project 3: Value-based analysis of integrated clinic - health management and economics

Mats Brommels, Clas Rehnberg, Carl Savage, Pamela Mazzocato, Clas Rehnberg, Pär Höglund. **PhD Student George Keel.**
Health economic analysis of outcomes from PhD project 1-2, and health management.
Study 1: Can time- and activity -based measures be used to estimate health care costs in both cardiac, renal and diabetes care, and at HND-centrum?
Study 2-3: Is Care-HND cost effective from a broader perspective?
Study 4: Can Care-HND re-define chronic disease management?

PhD Project 4: Clinical learning and improvement - guideline development and interdisciplinary learning

Terese Stenfors Hayes, Susanna Jäghult, Åsa Franzén Dalin
Study 1: How is interdisciplinary learning taking place at HND?
Study 2: What learning processes occur at team conferences?
Study 3: How to integrate this knowledge in health care?
Study 4: How can these processes be standardised and developed to increase value to patients?

Ethical Issues

The study is approved by the Regional Ethics Committee (Dnr 2014/1:3). Possibly, those randomised to Care-HND obtain a clinical benefit, which is our purpose to show. Previous studies are lacking to substantiate this. However, we will offer all patients in the control arm an opportunity to cross-over at the return visit after one year.

Description of the gender perspective

The study includes both men and women and we aim to get an even distribution to get an indication of the possible existence of gender-related differences. We believe we will find differences in, for example, the presence of sleep apnoea, and in the experience / PREM of the received care. However, we believe that Care-HND will have a similar effect on both genders regarding the primary outcome measures.

Preliminary results

Initial descriptive data of the patients so far admitted to the HND-centrum show that they are older, on average 72 years. Of all, 25% are below 64 years of age, while 58% are between 65 and 79 years, and 16% are over 80 years of age. Median age when they received their diabetes mellitus diagnosis is 60years. Of all, 85% have type 1 diabetes, and 15% type 2. Of all, 43% are on insulin only.
We have previously not studied these three entities together, but have focused on the cardiorenal interactions showing underteratment despite net benefit. The published results have been presented in context in the background. One example is that we have shown that warfarin treatment is associated with significant reduced mortality also in CKD patients [24]. We are currently looking into similar treatments (fondaparinux, ARB, statins). We are also studying combined treatment adherence and outcome (PhD project for Masih Khedri, J Spaak main supervisor), renal dysfunction and calcium-phosphate disturbances and vascular dysfunction (Kristina Lundwall, J Spaak main supervisor), renal dysfunction and haemostasis (Josefin Mörtberg, J Spaak main supervisor), and vascular function in stress cardiomyopathy/Takotsubo syndrome (Christina Ekenbäck, J Spaak main supervisor).

Research environment and Collaborators

Clinical integration at Danderyd University Hospital

HND-centrum is staffed by specialist doctors and specialist nurses in cardiology, endocrinology and nephrology, with a profound interest in the field, and share a common vision that we can do this better. All are deeply involved in the new clinic and are very positive about the planned CareHND study.

Clinical research expertise in the subject area

We have accumulated extensive expertise with active clinical researcher in cardiovascular, renal and diabetes. Stefan Jacobson, Professor of Nephrology and while CEO of Danderyd Hospital is responsible for the field of nephrology in CareHND trial. Gun Jörneskog, Associate Professor, Department of Internal Medicine, is responsible for the field of microcirculation and diabetes. Thomas Kahan, Professor, Department of Cardiology, is responsible for the field of cardiovascular function. Mårten Rosenqvist. Professor, Department of Cardiology, is responsible for the area of clinical implementation. Jonas Spaak. PhD, MD, Cardiology clinic is medically responsible for HND-centrum. Jonas is main responsible for the area of cardiovascular risk and treatment, and links national registries and outcome. Pia Lundman, PhD, Consultant in Cardiology is responsible for the field dyslipidemia and metabolic risk.

Research Expertise in qualitative research and empowerment:

Susanna Jäghult, program director of the medical clinic, RN, PhD and Åsa Franzén - Dahlin, RN, PhD, quality developer of the medical clinic, Danderyd Hospital are both very familiar with qualitative research methods and studies.

Research skills in the field of health economics and health care processes:

Carl Savage, PhD, a researcher at the Medical Management Centre, Karolinska Institutet. Broad expertise in the field. Louise Hagander, MD, PhD, business developer at the hospital management section at Danderyd Hospital. Pamela Mazzocato, post-doctoral researcher at LIME / KI.

Interprofessional teams, clinical microsystems and inter-professional learning

Terese Stenfors - Hayes, senior researcher, Department of Learning, Informatics, Management and Ethics (LIME), Center for Learning and Knowledge (CLK), did her Post-Doc fellowship at the world's first integrated HND clinic in Vancouver, Canada. Susanna Jäghult also contributes here in her role as an educational leader at the clinic.

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