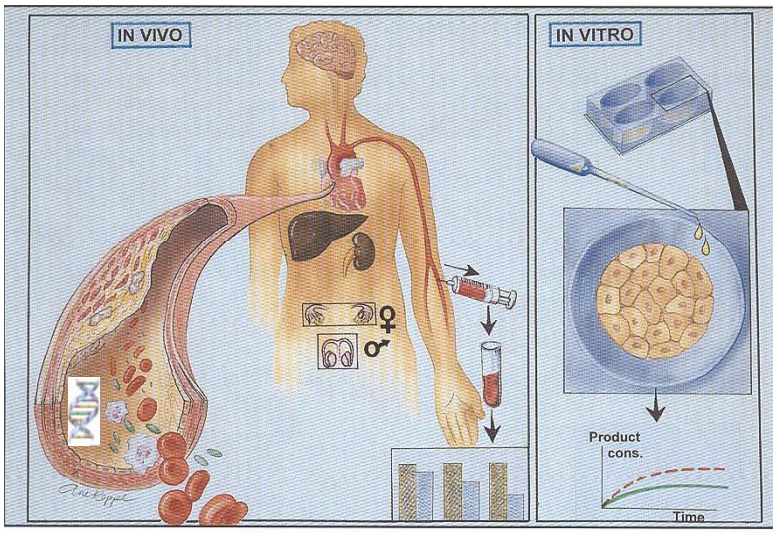
Center for Clinical Heart Research (CCHR)

Department of Cardiology
Medical Division
Oslo University Hospital, Ullevål

Annual Report 2012



Center for Clinical Heart Research, OUH, Ulleval

Oslo University Hospital

http://ous-research.no/clinicalheartresearch/

1. Preface

Center for Clinical Heart Research (CCHR) was grounded in 1991 and is now organized in Department of Cardiology, Division of Medicine, OUS Ullevål. CCHR is one of the formal Research Groups in Division of Medicine/Institute of Clinical Medicine, University of Oslo.

1.1 The main aim of the research in CCHR is to continously improve our competence in clinical translational research, achieve new knowledge broadly related to cardiovascular disease states, initiated by relevant clinical challenges in Oslo University Hospital (OUH) and other health institutions in Helse Sør-Øst.

"Researcher-initiated clinical, randomized intervention trials including studies on basic mechanisms in pathophysiology of the disease states and the intervention principles", are the trade mark of CCHR, and are conducted devotedly.

The milieu continously perform systematically researcher-initiated clinical heart research, based on accepted research methodology along with the flow of patients in OUH and Helse Sør-Øst. Projects related to acute myocardial infarction as well as chronic heart disease states like heart failure, atrial fibrillation and also diabetes are central. Studies on mechanisms/translational studies, especially of biochemical, cellular and genetic type are of major importance for pathogenetic and therapeutic understanding. Secondary aims in the projects are therefore to improve our knowledge on the pathophysiology of the disease states, especially related to inflammation, thrombotic processes and endothelial dysfunction, on the circulatory, cellular and genetic levels.
With regard to therapy, controlled life style intervention and individualized drug treatment are focused concepts.

Biobanking, including sampling, processing, freezing/storing according to given quality criteria and procedures are therefore a major part of the activity. To satisfy the high quality demands in this activity we have running costs for qualified technical support and large routine expenses. Many PhD students are allocated to and supervised by the milieu, and several post-doc researchers are closely associated.

The milieu is result oriented, as can be seen from the scientific section in this report.

1.2 Strategy

All research projects are in line with the strategy for research in Department of Cardiology OUH, and CCHR is a group within the network of Center for Heart Failure Research, OUH/UoO.
With new facilites (vide infra) our goal is to increase the national and international collaboration for instance by exchange of PhD-students.

1.3 Location

CCHR is located within Department of Cardiology, close to the patients, which is crucial for the activity. However, serious lack of space have represented a limiting factor and a challenging daily life for both PhD students and staff. This has been largely improved during the end of this year through our moving into larger, practically suitable localities, still in close proximity of the clinical ward of cardiology. The interrelation with the outpatient clinic has unfortunately been changed after the administrative re-construction of the hospital. Hopefully, this relation will be re-established again due to the constructive synergy between clinical work and clinical research, which is necessary and expected at a university hospital.

1.4 Finances

Budgets for the single projects as well as for the running laboratory expenses are totally based on external funding. The economical support from Stein Erik Hagens Foundation for Clinical Heart Research has been of fundamental importance for the activity in 2012.

April 2013

Ingebjørg Seljeflot (sign)	Harald Arnesen (sign)	Svein Solheim (sign)
professor dr. philos	professor em dr. med	MD post.doc

2. Organization

2. 1 Organization and working procedures.

2.1 Administration and organization aspects are undertaken in total by the center leaders.
A most important activity is the regular research 2-hour-meetings every 2-3 weeks.
PhD students, post docs and laboratory personell participate together with the professors, and the main projects are reported with progress, results and relevant discussion. Relevant international literature is referred to. Furthermore, external experts on special relevant topics and co-workers from other institutions, in addition to intramural experts in epidemiology and biostatistics are invited as lecturers.
Application issues for grants are discussed, and research-related scientific and administrative issues are reported, as well as other research meetings, conferences and congresses, reminding of Abstract deadlines etc.
PhD students are encouraged to participate on international congresses, primarily with presentation of own results.
Participation in the research meetings is counting in the PhD program at UoO. In 2012, 14 research meetings were arranged.
In addition, individual supervision of the single PhD student is undertaken, with an ”open-door-policy”, and specific projects are separately discussed in smaller groups.

A **Scientific Symposium** was organized for all PhD-students and other participants of the group in November 2012 at Hotel Bristol, Oslo. This was made possible by economic fundings from the Department of Medicine, OUS with the aim to make a social ”atmosphere” for the research group.
Two highly competent external guests were invited to present supplementory methodological aspects, in epidemiology/biostatistics and in imaging technology.

2.2 Personell

Leadership: The leader is also the head of the R&D Section at Department of Cardiology, 100% position, professor II at UoO. In addition, medical leaders are one post.doc in 50% position (financed from Health South East) and one professor emeritus (externally financed) who also is the Centers delegate in the Board for Stein Erik Hagens Foundation for Clinical Heart Research, OUH Ullevål.
Employees: 2 medical technologists of which one has a Master of Science in biomedicine, 0.5 study nurse.
10 PhD students and 4 post.docs are participating in the milieu. In addition, the scientific milieu and the lab are open for several other PhD-students at the Department of Cardiology and from other collaborating groups.

3. Scientific Activities

3.1 Defended theses with supervision from CCHR

Trine B. Opstad, MSC
" Selected Polymorphisms in Coronary Artery Disease. Influence on gene expression and circulating levels of atherothrombotic risk markers"
June 2012
Supervisors: Professor Ingebjørg Seljeflot, Professor em. Harald Arnesen

Thomas Weiss, MD
"Inflammation, Adipose tissue and Atherosclerosis"
September 2012
Supervisors: Professor Ingebjørg Seljeflot, Professor em. Harald Arnesen

Alf-Åge Pettersen, MD
" Platelet function testing in patients with stable coronary artery disease. Impact on clinical outcome. Results from the ASCET trial"
September 2012
Supervisors: Professor em. Harald Arnesen, Professor Ingebjørg Seljeflot

3.2 Defended theses with collaboration /co-supervision from CCHR

Jan Otto Beitnes, MD
"Cell therapy in acute myocardial infarction"
February 2012
Supervisor: Professor Svend Aakhus
Close collaborators: Svein Solheim MD, PhD, Professor em. Harald Arnesen

Hanna Dis Margeirsdottir, MD
Atherosclerosis and childhood diabetes"
January 2012
Supervisor: Professor Knut Dahl-Jørgensen
Close collaborator: Professor Ingebjørg Seljeflot

Kristin Angell, MD
"Anti-inflammatory therapy and cardiovascualr disease in inflammatory arthropathies – Effects of TNF-α antagonists on vascular function and structure"
August 2012
Supervisors: Professor Dan Atar, professor Tore K Kvien

3.3 Projects, mainly PhD

Main project:
Cand.med. Alf-Åge Pettersen

Thesis defended 2012 for the degree of PhD
Supervisors:
Professor em. Harald Arnesen, Professor Ingebjørg Seljeflot

The ASCET study (ASpirin non-responsiveness and clopidogrel Clinical Endpoint Trial)

In this study the primary aim was to investigate if patients with angiographically verified coronary artery disease respond adequately on aspirin as their single antithrombotic medication.
Thus, clinical relevant endpoints (death, myocardial infarction, new angina pectoris and stroke) were registered in 1001 patients and related to their initial laboratory response to aspirin. Thereafter patients were randomized to continue with aspirin or change to an alternative antiplatelet agent clopidogrel for follow-up after 1 month, 1 year and at end of study after 2 years. *The main study was finished 2012.*

A series of laboratory tests on platelet function have been performed at all time points, and from a large biobank special focus are related to possible influence of relevant genetic differences in the response to aspirin and clopidogrel, and also on polymorphisms in the genes for other risk factors (vide infra). Furthermore, studies on mechanisms behind the phenomonon that despite aspirin treatment, some patients have high platelet activation have been undertaken.

Vibeke Bratseth
Master of Science
Supervisors:
Professor Ingebjørg Seljeflot, Cand.med. Alf-Åge Pettersen

In this context, a substudy of the ASCET trial was conducted:
"Evaluation of thrombin generation in sub-groups of patients with coronary artery disease"
By use of new methodology ex vivo evaluation of thrombin generation (Endogenous Thrombin Potential with the Calibrated automated thrombogram (CAT)) as a thrombotic marker was evaluated against a traditional in vivo method for thrombin generation (Prothrombin Fragment 1+2) in samples from the 1001 patients. Special attention was paid to the levels of thrombin generation in different clinical subgroups (gender, smoking, diabetes, hypertension) and also to the effects of single treatment with aspirin or clopidogrel on thrombin generation.

3.3 Projects, mainly PhD (cont.)

Cand. med. Ida Unhammer Njerve
Supervisors: Professor Ingebjørg Seljeflot, Post doc. MD PhD Svein Solheim, Professor em. Harald Arnesen

"The influence of aspirin and clopidogrel on genetic regulation of inflammation with special emphasis on fractalkine (CXC3CL) and its receptor CXC3CR in diabetic patients"
Based on the ASCET biobank further studies on the effects of the antiplatelet drugs on inflammation are performed, with special emphasis on diabetes. The chemokine CXC3CL which has been shown to be induced by glucose in experimental studies are explored, both as circulating protein and on the genetic regulation of its receptor.

Master of Science Trine Baur Opstad.

Thesis defended 2012 for the degree of PhD
Supervisors: Professor Ingebjørg Seljeflot, professor em. Harald Arnesen

ASCET-Genetics: "Genetic regulation of atherothrombotic risk markers in patients with coronary artery disease"
Biobank material and clinical database from the ASCET study (vide supra) are used (n=1001). With application of new methodology possible differences in the genetic regulation of atherothrombotic risk markers (inflammation and haemostasis) in clinical subgroups of patients with coronary artery disease (diabetes, hypertension, gender, smoking) are investigated. Special focus are laid on selected genetic polymorphisms' influence on gene expression and phenotype (circulating proteins) of interleukin-18, matrix metalloproteinase 9, tissue factor and tissue factor pathway inhibitor.

This study continue with different aspects on genetics in the population. One goal is to explore any importance of genetic polymorphisms on clinical endpoints.

3.3 Projects, mainly PhD (cont.)

Main Project:
Cand.med. Rune Byrkjeland
Supervisors: Post doc. MD PhD Svein Solheim, Professor Ingebjørg Seljeflot, Professor em. Harald Arnesen

EXCADI (Exercise training in patients with coronary artery disease and diabetes). Patients with type 2-diabetes have a two- to four-fold increased risk for cardiovascular morbidity and mortality. Physical activity has a well-established role in prevention of coronary artery disease, as well as for the prevention and treatment of type 2-diabetes. Despite this, few studies have described the effects of physical training in patients suffering from *both* diseases. There is also limited knowledge about the mechanisms involved in beneficial effects of physical exercise.

The primary aims of the EXCADI study are to investigate the effects of one year of organized physical exercise in patients with both coronary heart disease and type 2-diabetes on pathophysiological mechanisms related to atherothrombosis, on glucometabolic state and also use of medication, risk factors for CVD, and co-morbidity associated with type 2-diabetes.

The project is a randomized, controlled, open study on physical exercise and 140 patients are included, based on power calculation. The exercise training is conducted in cooperation with the Norwegian School for Science in Sports.

A large biobank is founded for additional studies on the molecular level, including genetic expression in circulating leukocytes and in samples from adipose tissue.

The follow-up after 1 year of intervention will be ended March 2013

Sissel Åkra, Laboratory technologist.
Master of Sciense project;
Supervisor: Professor Ingebjørg Seljeflot

"The influence of glycemic control on genetic regulation of Inlerleukin-18"

Special emphasis is on the association between the degree of glycemic control and inflammation. Based on previous findings, extensive studies on the relationship between HbA1c and Interleukin-18 will be performed by genetic analyses in circulating celles and adipose tissue.

3.3 Projects, mainly PhD (cont.)

Cand.med. Thomas Weiss

Thesis defended 2012 for the degree of PhD
Supervisors:
Professor Ingebjørg Seljeflot, Professor em. Harald Arnesen

"Glycoprotein 130 (Gp130) – A crosstalk between inflammation, obesity and atherosclerosis"

GP130 is a transmembrane signaling protein, a part of the interleukin-6 signalling pathway, with important regulatory functions in several inflammatory reactions.

The importance of this system has been extensively investigated with regard to the metabolic syndrome.

Polymorphisms in the gene coding for Gp130 and their influence on phenotype (circulating proteins), association with clinical end-points and importance for a possible effect of intervention with diet and/or omega-3 fatty acids have further been studied in a population of 560 men with high risk for coronary heart disease. In addition, studies on genetic expression of inflammatory mediators in adipose tissue from these individuals have been undertaken. A predictive score for cardiovascular events based on the genetic expression of these mediators has been launched.

The main project was finished in 2012.

The investigation on the transsignalling system continue (vide infra). In addition, the influence of the polymorphisms is further investigated in a collaboration study with Wilehelminenspital, Vienna, Austria

Cand.med. Ragnhild Helseth
Supervisors:
Professor Ingebjørg Seljeflot, Post doc. MD PhD Svein Solheim, Professor Thomas Weiss

Gene expression in coronary thrombus

This project aims to explore genes related to atherothrombosis that are expressed in the coronary thrombus. Special attention will be paid to markers or mediators of fibrous cap rupture causing the acute myocardial infarction. The levels of gene expression in the coronary thrombus as related to different clinical disease entities (sub groups) will further be investigated, and also any associations with levels of corresponding or related markers in the circulation.

Coronary thrombus from approximately 80 patients with acute ST-elevation myocardial infarction undergoing percutaneous coronary intervention (PCI) will be included, with plasma samples from the same individuals.

Collaboration with Department of Cardiology, Wilhelminenhospital, Vienna, Austria.

3.3 Projects, mainly PhD (cont.)

Cand. med. Ida Unhammer Njerve
Supervisors: Professor Ingebjørg Seljeflot, Post doc. MD PhD Svein Solheim, Professor Thomas Weiss, Vienna.

SAXATH (Saxagliptin in atherosclerosis; effects beyond glucometabolic control) The main aim is to explore the effects of 3 months intervention with a dipeptidyl peptidase 4 (DPP-4) inhibitor on biomarkers related to atherosclerosis in patients with coronary artery disease (CAD) and type 2 diabetes, both circulating and on tissue and cellular levels, with the hypothesis that the medication would improve a proinflammatory profile in these patients; thus any pleiothropic effect of saxagliptin is explored.
Patients with stable CAD and type 2 diabetes (n=50) treated with either metformin or glimepirid are recruited at OUH, Ullevaal and randomized to either saxagliptin 5 mg per day or placebo and followed for 3 months. Blood samples, including PAX-gene tubes (for RNA analysis), will be collected at inclusion, after 6 weeks and after 3 months. At inclusion and after 3 months a subcutaneous fat tissue sample will be taken for gene expression studies.
The study is still ongoing, but recruitment of patients has turned up as a problem

Cand.med. Vibeke Ritschel
Supervisors: MD PhD Post.doc Geir Ø. Andersen, Professor Ingebjørg Seljeflot, MD
PhD Jan Eritsland,

Inflammatory biomarkers in patients with ST-elevation myocardial infarction. Atherosclerotic mechanisms and implication for clinical outcome.
This project is based on ”Biobanking of Acute Myocardial Infarction (BAMI)” (vide infra) in which patients admitted to the coronary care unit with an ST-elevation myocardial infarction at OUH, Ullevål, are included.
This project is a prospective cohort study on 1200 of these patients. A standardized biobank and a complete database with relevant clinical data are established. The patients will be followed for clinical events after 5 years, i.e. will be available during 2013.
In this specific project inflammatory signalling pathways will be explored, especially related to 1) the interleukin-6 axis (IL-6, IL-6 Receptor, Gp130), circulating as well as on gene expression in leukocytes, and 2) the insulin growth factor (IGF)-1 axis (IGF-1, IGF-1BP3, growth hormone). The goal is to extend our understanding of these novel signalling pathways along with the present acute infarction and the remodelling process, and their role as risk markers for future cardiovascular events.

3.3 Projects, mainly PhD (cont.)

Cand.med. Limalanathan Shanmuganath
Supervisors: MD PhD Jan Eritsland, MD PhD Post.doc Geir Ø. Andersen

POSTEMI (Post-conditioning in STEMI patients treated with primary PCI). A prospective, randomized trial undertaken at the coronary care unit to investigate the effect of 2 different regimes for PCI therapy in patients with acute ST-elevation myocardial infarction (n=260): traditional opening of the occluded artery or a "step-wise" opening/occlusion procedure, inducing so-called post-conditioning which is thought to contribute to diminished reperfusion injury after the PCI. The primary aim is infarct size measured with MRI. The mechanisms of post-conditioning are not fully understood, and a series of blood samples along the PCI procedure are gathered to elucidate the biochemical processes related to reperfusion injury (inflammatory, oxidative, apoptotic). The project is ongoing in the Acute Coronary Care Unit, and processing of samples, biobanking and biochemical analyses are undertaken at CCHR. The follow-up after 1 year will be finished during 2013.

Cand.med.Trygve Huseby
Supervisors: MD PhD Geir Ø. Andersen, MD PhD Jan Eritsland, Professor IngebjørgSeljeflot

LEAF (Safety and efficacy of Levosimendan in patients with Acute myocardial infarction complicated with symptomatic left ventricular Failure).
A randomized, placebo-controlled study to investigate the effect and safety of the relatively new drug Simdax (levosimendan) in patients with PCI-treated STEMI with complicating heart failure. Infusion of levosimendan for 24 hours is compared to placebo, and a broad specter of biochemical analyses are performed in addition to tests of cardiac function, repeatedly during the 6 weeks follow-up. The main aim is measure of wall motion score.
All patients (n=61) have been followd-up for the time period. Sampling, processing, biobanking and the biochemical analyses are undertaken at CCHR. Biochemical analyses will be part of the main project and have been ongoing during 2012.

3.3 Projects, mainly PhD (cont.)

Cand.med. Hilde Ulsaker
Supervisors: MD PhD Arnljot Flaa, MD PhD Eivind Berge, Professor Ingebjørg Seljeflot

CADENCE
(Markers of Coronary Artery Disease During Exercise Testing) The aim of this study, started out in 2011, is to examine whether measuring changes in N-terminal fragment of pro-BNP (NT-pro-BNP) and troponin T during exercise may improve the diagnostic accuracy of exercise ECG. All subjects (n=600) will be examined with coronary angiography, which is regarded as the gold standard for diagnosing CAD. Moreover, we aim to elucidate mechanisms related to sudden cardiac death in relation to exercise by studying whether there is an increase in biomarkers associated with haemostasis and inflammation during exercise, and examine whether ischemia may potentiate this increase. Furthermore, the relationship between exercise-induced changes in biomarkers and echocardiographic measures of systolic and diastolic function at rest will be performed. In a subsequent follow-up study, we aim to examine the predictive power of these markers on future cardiovascular mortality and morbidity.
The results may have important clinical implications for non-invasively diagnosing CAD, especially in women. Furthermore, the study may provide important insights into mechanisms responsible for exercise-related myocardial infarction.

Twin PhD students at OUHU and AHUH.
Cand. med. Kristian Laake
Cand. med. Peder Myhre
Supervisors: Post. doc Svein Solheim, professor Ingebjørg Seljeflot, professor em. Harald Arnesen, Professor Pål Smith, MD PhD Tone Nerdrum

OMEMI (OMega-3 fatty acids in Elderly patients with Myocardial Infarction) The aim of this study is to investigate the possible effects of supplementation with 2 g/day of n-3 PUFAs on cardiovascular morbidity and mortality during a follow-up period of 2 years in an elderly population after having experienced an acute MI.
The hypothesis is that this supplementation on top of modern therapy will reduce the combined cardiovascular end-point of death, non-fatal MI, stroke and revascularizations with at least 30%. Patients with acute MI discharged from hospital alive being ≥70-82 years of age, both gender will be included. The study will be a randomized, placebo-controlled, double blind multicenter study with study center at Center for Clinical Heart Research (CCHR), Oslo University Hospital Ullevål. Participating centers will be OUH Ullevål, Akershus university hospital (AHUH), Asker and Baerum Hospital (ABH) and Aalborg University Hospital, Denmark,
The study will, in addition give new knowledge into the acute myocardial infarction and related morbidity in the elderly.

3.3 Projects, mainly PhD (cont.)

Cand.med. Irene Grundvold
Supervisors: Professor em. Harald Arnesen/Professor Sverre Erik Kjeldsen/Dr.med. Johan Bodegard

"Atrial fibrillation - long-term risk predictors and importance for morbidity and mortality". The project comprises risk factors for atrial fibrillation, mainly epidemiological studies on a large database residing in Medical Research Laboratory, OUH Ullevål. Focus is on the predictive effects of upper normal systolic blood pressure, BMI, weight gain and physical fitness, as well as pulse rate at rest and during physical activity on atrial fibrillation after up to 35 years.

Cand.med.Sara Ulimoen
Supervisors: Dr.med. Arnljot Tveit/Professor em. HaraldArnesen

RATAF (RaTe control in Atrial Fibrillation):
So-called "rate control" has in recent years been claimed to be more important than "rhythm control" for patients with Atrial fibrillation. This randomized cross-over project (n=80) studies the effect of different drugs used in rhythm control to evaluate which drug gives optimal ventricular rate and at the same time improved quality-of-life. A biobank is mounted for relevant biochemical analyses. Joint project with Asker & Bærum Hospital, Vestre Viken HF.

3.4 Post.doc projects

MD PhD Svein Solheim

"Post ASTAMI" Dr.med. Svein Solheim received a 50% post doc. scholarship from Helse Sør-Øst on the project "Haemostatic factors in the ASTAMI study, with special reference to left ventricular thrombus" .

Based on the observation of 15% mural left ventricular thrombus in the ASTAMI (Autologous Stem cell Transplantation in Acute Myocardial Infarction) trial during dual antiplatelet therapy, studies on the coagulation system, systemic and at an expression level from blood samples in the biobank from this trial, are undertaken. Supplementary studies on inflammatory aspects are ongoing.

MD PhD Eva Cecilie Knudsen

GLUMIK (Glucometabolic status in patients with acute myocardial infarction).

MD PhD Eva Cecilie Knudsen who defended her thesis on this project 2011 are continuing in 50% post.doc position with supplementary investigations in this population. Special interests are paids to new markers in acute MI, antibodies to phosphorylcholine (PC), an important epitope on oxidized low-density lipoprotein (oxLDL.)

This is investigated in 220 patients with acute ST-elevation myocardial infarction (STEMI) related to clinical outcome after 3 years and to the presence of "abnormal glucose regulation".

In addition, the patients are planned for a follow-up in 2013 (after about 7 years) for new classification of glucometabolic state as well as for clinical endpoints.

MD PhD Arnljot Tveit

In the **CAPRAF (Candesartan in the Prevention of Relapsing Atrial Fibrillation)** trial in patients with atrial fibrillation no effect of the angiotensin-II-receptor antagonist candesartan on relapse of atrial fibrillation after initial successful electroconversion was observed (Thesis cand med Arnljot Tveit defended 2008). However, based on biobanking during the study, new light was shed on mechanisms of the arrhythmia itself and the tendency to relapse after electroconversion, mainly related to endothelial function and remodelling of the atrium.

Supplementary substudies are still ongoing.

3.5 Other projects with support/supervision from CCHR

Diabetes in children and atherosclerosis development
PhD project
(Cand.med. Martin Høyer)
Supervisor: Professor Knut Dahl-Jørgensen

Patients with type-1 diabetes from childhood have 20-30 times increased risk for premature death from cardiovascular diseases compared to non-diabetics. In the present study, initiated from Department of Pediatrics/Oslo Diabetes Center, 330 children/youth with type-1 diabetes are compared with 120 healthy controls matched for age and gender to investigate early signs of atherosclerosis as measured with various methods (anatomical, physiological, biochemical). Both groups will be followed for 5 and 10 years. All blood sampling/processing and facilities for biochemical translational research (biobanking, analyses) are undertaken at CCHR. The first 5 year follow-up is started in 2011.

NORCAST (Norwegian Cardiac Arrest Survival Trial)
Main initiators /responsible
Professor Kjetil Sunde, MD Espen Nakstad

Combined clinical-neurological, neurophysiological, neuroradiological and biochemical markers in prognostication after cardiac and/or respiratory arrest. A prospective observation study at Oslo University Hospital, Ullevål.
In this multidisiplanary study performed in acute seriously ill patients, 250 patients are planned to be included. Blood samples are taken and processed at CCHR for analysis of a series of biomarkers especially related to neuro-inflammation and thrombotic risk markers in the very acute phase and also after 3 days in those staying alive. The patients are followed for one year. A Steering Committee representing the different diciplines are involved, with *professor Kjetil Sunde, Department of Surgical Intensive Care Unit* as the leader of the project in close collaboration with the Acute Coronary Care Unit by Geir Ø. Andersen ao. The project is daily taken care of by *PhD-student Henrik Stær-Jensen*.

Deleterious cardiac effects of long-time use of anabolic steroids.
PhD project
Cand.med. Paul Vanberg
Supervisor:
Professor Dan Atar

The study is based on the assumption that doping with anabolic steroids increase the risk for and prevalence of ischemic heart disease. Body-builders with confessed use of anabolic steroids are compared to weight-lifting athletes not using stimulants. A multitude of cardiological methods (E-ECG, echocardiography, coloured tissue-Doppler, coronary CT) are used, and a series of biomarkers, including variables in coagulation and platelet activation are studied. The project, initiated from OUH Aker with all biochemical investigations being performed at CCHR is still ongoing.

3.5 Other projects with support/supervision from CCHR (cont.)

Biomarkers in Welders Inflammation and coagulation
Collaboratory study with National Institute of Occupational Health
MD PhD Dag.G. Ellingsen

The mechanisms behind why the cardiovascular and pulmonary system is vulnerable to the external environment pollution, is not known. Welders are especially exposed to particulate and gaseous components during work, and this study address the hypothesis that particles inhaled during work can result in a low-grade chronic pulmonary inflammation inducing a low-grade systemic inflammation. The main focus is to study if such low-grade systemic inflammation may activate endothelial cells and platelets and simultaneously induce a hyper-coagulable state. 160 russian welders are investigated before and after a 3-year period of daily/weakly work for inflammatory and haemostatic variables. Blood sampling is undertaken in Russia and samples are brought to our laboratory. The degree of pollution is examined throughout the study period.

The ABSENT-Study (Anesthesia in Abdominal Aortic Surgery)
Part of PhD project (MD Espen Lindholm)
Supervisor: professor Knut Arvid Kirkebøen

The primary aim in this study is to test if the volatile anesthetic agent sevoflurane is cardioprotective in open aortic aneurism surgery (AAA) as measured by troponines, time to extubation, inotropic medication, occurrence of atrial fibrillation, and the biochemical aspects like cytokine and chemokine production and degree of hypercoagulability. 200 patients are included and randomized to sevoflurane or TIVA (propofol/remifentanil) anesthesia. Blood samples are investigated before randomization, and after 8 hours, 1st and 2nd postoperative days. Cardiovascular events after 30 days are recorded.
Collaboratory study with Vestfold Hosital Trust

Inflammation and Frailty in elderly with colorectal cancer
Medical Student Benedicte Rønning
Supervisor: Professor Torgeir B. Wyller

Knowledge on long-term consequences of older survivors of colorectal cancer, in which frailty is frequently observed, is limited. This study is aimed to investigate predictive value of inflammatory biomarkers for frailty by Fried phenotype, and frailty indicators on functional state. 137 patients were included for biochemical analyses, and 84 patients were available for the clinical follow-up.
A study performed at Department of Geriatri with a Medical student's in the Research Program

3.5 Other projects with support/supervision from CCHR (cont.)

Pulmonal arterial hypertension and right ventricle function in patients with chronic obstructive lung disease (COLD).
PhD project
(Cand.med. Janne Mykland Hilde)
Supervisor: Amanuensis Kjetil Steine

This study is aimed to evaluate non-invasive 3-D eccho cardiography and Doppler method and ergospirometry, to diagnose pulmonal arterial hypertension (PAH) and systolic function of right ventricle in patient with COLD, and compare with magnetic resonnance imaging (MR) and right ventricle cateterization. Biomarkers both venous and mixed arterial/venous, as related to the diagnosis and also to the severity of COLD (GOLD-calssification), are collected. The laboratory analysis and biochemical supervision are undertaken at CCHR.

Biomarkers for diagnosis of DVT in unselected patients
PhD project
(Cand.med. Fredrik Wexels)
Supervisors: MD PhD Ola Dahl, PhD Are Pripp, Professor Ingebjørg Seljeflot

Patients with clinically suspect DVT and Pulmonary embolism (PE) are usually hospitalized. The diagnosis is unspecific and radiological confirmation is necessary. In this study we want to evaluate the accuracy of the spot urine stix test in patients with clinically suspect DVT or PE. Our hypothesis is that the urine stix has a high negative predictive value and thus will exclude a number of patients from unnecessary radiological examinations.
We further want to follow those patients that do not have any confirmatory thrombotic findings on our radiological examinations, to observe if they develop some thrombin driven clinical events like stroke, myocardial infarction or venous events. Finally, we want to analyse stored blood samples from a biobank on markers on activation of coagulation and fibrinolysis, proteomics and other biomarkers for comparison with clinical outcome.

BAMI ("Biobanking in patients with Acute Myocardial Infarction").
A Steering committee for BAMI is established.

In this joint project between the the Cardiac Care Unit, General Cardiology Section and CCHR in Department of Cardiology, an extended biobank is mounted along with prospectively registered clinical data and will be the basis for studies on predictive markers for later clinical events. Consecutive patients with STEMI are included after consent. At the end of 2011 about 1100 patients have been included and a PhD project on baseline biochemical variables is started (vide supra). Furthermore, when about 3000 patients are included, genetic analyses will be undertaken. All logistics for processing of blood samples in the acute phase and the biochemical translational research are undertaken by CCHR.

3.5 Other projects with support/supervision from CCHR (cont.)

Endothelial dysfunction in relation to microbial translocation
Studies in collaboration with Department of Infectious Disease
MD PhD Marius Trøseid

Microbial translocation has been suggested as a driving force of immune activation in several disease states.
In chronic HIV-infected individuals the gastrointestinal mucosal barrier is distorted. Markers of microbial translocation have been shown to be independent predictors of future hypertension in HIV-infected patients. We hypothesize that markers of microbial translocation would be associated with asymmetric dimethylarginine (ADMA), a marker of endothelial dysfunction, and its structural isomer, symmetric dimethylarginine (SDMA) in HIV patients. We further want to explore the impact of microbial translocation in treated vs non-treated HIV-patients.

Any association between endothelial dysfunction/microbial translocation and obesity are explored in a study on obese individuals, who undergo weight reduction and additional gastric bypass surgery. An ongoing study in collaboration also with Bodø Hospital Trust.

3.6 Planned projects

Regulation of the proinflammatory cytokine Interleukin-18 related to the presence of diabetes and the metabolic syndrome
MSc PhD Trine B. Opstad

We have previously shown circulating levels of IL-18 to be predictive of cardiovascular events, and also a close relationship to the presence of MetS and hyperglycemia. We have also shown that IL-18 gene expression in adipose tissue in MetS patients is elevated compared to non-MetS individuals, related to high glucose, also confirmed in vitro. Furthermore, we have shown that genetic polymorphisms (SNPs) on the IL-18 gene, especially the +187 A/G induces lower levels of IL-18 compared to wild type and the distribution of this SNP was specifically important in patients with MetS and diabetes. We want to further explore regulatory mechanisms of IL-18 with special reference to MetS and type 2 diabetes.
The pro-inflammatory properties IL-18 might be in synergism with IL-12, and this will be explored by measure of circulating IL-12 as well as genetic expression. We also want to explore any association between circulating micro RNAs (i.e. miR-146) and gene expression/circulating protein level of IL-18 to elucidate other regulatory pathways of IL-18.

MMP's during Autologous Stem Cell Transplantation in Acute Myocardial Infarction (ASTAMI)
Planned PhD project
(cont. Med.Stud. Res. Program)
MD Eline B. Furenes
Supervisors:
professor Ingebjørg Seljeflot
Post.doc.MD PhD Svein Solheim

The role of different metalloproteinases in acute myocardial infarction is still debatable, and there is limited knowledge on any influence of bone marrow stem cell (BMSC) therapy on these proteinases. We want to investigate any role of BMSC on MMP-9 and its inhibitor TIMP-1 and pregnancy associated plasmaprotein (PAPP-A) in such patients, on circulating protein levels as well as on gene expression. Relation to pro-inflammatory markers known to induce PAPP-A in leukocytes will be explored.
We also plan to search for any predictive value of serum levels of PAPP-A on cardiovascular endpoints in a previously investigated cohorte of high risk individuals.

4. Laboratory Methods

4.1 Locally

- Facilities for blood sampling and prosessing for biobanking after SOPs (Centrifuges, cooling centrifuges, freezers (-30°C and -80°C))

- Platelet function testing with
  Aggregometry
  PFA100
  VerifyNow (”bedside” screening tests)

- Flow-cytometry

- ELISA’s

- RT-PCR (ViiA7 Applied Biosystems)
  Studies on gene expression
  Studies on genetic polymorphisms
  (Locally from November 2012)

4.2 Located outside (in related laboratories)

- HPLC, specially used for elucidation of endothelial function and peroxidation

5. Collaborators

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6. Publications

6.1 Articles

Abdelnoor M, Eritsland J, Brunborg C, Halvorsen S (2012)
Ethnicity and acute myocardial infarction: risk profile at presentation, access to hospital management, and outcome in Norway
Vasc Health Risk Manag, 8, 505-15
PubMed 22956878

Angel K, Provan SA, Mowinckel P, **Seljeflot I**, Kvien TK, Atar D (2012)
The l-arginine/asymmetric dimethylarginine ratio is improved by anti-tumor necrosis factor-α therapy in inflammatory arthropathies. Associations with aortic stiffness
Atherosclerosis, 225 (1), 160-5. PubMed 23014354

Bliksøen M, Mariero LH, Ohm IK, Haugen F, Yndestad A, **Solheim S**, **Seljeflot I**, Ranheim T, **Andersen GØ**, Aukrust P, Valen G, Vinge LE (2012)
Increased circulating mitochondrial DNA after myocardial infarction
Int J Cardiol, 158 (1), 132-4. PubMed 22578950

Bratseth V, **Pettersen AÅ**, **Opstad TB**, **Arnesen H**, **Seljeflot I** (2012)
Markers of hypercoagulability in CAD patients. Effects of single aspirin and clopidogrel treatment
Thromb J, 10 (1), 12. PubMed 22883224 SFX Cristin 983291 (Details)

De Caterina R, Husted S, Wallentin L, Andreotti F, **Arnesen H**, Bachmann F, Baigent C, Huber K, Jespersen J, Kristensen SD, Lip GY, Morais J, Rasmussen LH, Siegbahn A, Verheugt FW, Weitz JI, Coordinating Committee (2012)
New oral anticoagulants in atrial fibrillation and acute coronary syndromes: ESC Working Group on Thrombosis-Task Force on Anticoagulants in Heart Disease position paper
J Am Coll Cardiol, 59 (16), 1413-25. PubMed 22497820 SFX WOS 000302785500002 Cristin 949198

Fraser DA, Diep LM, Hovden IA, Nilsen KB, Sveen KA, **Seljeflot I**, Hanssen KF (2012)

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Diabetes Care, 35 (5), 1095-7
PubMed 22446172 SFX WOS 000303218900029 Cristin 945667

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Response to Comment on: Fraser et al. The Effects of Long-Term Oral Benfotiamine Supplementation on Peripheral Nerve Function and Inflammatory Markers in Patients With Type 1 Diabetes: A 24-Month, Double-Blind, Randomized, Placebo-Controlled Trial. Diabetes Care 2012;35:1095-1097
Diabetes Care, 35 (11), E80 WOS 000311424100005

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Upper normal blood pressures predict incident atrial fibrillation in healthy middle-aged men: a 35-year follow-up study
Hypertension, 59 (2), 198-204
PubMed 22252392 SFX WOS 000299315800021 Cristin 930526

Grundvold I, Skretteberg PT, Liestøl K, Gjesdal K, Erikssen G, Kjeldsen SE, **Arnesen H**, Erikssen J, Bodegard J (2012)
Importance of physical fitness on predictive effect of body mass index and weight gain on incident atrial fibrillation in healthy middle-age men
Am J Cardiol, 110 (3), 425-32
PubMed 22579085 SFX WOS 000307321000019 Cristin 970132, 988123

Halvorsen S, **Seljeflot I**, **Weiss T**, Bøhmer E, **Arnesen H** (2012)
Inflammatory and thrombotic markers in patients with ST-elevation myocardial infarction treated with thrombolysis and early PCI: a NORDISTEMI substudy
Thromb Res, 130 (3), 495-500
PubMed 22607887 SFX WOS 000308078800068 Cristin 972965

Lindholm E, **Seljeflot I**, Aune E, Kirkebøen KA (2012)
Proinflammatory cytokines and complement activation in salvaged blood from abdominal aortic aneurism surgery and total hip replacement surgery
Transfusion, 52 (8), 1761-9
PubMed 22304534 SFX WOS 000307392800018 Cristin 943227

Njerve IU, **Pettersen AÅ**, **Opstad TB**, **Arnesen H**, **Seljeflot I** (2012)
Fractalkine and its receptor (CX3CR1) in patients with stable coronary artery disease and diabetes mellitus
Metab Syndr Relat Disord, 10 (6), 400-6
PubMed 22897138 SFX WOS 000311828900004 Cristin 978120

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Genetic variation, gene-expression and circulating levels of matrix metalloproteinase-9 in patients with stable coronary artery disease
Clin Chim Acta, 413 (1-2), 113-20
PubMed 21963461 SFX WOS 000298462400017 Cristin 919090

Pettersen AÅ, **Arnesen H**, **Opstad TB**, **Bratseth V**, **Seljeflot I** (2012)
Markers of endothelial and platelet activation are associated with high on-aspirin platelet reactivity in patients with stable coronary artery disease
Thromb Res, 130 (3), 424-8
PubMed 22795340 SFX WOS 000308078800055 Cristin 972567

Seljeflot I, Ulimoen S, Enger S, Bratseth V, Arnesen H, Tveit A (2012) ADMA levels as measure of endothelial dysfunction are highly associated with the presence of atrial fibrillation in an elderly population.
Cardiol Res (3), 109-115
Cristin 978095 (Details)

Pettersen AÅ, **Seljeflot I**, **Abdelnoor M**, **Arnesen H** (2012)
High On-Aspirin Platelet Reactivity and Clinical Outcome in Patients With Stable Coronary Artery Disease: Results From ASCET (Aspirin Nonresponsiveness and Clopidogrel Endpoint Trial)
J Am Heart Assoc, 1 (3), e000703
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Plasma asymmetric dimethylarginine in patients with acute decompensation of chronic heart failure
Heart, 98 (11), 831-2
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Solheim S, **Seljeflot I**, Lunde K, **Bratseth V**, Aakhus S, Forfang K, **Arnesen H** (2012)
The influence of intracoronary injection of bone marrow cells on prothrombotic markers in patients with acute myocardial infarction
Thromb Res, 130 (5), 765-8
PubMed 22192151 SFX WOS 000311025700021 Cristin 996157 (Details)

Task Force on the management of ST-segment elevation acute myocardial infarction of the European Society of Cardiology (ESC), Steg PG, James SK, Atar D, Badano LP, Blömstrom-Lundqvist C, Borger MA, Di Mario C, Dickstein K, Ducrocq G, Fernandez-Aviles F, Gershlick AH, Giannuzzi P, **Halvorsen S**, Huber K, Juni P, Kastrati A, Knuuti J, Lenzen MJ, Mahaffey KW, Valgimigli M, van 't Hof A, Widimsky P, Zahger D (2012)
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Eur Heart J, 33 (20), 2569-619
PubMed 22922416 SFX (Details)

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Njerve IU, Pettersen AA, Opstad TB, Bratseth V, Arnesen H, Seljeflot I. Circulating fractalkine (CX3CL1) in patients with stable coronary artery disease (CAD) with and without diabetes mellitus. Frontiers in Cardiovascular Biology (FCVB/ESC) Londom 2012

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Solheim S, Arnesen H, Lunde K, Aakhus S, Bjørnerheim R, Bratseth V, Forfang K, Seljeflot I. Prothrombotic markers in patients with acute myocardial infarction and left ventricular thrombus formation treated with PCI and dual antiplatelet therapy. 10th Chronic Heart Failure Research Symposium 2012, Oslo Abstract P05

Pettersen A-Å, Arnesen H, Opstad TB, Bratseth V, Seljeflot I. Markers of endothelial and platelet activation are associated with high on aspirin residual platelet reactivity. 10th Chronic Heart Failure Research Symposium 2012, Oslo Abstract P06

Knudsen EC, Seljeflot I, Müller C, Andersen GA. Levels of IgM antibodies against phosphorylcholine (IgM anti-PC) are not associated with glucometabolic disturbances in patients with acute ST-elevation myocardial infarction. 10th Chronic Heart Failure Research Symposium 2012, Oslo Abstract P07

Tveit A, de Caterina R, Smith P, Arnesen H, Seljeflot I. Effects of plasma levels of angiotensin receptor blockade and maintained sinus rhythm after electrical cardioversion for persistent atrial fibrillation. 10th Chronic Heart Failure Research Symposium 2012, Oslo Abstract P44

Husebye T, Eritsland J, Arnesen H, Seljeflot I, Sandvik L, Mangschau A, Bjørnerheim R, Andersen GØ. Levosimendan improves regional contractility in post-ischemic myocardium in patients with acute PCI-treated STEMI complicated by symptomatic heart failure. 10th Chronic Heart Failure Research Symposium 2012, Oslo Abstract P46

Opstad TB, Pettersen AÅ, Åkra S, Arnesen H, Seljeflot I. The IL-18 A/G polymorphism is associated with clinical events in CAD. 10th Chronic Heart Failure Research Symposium 2012, Oslo Abstract P51

Njerve IU, Pettersen AÅ, Bratseth V, Arnesen H, Seljeflot I. Effect of clopidogrel and aspirin on circulating fractalkine (CX3CL1) levels in patients with coronary artery disease. 10th Chronic Heart Failure Research Symposium 2012, Oslo Abstract P52