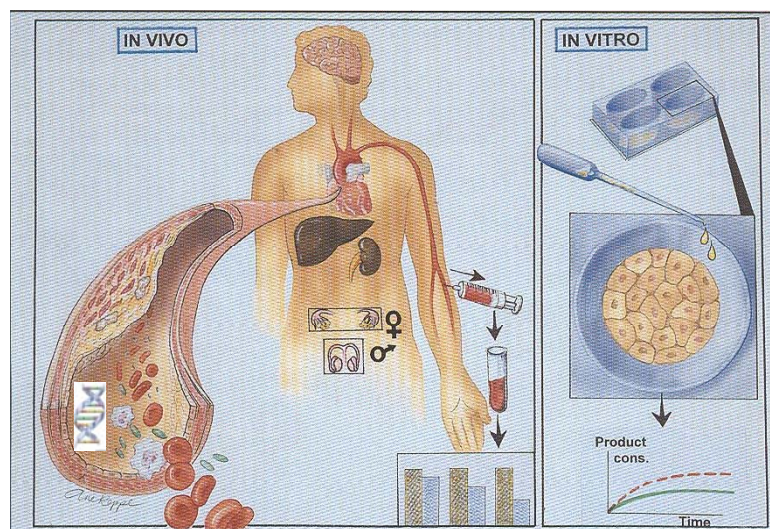


# Center for Clinical Heart Research (CCHR)

Department of Cardiology  
Medical Division  
Oslo University Hospital, Ullevål



## Annual Report 2011

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## 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.

**1.1 The main aim of the research in CCHR is to continuously 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.**

**”Independent 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 continuously 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 diabetes are central.

Studies on mechanisms/translational studies, especially of biochemical 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, haemostasis and peroxidative processes on the circulatory, cellular and genetic levels.

With regard to therapy, controlled life style intervention and individualised 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.

**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 represents a limiting factor and a challenging daily life for both PhD students and staff. The interrelation

with the outpatient clinic has unfortunately been changed after the administrative re-construction of the hospital. Hopefully, this 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 2011.

March 2012

Ingebjørg Seljeflot (sign)  
professor dr. philos

Harald Arnesen (sign)  
professor em dr. med

Svein Solheim (sign)  
MD post.doc

## 2. Organization and working procedures.

**2.1** Administration and organization aspects are undertaken in total by the center leaders.

Of 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. Authors of published papers are congratulated, and the 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 2011, 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 October 2012 at Noreheim/Norefjell, a most suitable location for our group size with about 20 persons. Two highly competent external guests were invited as discussants to the presentations which were given by all participants related to their individual research projects. The distinguished guests, professor Steen Dalby Kristensen from Aarhus University, Denmark and professor Jens Petter Berg from Oslo University also gave their special lectures. An invited lecture on "Team building for individual excellence" was given by former head coach of the national alpine ski team Marius Arnesen.

With scientific work from Friday afternoon till Sunday noon, interrupted by physical activity in the mountain terrain on Saturday and a great dinner on Saturday night, the symposium turned out very successful, scientifically and socially.

### 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 (external financed) which 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 is open for several other PhD-students at the Department of Cardiology and from other collaborating groups.

### 3. Scientific Activities

#### 3.1 Defended thesis with supervision from CCHR

Jostein Grimsmo, MD

*"Cardiorespiratory function, atrial fibrillation and cardiovascular health effects of long-term endurance training in three different age groups of former or current long distance cross-country skiers. A 28-30 year follow-up study. "The Birkopp study""*

January 2011

Supervisors: Professor Sverre Mæhlum/Professor em. Harald Arnesen

Ellen Bøhmer, MD

*"Studies on patients with ST-elevation myocardial infarction and long transfer distance to PCI centres"*

May 2011

Supervisors: MD PhD Sigrun Halvorsen, Professor em. Harald Arnesen

Haakon Kihl-Grøgaard, MD

*"Progenitor cells, growth factors and inflammation in acute myocardial infarction"*

September 2011

Supervisors: Professor em. Arnfinn Ilebekk, Professor em. Harald Arnesen

Eva Cecilie Knudsen, MD

*"Abnormal glucose regulation in patients with acute ST-elevation myocardial infarction"*

November 2011

Supervisors: MD PhD Geir Ø. Andersen, Professor Ingebjørg Seljeflot

Eline Bredal Furenes, Medical Student in research

*" Studies on matrix metalloproteinases in atherosclerosis and coronary heart disease"*

April 2011

Medical Student Research Program, Faculty of Medicine, UoO

Supervisors: Professor Ingebjørg Seljeflot/Professor em. Harald Arnesen/Post doc. Svein Solheim

#### 3.2 Defended thesis with collaboration /co-supervision from CCHR

Skjalg Hassellund, MD

*"Effects of anticyanin supplementation on pathophysiological markers of cardiovascular disease"*

December 2011

Supervisors: MD PhD Morten Rostrup, Professor Sverre E. Kjeldsen

Inger Ariansen, MD

*"Impact of permanent atrial fibrillation on 75-years olds. A cross-sectional study of quality of life, exercise capacity, lung function and heart rate in a general population"*

December 2011

Supervisors: Professor Knut Gjesdal, MD PhD Arnljot Tveit

Nisha Mistry MD

*"Assesment of left ventricular function in patients with recent ST-elevation myocardial infarction"*

November 2011

Supervisors: MD PhD Reidar Bjørnerheim, MD PhD Sigrun Halvorsen, Professor Sverre E. Kjeldsen.



### **3.3 Ongoing projects, mainly PhD-projects (short version)**

#### **"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 is extensively investigated with regard to the metabolic syndrome.

Polymorphisms in the gene coding for Gp130 and their influence on phenotype (circulating proteins), for clinical end-points and for a possible effect of intervention with diet and/or omega-3 fatty acids are further 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 are undertaken. A predictive score for cardiovascular events based on the genetic expression of these mediators has been launched.

Project for the PhD degree (Cand.med. Thomas Weiss)

*Supervisors: Professor Ingebjørg Seljeflot/Professor em. Harald Arnesen*

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

In this study the primary aim is 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) are registered in 1001 patients and related to their initial laboratory response to aspirin. Thereafter patients are 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. A series of laboratory tests on platelet function are 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 phenomenon that despite aspirin treatment, some patients have high platelet activation.

Project for the PhD degree (Cand.med. Alf-Åge Pettersen).

*Supervisors: Professor em. Harald Arnesen/Professor Ingebjørg Seljeflot*

#### **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)

on interleukin-18, matrix metalloproteinase 9, tissue factor and tissue factor pathway inhibitor.

Project for the PhD degree (Master of Science Trine Baur Opstad).

*Supervisors: Professor Ingebjørg Seljeflot/Professor em. Harald Arnesen*

**ASCET-Thrombo: "Evaluation of thrombin generation in sub-groups of patients with coronary artery disease".**

In this substudy of the ASCET trial (vide supra), new methodology for ex vivo evaluation of thrombin generation (Endogenous Thrombin Potential with the Calibrated automated thrombogram (CAT)) as a thrombotic marker is evaluated against a traditional in vivo method for thrombin generation (Prothrombin Fragment 1+2) in samples from the 1001 patients. Special attention is 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.

Part of it being the basis for the Master of Science project (defended October 2010; Medical technologist Vibeke Bratseth).

*Supervisors: Professor Ingebjørg Seljeflot/Cand.med. Alf-Åge Pettersen*

**EXCADI (Exercise training in patients with coronary artery disease and diabetes).**

Based on the population from the ASCET study (vide supra) a study was started aiming at evaluating the effect of systematic physical exercise training in a randomised trial including patients with documented coronary artery disease and diabetes type-2. Primary aims are effect on glucometabolic regulation and biomarkers of atherothrombosis. Power calculation resulted in the need for 160 patients to be included. 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 exercise training is conducted in cooperation with the Norwegian School for Science in Sports, including 2 students for the degree of Master of Science.

Project for the PhD degree (Cand.med. Rune Byrkjeland).

*Supervisors: Post doc. MD PhD Svein Solheim / Professor Ingebjørg Seljeflot / Professor em. Harald Arnesen*

**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.

Project for the PhD degree (Cand.med. Ida Unhammer Njerve).

*Supervisors: Professor Ingebjørg Seljeflot, Post doc. MD PhD Svein Solheim /Post doc Thomas Weiss, Vienna.*

**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.

Project for the PhD degree (Cand.med. Sara Ulimoen).

*Supervisors: Dr.med. Arnljot Tveit/Professor em. Harald Arnesen*

**"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.

Project for the PhD degree. (Cand.med. Irene Grundvold).

*Supervisors: Professor em. Harald Arnesen/Professor Sverre Erik Kjeldsen/Dr.med. Johan Bodegard*

**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. Sampling, processing, biobanking and the biochemical analyses are undertaken at CCHR. Biochemical analyses will be part of the main project.

Project for the PhD degree (Cand.med. Trygve Huseby)

*Supervisors: MD PhD Geir Ø. Andersen, MD PhD Jan Eritsland, Professor Ingebjørg Seljeflot*

### **POSTEMI (Post-conditioning in STEMI 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). Processing of samples, biobanking and biochemical analyses are undertaken at CCHR.

Project for the PhD degree. (Cand.med. Limalanathan Shanmuganath)

*Supervisors: MD PhD Jan Eritsland, MD PhD Post.doc Geir Ø. Andersen*

### **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 (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-6Receptor, Gp130, cardiotropin-1 and leukemia inhibitory factor), 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.

Project for the PhD degree. (Cand.med. Vibeke Ritschel)

*Supervisors: MD PhD Post.doc Geir Ø. Andersen, Professor Ingebjørg Seljeflot, MD PhD Jan Eritsland,*

### **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 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 clarify mechanisms related to sudden cardiac death related 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.

Project for the PhD degree. (Cand.med. Hilde Ulsaker)

*Supervisors: MD PhD Arnljot Flaa, MD PhD Eivind Berge, Professor Ingebjørg Seljeflot*

### 3.4 Post doc. Projects

#### **"Post ASTAMI".**

Dr.med. Svein Solheim who defended his thesis in 2008 has 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 in vitro studies in cell cultures are further planned.

Post doc. project (MD PhD Svein Solheim)

#### **GLUMIIK (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 paid 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"

Post.doc project (MD PhD Eva Cecilie Knudsen, Post.doc MD PhD Geir Øystein Andersen, Professor Ingebjørg Seljeflot)

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.

Post doc. project (MD PhD Arnljot Tveit)

**ABAF (Asker and Bærum Atrial Fibrillation study).** A population study to map the prevalence of atrial fibrillation (AF) in individuals above 75 years. A total of 1200 individuals participated and AF was diagnosed in 12%. A case-control study (60 cases/120 controls) is conducted to study risk factors, quality of life, sosio-economic conditions etc. A biobank is established in ABAF and a series of analyses are performed to increase the understanding of trigger mechanisms and potentially new therapeutic principles. Genetic aspects are also studied. The biochemical analyses are undertaken at CCHR.

Post doc. project (MD PhD Arnljot Tveit)

**NORDISTEMI (NORwegian Distance ST-Elevation Myocardial Infarction study).**

This regional study in Helse Sør-Øst where 240 patients with acute ST-elevation myocardial infarction, all receiving thrombolytic therapy because of long distance(>90 minutes) to the PCI center, randomized to direct transport to OUH-Ullevål for primary coronary angiography ± PCI or to clinical stabilization at the local hospital for later referral to coronary angiography ± PCI when indicated (according to previous routine), was finished and defended in 2011. Additional studies on mechanisms related to Haemostasin and inflammation are ongoing.

Project ("post.doc") MD PhD Sigrun Halvorsen, Professor Ingebjørg Seljeflot, professor em. Harald Arnesen

### **3.5 Other projects with support/supervision from CCHR**

#### **NORCAST (Norwegian Cardiac Arrest Survival Trial)**

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 multidisciplinary 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 disciplines 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*.

#### **Diabetes in children and atherosclerosis development.**

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.

PhD project (Cand.med. Martin Høyer)

*Supervisor: Professor Knut Dahl-Jørgensen*

**Effect of benfothiamin in type-1 diabetes** ("Influence of oral benfothiamine supplementation on the progression of micro-and macrovascular complications in type-1 diabetes").

This principle is being tested in a randomized, placebo-controlled study over 2 years in 70 patients with long-standing type-1 diabetes. The aim is to evaluate whether this simple "drug" (vitamin B-type) might influence positively the glucose regulation in such patients. The participants undergo neurophysiological examination and a biobank is established to study any influence on markers of atherosclerosis at CCHR. Also, monocytes are isolated for *ex vivo* studies on potential effects of thiamin.

*Post doc. David Frazer and Professor Kristian Hanssen are primarily responsible for the project.*

**Deleterious cardiac effects of long-time use of anabolic steroids evaluated with different cardiological methods.**



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 used 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 (in detail by flowcytometry and aggregation) are studied. The project is initiated from OUH Aker with all biochemical investigations being performed at CCHR.

PhD project (Cand.med. Paul Vanberg)

*Supervisor: Professor Dan Atar*

### **Pulmonal arterial hypertension and right ventricle function in patients with chronic obstructive lung disease (COLD).**

This study is aimed to evaluate non-invasive 3-D echo 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 resonance 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-calsification), are collected. The laboratory analysis and biochemical supervision will be undertaken at CCHR. The study is performed at OUS Aker.

PhD project (Cand.med. Janne Mykland Hilde)

*Supervisor: Amanuensis Kjetil Steine*

### **BAMI ("Biobanking in patients with Acute Myocardial Infarction").**

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. (Professor Ingebjørg Seljeflot)

A Steering committee for BAMI is established.

### **Biomarkers of inflammation and haemostasis in welders; exposed to high-grade pollution**

Increased mortality due to pulmonary and cardiovascular diseases by increasing pollution in the external environment is shown. The mechanisms behind why the cardiovascular and pulmonary system is vulnerable to such 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 to a hyper-coagulable state. If this is the case, it may constitute a work-related risk factor for the development of certain cardiovascular diseases. 160 Russian welders are investigated before and after a 3-year period of daily/weekly work for inflammatory and haemostatic variables. Blood sampling is undertaken in Russia and brought to our laboratory. The degree of pollution is examined throughout the study period. In collaboration with National Institute of Occupational Health (professor Dag Ellingsen).

#### **A comparison between two types of anesthesia for open abdominal aortic surgery (ABSENT-study)**

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

A study in collaboration with Vestfold HF, Tønsberg (MD Espen Lindholm, PhD-student) and Department of Anesthesia, OUH, Ullevål (professor Knut Arvid Kirkebøen)

#### **Markers of inflammation in cerebrospinal fluid (CSF) in delirium associated with hip-fracture**

Potential biomarkers that may shed light over the possible mechanisms related to delirium; association with exaggerated neuroinflammatory response, increased macrophage and neutrophil chemotaxis into CNS, damage of myelin along with low-grade ischemia and blood-brain barrier dysfunction. Inflammatory biomarkers that might be present also in CSF are investigated. Little knowledge exists on which biomarkers are present. We try to sort out any presence of CRP and components in the interleukin-6 transsignaling pathway, in serum and CSF. About 100 patients are included.

A collaboration with Department of Geriatric, OUH Ullevål (professor Torgeir Bruun Wyller and MD Leiv Otto Watne, PhD-student)

### **3.6 Planned projects**

#### **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 drawn 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 circulating 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.

PhD project (Cand.med. Ragnhild Helseth)

*Supervisors: Professor Ingebjørg Seljeflot, Post doc. MD PhD Svein Solheim / Post doc Thomas Weiss, Vienna.*

#### **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  $\geq 70$ -80 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 Oslo university hospital Ullevål (OUHU), Aalborg university hospital (AaUH), Akershus university hospital (AHUH) Asker and Baerum Hospital (ABH)

Twin PhD students at OUHU and AaUH, potentially also at AHUH.

*Responsible: Professor em. Harald Arnesen, post. doc Svein Solheim, professor Dan Atar and professor Ingebjørg Seljeflot*

## 4. Laboratory Methods

### 4.1 Locally

- Facilities for blood sampling and processing for biobanking after SOPs (Centrifuges, cooling centrifuges, freezers (-30°C and -80°C))
- Platelet function testing with aggregometry and flow-cytometry in addition to "bedside" screening tests (PFA100, VerifyNow)
- ELISA's

### 4.2 Located outside (in related laboratories)

- HPLC, specially used for elucidation of endothelial function and peroxidation
- ViiA7 RT-PCR (Applied biosystems)  
Studies on gene expression  
Studies on genetic polymorphisms

As several of our own laboratory instruments are placed in different facilities in collaborating laboratories, due to serious lack of space "at home", it is a limitation factor and challenging daily life for both PhD students and staff and therefore for the research activity.

## 5. Collaborators

Tonje Amb Aksnes MD, PhD

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## 6. Publications 2011

### Articles

Andersen GØ, Knudsen EC, Aukrust P, Yndestad A, Oie E, Müller C, Seljeflot I, Ueland T. Elevated serum osteoprotegerin levels measured early after acute ST-elevation myocardial infarction predict final infarct size. *Heart* 2011; 97 (6), 460-5

Andersen GØ, Ueland T, Knudsen EC, Scholz H, Yndestad A, Sahraoui A, Smith C, Lekva T, Otterdal K, Halvorsen B, Seljeflot I, Aukrust P. Activin A levels are associated with abnormal glucose regulation in patients with myocardial infarction: potential counteracting effects of activin A on inflammation. *Diabetes* 2011; 60 (5), 1544-51

Bendz B, Endresen K, Eritsland J, Arnesen H. Don't withdraw all blood platelet inhibitors. *Tidsskr Nor Laegeforen* 2011; 131 (8), 800; author reply 800

Byrkjeland R, Nilsson BB, Westheim AS, Arnesen H, Seljeflot I. Inflammatory markers as related to disease severity in patients with chronic heart failure: limited effects of exercise training. *Scand J Clin Lab Invest* 2011; 71 (7), 598-605

Bøhmer E, Kristiansen IS, Arnesen H, Halvorsen S. Health and cost consequences of early versus late invasive strategy after thrombolysis for acute myocardial infarction *Eur J Cardiovasc Prev Rehabil* 2011; 18 (5), 717-23

Grøgaard HK, Solheim S, Landsverk KS, Seljeflot I, Hoffmann P, Arnesen H, Ilebekk A. Circulating CD34<sup>+</sup> progenitor cells and growth factors in patients treated with PCI for acute myocardial infarction or stable angina pectoris. *Scand J Clin Lab Invest* 2011; 71 (4), 322-9

Karlsen A, Svendsen M, Seljeflot I, Sommernes MA, Sexton J, Brevik A, Erlund I, Serafini M, Bastani N, Remberg SF, Borge GI, Carlsen MH, Bøhn SK, Myhrstad MC, Dragsted LO, Duttaroy AK, Haffner K, Laake P, Drevon CA, Arnesen H, Collins A, Tonstad S, Blomhoff R. Compliance, tolerability and safety of two antioxidant-rich diets: a randomised controlled trial in male smokers. *Br J Nutr* 2011; 106 (4), 557-71

Knudsen EC, Seljeflot I, Abdelnoor M, Eritsland J, Mangschau A, Müller C, Arnesen H, Andersen GO. Impact of newly diagnosed abnormal glucose regulation on long-term prognosis in low risk patients with ST-elevation myocardial infarction: A follow-up study. *BMC Endocr Disord* 2011; 11, 14

Knudsen EC, Seljeflot I, Abdelnoor M, Eritsland J, Mangschau A, Müller C, Arnesen H, Andersen GØ. Elevated levels of PAI-1 activity and t-PA antigen are associated with newly diagnosed abnormal glucose regulation in patients with ST-elevation myocardial infarction. *J Thromb Haemost* 2011; 9 (8), 1468-74

Kringen MK, Narum S, Lygren I, Seljeflot I, Sandset PM, Trøseid AM, Johansen PW, Brørs O, Holthe MR. Reduced platelet function and role of drugs in acute gastrointestinal bleeding

*Basic Clin Pharmacol Toxicol* 2011; 108 (3), 194-201

Mistry N, Abdelnoor M, Seljeflot I, Hoffmann P, Bøhmer E, Bjørnerheim R, Kjeldsen SE, Halvorsen S. Amino-terminal pro-B-type natriuretic peptide (NT-proBNP) levels 3 months after myocardial infarction are more strongly associated with magnetic resonance-determined ejection fraction than NTproBNP levels in the acute phase. *J Card Fail* 2011; 17 (6), 479-86

Mistry N, Beitnes JO, Halvorsen S, Abdelnoor M, Hoffmann P, Kjeldsen SE, Smith G, Aakhus S, Bjørnerheim R. Assessment of left ventricular function in ST-elevation myocardial infarction by global longitudinal strain: a comparison with ejection fraction, infarct size, and wall motion score index measured by non-invasive imaging modalities. *Eur J Echocardiogr* 2011; 12 (9), 678-83

Patrono C, Andreotti F, Arnesen H, Badimon L, Baigent C, Collet JP, De Caterina R, Gulba D, Huber K, Husted S, Kristensen SD, Morais J, Neumann FJ, Rasmussen LH, Siegbahn A, Steg PG, Storey RF, Van de Werf F, Verheugt F. Antiplatelet agents for the treatment and prevention of atherothrombosis. *Eur Heart J* 2011; 32 (23), 2922-32

Pettersen AA, Arnesen H, Opstad TB, Seljeflot I. The influence of CYP 2C19\*2 polymorphism on platelet function testing during single antiplatelet treatment with clopidogrel *Thromb* 2011; 9, 4

Seljeflot I, Nilsson BB, Westheim AS, Bratseth V, Arnesen H. The L-arginine – asymmetric dimethylarginine ratio is strongly related to the severity of chronic heart failure. No effects of exercise training. *J Card Fail* 2011; 17 (2), 135-42

Steg PG, Huber K, Andreotti F, Arnesen H, Atar D, Badimon L, Bassand JP, De Caterina R, Eikelboom JA, Gulba D, Hamon M, Helft G, Fox KA, Kristensen SD, Rao SV, Verheugt FW, Widimsky P, Zeymer U, Collet JP. Bleeding in acute coronary syndromes and percutaneous coronary interventions: position paper by the Working Group on Thrombosis of the European Society of Cardiology. *Eur Heart J* 2011; 32 (15), 1854-64

Weiss TW, Arnesen H, Trøseid M, Kaun C, Hjerkin EM, Huber K, Wojta J, Seljeflot I. Adipose tissue expression of interleukin-18 mRNA is elevated in subjects with metabolic syndrome and independently associated with fasting glucose. *Wien Klin Wochenschr* 2011; 123 (21-22), 650-4

Weiss TW, Rosenthal SL, Zimet GD. Attitudes toward HPV Vaccination among Women Aged 27 to 45. *ISRN Obstet Gynecol*, 2011, 670318

Weiss TW, Seljeflot I, Hjerkin EM, Arnesen H. Adipose tissue pro-inflammatory gene expression is associated with cardiovascular disease. *Int J Clin Pract* 2011; 65 (9), 939-44



Grimsmo J, Grundvold I, Maehlum S, Arnesen H. Echocardiographic evaluation of aged male cross country skiers. *Scand J Med Sci Sports* 2011; 21 (3), 412-9

Hopp E, Lunde K, Solheim S, Aakhus S, Arnesen H, Forfang K, Edvardsen T, Smith HJ. Regional myocardial function after intracoronary bone marrow cell injection in reperfused anterior wall infarction - a cardiovascular magnetic resonance tagging study. *J Cardiovasc Magn Reson* 2011; 13, 22

Beitnes JO, Gjesdal O, Lunde K, Solheim S, Edvardsen T, Arnesen H, Forfang K, Aakhus S. Left ventricular systolic and diastolic function improve after acute myocardial infarction treated with acute percutaneous coronary intervention, but are not influenced by intracoronary injection of autologous mononuclear bone marrow cells: a 3 year serial echocardiographic sub-study of the randomized-controlled ASTAMI study. *Eur J Echocardiogr* 2011; 12 (2), 98-106

Grimsmo J, Maehlum S, Moelstad P, Arnesen H. Mortality and cardiovascular morbidity among long-term endurance male cross country skiers followed for 28-30 years. *Scand J Med Sci Sports* 2011; 21 (6), e351-8

## Congress Abstracts

1. Falch E, Kirkhus B, Lamglait A, Eilertsen KE, Haider T, Vik H, Hoem N, Habve TA, Basu S, Olsen E, Seljeflot I, Nyberg L, Elind E, Ulven SM. Bioavailability of marine n-3 fatty acids from enriched food products and fish oil supplement in healthy humans. Lipidforum, Ålesund 2011
2. Byrkjeland R, Arnesen H, Nilsson BB, Westheim AS, Seljeflot I. Inflammatory markers and disease severity in patients with chronic heart failure. Limited effects of exercise training. Eur Congress on Atherosclerosis. Gøteborg 2011
3. Opstad TB, Pettersen AÅ, Åkra S, Bratseth V, Weiss T, Arnesen H, Seljeflot I. The influence of TF and TFPI polymorphisms on thrombin generation in patients with stable CAD. Eur Congress on Atherosclerosis. Gøteborg 2011
4. Opstad TB, Pettersen AÅ, Åkra S, Weiss T, Arnesen H, Seljeflot I. Genetic variations, mRNA expression and circulating levels of matrix metalloproteinase-9 in patients with CAD. Eur Congress on Atherosclerosis. Gøteborg 2011
5. Solheim S, Seljeflot I, Lunde K, Aakhus S, Bratseth V, Forfang K, Arnesen H. The influence of intracoronary injection of mononuclear bone marrow cells on haemostatic factors in patients with acute myocardial infarction. Eur Congress on Atherosclerosis. Gøteborg 2011
6. Solheim S, Arnesen H, Lunde K, Aakhus S, Bjørnerheim R, Bratseth V, Forfang K, Seljeflot I. Haemostatic factors in patients with acute myocardial infarction and left ventricular thrombus formation treated with dual antiplatelet therapy. Congress of the European Society of Cardiology 2011, Paris Eur H J 2011
7. Kristin Angel<sup>1</sup>, Sella Aarrestad Provan<sup>2</sup>, Petter Mowinckel<sup>2</sup>, Ingebjørg Seljeflot<sup>3,4</sup>, Tore Kristian Kvien<sup>2,4</sup>, Dan Atar<sup>1,4</sup>. The L-arginine/asymmetric dimethylarginine (ADMA) ratio is improved during anti-Tumor Necrosis Factor – $\alpha$  therapy in patients with inflammatory arthropathies. Association with aortic stiffness. 9<sup>th</sup> Chronic Heart Failure Research Symposium 2011, Oslo Abstract P 10.
8. Hanna Dis Margeirsdottir, Martin Heier, Jakob Roald Larsen, Cathrine Brunborg, Knut Dahl-Jørgensen, Ingebjørg Seljeflot. Evidence for low grade inflammation in diabetic children on intensive insulin treatment: a population based study. Int Soc Pediatric and Adolescent Diabetes (ISPAD), 2011 Miami.
9. Hanna Dis Margeirsdottir, Mette Ree Holthe, Martin Heier, Knut Dahl-Jørgensen, Ingebjørg Seljeflot. Platelet activation in diabetic children on intensive insulin treatment. Int Soc Pediatric and Adolescent Diabetes (ISPAD), 2011 Miami.

10. Martin Heier, Hanna Dis Margeirsdottir, Peter A. Torjesen, Ingebjørg Seljeflot, Cathrine Brunborg, Kristian F. Hanssen and Knut Dahl-Jørgensen. Methylglyoxal-derived hydroimidazolone and early atherosclerosis in children with type 1 diabetes. Int Soc Pediatric and Adolescent Diabetes (ISPAD), 2011 Miami.
11. Svendsen M, Klemsdal TO, Heggen E, Holme I, Pedersen TR, Seljeflot I, Blomhoff R, Tonstad S. Effect of Dietary Intake of Kiwi Fruit on 24-Hour Ambulatory Blood Pressure. Am Heart Ass Scientific Session 2011, Orlando
12. Njerve IU, Pettersen AA, Bratseth V, Arnesen H, Seljeflot I. Circulating fractalkine (CX3CL1) in patients with stable coronary artery disease (CAD) with and without diabetes mellitus. 9<sup>th</sup> Chronic Heart Failure Research Symposium 2011, Oslo Abstract P52
13. Opstad, TB, Pettersen, AÅ, Bratseth, V, Arnesen, H, Seljeflot, I. The influence of tissue factor and tissue factor pathway inhibitor polymorphisms on thrombin generation in stable CAD patients. 9<sup>th</sup> Chronic Heart Failure Research Symposium 2011, Oslo Abstract P 12.
14. Opstad, TB<sup>1,2</sup>, Pettersen, AÅ<sup>1,2</sup>, Åkra, S<sup>1,2</sup>, Arnesen, H<sup>1,2,3</sup>, Seljeflot, I<sup>1,2,3</sup> The influence of the IL-18 +183 A/G polymorphism on gene- and protein expression in stable CAD patients. 9<sup>th</sup> Chronic Heart Failure Research Symposium 2011, Oslo Abstract P09
15. Ohm IK, Sandanger Ø, Nymo SH, Finsen AV, Bliksøen M, Mariero LH, Valen G, Seljeflot I, Solheim S, Aukrust P, Yndestad A, Vinge LE. Extracellular mitochondrial DNA is a putative toll-like receptor 9 agonist on cardiac fibroblasts during myocardial infarction. Am Heart Ass Scientific Session 2011, Orlando.
16. Svendsen M, Klemsdal TO, Heggen E, Holme I, Pedersen TR, Seljeflot I, Blomhoff R, Tonstad S. Effect of dietary intake of kiwi fruit on 24-hour ambulatory blood pressure. Am Heart Ass Scientific Session 2011, Orlando.