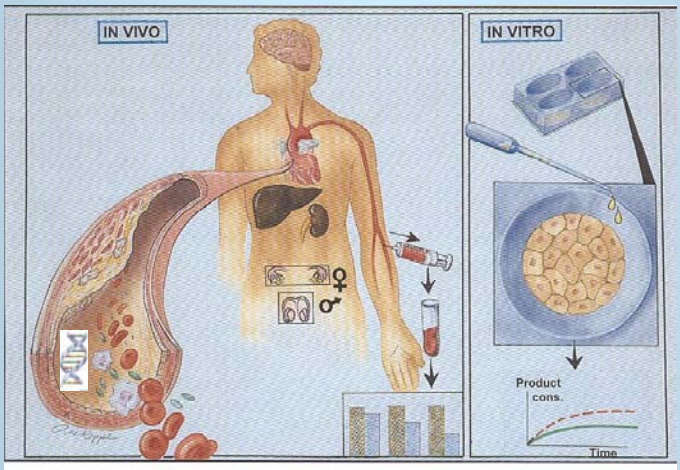
Center for Clinical Heart Research (CCHR)

Department of Cardiology
Medical Division
Oslo University Hospital, Ullevål

"Team building for individual excellence"



Annual Report 2014

Oslo University Hospital

UiO : University of Oslo

Center for Clinical Heart Research, OUH, Ulleval

Content

Preface

Center for Clinical Heart Research (CCHR) was grounded in 1991 and is now organized as a part of the Department of Cardiology, Medical Division, OUH Ullevål.

The trademark of CCHR is researcher-initiated clinical, randomized intervention trials including studies on basic mechanisms in pathophysiology in cardiovascular disease states

The Center is one of the resarch groups within Department of Cardiology. In addition, the Center plays an important role as a core laboratory for other research groups in the Department as well as for other in the Division and others.
CCHR is located within the Department, close to the patients, which is crucial for the scientific activity.
The Center has from an early stage close collaboration with Vestre Viken Trust, Asker & Bærum Hospital and Akershus University Hospital by having common PhD-projects and students. This has continued also after the new group structure given by OUH and the University of Oslo.

Our new locations/facilities that have been in use since 2013 have resulted in an improved milieu both for research and socially, by connecting phd-students, technologists and supervisors closer together.

We are pleased to give this annual report for 2014.

April 2015

Ingebjørg Seljeflot (sign)
professor dr. philos

Harald Arnesen (sign)
professor em dr. med

Svein Solheim (sign)
MD post.doc

Finances

The leader is financed from the Department of Cardiolgy Ullevål by a combined position for the Center and for being Head of the Research and Development Section in the Department.
Budgets for the single projects, including salary for PhD-studnents, technical personell and running laboratory expenses are based on external funding from different sources.

The economical support from Stein Erik Hagens Foundation for Clinical Heart Research has been of fundamental importance for the activity also in 2014.

Strategy

- Systematic researcher-initiated clinical heart research, based on accepted research methodology along with the flow of patients in OUH

- Projects related to acute myocardial infarction, chronic heart diseases like heart failure, atrial fibrillation and diabetes

- Focus on ischemic heart disease in the elderly

- Biobanking, standardized sampling and processing
  About 90 % of all publications are based on biobanks

- Main issue: Studies on mechanisms/translational studies, on biochemical, cellular and genetic aspects especially related to inflammation, thrombotic processes and endothelial dysfunction

- All projects are in line with the strategy for research in Department of Cardiology

- CCHR is a group within the network of Center for Heart Failure Research, OUH/UiO

- To be an interdisciplinary composed group, including researchers at post.doc level

Main Goals

- to increase understanding of disease mechanisms, pathogenetic factors, as well as effects of interventions in patients with cardiovascular disease

- to design and carry out randomized clinical trials, and to further expand on translational research in light of new knowledge and by use of new technology in materials from extended biobanking

- to constitute a dynamic research group with highly motivated participants where group adherence and common efforts lead to progression – for the research group as well as for the individual researcher
  (”Team building for individual excellence”)

- to exert research of high quality, aiming at publications in high ratet international journals

- to create an arena for scientific discussions, and for structured research supervision and teaching

- to educate competent PhD candidates a.o. who contribute to academic skill in clinical medicine and research

- to contribute to extended research skill on a post doc level

- to strengthen collaboration with national and international research groups

Organization

Administration and organization aspects are undertaken by the Center leaders.

Our 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. Furthermore, external experts on special relevant topics and co-workers from other groups and 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. The PhD students are encouraged to prepare abstracts and participate on international congresses, primarily with presentation of own results. In 2014, 12 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. Decisions and ”Contracts” for collaboration with other research groups are made by the leaders, all based on common scientific interests.

Scientific Symposium, ”Team building for individual excellence”, are organized every second year. It was organized in 2013 and the next will be prepared for October 2015.

In 2014, thanks to the economic possibilites from Stein Erik Hagens Foundation for Clinical Heart Research, PhD-student, Ida U.Njerve has been working at Mount Sinai School of Medicine, New York, for one year, resulting in increased scientific knowledge and new important international collaborators.

Several members of CCHR have participated in larger international congresses, all as invited speakers or, mostly, by presenting selected scientific abstract from the group (See abstract list).

Organization (cont.)

Personell

Leadership: The leader is also the head of the R&D Section at Department of Cardiology, 100% position, professor II at UiO. In addition, medical leaders are one previous post.doc and one professor emeritus, the latter is also the Centers delegate in the Board for Stein Erik Hagens Foundation for Clinical Heart Research, OUH Ullevål.
Employees: 2 medical technologists, both with a Master of Science in biomedicine and 0.5 study nurse.

11 PhD students, 5 post.docs and 1 epidemiologist participate in the milieu.
In addition, the scientific milieu and the laboratory facilities are open for several other PhD-students, partially supervised at the Department of Cardiology and from other collaborating groups.

Scientific Activities Defended PhD-thesis 2014

Irene Grundvold, MD
Long-term Predictors of Atrial Fibrillation in Healthy Middle-aged Men

Supervisors: Johan Bodegård, Harald Arnesen, Sverre Erik Kjeldsen

In a long-term observational study of 2014 initially healthy middle-aged Norwegian men aged 40-60 years, included in a prospective cardiovascular survey in 1972-75, 270 participants (13%) developed atrial fibrillation (AF) during median 30 years of follow-up. The mean age at the diagnosis of AF was 71 years (range 40-88 years).

The results indicated that not only high systolic blood pressure (SBP), which is well known, but also SBP values in the upper normal range (128-138 mmHg) were significantly predictive of incident AF in the present population.

In addition, high baseline body mass index (BMI $\geq$ 28 kg/m2) and weight gain $\geq$ 10kg from the age of 25 to mid-life were long-term predictors of incident AF, but only in men with physical fitness below the population median when tested on a standardized bicycle exercise ECG test.

Finally, low exercise heart rate (HR $<$100 bpm) after 6 min exercise on a moderate workload (100 W) was predictive of incident AF, significant also after adjustment for age, SBP and physical fitness. These men (n=260) were characterized by high physical fitness, low resting and low maximum HR. The risk for incident AF was especially high when hypertensive SBP measurements were present at baseline.
These data suggest a relationship between increased vagal tone, high stroke volume and incident AF, particularly in physically fit men.

Eline Bredal Furenes, MD
Studies on matrix metalloproteinases in atherosclerosis and coronary heart disease

Supervisors: Ingebjørg Seljeflot, Svein Solheim, Harald Arnesen, Trine B. Opstad

Matrix metalloproteinase-9 (MMP-9), tissue inhibitor of matrix metalloproteinase-1 (TIMP-1) and -2, extracellular matrix metalloproteinase inducer (EMMPRIN) and pregnancy associated plasma protein A (PAPP-A) were explored in patients with atherosclerosis and coronary heart disease (CHD). MMPs contributes to thrombotic complications in atherosclerosis by degrading the fibrous cap of the plaque. EMMPRIN has been discussed to be involved in the synthesis and release of MMP-9, whereas TIMP-1 is a specific endogenous inhibitor of MMP-9.

In the present work three different patient populations were investigated. Subjects participating in the DOIT study were elderly men with high risk for CHD, and baseline results showed that smokers had significantly higher circulating levels of MMP-9 and MMP-9/TIMP-1 ratio. MMP-9 was significantly correlated to LDL-cholesterol and inversely correlated to HDL-cholesterol. Intervention with diet and/or n-3 PUFA supplementation did not influence the measured markers. MMP-9 was associated with cardiovascular (CV) events in the 36 months follow-up period. Elevated MMP-9 levels predicted CV events in individuals with hypertriglyceridemia.
In a population with acute myocardial infarction (AMI) or stable angina pectoris (AP) undergoing PCI, higher levels of MMP-9 were observed in the AMI group compared to the AP group three hours after PCI.
In the third study population patients with ST-elevation myocardial infarction were randomized to injection of bone marrow-derived mononuclear cells (mBMC) in the index coronary artery, or controls without injection. A more pronounced increase in MMP-9 levels were observed from before transplantation to 2-3 weeks and 3 months after compared to the control group. EMMPRIN levels were reduced from baseline to later time points in both groups, whereas TIMP-1 levels did not change in either groups. Furthermore, MMP-9 and EMMPRIN gene expression levels in circulating leucocytes were significantly reduced from baseline to 3 months in the mBMC group. Peak levels of CK, and infarct size measured by SPECT, correlated significantly to both MMP-9 and EMMPRIN.

These results strenghten the hypothesis that metalloproteinases play an important role in atherosclerosis and plaque instability, and might be useful tools in identifying individuals at risk for CV events.

Scientific Activities Defended Master of Science 2014

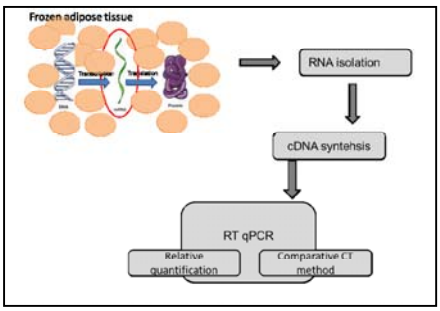
Sissel Åkra

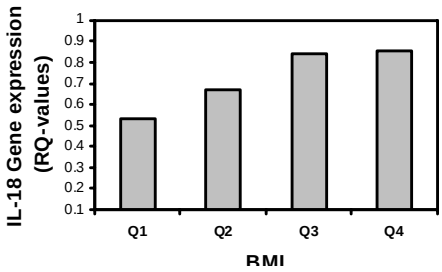
Glucometabolic variables, adipose tissue and Interleukin-18 in patients with established CAD and Type-2 diabetes

Supervisors: Ingebjørg Seljeflot and Rune Byrkjeland

The aim of this study was to elucidate the role of gluco-metabolism on IL-18 regulation; specifically by studying the relationship between gluco-metabolic variables and the genetic expression of IL18 in adipose tissue and circulating levels of IL18.

Patients with combined coronary artery disease (CAD) and diabetes type-2 (T2DM), included in the EXCADI-study, a prospective, randomized study on the effect of exercise training, were investigated at study baseline. Fasting blood samples were collected and subcutaneous adipose tissue was collected from the gluteal region for IL-18 gene expression analysis. RNA isolation was performed from adipose tissue by use of "High Pure RNA Tissue kit". RT-PCR (ViiA^{TM}7 Instrument, ABI System) was used to determine the level of gene expression (mRNA) and a commercially ELISA was used to measure circulating levels of IL-18. Of 137 patients included in the study 102 fat samples were suitable for gene expression analysis.





IL-18 gene expression assoiated with BMI.

No significant correlation between gene expression or circulating levels of IL-18 and fasting glucose or HbA1c were found. However, significant correlations between the adipose tissue expression of IL-18 and insulin ($r=0.352$, $p<0.001$), HOMA2-IR ($r=0.294$, $p=0.004$) and body mass index (BMI) ($r=0.306$, $p=0.002$) were observed. When dichotomizing BMI by median (28.7 kg/m^2) we observed significantly higher IL-18 expression in patients with high vs low BMI ($p=0.01$).

Summary/ conclusion

The genetic expression of IL-18 in adipose tissue was significantly associated with HOMA2-IR, insulin and BMI, indicating the adipose tissue to be more inflammatory active when BMI is increasing, and also more active in patients with insulin resistance. This may reflect the reduced glucose tolerance in overweight patients.,

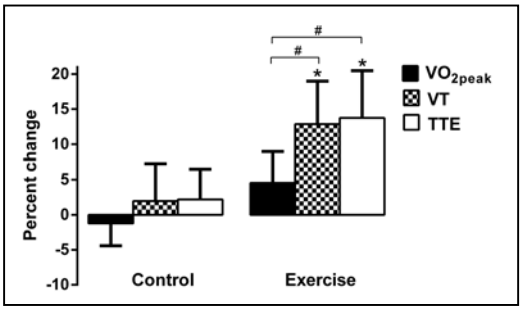
EXCADI (Exercise training in patients with coronary artery disease and diabetes)

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

The primary aims of the EXCADI study are to investigate the effects of one year organized physical exercise in patients with both coronary artery disease (CAD) and type 2-diabetes on pathophysiological mechanisms related to i) atherothrombosis ii) glucometabolic state iii) risk factors for CVD iv) co-morbidity associated with type 2-diabetes.
Despite that physical activity has a well-established role in prevention of CAD *per se* and also for the progression and treatment of type 2-diabetes, 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 project is a randomized, controlled, open study. 137 patients are included, based on power calculation. The exercise training is conducted in cooperation with the Norwegian School for Science in Sports.

Changes in exercise performance after 1 year



VT: Ventilatory treshold. TTE: Time to exhaustion.
*p<0.05, changes in the exercise group compared to controls.
#p<0.05, differences in relative changes between VO2peak and VT/ TTE in the exercise group.

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

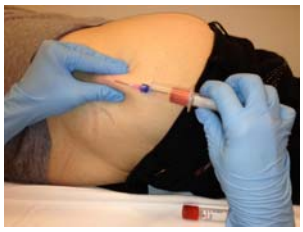
Scientific Activities PhD projects

Based on the EXCADI biobank

The influence of glycemic control and effects of exercise training on genetic regulation of inflammation with special emphasis on fractalkine (CXC3CL) and its receptor CXC3CR

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

The chemokine fractalkine and it´s receptor CX3CR1, associated with inflammation and atherosclerosis, are expressed in endothelial cells, macrophages and adipocytes amongst others. Conflicting results regarding associations between fractalkine levels and coronary artery disease (CAD) and glucometabolic state exist.
We specifically aimed to investige whether there are any associations between glucometabolic control (HbA1c), insulin resistance (HOMA2-IR), BMI and fractalkine in patients with both CAD and type 2 diabetes, and furter the effects of exercise training.



Further explorative studies on the relationship between inflammation and glucose regulation by use of gene array in circulating leukocytes and adipose tissue will be performed.

SAXATH (Saxagliptin in atherosclerosis; effects beyond glucometabolic control)

Main Project: Cand.med. Ida Unhammer Njerve.
Supervisors: Professor Ingebjørg Seljeflot, Post doc. MD PhD Svein Solheim

The main aim of this study is to explore the effects of 3 months intervention with a dipeptidyl peptidase 4 (DPP-4) inhibitor on inflammation on a cellular level in patients with CAD and type 2 diabetes. Circulating and tissue levels of selected markers will also be investigated. As atheroscleris is an inflammatory disease, we hypothesise that the medication would improve a proinflammatory profile in these patients; thus any pleiotrophic effect of saxagliptin is explored.
Patients with stable CAD and type 2 diabetes (n=12) treated with either metformin or glimepirid were recruited at OUH, Ullevaal and randomized to either saxagliptin 5 mg per day or placebo and followed for 3 months. Blood samples, PAX-gene tubes (for RNA analysis), subcutaneous fat tissue sample are collected, and polymorphonuclear cells (PBMS) are isolated at inclusion and the end of study.

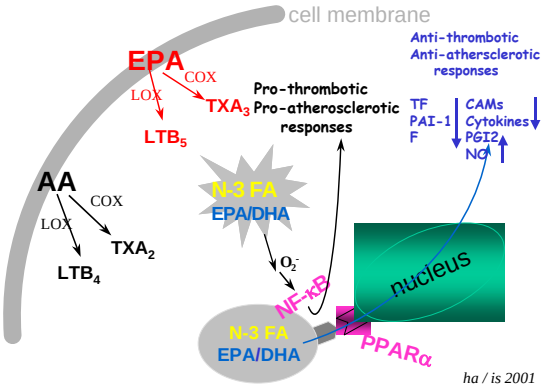
Scientific Activities PhD projects

OMega-3 fatty acids in Elderly patients with Myocardial Infarction

Twin PhD students, Cand. med Kristian Laake at OUHU and Cand. med Peder Myhre at AUH.
Responsible/supervisors: Professor em. Harald Arnesen, post. doc Svein Solheim, professor Pål Smith, MD PhD Arnljot Tveit, professor Ingebjørg Seljeflot

Knowledge about elderly with CAD is limited. The aim of this study is to investigate the possible effects of supplementation with 1.8 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, revascularizations and re-hospitalization for heaart failure with at least 30%. Patients with acute MI discharged from hospital alive being ≥70-82 years of age, both gender will be included. Special emphasis will be paid on the incidence of atrial fibrillation and heart failure in this elderly population.
In addition, the study will generate important new knowledge about such an elderly population with CAD.

The study is a randomized, placebo-controlled, double blind multicenter study with study center at CCHR.
Participating centers are OUH Ullevål, Aalborg University Hospital, Denmark, Akershus University Hospital, Asker and Baerum Hospital and Stavanger University Hospital.



Suggested effects of n-3 PUFA

A large biobank will be established and several sub-studies are planned related both to the intervention principles and to CAD in this elderly population.

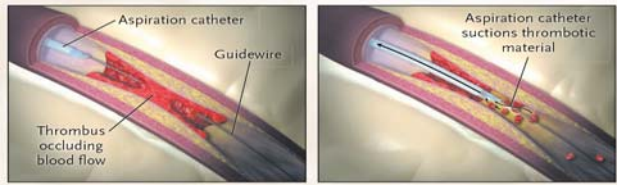
Scientific Activities PhD-projects

Coronary thrombus genes and neutrophil cell activation in acute myocardial infarction

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

This project aims to explore regulation of genes that are expressed in the coronary thrombus in an acute MI - related to atherothrombosis. Markers or mediators of fibrous cap rupture causing the acute myocardial infarction are focused. The levels of gene expression in the coronary thrombus as related to different clinical disease entities (sub groups), and also any associations with circulating levels of corresponding or related markers are investigated.

Special attention will also be drawn to neutrophile leukocyte activation which lately has been given attention.



Coronary thrombus from approximately 80 patients with acute MI undergoing percutaneous coronary intervention (PCI) are included, with blood samples from the same individuals.

Genes expresses according to ischemic time

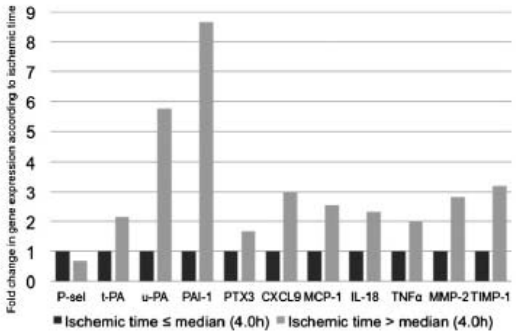


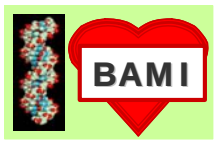
Fig. 1. Fold regulation of the selected mediators as related to total ischemic time ≤ 4 hours as reference (=1).

Thromb Res 2015; 135: 329-333

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

Scientific Activities PhD-projects

Inflammatory biomarkers in patients with ST-elevation myocardial infarction.
Atherosclerotic mechanisms and implication for clinical outcome.



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

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 1000 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 4-5 years (will be available during 2014).
In this specific project inflammatory signalling pathways are explored, especially related to 1) the interleukin-6 axis (IL-6, IL-6 Receptor and Gp130) circulating levels as well as gene expression in leukocytes, and 2) the connective tissue growth factor (CTGF) and further the IL-8 pathway.
Association studies at inclusion and prospective studies on the predictive role of these markers on clinical endpoints are undertaken.

The goal is to extend our understanding of these novel signalling pathways along with the present acute myocardial infarction and the remodelling process, and their role as risk markers for future cardiovascular events.

Scientific Activities PhD-projects

CADENCE (Markers of Coronary Artery Disease During Exercise Testing)

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

The aim of this study, 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 in the diagnosis of CAD.

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.

In a substudy, patients treated with PCI will repeat the exercise ECG after 4 months in order to explore any difference in their secretion of NT-proBNP and troponin T.

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.

Scientific Activities PhD-projects

RATAF (RaTe control in Atrial Fibrillation)

Cand.med. Sara Ulimoen
Supervisors: Dr.med. Arnljot Tveit/Professor em. Harald Arnesen/Professor Knut Gjesdal

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=60) studies the effect of 4 different drugs (2 Calcium channel blockers and 2 beta-blockers) used in rhythm control to evaluate which drug gives optimal ventricular rate and at the same time improved quality-of-life. In addition the influence on exercise capacity is investigated. Furthermore, a biobank is mounted for relevant biochemical analyses, and initial focus will be on NT-proBNP at rest and at peak exercise, as well as on Cardiac Troponin T at rest and after maximal exercise test. Joint project with Asker & Bærum Hospital, Vestre Viken HF.

Biomarkers for diagnosis of deep venous thrombosis (DVT) in unselected patients

Cand.med. Fredrik Wexels
Supervisors: MD PhD Ola Dahl, PhD Are Hugo Pripp, Professor Ingebjørg Seljeflot

Patients with clinically suspect DVT and Pulmonary embolism (PE) are usually hospitalized. The clinical 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.
The study is in collaboaration with and initiated at Vestre Viken HF, Drammen.

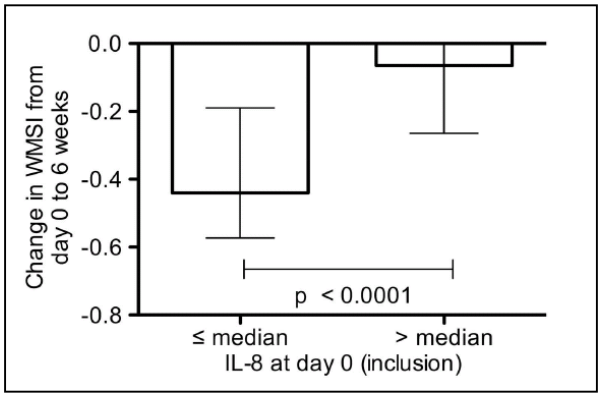
Scientific Activities PhD-projects

LEAF (Safety and efficacy of Levosimendan in patients with Acute myocardial infarction complicated with symptomatic left ventricular Failure).

Project for the PhD degree: Cand.med.Trygve Huseby
Supervisors: MD PhD Geir Ø. Andersen, MD PhD Jan Eritsland, Professor Ingebjørg Seljeflot

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.

No effects of levosimendan on selected markers of inflammation were observed. However, Interleukin-8 was associated with wall motion score (WMS), and patients with the lowest level of IL-8 had the most pronounced improvement in WMS after 5 days.



Changes in left ventricular function according to IL-8 levels

PlosOne November, 9 2014

Scientific Activities Post doc projects

”Glycoprotein 130 (Gp130) – interleukin-6 signalling pathway

Post doc project: Thomas Weiss MD PhD

Professor Ingebjørg Seljeflot/Professor em. Harald Arnesen

GP130 is a transmembrane signaling protein, a part of the interleukin-6 signalling pathway, with important regulatory functions in several inflammatory reactions. Polymorphisms (SNP’s) 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 Norwegian population of 560 men with high risk for coronary heart disease. The SNP’s were studied in joint with a population from Vienna, Austria for the importance for clinical outcome.

Glycoprotein 130 polymorphism predicts soluble glycoprotein 130 levels

Table 3 – Soluble gp130 levels, IL-6 levels and sIL-6R levels according to genotype in OSLO and VIENNA subjects.

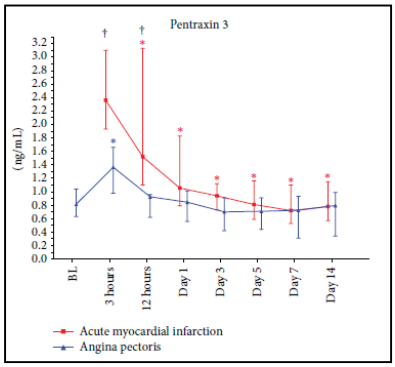
Allele G148C	GG	GC/CC	p
Sgp130 (ng/ml)			
OSLO	324.1 ± 40.1	338.1 ± 43.9	0.001
VIENNA	392.1 ± 95.4	424.5 ± 95.1	0.031

METABOLISM CLINICAL AND EXPERIMENTAL 63 (2014) 647–653

Post ASTAMI”

MD PhD Svein Solheim

In this projects the main goal was to study ”Haemostatic factors in the ASTAMI study, with special reference to left ventricular thrombus”, by which a 50% post doc. scholarship from Helse Sør-Øst was received. This was 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. Thus, studies spesific on the coagulation system, as well as furter studies on the inflammatory aspects are undertaken, both systemic and at a regulatory level. The importance of GDF-15, CTGF and PTX3 are especially further focused.



Time profile of PTX3 in STEMI and SAP

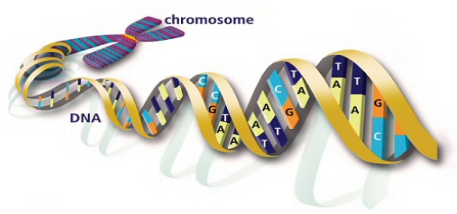
Helseth et al.
Mediators of Inflammation 2014

Scientific Activities Post doc projects

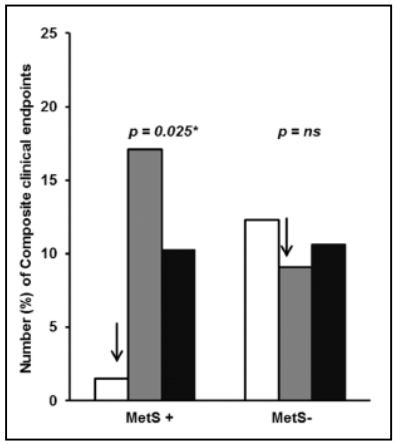
”Genetic regulation of Interleukin-18 and MMP-9. Type 2 diabetes, MetS, clinical outcome”

MSc PhD Trine B. Opstad
Professor IngebjørgSeljeflot, MD PhD Alf-Åge Pettersen

In this project we want to further explore the regulatory mechanisms of IL-18 and MMP-9 with special reference to the metabolic syndrome (MetS) and type 2 diabetes. 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. Furthermore, we have shown that genetic polymorphisms (SNPs) in the IL-18 gene, especially the +187 A/G induces lower levels of IL-18 compared to wild type. We further want to explore the importance of the co-existence of the IL-18 +183 A/G and the MMP-9 -1562C/T polymorphisms which has been associated with elevated levels of MMP-9, on clinical prognosis.



Any particular importance of these SNP’s and proteins in patients with diabetes type-2 and MetS is investigated as well as the regulation of MMP-9 by further studying both inhibitors and stimulators in addition to the SNP’s per se.
The pro-inflammatory properties of IL-18 might be in synergism with IL-12, and this will be investigated by measuring circulating levels of IL-12 as well as genetic expression. We also intend to explore any association between circulating micro RNAs (i.e. miR-146, miR-21) and gene expression/circulating protein levels of IL-18 to elucidate other regulatory pathways of IL-18.
Initial results:



Clinical endpoints as related to tertiles of circulating levels og MMP-9 and the presence of MetS or not

PlosOne 2014

Scientific Activities Post doc projects

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

Post doc project: MD PhD Alf-Åge Pettersen
Professor em. Harald Arnesen/Professor IngebjørgSeljeflot

This main study which was to investigate the clinical importance of non-responsiveness to aspirin, was finalized in 2012. However, several questions with regard to response to both aspirin and clopidogrel are still not fully answered. Thus, different sub-studies based on the biobank obtained – on the stability of the response-phenomenon as well as further studies on the mechanisms behind, are ongoing and additionally planned. Special focus has been 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).

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

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

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”. In addition, the cohort was re-investigated during 2013 for their glucometabolic status as well as for clinical outcome after 5.5 years.

NORDISTEMI (NORwegian DIstance ST-Elevation Myocardial Infarction tudy).

Post doc project: MD PhD Sigrun Halvorsen, in collaboration with
Professor Ingebjørg Seljeflot, professor em. Harald Arnesen

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 (Ellen Bøhmer, MD). Additional studies on mechanisms related to haemostasis and inflammation are ongoing.

Inflammation in Atrial Fibrillation

Post doc. Project: MD PhD Arnljot Tveit

In two different studies, the **CAPRAF (Candesartan in the Prevention of Relapsing Atrial Fibrillation)** trial in patients with atrial fibrillation and the ABAF **(Asker and Bærum Atrial Fibrillation study)** - a population study to map the prevalence of atrial fibrillation (AF) in individuals above 75 years, large biobanks were established. Supplementary substudies are still ongoing. Studies especially related to the importance of inflammation are performed to increase the understanding of trigger mechanisms and potentially new therapeutic principles for the disease.

Other projects with supervision and/or support from CCHR

POSTEMI (Post-conditioning in STEMI treated with primary PCI).

Project for the PhD degree. (Cand.med. Limalanathan Shanmuganath)
Supervisors: MD PhD Jan Eritsland, MD PhD Post.doc Geir Ø. Andersen

A prospective, randomized trial undertaken at the coronary care unit to investigate the effect of 2 different regimes for PCI treatment 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, with main focus on inflammation.

NORCAST (Norwegian Cardiac Arrest Survival Trial)

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, also supervised by MD Espen Rostrup 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 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.

Other projects with supervision and/or support 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” was completed during 2013.

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

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 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.

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

PhD project (Cand.med. Janne Mykland Hilde)
Supervisor: Professor 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 catheterization. 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 analyses and biochemical supervision have been undertaken at CCHR.
The study was performed at OUS Aker and the main results were defended in the thesis in 2014.

BAMI ("Biobanking in patients with Acute Myocardial Infarction")

A Steering committee for BAMI is established (*Professor em. Harald Arnesen, MD PhD Geir Øystein Andersen, MD PhD Sigrun Halvorsen, MD PhD Jan Eritsland, MD PhD Reidar Bjørnerheim, MD PhD Arild Mangschau, Professor Ingebjørg Seljeflot)*

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 2013 about 1500 patients have been included and a PhD project on baseline biochemical variables is started (vide supra). In addition, studies on the response to clopidogrel, which initially is used by all patients are undertaken. Furthermore, when about 2000 patients are included, genetic analyses are planned. All logistics for processing of blood samples in the acute phase and the biochemical translational research are undertaken by CCHR.

Biomarkers of inflammation and haemostasis: welders under exposure to high- grade pollution

In collaboration with National Institute of Occupational Health (professor Dag Ellingsen)

Increased mortality due to pulmonary and cardiovascular diseases by increasing pollution in the external environment has been documented. The mechanisms behind the cardiovascular and pulmonary systems vulnerability to such pollution, are 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 a hyper-coagulable state. If this is the case, it may constitute a work-related risk factor for the development of certain cardiovascular diseases. A total of 160 russian welders are investigated before and after a 3-year periode of daily/weakly 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.

Other projects with supervision and/or support from CCHR

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

*A study in collaboration with Vestfold HF, Tønsberg (**MD Espen Lindholm, PhD-student,** MD PhD Jan Erik Otterstad) and Department of Anesthesia, OUH, Ullevål (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. A total of 200 patients will be 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. Biochemical analyses are undertaken at CCHR.

Markers of inflammation in cerebrospinal fluid (CSF) in delirium assocated with hip-fracture

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

Potential biomarkers that may shed light on 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, as little knowledge exists on this issue. We try to sort out any presence of CRP and components of the interleukin-6 transsignalling pathway, in serum and CSF. About 100 patients are included.
Some results were included in thesis defended 2014, and other aspects are further studied.

Other projects with supervision and/or support from CCHR

Lifestyle intervention: Effects on cardiovascular disease risk factors in high risk individuals.

PhD project (Cand.med. Eli Heggen)
Supervisor: Serena Tonstad MD PhD

In young adults with a familiy history of premature coronary heart disease, the risk for developing atherosclerosis and coronary artery disease is high. In this project the effect of lifestyle intervention (diet and smoking sessetion) is investigated, especially with regard to so-called novel biomarkers, i.e. biomarkers of inflammation, endothelial activation and haemostasis. About 150 individuals are randomized to the intervention or not for 6 months. The laboratory analyses are performed at CCHR.

Endothelial dysfunction in relation to microbial translocation

Main investigator post doc Marius Trøseid, *in collaboration with Bodø Hospital Trust, Rikshospitalet København and Department of Infectious disease OUH.*

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. Further ongoing studies on this topic.

Other projects with supervision and/or support from CCHR

DIALONG (Diabetes type-1: long-term survivors with a new syndrome of late complications?)

PhD project (Cand.med. Kristine Holte)
Supervisor: Professor Tore Julsrud Berg

With the hopothesis that in patients with diabetes type-1 there exists a diabetic late complication syndrome consisting of cheiropathy and fatigue, in addition to the traditional micro-and microvascular complications. Markers of glycaemic burden, HbA1c and AGE's, as well as markers of inflammation and endothelial dysfunction are associated with this syndrome. The main aims are to study 150 patients with a duration of diabetes type-1 for 40 years in comparison with age-matched controls without any signs of related disease - for the presence of cheiropathy, levels of AGE's in collagen from the shoulder region, inflammatory biomarkers, glycemic control as well as genetic factors. All subjects are also investigated for their prevalence of coronary artery disease (by CT coronary angiography).
The inclusion of subjects started in 2014 and is assumed to continue duribng 2015. All blood sampling/biobanking and analyses of biomarkers for inflammation and endothelial activation are performed at CCHR.

Laboratory Methods

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
- PCR instruments and centrifuges for molecular biology
- ViiA7 RT-PCR (Applied biosystems)
  Studies on gene expression
  Studies on genetic polymorphisms

Located at Institute of Experimental Medical Research

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

For cell-culture studies

- In collaboration with Department of Medical Biochemistry, R&D Unit OUS Ullevål

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Publications 2014

Articles

Abdelnoor M, Sandven I, Limalanathan S, Eritsland J (2014)
Postconditioning in ST-elevation myocardial infarction: a systematic review, critical appraisal, and meta-analysis of randomized clinical trials. Vasc Health Risk Manag, 10, 477-91

Byrkjeland R, Edvardsen E, Njerve IU, Arnesen H, Seljeflot I, Solheim S (2014)
Insulin levels and HOMA index are associated with exercise capacity in patients with type 2 diabetes and coronary artery disease. Diabetol Metab Syndr, 6 (1), 36

Bøhmer E, Kristiansen IS, Arnesen H, Halvorsen S (2014)
Health-related quality of life after myocardial infarction, does choice of method make a difference? Scand Cardiovasc J, 48 (4), 216-22

Claussen PA, Abdelnoor M, Kvakkestad KM, Eritsland J, Halvorsen S (2014)
Prevalence of risk factors at presentation and early mortality in patients aged 80 years or older with ST-segment elevation myocardial infarction. Vasc Health Risk Manag, 10, 683-9

Engeseth K, Hodnesdal C, Grundvold I, Liestøl K, Gjesdal K, Erikssen G, Kjeldsen SE, Erikssen JE, Bodegard J, Skretteberg PT (2014)
Heart rate reserve predicts cardiovascular death among physically unfit but otherwise healthy middle-aged men: a 35-year follow-up study. Eur J Prev Cardiol PubMed 25281482

Furenes EB, Opstad TB, Solheim S, Lunde K, Arnesen H, Seljeflot I (2014)
The influence of autologous bone marrow stem cell transplantation on matrix metalloproteinases in patients treated for acute ST-elevation myocardial infarction
Mediators Inflamm, 2014, 385901. PubMed 25294955

Heier M, Margeirsdottir HD, Brunborg C, Hanssen KF, Dahl-Jørgensen K, Seljeflot I (2014)
Inflammation in childhood type 1 diabetes; influence of glycemic control. Atherosclerosis, 238 (1), 33-7

Helseth R, Seljeflot I, Opstad T, Solheim S, Freynhofer M, Arnesen H, Huber K, Weiss T (2014)
Genes expressed in coronary thrombi are associated with ischemic time in patients with acute myocardial infarction. Thromb Res, 135 (2), 329-33

Helseth R, Solheim S, Opstad T, Hoffmann P, Arnesen H, Seljeflot I (2014)
The time profile of Pentraxin 3 in patients with acute ST-elevation myocardial infarction and stable angina pectoris undergoing percutaneous coronary intervention
Mediators Inflamm, 2014, 608414, PubMed 24737925

Publications 2014 (cont.)

Horn MA, Retterstøl L, Abdelnoor M, Skjeldal OH, Tallaksen CM (2014)
Age-dependent penetrance among females with X-linked adrenoleukodystrophy
Brain, 138 (Pt 2), e325. PubMed 25149409

Husebye T, Eritsland J, Arnesen H, Bjørnerheim R, Mangschau A, Seljeflot I, Andersen GØ (2014). Association of interleukin 8 and myocardial recovery in patients with ST-elevation myocardial infarction complicated by acute heart failure. PLoS One, 9 (11), e112359

Husted S, de Caterina R, Andreotti F, Arnesen H, Bachmann F, Huber K, Jespersen J, Kristensen SD, Lip GY, Morais J, Rasmussen LH, Siegbahn A, Storey RF, Weitz JI, ESC Working Group on Thrombosis Task Force on Anticoagulants in Heart Disease (2014)
Non-vitamin K antagonist oral anticoagulants (NOACs): No longer new or novel
Thromb Haemost, 111 (5), 781-2

Limalanathan S, Andersen GØ, Kløw NE, Abdelnoor M, Hoffmann P, Eritsland J (2014)
Effect of ischemic postconditioning on infarct size in patients with ST-elevation myocardial infarction treated by primary PCI results of the POSTEMI (POstconditioning in ST-Elevation Myocardial Infarction) randomized trial. J Am Heart Assoc, 3 (2), e000679. PubMed 24760962

Laake K, Myhre P, Nordby LM, Seljeflot I, Abdelnoor M, Smith P, Tveit A, Arnesen H, Solheim S (2014). Effects of ω3 supplementation in elderly patients with acute myocardial infarction: design of a prospective randomized placebo controlled study. BMC Geriatr, 14, 74

Njerve IU, Solheim S, Lunde K, Hoffmann P, Arnesen H, Seljeflot I (2014)
Fractalkine levels are elevated early after PCI-treated ST-elevation myocardial infarction; no influence of autologous bone marrow derived stem cell injection. Cytokine, 69 (1), 131-5

Opstad TB, Arnesen H, Pettersen AÅ, Seljeflot I (2014)
The MMP-9 -1562 C/T polymorphism in the presence of metabolic syndrome increases the risk of clinical events in patients with coronary artery disease. PLoS One, 9 (9), e106816

Pedersen KK, Manner IW, Seljeflot I, Kvale D, Os I, Gerstoft J, Nielsen SD, Trøseid M (2014)
Monocyte activation, but not microbial translocation, is independently associated with markers of endovascular dysfunction in HIV-infected patients receiving cART
J Acquir Immune Defic Syndr, 67 (4), 370-4.

Publications 2014 (cont.)

Sveen KA, Dahl-Jørgensen K, Stensaeth KH, Angel K, Seljeflot I, Sell DR, Monnier VM, Hanssen KF (2014). Glucosepane and oxidative markers in skin collagen correlate with intima media thickness and arterial stiffness in long-term type 1 diabetes. J Diabetes Complications (in press) PubMed 25600701

Svendsen M, Tonstad S, Heggen E, Pedersen TR, Seljeflot I, Bøhn SK, Bastani NE, Blomhoff R, Holme IM, Klemsdal TO (2014)
The effect of kiwifruit consumption on blood pressure in subjects with moderately elevated blood pressure: a randomized, controlled study. Blood Press, 24 (1), 48-54

Ulimoen SR, Enger S, Norseth J, Pripp AH, Abdelnoor M, Arnesen H, Gjesdal K, Tveit A (2014) Improved rate control reduces cardiac troponin T levels in permanent atrial fibrillation Clin Cardiol, 37 (7), 422-7.

Wexels F, Dahl OE, Pripp AH, Seljeflot I, Borris LC, Haslund A, Gudmundsen TE, Lauritzen T, Lassen MR (2014). Prothrombin fragment 1+2 in urine as a marker on coagulation activity in patients with suspected pulmonary embolism. Thromb Res 134 (1), 68-71.

Wonnerth A, Katsaros KM, Krychtiuk KA, Speidl WS, Kaun C, Thaler K, Huber K, Wojta J, Maurer G, Seljeflot I, Arnesen H, Weiss TW (2014). Glycoprotein 130 polymorphism predicts soluble glycoprotein 130 levels. Metabolism, 63 (5), 647-53.

Publications 2014 (cont.)

Abstracts

Wexels F, Pripp AH, SeljeflotI, Haslund A, Gudmundsen TG?, Dahl OE.
Prothrombin fragment 1 + 2 in urine in patients with clinical suspected venous thromboembolism. Mediterranian Leage against Thrombotic Disease (MLTD), Valenzia 2014

Husebye T, Eritsland J, Arnesen H, Bjørnerheim R, Mangschau A, Müller C, Seljeflot I, Andersen GØ. No effect of levosimendan on inflammation in ST-elevation myocardial infarction complicated by acute heart failure: A substudy of the LEAF trial
Congress of the European Society of Cardiology 2014 Barcelona

Hansen CH, Ritschel V, Arnesen H, Halvorsen H, Andersen GØ, Eritsland J, Mangskou A, Bjørnerheim R, Seljeflot I. Markers of thrombin generation are associated with myocardial necrosis and left ventricular impairment in patients with ST-elevation myocardial infarction
Congress of the European Society of Cardiology 2014 Barcelona

Helseth R, Seljeflot I, Opstad T, Solheim S,, Freynhofer M, Arnesen H, Huber K, Weiss TW.Expression of genes in aspirated coronary thrombi in patients with acute myocardial infarction. Congress of the European Society of Cardiology 2014 Barcelona

Njerve IU, Byrkjeland R, Arnesen H, Åkra S, Solheim S, Seljeflot I. Expression of Fractalkine and its receptor (CX3CR1) in subcutanous adipose tissue from patients with coronary artery disease and type 2 diabetes. European Society of Atherosclerosis 2014 Madrid.

Heier M, Margeirsdottir HD, Torjesen PA, Brunborg C, Hanssen KF, Dahl-Jørgensen K, Seljeflot I. Inflammation in childhood type 1 diabetes, influence of glycemic control. European Society of Atherosclerosis 2014 Madrid.

Opstad TB, Pettersen AÅ, Arnesen H, Seljeflot I. The MMP-9 -1562 C/T polymorphism increase the risk of future events in patients with MetS, partiallly mediated through circulating MMP-9 and EMMPRIN. European Society of Atherosclerosis 2014 Madrid.

ByrkjelandR, Njerve IU, Arnesen H, Anderssen S, Seljeflot I, Solheim S.Effects of exercise training in patients with type 2-diabetes and coronary artery disease. American College of Sports Medicine (ACSM) 61st Annual Meeting 2014, Orlando

Laake K, Seljeflot I, Fagerland M, Arnesen H, Solheim s: Effects of diet and omega-3 fatty acid intervention on serum fractalkinein elderly men at high risk of coronary artery disease. 12th Chronic Heart Failure Research Symposium 2014, Oslo Abstract P4

Publications 2014 (cont.)

Myhre P, Laake P , Arnesen H, Seljeflot I, Smith P, Nerdrum T, Solheim S. Baseline characteristics of a cohort from the randomized OMEMI Study. 12th Chronic Heart Failure Research Symposium 2014, Oslo Abstract P11

Byrkjeland R, Njerve IU, Arnesen H, Anderssen S, Seljeflot I, Solheim S. Effects of exercise training in patients with type 2-diabetes and coronary artery disease. a randomised clinical trial - effects on glycemic control and exercise capacity . 12th Chronic Heart Failure Research Symposium 2014, Oslo Abstract P24

Opstad TB, Arnesen H, Pettersen AP, Seljeflot I. Combined high levels of IL-12 and IL-18 predict new clinical events in CAD patients. 12th Chronic Heart Failure Research Symposium 2014, Oslo Abstract P09

Opstad TB, Pettersen AÅ, Arnesen H, Seljeflot I. The MMP-9 -1562 C/T polymorphism increase the risk of future events in patients with MetS, partiallly mediated through circulating MMP-9 and EMMPRIN. 12th Chronic Heart Failure Research Symposium 2014, Oslo Abstract P62

Husebye T, Eritsland J, Arnesen H, Bjørnerheim R, Mangschau A, Müller C, Seljeflot I, Andersen GØ.IL-8 is associated with myocardial recovery in patients with ST-elevation myocardial infarction complicated by acute heart failure
12th Chronic Heart Failure Research Symposium 2013, Oslo Abstract P60

Furenes EB, Opstad TB, Solheim S, Lunde K, Arnesen H, Seljeflot I. The influence of autologous bone marrow stem cell transplantation on matrix metalloproteinases in patients tretaed for acute ST-elevation myocardial infarction. 12th Chronic Heart Failure Research Symposium 2014, Oslo Abstract P59

Husebye T, Eritsland J, Arnesen H, Bjørnerheim R, Mangschau A, Müller C, Seljeflot I, Andersen GØ. No effect of levosimendan on inflammation in ST-elevation myocardial infarction complicated by acute heart failure: A substudy of the LEAF trial. 12th Chronic Heart Failure Research Symposium 2014, Oslo Abstract P58

Opstad TB, Arnesen H, Pettersen AP, Seljeflot I. Combined high levels of IL-12 and IL-18 predict new clinical events in CAD patients. Eurothrombosis Summit 2014 Paris, Abstract P14

Furenes EB, Opstad TB, Solheim S, Lunde K, Arnesen H, Seljeflot I. The influence of autologous bone marrow stem cell transplantation on matrix metalloproteinases in patients with acute ST-elevation myocardial infarction. Eurothrombosis Summit 2014 Paris, Abstract P04

Publications 2014 (cont.)

Opstad TB, Arnesen H, Pettersen AP, Seljeflot I. MMP-9 and its regulators EMMPRIN and TIMP-1 in Metabolic Syndrome. Eurothrombosis Summit 2014 Paris, Abstract P12

Byrkjeland, NjerveIU, Anderssen S, ArnesenH, Seljeflot I, Solheim S. Modest effects of exercise training on HbA_{1c} and VO_{2peak} in patients with type 2 diabetes and coronary artery disease: a randomised clinical trial. NCS Høstmøte, Oslo 2014

Helseth R , Seljeflot I, Opstad TB, Solheim S, Freynhofer M, Arnesen H, Huber K, Weiss T. Expression of selected genes in aspirated coronary thrombi in patients with acute myocardial infarction. NCS Høstmøte, Oslo 2014

Santos-Gallego CG, Njerve IU, Ishikawa K, Aguero J, Vahl TP, Picatoste B, Hammoudi N, Hajjar RJ, Fuster V, Badimon J, Sanz J. Validating the Gold-standard: Steady-State Free Precession Sequence for Assessment of Left Ventricular and Right Ventricular Mass. AHA Scientific Session Chicago 2014. APS.108.02

Santos-Gallego CG, Picatoste B, Njerve IU, Vahl TP, Ishikawa K, Sanz J, Hajjar RJ, Fuster V, Badimon J. "Pharmacological Inhibition of PTEN Increases Myocardial Salvage, Reduces Infarct Size, and Decreases Adverse Post-infarction Left Ventricular Remodeling in a Porcine Model of Reperfused Myocardial Infarction» AHA Scientific Sessions Chicago 2014, APS.514.05