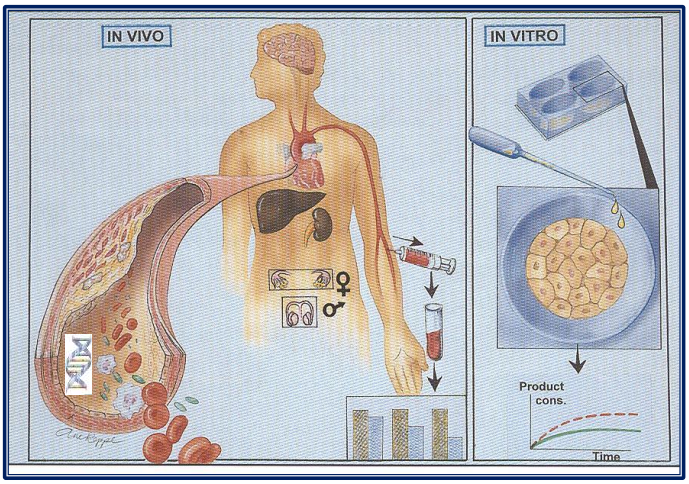


Center for Clinical Heart Research (CCHR)

Department of Cardiology
Division of Medicine
Oslo University Hospital, Ullevål

Annual Report 2017

"Team building for individual excellence"

http://research.no/clinicalheartresearch/

Content

Preface

Center for Clinical Heart Research (CCHR) is organized as a part of the Department of Cardiology, Medical Division, OUS Ullevål. The Center plays an important role as a core laboratory for other research groups in the Department as well as for others in the Division of Medicine and other collaborators.
CCHR is located close to the patients, which is crucial for the scientific activity.

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

The Center has fruitful collaboration with many centers and institutions in which Vestre Viken Trust, Asker & Bærum Hospital, Akershus University Hospital and OUH Rikshospitalet are of special importance by having common PhD-projects and students.
In 2017 the establishment of new laboratory methods has been successfully implemented, especially for the understanding of ageing and the ageing process, as our patient populations are getting older. Also, the focus on laboratory methods for understanding of the innate immune system and for microbial translocation have been successfully implemented.

The high scientific activity has this year resulted in 4 PhD theses directly from the center, and 2 in addition with supervision from the center, 1 medical student in research with an international publication, 20 internationally published papers and further 24 published congress abstracts.
One of the highlights this year was the Scientific Symposium ”Team building for individual excellence”, organized October 2017 at Noreheim, Norefjell which also was a celebration of **10 years of Stein Erik Hagens Foundation for Clinical Heart Research**, and we were happy to have him with us for the occation.

We are very pleased to give this annual report for 2017

April 2018

Ingebjørg Seljeflot (sign)
professor dr. philos

Harald Arnesen (sign)
professor em dr. med

Svein Solheim (sign)
MD post.doc

Strategy

The strategies are unchanged

- Systematic researcher-initiated clinical heart research, based on accepted research methodology along with the flow of patients in OUS
- Projects related to acute myocardial infarction, chronic heart diseases like heart failure and atrial fibrillation
- Further focus on ischemic heart disease in diabetics and in the elderly
- Biobanking, standardized sampling and processing of blood and tissue
  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
- To be an interdisciplinary composed group, including researchers at post.doc level
- CCHR is a group within the network of Center for Heart Failure Research, OUS/UiO

Main Goals

The main goals are unchanged

- to increase the 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 rated 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 organizational aspects are undertaken by the Center leaders. Our most important activity is the regular 2-hour-scientific meetings every 2-3 weeks with PhD candidates, post.docs, laboratory staff, professors and seniors. The main projects are reported with progress, results and relevant discussions. External experts on special relevant topics and co-workers from other groups and institutions, as well as 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 candidates are encouraged to give presentations at the meetings and to prepare abstracts for international congresses. In addition, individual supervision of the single PhD candidate is undertaken, with a ”supervisor-open-door-policy”, and specific projects are separately discussed in smaller groups.
Decisions and ”Contracts” for collaboration with other research groups are all based on common scientific interests.

Personnel

Leadership: The leader is also the Head of the R&D Section at Department of Cardiology, 100% position, and professor II at UiO. In addition, medical responsibles 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, OUS Ullevål.
Employees: 2 medical technologists, both with a Master of Science in Biomedicine, 1 post.doc researcher (PhD) and 0.5 study nurse.
10 PhD students, 4 post.docs/seniors participate in the milieu. One student from the research program for medical students has been participating, funded by the Norwegian Research Council via UiO. A biostatistician /epidemiologist participate occationally. In addition, the scientific milieu and the laboratory facilities are open for several other PhD-students, mainly supervised in collaboration with other groups at the Department of Cardiology, but also from other collaborating groups.

Finances

Budgets for the single projects, including salary for PhD-students, technical personnel and running laboratory expenses are based on external fundings from different sources. Also in 2017 we were happy to receive fundings for one of the PhD-projects related to elderly patients with acute myocardial infarction from Olav Thon Stiftelsen. The Head is financed from the Department of Cardiology, OUS, Ullevål by a combined position for the Center and for being Head of the Research and Development Section in the Department.

The major economic support from Stein Erik Hagens Foundation for Clinical Heart Research, anchored at Institute of Clinical Medicine, University of Oslo, has been of crucial importance for the activity also in 2017.

Scientific Activities

PhD-theses defended 2017

"Coronary heart disease and associations with omega-3 fatty acids in the elderly"

Kristian Laake, Cand. Med.

Supervisors: Svein Solheim MD, PhD, Ingebjørg Seljeflot Professor, Harald Arnesen Professor em

The large scale clinical trial (OMEMI) evaluating the effects of omega-3 fatty acids on clinical outcomes in elderly patients with acute myocardial infarction (AMI), is still ongoing. The aims of the thesis were to evaluate any associations between omega-3 fatty acids in serum measured at inclusion and markers of atherosclerosis, infarct size and indices of heart failure in a subgroup of 299 patients. No significant associations between any serum fatty acids and myocardial injury during the index AMI assessed by Troponin T was found. However, an association between omega-3 fatty acid levels and Galectin-3, a biomarker of fibrosis, was found, indicative of a potential role of omega-3 fatty acids in adverse cardiac remodeling and heart failure development. Furthermore, patients with a history of atrial fibrillation (AF) had lower docosahexaenoic acid (DPA) levels, indicative of an association between omega-3 fatty acids and AF. Taken together, omega-3 fatty acids could be protective of atrial fibrillation development in elderly and potentially beneficial on cardiac fibrosis and remodeling after an AMI.

"Fractalkine (CX3CL1) and its receptor (CX3CR1) in acute myocardial infarction, stable coronary artery disease and diabetes. Emphasis on adipose tissue inflammation"

Ida Unhammer Njerve, Cand. Med.

Supervisors: Ingebjørg Seljeflot Professor, Svein Solheim MD, PhD

In this thesis degree of inflammation was studied by the chemokine fractalkine in various populations of patients with coronary artery disease (CAD) and type 2 diabetes (T2DM). Serum fractalkine were elevated in the acute and subacute phase of acute myocardial infarction (AMI), but did not associate with measures of myocardial injury. Intracoronary injection of autologous bone marrow derived stem cells, did not affect fractalkine levels in patients with AMI. In patients with combined CAD and T2DM, randomized to exercise training or not, no significant beneficial influence of training was observed on fractalkine gene expression in subcutaneous adipose tissue. In addition to adding to the knowledge on fractalkine in various populations of patients with CAD, the antidiabetic drug saxagliptin was investigated in a randomized placebo-controlled study in patients with combined CAD and T2DM. In peripheral blood leukocytes and mononuclear cells from patients on active drug for 3 months, an increased expression of the anti-inflammatory interleukin-10 was observed.

"Effects of exercise training on exercise capacity, glycemic control and atherosclerosis in patients with type 2 diabetes and coronary artery disease"

Rune Byrkjeland, Cand. Med.

Supervisors: Svein Solheim MD PhD, Ingebjørg Seljeflot Professor, Harald Arnesen Professor em

The primary aims of the EXCADI study were 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.

There is limited knowledge about the mechanisms involved in the beneficial effects of physical exercise.

The project was a randomized, controlled, open study. 137 patients were included, based on power calculation. The combined exercise training was conducted in collaboration with the Norwegian School for Science in Sports.

In the total population no significant effect of the exercise training could be demonstrated on VO_2peak or HbA_1c, whereas in a subgroup without cardiovascular complications, significant improvements were obtained in these variables. Likewise, no overall effect of exercise on progression of carotid intima-media thickness was demonstrated, whereas beneficial effects were observed in patients without carotid atherosclerotic plaques.

In conclusion, the results indicate that the effects of exercise training may be attenuated in diabetic patients with more advanced vascular disease, and that the most beneficial effects may occur in patients with less severe vascular complications.

"Safety and efficacy of levosimendan in patients with acute myocardial infarction complicated with symptomatic heart failure"

Trygve Husebye, Cand. Med.

Initiated at CCU, Dept of Cardiology, OUS

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

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 acute heart failure (AHF). Infusion of levosimendan for 24 hours was compared to placebo, and a broad specter of biochemical analyses were performed in addition to tests of cardiac function, repeatedly during the 6 weeks follow-up. Sampling, processing, biobanking and the biochemical analyses have been undertaken at CCHR. Levosimendan treatment did not affect the levels of inflammatory markers during the first 6 weeks after the PCI-intervention in STEMI-AHF patients. However, high levels of IL-8 were associated with less improvement in LV systolic function during the first 6 weeks, suggesting a possible role of IL-8 in the adverse LV remodeling of post-ischemic myocardium.

"Effect of ischemic postconditioning on infarct size and left ventricular function. Results of the POstconditioning in ST-Elevation Myocardial Infarction (POSTEMI) randomized trial"

Limalanathan Shanmuganath, Cand.med.

Initiated at CCU, Dept of Cardiology, OUH

Supervisors: Jan Eritsland MD PhD, Geir Ø. Andersen MD PhD, Pavel Hoffmann MD PhD

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=272): traditional opening of the occluded artery or a "step-wise" opening/occlusion procedure, inducing post-conditioning which is thought to contribute to diminished reperfusion injury after the PCI. The primary aim was infarct size measured with MRI. The mechanisms of post-conditioning are not fully understood, and a series of blood samples along the PCI procedure were gathered to elucidate the biochemical processes related to reperfusion injury (inflammatory, oxidative, apoptotic). Processing of samples, biobanking and biochemical analyses were undertaken at CCHR, with main focus on inflammation. The post-conditioning procedure did not reduce infarct size measured by MRI after 4 months. Patients with microvascular obstruction on early MRI ended up with larger infarct size, lower myocardial salvage and left ventricular ejection fraction after 4 months.

"Cardiovascular biomarkers in high-risk patients"

Cand.med. Peder Langeland Myhre

Initiated and mainly conducted at Akershus University Hospital (AHUS)

Supervisors: Helge Røsjø MD PhD, Pål Smith Professor em, Ingebjørg Seljeflot Professor

The studies on cardiovascular biomarkers in high-risk patients were undertaken at AHUS without contribution from CCHR.

However, the candidate contributed largely to the inclusion and follow-up of the initial patients from AHUS in the OMEMI trial and the design article on this randomized study was a part of his thesis.

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

Cand. Med. Fredrik Wexels

Supervisors: Ola Dahl MD PhD, Are Hugo Pripp PhD, Ingebjørg Seljeflot Professor

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 the initial idea was to evaluate the accuracy of a "spot urine stix test" in patients with clinically suspect DVT or PE. Our hypothesis was that the urine stix would have a high negative predictive value and thus a number of patients could be excluded from unnecessary radiological examinations.
We have also investigated stored blood samples from a biobank on markers of activation of coagulation and fibrinolysis, proteomics and other biomarkers for comparison with clinical outcome in the population. The study is in collaboration with and initiated at Vestre Viken HF, Drammen, and the doctoral thesis including four published papers will be ***defended for the PhD degree March 2018.***

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

Cand. Med. Vibeke Ritschel

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

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 OUS, Ullevål, are included. A standardized biobank and a complete database with relevant clinical data are established. This cohort of patients have been followed for clinical events after 4-5 years (available during 2015). In this specific project inflammatory signalling pathways are explored, especially related to the interleukin-6 axis (IL-6, IL-6 Receptor and Gp130) and CTGF. 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. Four papers on the topic have been published and the work will be *submitted for the doctoral thesis evaluation Spring 2018*.

CADENCE (Markers of Coronary Artery Disease During Exercise Testing)

Cand. Med. Joanna Cwikiel

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

The aim of this study, is to examine whether 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=300) are being examined with coronary angiography, which is regarded as the gold standard for diagnosing CAD. We further aim to clarify mechanisms related to sudden cardiac death as related to exercise by studying whether ischemia may potentiate increase in biomarkers of thrombosis and inflammation.
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. The inclusion is finalized and the main results, combined into the doctoral thesis, are *planned to be submitted for evaluation during 2018.*

Inflammation and ischemia/reperfusion injury in STEMI patients treated by PCI and ischemic postconditioning

Cand. Med. Christian Shetelig

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

From the POSTEMI study (vide supra), the purpose of this investigation is to identify novel inflammatory pathways involved in acute MI, reperfusion injury and cardiac remodelling. The main objectives are to specifically explore potential chemokines/growth factors, which, based on previous research may be involved in both reperfusion damage but also potential salvage of the vulnerable reperfused myocardium. Studies on osteoprotegerin (OPG), a member of the TNF receptor superfamily, Interleukin-8, and CTGF have been explored. In addition, the IL-1β-pathway will thoroughly be investigated in the project and will be part of the doctoral thesis*, planned to be submitted for evaluation during 2018.*

High-sensitivity Troponin I in atrial fibrillation - Impact of rate and rhythm control and associations to other biomarkers

Initiated at Vestre Viken HF, Asker & Bærum Hospital

Cand. Med. Anja Wiedswang Horjen

Supervisors Arnljot Tveit Professor, Sara Ulimoen MD PhD, Ingebjørg Seljeflot Professor

In the ABAF (Atrial fibrillation in Asker and Bærum community), CAPRAF (Candesartan in the Prevention of Relapsing Atrial Fibrillation) trial and the RATAF-study on patients with atrial fibrillation, the importance of cardiac biomarkers (troponins) is explored, as related to AF per se, but also to electrical cardioversion, exercise ECG and use of anti-hypertensive medications, like angiotensin receptor blockers, calcium channel blockers and beta-blockers. In addition, procoagulant activity, assessed by *in vivo* and *ex vivo* thrombin generation *(vide infra*), in AF patients, related to cardioversion is investigated.

The project is finalized and four papers, combined into the doctoral thesis, are planned to be *submitted for evaluation Spring 2018.*

Scientific Activities

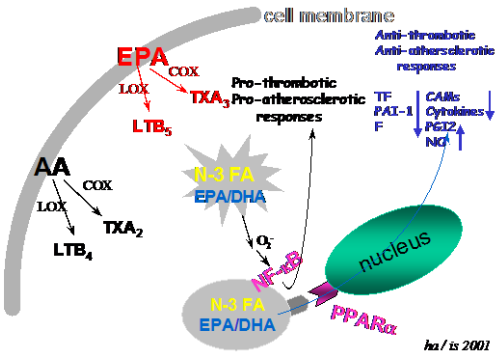
Ongoing projects (mainly PhD)

Studies on Omega-3 fatty acids

Twin PhD students, Cand. Med. Are Annesønn Kalstad at OUS and Cand. Med.Sjur Hansen Tveit at AUH

Responsible/supervisors: Ingebjørg Seljeflot Professor, Svein Solheim MD PhD, Harald Arnesen Professor em, Pål Smith Professor em, Arnljot Tveit Professor

An ongoing clinical trial, started out in 2013 based on the suspected beneficial effects of omega-3 fatty acid supplementation and the limited knowledge about elderly with CAD. The aim is to investigate the effects of supplementation with 1.8 g/day of n-3 PUFAs on top of modern therapy, on cardiovascular morbidity and mortality during a follow-up period of 2 years in an elderly population after having experienced an acute MI. 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 the elderly population with CAD.
The study is a randomized, placebo-controlled, double blind multicenter study with study center at CCHR. Participating centers are OUS Ullevål, Aalborg University Hospital, Denmark, Akershus University Hospital, Asker and Baerum Hospital and Stavanger University Hospital. The inclusion is planned to be finalized by end of June 2018. A large biobank is established.



Suggested effects of n-3 PUFA

Serum Omega-3 fatty Acids as related to traditional CVD risk factors and co-morbidities in elderly patients with myocardial infarction (Laake K et al).

Serum Omega-3 Fatty Acids levels and the importance for myocardial function and cardiac remodeling (Laake K et al).

Serum Omega-3 Fatty Acids according to "Leukocyte Telomere Length", a suggested marker of longevity as well as proneness for CVD in this special population of elderly patients with AMI is under investigation.

Serum Omega-3 fatty Acids as related to the presence of atrial fibrillation in the elderly.

Studies on Microbial Translocation

An altered gut microbiota has been linked to several chronic disease states, including obesity and type-2 diabetes. Translocation of parts of the gut microbiota, and in particular endotoxins or lipopolysaccharides (LPS) to the systemic circulation, has been proposed to be an early trigger of inflammation, insulin resistance and subsequent cardiovascular risk. LPS promotes inflammation mainly by signaling through Toll like receptor (TLR) 4 on cells of the innate immune system, and CD14 plays a central role by transferring LPS to the TLR4 receptor complex.

Microbial translocation and the metabolic syndrome

Cand. Med. Ayodeji Awoyemi, PhD student

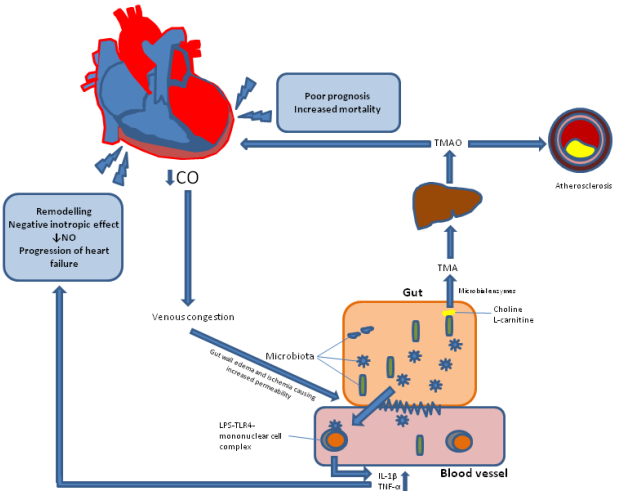
Supervisors: Ingebjørg Seljeflot Professor, Svein Solheim MD PhD, Marius Trøseid Professor

This project will focus on the potential role of microbial translocation and gut leakage in metabolic syndrome (MetS) and diabetes type-2. Any association between LPS, LPS-binding protein (LPSBP), CD14 and markers of endothelial dysfunction, the degree of atherosclerosis, measured by carotid intima media thickness (cIMT) and clinical end points will be explored.

Microbial translocation and chronic heart failure

Cand. Med. Ayodeji Awoyemi

In an intervention study on patients with chronic heart failure in collaboration with OUS Rikshospitalet (GutHeart) the effect of treatment with antibiotics and/or probiotics on heart function (ejection fraction) and the leakage markers will be investigated.



Ayodeji Awoyemi: Suggested action.

Microbial translocation related to endothelial dysfunction, HIV, Hypertension, Diabetes and Obesity

Main investigator Professor Marius Trøseid, *in collaboration with Rikshospitalet København and Department of Infectious disease OUH.*

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, treated and non-treated. We also explored the impact of microbial translocation in HIV-infected patients with and without diabetes and in obese people undergoing weight reduction and additional gastric bypass surgery.

Microbial translocation in HIV patients. Effects of probiota treatment

Main investigator MD PhD Dag H. Reikvam, Dept of Infection diseases OUS Ullevål

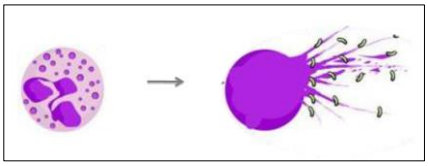
Patients with HIV-infection who do not respond on antiviral treatment, so-called immunological non-responders (INR) have an increased low-grade inflammation and systemic immune activation. A relevant hypothesis is that these patients have reduced mucosal barrier, and thus an increased leakage from the gut. We investigate such patients in comparison with responders to antiviral treatment as well as the effect of probiota treatment for 8 weeks.

Microbial translocation in primary sclerosing cholangitis

Main investigator MD PhD Johannes Hov, *OUS Rikshospitalet*

Primary sclerosing cholangitis is a chronic inflammatory liver disease of unknown etiology affecting both intrahepatic and extrahepatic bile ducts, eventually progressing to end-stage liver disease. Recent studies have identified an altered gut microbiota in PSC patients, and the gut leakage hypothesis could be relevant in the pathogenesis. We hypothesize that circulating markers of gut barrier function are elevated in PSC compared with controls and that high levels of these markers are associated with a reduced liver transplantation-free survival.

Studies on Neutrophil extracellular traps (NETs)



Lately, it became evident that neutrophils upon activation are able to release parts of their nuclear content with residing neutrophil granule proteins into the extracellular space to form spindle-like networks, called neutrophil extracellular traps (NETs). Although NETs initially were thought to have their main role in infectious diseases ensuring entrapment of microorganisms, NETs have lately been identified in coronary artery disease (CAD). Cell free deoxyribonucleic acid (DNA) and MPO-DNA have been used as a surrogate marker of NETs, and are reported to be elevated in acute myocardial infarction.

NETs in acute and stable coronary heart disease

Cand Med Miriam S. Langseth, PhD student

Supervisors: Ragnhild Helseth MD PhD, Trine B. Opstad MSc PhD, Ingebjørg Seljeflot Professor

For this project we aimed to explore the relationship between the surrogate markers of NETs, double-stranded deoxyribonucleic acid (dsDNA) and nucleosomes (DNA-histone complexes) in patients with STEMI or stable angina pectoris undergoing coronary angiography with percutaneous coronary intervention (PCI) and their relation to myocardial injury and left ventricular function.

Results showing NETs markers to be related to clinical outcome in patients with stable CAD have been published.

NETs in acute and stable coronary heart disease

Cand med Christian Schetelig and post doc MD Ragnhild Helseth

To further explore any impact of NETs on the the degree of myocardial injury and left ventricular function assessed by coronary magnet resonance imaging will be explored by use of the biobank from the POSTEMI study (vide supra).

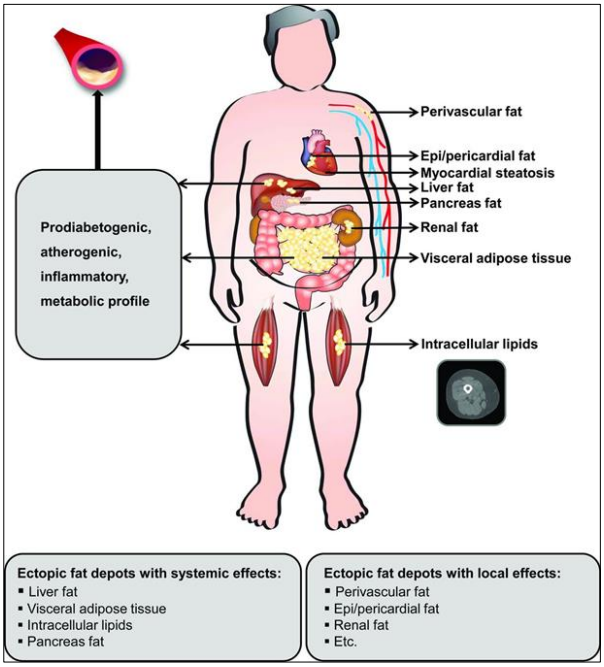
Impact of glucose regulation on Netosis in patients with acute myocardial infarction

Post doc MD Ragnhild Helseth and MD PhD Eva C Knudsen

An early event during NETs release is decondensation of nuclear chromatin by the enzyme peptidylarginine deiminase (PAD4). In experimental studies NETosis is suggested to be glucose dependent. This project is aimed to assess whether plasma glucose associate with the NETs marker in the acute phase and in stable condition in patients with acute ST-elevation myocardial infarction and further, whether an acute increase in glucose by an oral glucose tolerance test leads to upregulated NETosis by PAD4 mRNA levels as well as increased release of dsDNA.

Studies on Adipose Tissue inflammation

We have for several years focused on inflammation in relation to the metabolic syndrome, adipose tissue, atherosclerosis and cardiovascular disease states, also with respect to genetic expression of inflammatory mediators, visualized in several previous and ongoing projects. Furthermore, differences in fat compartments have been focused.



J-P. Despres, Circulation 2012;126:1301-1313

Inflammatory gene expression in adipose tissue and glucometabolism in healthy men

MSc Sissel Åkra. In collaboration with MD PhD Tonje A. Aksnes, Section of Cardiovascular and Renal Research, OUS Ullevål

In a cross sectional sub-study of INFO we investigate the association between insulin sensitivity assessed by glucose clamp and inflammatory genes expressed in adipose tissue as well as circulating levels of corresponding inflammatory biomarkers with special emphasis on the regulatory mechanisms of the inflammasome axis. And further whether these mediators are related to the amount of abdominal adipose tissue assesses by CT-scan.

Adipose tissue inflammation in patients with coronary artery disease and type 2 diabetes - effects of exercise training. Based on the EXCADI biobank

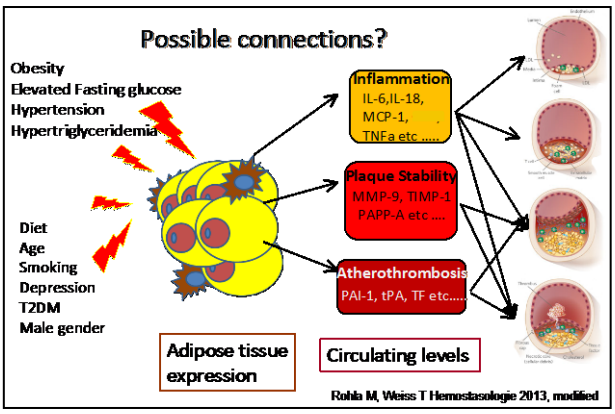
Cand. Med. Hani Zaidi (50% PhD position)

Supervisors: Trine B. Opstad Senior Scientist, Ingebjørg Seljeflot Professor, Rune Byrkjeland MD PhD

In this project the adipose tissue regulatory mechanisms of :

- the IL-18/IL-12/miR-21/NLRP3/Caspase-1 axis
- the MMP-9/TIMP-1/EMMPRIN/miR-21 axis
- the adiponectin/visfatin/PAI-1 axis

as related to glucometabolic variables, and effects of exercise training from the EXCADI biobank (i.e. patients with CAD and Type-2 diabetes((vide supra) will be further explored.



Connections between metabolic related risk factors and the different regulatory pathways

Differences between various compartments of adipose tissue regarding inflammatory activity in patients with coronary heart disease (ATICH)

In collaboration with Department of Thoracic surgery

Steering Committee: Professor Ingebjørg Seljeflot, MD PhD Svein Solheim, Professor em Harald Arnesen, Professor Theis Tønnesen, MD PhD Bjørn Braathen.

Executers: In addition to the surgeons

MSc Sissel Åkra: Sample handling

Study nurse Charlotte Holst Hansen: Patient information

Different compartments of adipose tissue like subcutaneous, visceral, perivascular, pericardial and epicardial fat have been claimed to exert different proinflammatory profiles with different associations with cardiovascular disease states.

The aims of this project are to study possible differences in inflammatory gene expression and protein secretion in various compartments of adipose tissue being exposed during open cardiac surgery on patients with coronary heart disease, and valvular disease for control. Inclusion of patients and sample collection have successfully been performed.

Studies on Thrombogenicity

Study on pro-thrombotic activity in STEMI from the BAMI cohort

Study nurse Charlotte Holst Hansen

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

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

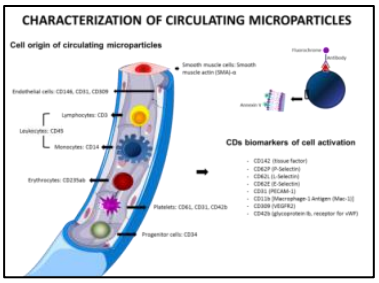
In this joint project between the Cardiac Care Unit, General Cardiology Section and CCHR in Department of Cardiology, an extended biobank is mounted along with prospectively registered clinical data and will be the basis for studies on predictive markers for later clinical events. Consecutive patients with STEMI are included after consent. At the end of 2017 about 2000 patients have been included and a PhD project on selected biomarkers are underway (vide supra).

Pro-coagulant activity, evaluated by both in vivo and ex vivo thrombin generation analyses has previously been studied for its influence on infarct size and development of heart failure from the first approximately 1000 patients.
We have further studied the impact of increased pro-coagulant activity on clinical outcome, showing especially levels of D-dimer to have prognostic value.
Further projects are planned, including genetic studies.

Hypercoagulability, thrombin generation and microvesicles in diabetes - with and without coronary artery disease

MSc Vibeke Bratseth, PhD student
Supervisors: Ingebjørg Seljeflot Professor, Svein Solheim MD PhD, Harald Arnesen Professor em.

The main aims of this project are to assess the importance of glucose control on the hypercoagulable state and on circulating microvesicles (cMVs) in patients with T1DM and in T2DM combined with CAD, and further any association with the degree of atherosclerosis and disease severity. This will be explored in two different cohorts: the EXCADI-biobank of patients with CAD and type-2 diabetes (vide supra) and the Atherosclerosis in Childhood Diabetes study (vide infra) including type-1 diabetics. Special attention will be paid to diabetes patients with albuminuria in whom we previously have shown a hypercoagulable state.
The Calibrated Automated Thrombogram (CAT- assay) for *ex vivo* thrombin generation and *in vivo* thrombin generation measurements will be undertaken in addition to flow-cytometry analyses of circulating micro-vesicles (cMVs).



cMVs from different cells are investigated based on their specific cell surface properties

In the EXCADI study the effects of 12-months exercise training on hypercoagulability and cMVs are investigated.

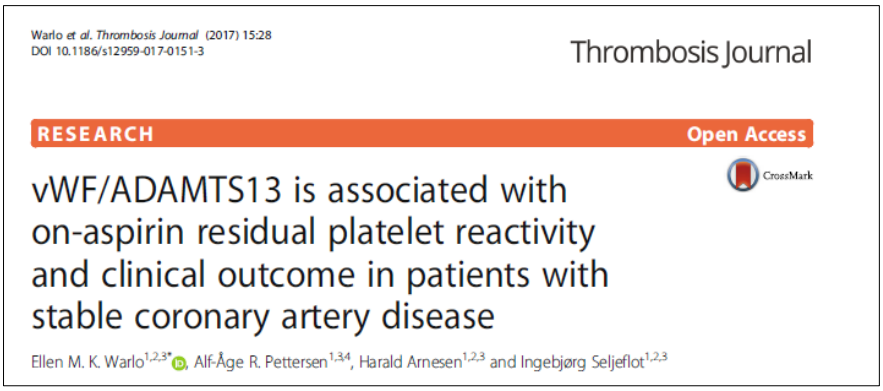
Biomarkers for diagnosis of deep venous thrombosis (DVT) in unselected patients

Cand. Med. Fredrik Wexels, PhD student (vide supra)
Supervisors: MD PhD Ola Dahl, PhD Are Hugo Pripp, Professor Ingebjørg Seljeflot
Initiated at Vestre Viken HF, Drammen.

In this study the initial idea was to evaluate the accuracy of a "spot urine stix test" for prothrombin fragment 1+2, a marker of ongoing coagulation in patients with clinically suspect DVT or PE. Our hypothesis was that the urine stix would have a high negative predictive value and thus a number of patients could be excluded from unnecessary radiological examinations. Markers of activation of coagulation and fibrinolysis according to clinical outcome were investigated.

The importance of ADAMTS-13 on von Willebrand factor regulation in patients with coronary artery disease – with special reference to aspirin treatment

Medical Student in Research, University of Oslo *(vide infra)*
Supervisors: MD PhD Alf-Åge Pettersen, Professor Ingebjørg Seljeflot


Warlo et al. Thrombosis Journal (2017) 15:28
DOI 10.1186/s12959-017-0151-3

Thrombosis Journal

RESEARCH Open Access

vWF/ADAMTS13 is associated with on-aspirin residual platelet reactivity and clinical outcome in patients with stable coronary artery disease

Ellen M. K. Warlo[1,2,3*], Alf-Åge R. Pettersen[1,3,4], Harald Arnesen[1,2,3] and Ingebjørg Seljeflot[1,2,3]

Elevated levels of von Willebrand factor (vWF) are reported in coronary artery disease (CAD) patients with high on-aspirin residual platelet reactivity (RPR) despite aspirin treatment. VWF has pro-thrombotic properties and plays a central role in platelet adhesion and aggregation upon vessel wall injury. ADAMTS-13 (a disintegrin and metalloprotease with thrombospondin 1 repeats) is a member of the ADAMTS family of metalloproteinases), responsible for the regulation of vWF by cleaving ultra large vWF multimers into less active fragments. Deficiency of this protease promotes vWF-induced platelet aggregation. In this project we have shown both reduced ADAMTS13 and increased vWF/ADAMTS13 ratio to be present with high RPR and also to be important for clinical outcome after 2 years.

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.

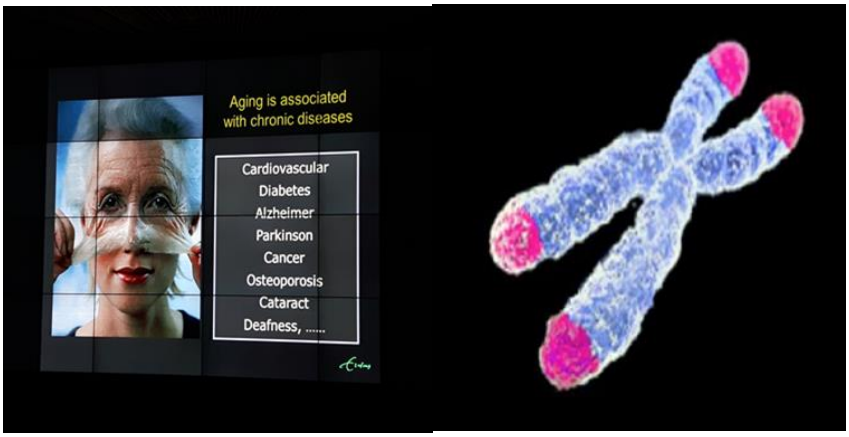
A total of 160 russian welders were investigated before and after a 3-year period of daily/weakly work for inflammatory and haemostatic variables. Blood sampling was undertaken in Russia and brought to our laboratory. The degree of pollution is examined throughout the study period.

Results from the study were published 2017, showing increased endothelial activation, but reduced inflammation and platelet activation during the work exposition. The clinical significance remains to be elucidated.

Studies on Telomere lengths and Ageing

Trine B. Opstad MSc PhD
Are A. Kalstad MD PhD student a.o

A telomere is a region of repetitive nucleotide sequences at the ends of each chromosome which protects DNA at the ends from deterioration. The telomeres become truncated during cell division and about 7 kilobases of telomere length is lost during life. The rate of shortening is thought to be greater in men than in women. Lifestyle and environmental factors have been reported to influence the rate of telomere shortening. Telomere attrition is counteracted by the enzyme telomerase, adding nucleotides to the telomere length during cell-division.



Telomere Length as a suggested marker of longevity, in relation to serum Omega-3 Fatty Acids and dietary pattern in the OMEMI population of elderly patients with AMI (vide supra), based on reports showing omega-3 fatty acids to reduce telomere shortening.

Telomere Length as related to myocardial injury and dysfunction in acute myocardial infarction

Telomere lengths and relation to other rejuvenating factors in patients with coronary artery disease
As certain growth hormones also have been associated with the process of ageing, we will explore the expression of different growth factors and inflammatory factors that are thought to be their regulators.

Telomere lengths and other rejuvenating factors in young people
To study the ageing phenomenon and the regulatory mechanisms we are planning to investigate these associations in a healthy young cohort.

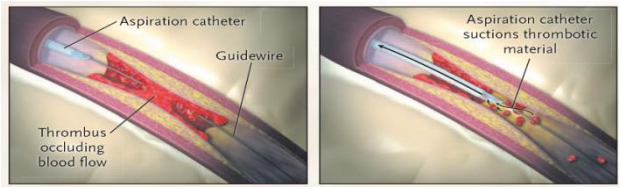
Polymorphisms within the telomerase gene, which have been reported to change the enzyme activity is further planned .

Scientific Activities - Other

Thrombus Aspiration in acute ST-elevation myocardial Infarction (TASTI)

Jostein Nordeng MD

Based on results from the "Coronary thrombus genes in acute myocardial infarction", we aim to further explore the cell types and content, in addition to the genetic profile in the aspirated coronary thrombus. Both cellular and non-cellular content of the thrombus will be examined with morphological and immunhistochemical methods and related to time from onset of symptoms to PCI, as well as to the degree of myocardial necrosis. Furthermore, mRNA expression of selected signal molecules will be performed. In addition, peripheral venous blood samples will be analysed for signalling molecules and corresponding mRNA expression in circulating leukocytes. The study is in close collaboration with Department of Pathology, OUS Ullevål, and collection of thrombi will be finalized during 2018.



Metalloproteinase-9 and its regulators in acute myocardial infarction (NORDISTEMI (NORwegian DIstance ST-Elevation Myocardial Infarction Study)).

Sigrun Halvorsen MD PhD Professor

Professor Ingebjørg Seljeflot, professor em. Harald Arnesen, post doc Trine B. Opstad

This regional study of 240 patients with acute ST-elevation myocardial infarction, all receiving thrombolytic therapy, was performed in 2010-11. A biobank was established and studies on mechanisms related to metalloproteinases (MMP-9), their inhibitors (TIMP-1) and inducers (EMMPRIN) were performed with special emphasis on infarct injury and the development of heart failure, assessed by MRI and SPECT. TIMP-1 measured in the subacute phase after STEMI associated significantly with infarct size and NT-proBNP, indicating a role of TIMP-1 beyond MMP-9 inhibition that influences extracellular matrix remodeling after MI.

The subacute levels of MMP-9 and MMP-9/TIMP-1 ratio were further associated with new clinical events within 1 year, which emphasizes MMP-9s' influence on plaque instability and rupture. Published 2018.

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

MD PhD Eva Cecilie Knudsen Post.doc-projects

MD PhD Eva Cecilie Knudsen who defended her thesis on this project 2011 are continuing 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.

NORCAST (Norwegian Cardiac Arrest Survival Trial)

A project initiated by **Professor Kjetil Sunde,** Department of Surgical Intensive Care Unit in close collaboration with the Acute Coronary Care Unit **by MD PhD Geir Ø. Andersen** ao. The project has daily been 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. In this multidisciplinary study performed in acute seriously ill patients, 250 patients have been 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 three years, the last patient during 2018.

Diabetes in children and atherosclerosis development

Aida Simeunovic MD PhD-student

Supervisors: MD PhD Hanna Dis Margeirsdottir, 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 this follow-up 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 have been followed for 5 years and the 10 years follow-up started in 2017. All blood sampling/processing and facilities for biochemical translational research (biobanking, analyses) are undertaken at CCHR. Results from the first ”5 year follow-up” was completed during 2013. Two PhD theses have been based on data from this study so far. Part of this study is the basis for the Phd-project of Vibeke Bratseth (vide supra) on hypercoagulability in diabetics.

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

Cand. Med. Kristine Holte PhD Student

Supervisor: Professor Tore Julsrud Berg, Professor em. Kristian Hanssen, MD PhD Svein Solheim

The hypothesis is that patients with diabetes type-1 have late complication syndrome consisting of cheiropathy and fatigue, in addition to the traditional micro-and macrovascular 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 to age-matched controls without any signs of related disease for the presence of coronary heart disease assessed by CT coronary angiography, cheiropathy, levels of AGE's in collagen from the shoulder region, inflammatory biomarkers, glycemic control as well as genetic factors.
The inclusion of subjects is finalized and analyses ongoing. Blood sampling/biobanking and analyses of biomarkers for inflammation and endothelial activation are performed at CCHR.

Effectiveness of 24/7 hotline on 30-day readmission following surgical aortic valve replacement surgery: the AVRre randomized controlled trial.

MSc. Stein Ove Danielsen, PhD student

Supervisors: Post doc Irene Lie, Professor Theis Tønnessen, MD PhD Svein Solheim

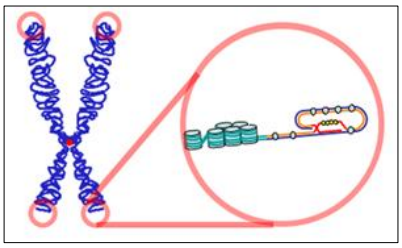
30-day all-cause readmission after surgical aortic valve replacement (SAVR) yields high readmission rates. Main objective was to determine whether a post-discharge intervention with a structured telephone follow-up and a 24/7 hotline reduces 30-day all-cause readmissions after SAVR. A prospective randomised controlled trial was conducted and 288 randomly allocated to either usual care or a telephone follow-up system after discharge. Status: All the patients have been included and the main results of the study will be published during 2018.

Laboratory Methods

has been further developed and established according to recent knowledge and available equipments.

- Method for micro RNA, used as a tool for gene regulation of proteins as well as use as biomarkers has been further developed

- Method for telomere length



- Arrays for gene regulation
- Use of Luminex for protein measures
- Use of Proseek, the OLINK platform (Uppsala)
- Gut-leakage markers
- Netosis markers
- Flow cytometry
- Adipose tissue sample handling/embedding

Methods, equipments

- Facilities for blood sampling and processing for biobanking after SOPs (Centrifuges, cooling centrifuges, freezers (-30°C and –80°C))
- Platelet function testing (aggregometry and ”bedside” screening tests (PFA100, VerifyNow)
- Flowcytomtry (BD Accuri C6)
- ELISA’s
- Fluoroscan
- PCR instruments and centrifuges for molecular biology
- ViiA7 RT-PCR (Applied Biosystems)
- HPLC (Located at Institute for Experimental Medical Research, OUH Ullevål)

Cell-culture studies and Luminex analyses
In collaboration with Department of Medical Biochemistry, R&D Unit OUS Ullevål

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  Mt. Sinai Hospital New York, USA
- Thomas Weiss Professor, MD PhD
  Department of Cardiology and Intensive Care, Wilhelminenhospital, Vienna, Austria

Publications 2017

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13. **Ritschel V,** Shetelig C**, Seljeflot I,** Limalathan S, Hoffmann P, Halvorsen S, **Arnesen H,** Eritsland J, Andersen GØ. Circulating levels of connective tissue growth factor/CCN2 in ST-elevation myocardial infarction: Associations to myocardial injury, function and long-term clinical outcome. Scientific Report 2017;doi: 10.1038/s41598-017-12372-w.
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21. Åkra S, Opstad T.B, Skårn S.N, Aksnes T.A, Seljeflot I. Gene expression of IL-18 and NLRP3 in adipose tissue strongly associate with glucometabolic variables and with the amount of abdominal adipose tissue assessed by CT. Nordcoag 2017, Helsinki
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23. Joanna Cwikiel, Ingebjørg Seljeflot, Eivind Berge, Ida Unhammer Njerve, Hilde Ulsaker, Harald Arnesen, Arnljot Flaa, Effect of strenuous exercise on mediators of inflammation in patients with coronary artery disease. NCS Høstmøte2017
24. Gemma Chiva-Blanch, Lina Badimon, Ingebjørg Seljeflot, Teresa Padró. Novel markers of platelet activation in cardiovascular disease. Summeschool on proteomics, Hamburg 2017

One of the highlights this year was the Scientific Symposium ”Team building for individual excellence” with guest professors, organized October 2017 at Noreheim, Norefjell which also was a celebration of **10 years of Stein Erik Hagens Foundation for Clinical Heart Research.**