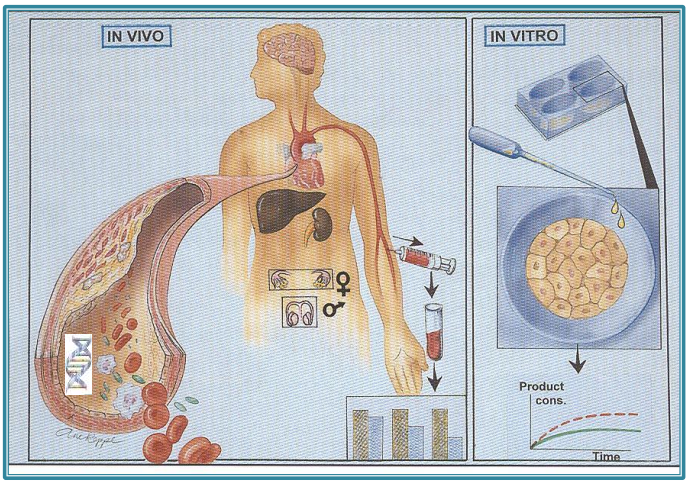



# Center for Clinical Heart Research (CCHR)

Department of Cardiology
Division of Medicine
Oslo University Hospital,
Ullevål

# Annual Report 2016

"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, OUH Ullevål and is one of the research groups within the Department. 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 2016 very much focus has been on development and establishment of new laboratory methods to expand our knowledge on cellular and molecular biology level, for further use in forthcoming projects. Much focus has been paid to improve our understanding of ageing, and how to determine the ageing process, as our patient populations are getting older.
The activity has been scientifically high. Three theses, supervised from the Center, have been submitted for the PhD degree to be defended early 2017, 17 internationally published papers and further 20 published congress abstracts.
The 6 months post.doc period for Gemma Chiva-Blanch from the prestigious ICIC in Barcelona ended March 2016, with the results of 3 scientific papers whereof 1 published in 2016, and 1 early 2017.
The Scientific Symposium ”Team building for individual excellence”, are organized every second year. It was organized in 2015 and the next, 6$^{th}$, will be prepared for October 2017 which also will be a celebration of 10 years of Stein Erik Hagens Foundation for Clinical Heart Reserch.

We are very pleased to give this annual report for 2016 which is a
**25 years anniversary for CCHR.**

April 2017

Ingebjørg Seljeflot (sign)
professor dr. philos

Harald Arnesen (sign)
professor em dr. med

Svein Solheim (sign)
MD post.doc

# Finances

Budgets for the single projects, including salary for PhD-students, technical personal and running laboratory expenses are based on external fundings from different sources. Also in 2016 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 leader is financed from the Department of Cardiology, OUH, 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 2016.

# Strategy

## The strategies are unchanged

- 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 and atrial fibrillation
- 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, OUH/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. PhD candidates, post.docs and laboratory staff participate together with the professors and seniors. The main projects are reported with progress, results and relevant discussions. 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 candidates are encouraged to give presentations at the meetings and to prepare abstracts for international congresses. In 2016, 12 such meetings were arranged.
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.

## Personell

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 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, 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 full time 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.

# Scientific Activities

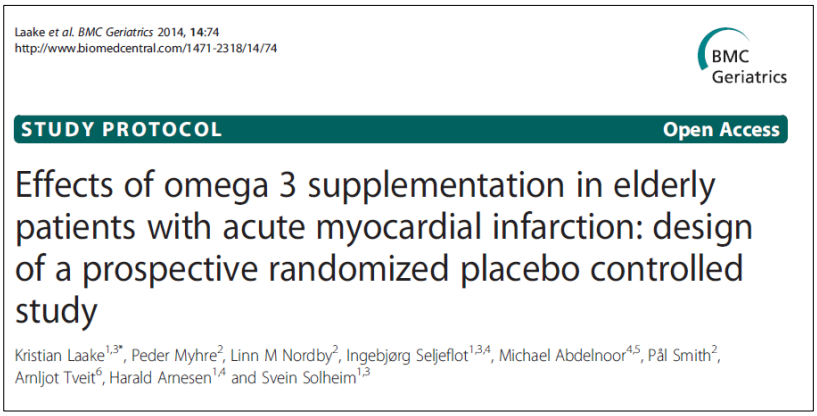
# PhD-thesis to be defended early 2017

## Kristian Laake, Cand. Med.

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

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

A large scale clinical trial (OMEMI) evaluating the effects of omega-3 fatty acids on clinical outcomes in elderly patients with acute myocardial infarction (AMI) was initiated in 2013.


Laake *et al. BMC Geriatrics* 2014, **14**:74
http://www.biomedcentral.com/1471-2318/14/74

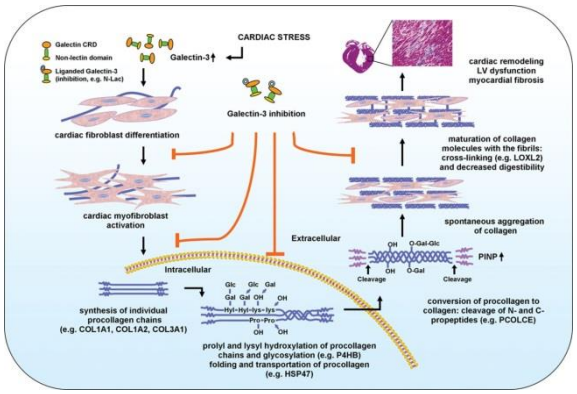
BMC Geriatrics

STUDY PROTOCOL Open Access

Effects of omega 3 supplementation in elderly patients with acute myocardial infarction: design of a prospective randomized placebo controlled study

Kristian Laake[1,3*], Peder Myhre[2], Linn M Nordby[2], Ingebjørg Seljeflot[1,3,4], Michael Abdelnoor[4,5], Pål Smith[2], Arnljot Tveit[6], Harald Arnesen[1,4] and Svein Solheim[1,3]

As the OMEMI study is still ongoing, the aims of the thesis were to evaluate the associations between omega-3 fatty acids in serum measured at inclusion (2-8 weeks after the index AMI) and infarct size and indices of heart failure in a subgroup of 299 patients.
The elderly patients with a history of atrial fibrillation (AF) had significantly lower docosahexaenoic acid (DHA) levels, indicative of an association between omega-3 fatty acids and AF.




Galectin-3, a recently described biomarker of fibrosis, correlated inversely to the concentration of omega-3 fatty acids at inclusion, indicating a potential role of omega-3 fatty acids in adverse cardiac remodeling and heart failure development.

# Scientific Activities

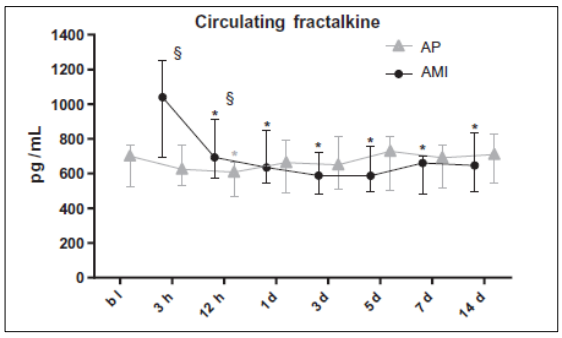
# PhD-thesis to be defended early 2017

## Ida Unhammer Njerve, Cand. Med.

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

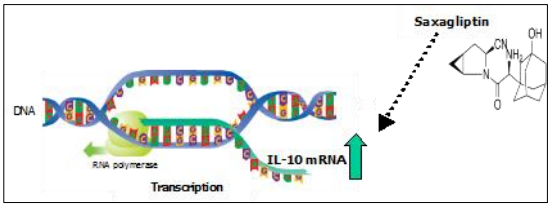
*Supervisors: Professor Ingebjørg Seljeflot, MD PhD Svein Solheim*

To elucidate the role and regulation of the chemokine CX3CL1 (fractalkine) and its receptor CX3CR1, various populations of patients with acute myocardial infarction, stable coronary artery disease and / or T2DM were investigated, also with emphasis on adipose tissue inflammation.




Fractalkine levels are elevated early after PCI-treated ST-elevation myocardial infraction.
*Cytokine 2014; 69; 131-134*

In patients with combined CAD and T2DM, randomized to exercise training or not, no significant beneficial influence of training was observed on pro-inflammatory genes expressed in subcutaneous adipose tissue.
The antidiabetic drug saxagliptin, thought to have anti-inflammatory properties, were investigated in a randomized placebo-controlled intervention study in patients with combined stable CAD and T2DM. In peripheral blood mononuclear cells and circulating leukocytes from patients on active drug for 3 months, an increase in the gene expression of the anti-inflammatory interleukin-10 was observed.



# Scientific Activities

# PhD projects

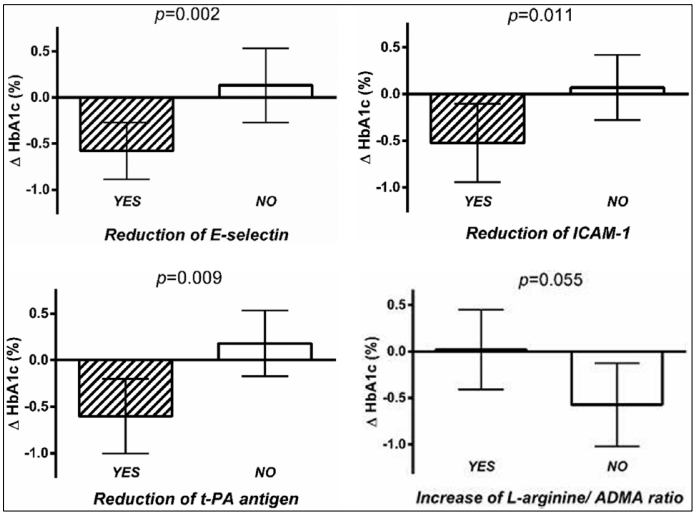
## EXCADI (Exercise training in patients with coronary Artery disease and diabetes)

### 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.
There is limited knowledge about the mechanisms involved in the 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 collaboration with the Norwegian School for Science in Sports.

*Reduced endothelial activation after exercise is associated with improved HbA1c in patients with type 2 diabetes and coronary artery disease*




*Byrkjeland R et al. Diabetes & Vascular Disease Research 2017; 1-7*

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**

## Adipose tissue inflammation in patients with coronary artery disease and type 2 diabetes; effects of exercise training

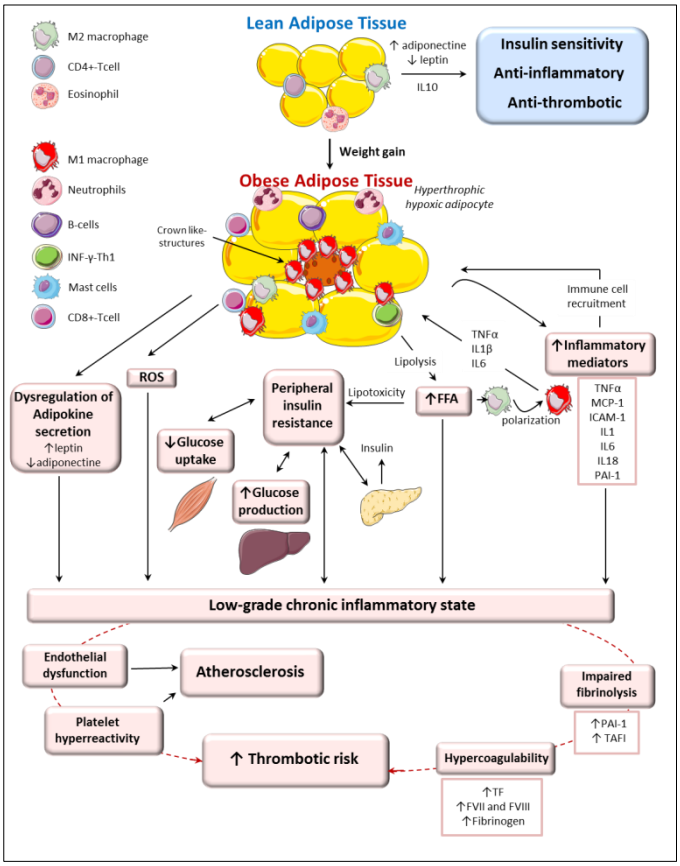
### Cand. Med. Hani Zaidi

*Supervisors: Professor Ingebjørg Seljeflot, Post.doc Trine B. Opstad*
*Phd-student Rune Byrkjeland, Post doc Svein Solheim*

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) will be further explored.




*G.Vilahur 2017, with permission*

# Scientific Activities

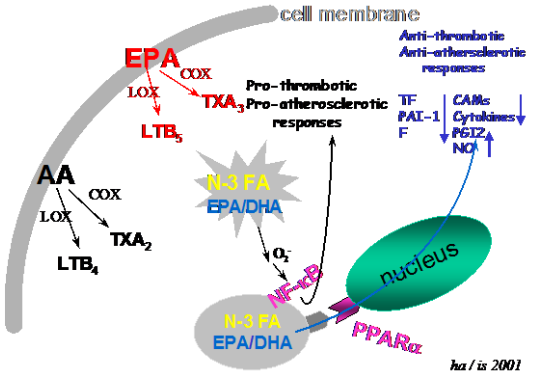
# PhD projects

## OMEMI (OMega-3 fatty acids in Elderly patients with Myocardial Infarction)

### Twin PhD students, Cand. Med. Are Annesønn Kalstad at OUHU and Cand. Med. Peder Myhre at AUH

*Responsible/supervisors: Professor Ingebjørg Seljeflot ,*
*Professor em. Harald Arnesen, post. doc Svein Solheim, Professor Pål Smith, Professor Arnljot Tveit*

This is an ongoing study, 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. A reduction in the combined cardiovascular end-point of death, non-fatal MI, stroke, revascularizations and re-hospitalization for heart failure with at least 25% is estimated. 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 is established and several sub-studies are ongoing related both to the intervention principles and to CAD in this elderly population. In a substudy including the first 299 patients a significant inverse correlation between omega-3 fatty acids and Galectin-3, a marker of left ventricular remodeling was observed (conf. Laake Thesis, page 8).

## Scientific Activities

# PhD projects

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

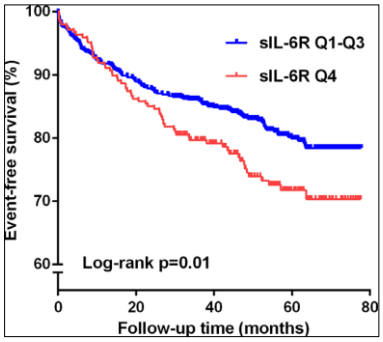
## Cand. Med. Vibeke Ritschel

*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 as previously reported on.
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 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.

*The prognostic value of IL-6R on cardiovascular endpoints*




*Ritschel V et al JAHA 2016; 2016;5:e003014*

## Scientific Activities

# PhD-projects

### CADENCE (Markers of Coronary Artery Disease During Exercise Testing)

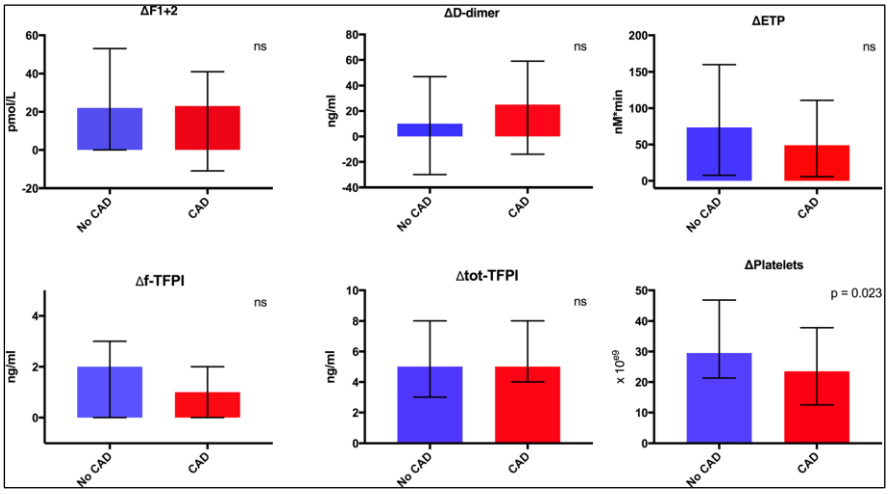

**Cand. Med. Joanna Cwikiel**

*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=300) 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 as related to exercise by studying whether there is an increase in biomarkers associated with haemostasis and inflammation during exercise, and examine whether ischemia may potentiate this increase.
Furthermore, the relationship between exercise-induced changes in biomarkers and echocardiographic measures of systolic and diastolic function at rest are performed.

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.




*Pro-thrombotic activity after strenuous exercise*

## Scientific Activities

# PhD-projects

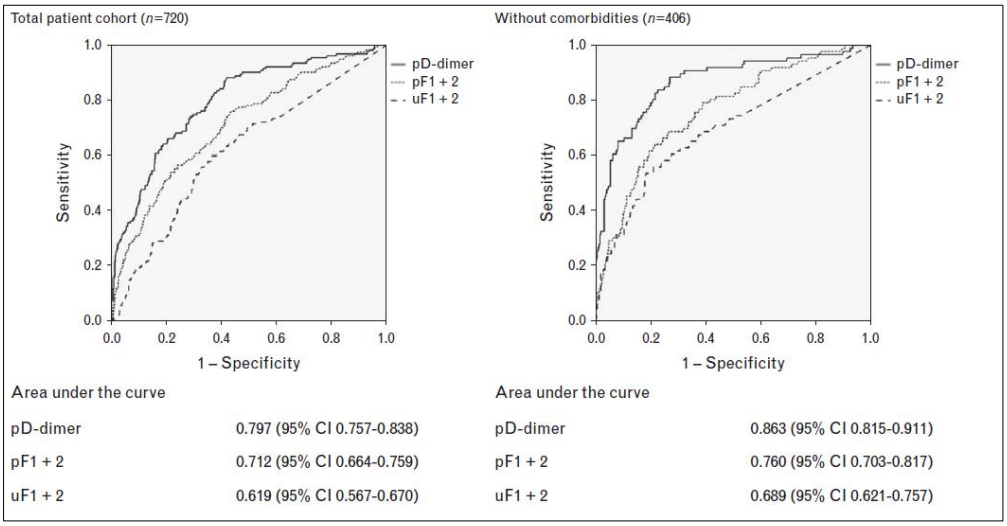
### Biomarkers for diagnosis of deep venous thrombosis (DVT) in unselected patients

### 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 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 also want to analyse 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.

*Rock curve analyses illustrating the prognostic values of the biomarkers*




*Wexels F et al. Blood Coag Fibrinolysis* 2016

## Scientific Activities

# PhD-projects

**Cardiac and prothrombotic markers in Atrial Fibrillation**
Initiated at Vestre Viken HF, Asker & Bærum Hospital

### Project for the PhD degree: Cand. Med. Anja Wiedswang Horjen

*Supervisors MD PhD Arnljot Tveit, Professor Ingebjørg Seljeflot*

In the **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.

# PhD-projects

**LEAF (Safety and efficacy of Levosimendan in patients with Acute myocardial infarction complicated with symptomatic left ventricular Failure)**.
Initiated at CCU, Dept of Cardiology, OUH

### 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 have been undertaken at CCHR, and results presented during 2015/16. The study will be the basis for the thesis to be submitted January 2017.

## Scientific Activities

# PhD-projects

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

### Cand. Med. Christian Shetelig

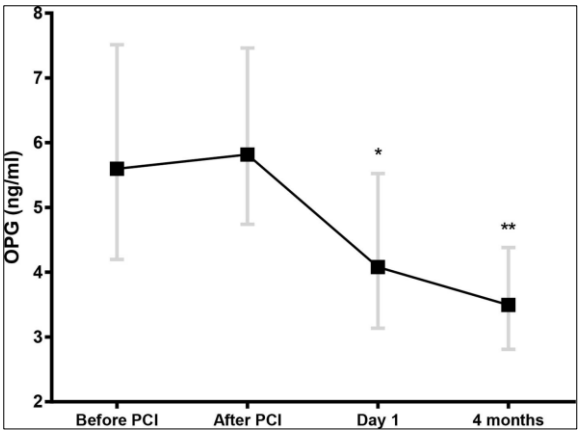
*Supervisors: MD PhD Geir Ø. Andersen, MD PhD Jan Eritsland, professor Ingebjørg Seljeflot*

From the POSTEMI study (vide infra), the purpose of the present 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. In addition, any importance of netosis (vide infra) will be explored in the project.

The study is also a cross-modality imaging study, which may enable us to explore and compare the use of CMR and novel echocardiographic methods to assess myocardial function during the development of an acute MI.

Study on osteoprotegerin (OPG), a member of the TNF receptor superfamily acting as a soluble decoy receptor of the receptor activator of NFkappa B ligand (RANKL), has been explored.

*Temporal profile of osteoprotegrin (OPG) during the* course of STEMI




*Schetelig C et al doi:10.1371/journal.pone.0173034.g002*

## Scientific Activities

# PhD-projects

### Microbial translocation and cardiovascular disease states. Emphasis on chronic heart failure, diabetes and the metabolic syndrome

**Cand. Med. Ayodeji Awoyemi**

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

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) on the surface of gram negative bacteria 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.

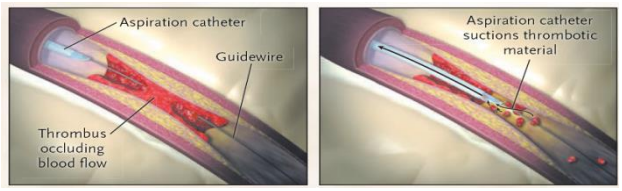
This project will focus on the potential role of microbial translocation and gut leakage in different cardiovascular disease (CVD) states, including metabolic syndrome (MetS), diabetes type-2 and chronic heart failure, with reference to degree of the disease states, intervention effects and also for clinical outcome.
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 to clinical end points in a population at high-risk for CVD will be explored. Furthermore, 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.

# Scientific Activities; Other

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

### Cand. Med. Jostein Nordeng

Based on results from the "Coronary thrombus genes in acute myocardial infarction", in this study 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, OUH Ullevål, and collection of thrombi, is still ongoing.

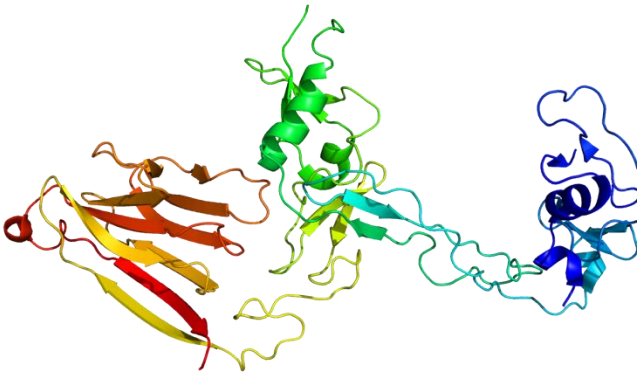


## Scientific Activities; Other

### 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)*

The mechanisms behind residual platelet reactivity (RPR) despite aspirin treatment are still not established.
Elevated levels of von Willebrand factor (vWF) are reported in coronary artery disease (CAD) patients with high on-aspirin RPR. VWF) is a well-established marker of endothelial activation and vascular injury. It 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 any relationship between ADAMTS13 and the vWF/ADAMTS13 ratio and the presence of high RPR are explored. Also, any importance for clinical outcome after 2 years is investigated.



# Scientific Activities; Other

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

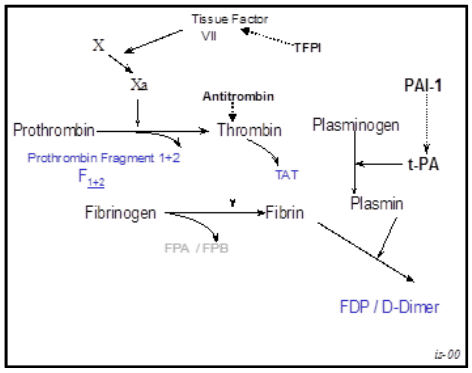
*A Steering committee for BAMI is established (Professor em. Harald Arnesen, MD PhD Geir Øystein Andersen, MD PhD Sigrun Halvorsen, MD PhD Jan Eritsland, MD PhD Reidar Bjørnerheim, Professor Ingebjørg Seljeflot)*

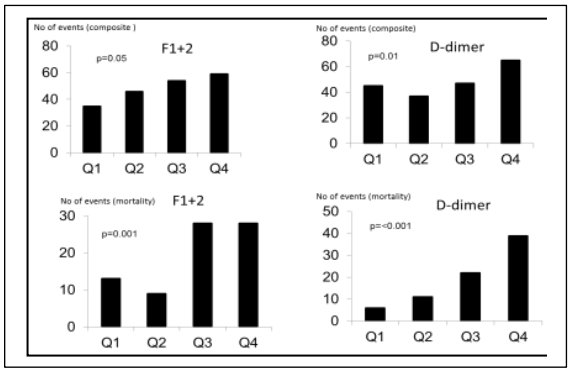
In this joint project between the Cardiac Care Unit, General Cardiology Section and CCHR in Department of Cardiology, an extended biobank is mounted along with prospectively registered clinical data and will be the basis for studies on predictive markers for later clinical events. Consecutive patients with STEMI are included after consent. At the end of 2015 about 1800 patients have been included and a PhD project on selected biomarkers are underway (vide supra).
Further projects are planned, including genetic studies. All logistics for processing of blood samples in the acute phase and the biochemical translational research are undertaken by CCHR.

## Based on the BAMI Cohort: Study on pro-thrombotic activity

### Study nurse Charlotte Holst Hansen

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.
In this project the impact of increased pro-coagulant activity on clinical outcome has been explored, showing especially levels of D-dimer to have prognostic value.




*Levels of F1+2 and D-dimer in quartiles as related to composite endpoints and total mortality*

# Scientific Activities; Other

## Based on the EXCADI biobank: Study on pro-thrombotic activity

MSc Vibeke Bratseth

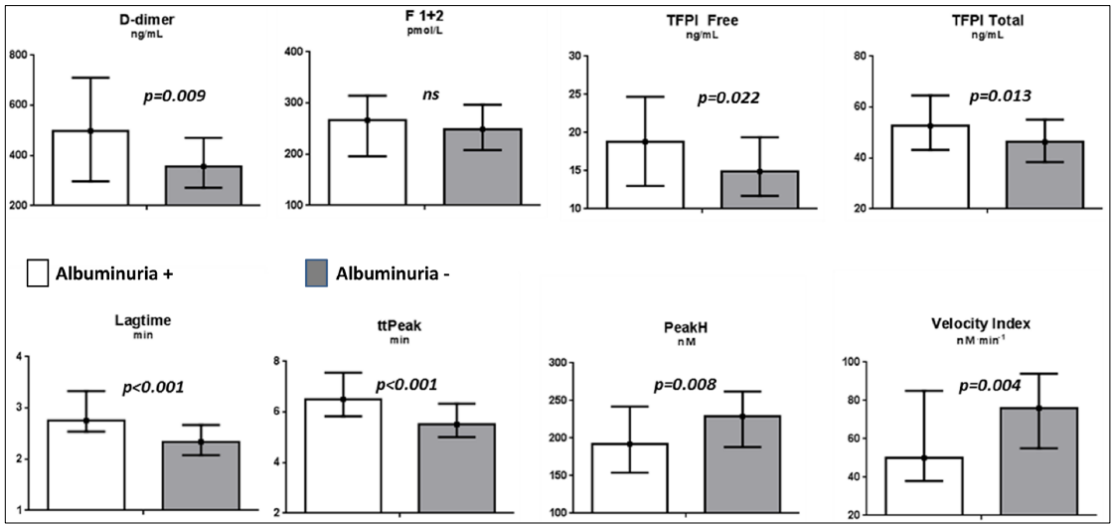
Patients with combined type 2 diabetes mellitus (T2DM) and coronary artery disease (CAD) represent a high risk population regarding athero-thrombotic events.
In this sub-study the effects of 12-months exercise training on markers of coagulation, in patients with combined T2DM and CAD are explored. The hypothesis is that exercise has a beneficial effect on the hypercoagulable state in these patients.
The Calibrated Automated Thrombogram (CAT- assay) for *ex vivo* thrombin generation, in addition to *in vivo* thrombin generation measurements (prothrombin fragment 1+2 and D-dimer) and TFPI are undertaken.

A significant association between poor glycaemic control and levels of TFPI was demonstrated, potentially due to endothelial activation.

We could, however, not demonstrate any effects of exercise training on markers of pro-coagulant activity in our population.

Increased pro-coagulant activity was, however, observed in patients with more severe diabetes i.e. presenting with microalbuminuria.

*In vivo and ex vivo thrombin generation according to patients with albuminuria (white column) and without (black column)*




*Bratseth V et al. Diabetes & Vascular Disease Research 2017; 1–8*

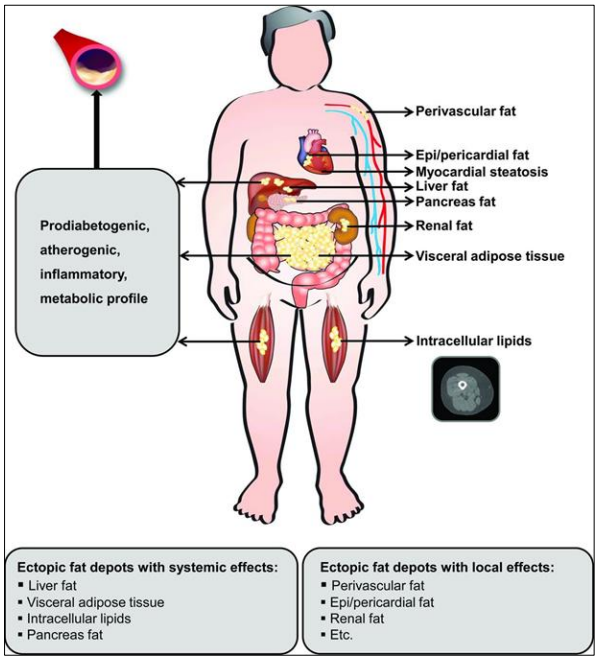
# Scientific Activities; Other

## 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

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, visualised in several previous and ongoing projects.
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.




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

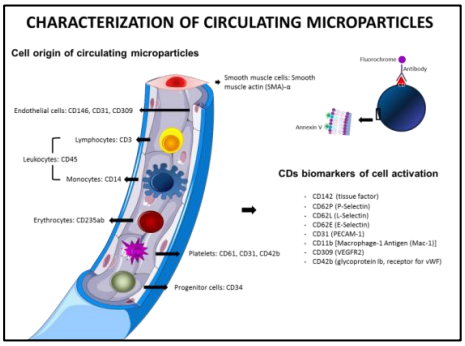
## Scientific Activities

# Post.doc-projects

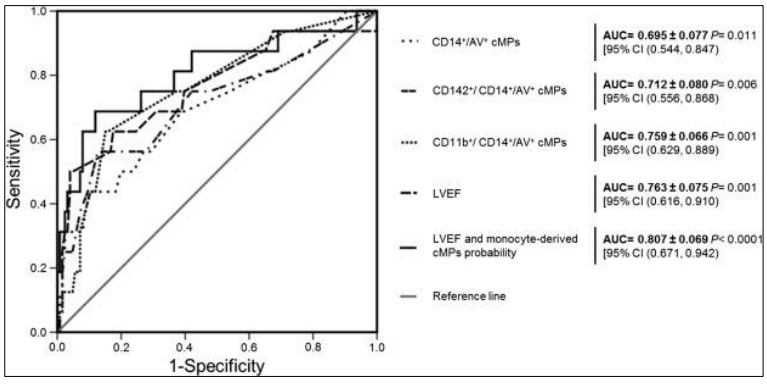
### Quantification of circulating microparticles in patients with cardiovascular disease

**Post doc Gemma Chiva Blanch, Cardiovascular Research Center (CSIC-ICCC), Hospital de la Santa Creu i Sant Pau, Barcelona**

This project continued until March 2016 and 2 scientific papers were accepted in 2016. The background for this project was related to the important role of microparticles in CVD states. Cell membrane microparticles (MPs) are phospholipid blebs of 0.2–1.0 µm in size shed from the plasma membrane of eukaryotic cells when injured, activated, or undergoing apoptosis. MPs are shed from several cell types, including platelets, endothelial cells, erythrocytes and leukocytes, and have been shown to reflect cellular activation and/or tissue degeneration occurring in vivo.
MPs are suggested to be of relevance in clinical applications, including their potential both as biomarkers of disease for improving cardiovascular risk prediction and as novel therapeutic targets.




From the OMEMI study (vide supra), MPs have been investigated with regard to their relation to myocardial injury and heart failure and in the BAMI study (vide supra) in relation to clinical endpoints.




*ROC curve analyses to evaluate the predictive power of monocyte-derived cMPs and ejection fraction for cardiovascular death.*

*Chiva Blanch G. Int J Cardiol 2016; doi.org/10.1016/j.ijcard.2016.11.302*

## Scientific Activities

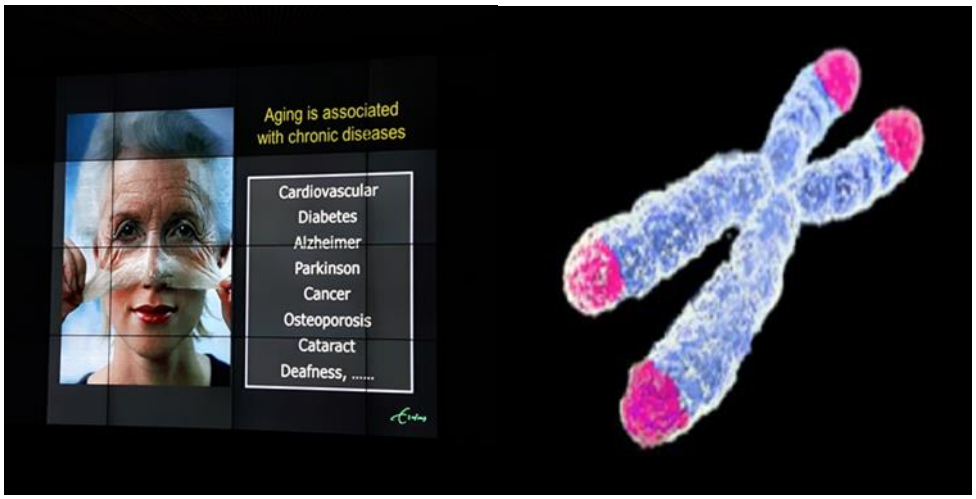
# Post.doc-projects

### Telomere lengths and Ageing

MSc PhD Trine B. Opstad

A telomere is a region of repetitive nucleotide sequences at the ends of each chromosome which protects DNA at the ends from deterioration. The sequence (TTAGGG) of nucleotides is repeated approximately 2.500 times in humans. 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. Additionally, lifestyle and environmental factors are recently 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. However, this enzyme is missing or holds very low activity in most somatic cells and is only present in stem cells and cancer cells and cells that need to divide regularly.

In this project, we will explore associations between telomere lengths and comorbidities in patients with coronary artery disease.
As telomere lengths have been associated with ageing, we will further investigate potential upstream regulatory mechanisms of telomere shortening, by measuring polymorphisms within the telomerase gene, which have been reported to change the enzyme activity.
As certain growth hormones also have been associated with the process of ageing, we will explore the expression of growth differentiate factor 11 and fibroblast growth factor 21 in relation to telomere length to search for potential covariation. Both markers are suggested as rejuvenating factors, however debated in the literature.



## Scientific Activities

# Post.doc-projects

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

**MD PhD Eva Cecilie Knudsen**

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.

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

**MD PhD Alf-Åge Pettersen**

**Ellen Warlo, Medical Student Research program** *(vide supra)*
*Professor IngebjørgSeljeflot*

This main study which was to investigate the clinical importance of non-responsiveness to aspirin in 1000 CAD-patients, 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 mechanisms behind, are ongoing. Special focus has been related to the impact of von Willebrand factor and ADAMTS-13 on the responsiveness to aspirin (vide supra). Possible influence of relevant genetic differences in this regard is further explored.

## Scientific Activities

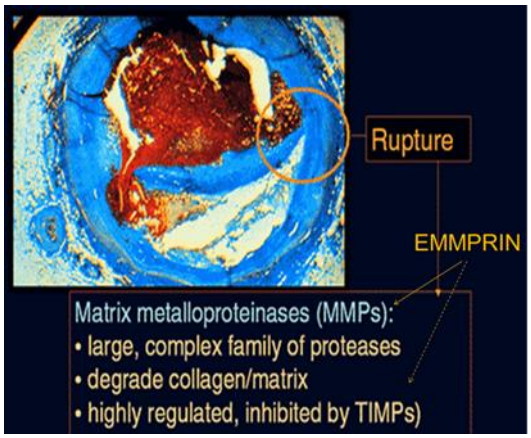
# Post.doc-projects

**NORDISTEMI (NORwegian DIstance ST-Elevation Myocardial Infarction Study).**

### MD PhD Professor Sigrun Halvorsen

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

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, were 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 PhD thesis defended in 2011(Ellen Bøhmer, MD).
Additional studies, based on an established biobank, on mechanisms related to metalloproteinases (MMP-9), their inhibitors (TIMP-1) and inducers (EMMPRIN) are ongoing, 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.



## Scientific Activities

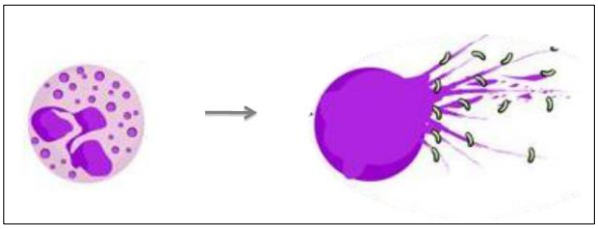
# Post.doc-projects

### Neutrophil extracellular traps (NETs) in coronary heart disease patients


## MD PhD Ragnhild Helseth

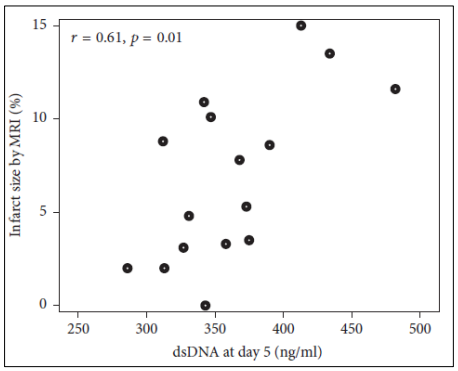
*Post doc Trine B. Opstad, MD PhD Svein Solheim, Professor em. Harald Arnesen, Professor Ingebjørg Seljeflot,*


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), a surrogate marker of NETs, have been reported in acute myocardial infarction.



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

*Correlation between dsDNA and infarct size assessed by MRI*





*Helseth R et al. Mediators of Inflam 2016; 2182358.*
*doi: 10.1155/2016/2182358*

# 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 *(vide supra).* Results from the study are the basis for thesis to be submitted early 2017.

### 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 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 one year.

### Markers of inflammation in the elderly. Special emphasis on cerebrospinal fluid (CSF) in delirium associated with hip-fracture

*A collaboration with Department of Geriatrics, OUH Ullevål*
*(Professor Torgeir Bruun Wyller and Associate professor Siri Rostoft).*

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 have been investigated. CRP and components of the interleukin-6 transsignalling pathway in serum and CSF have been extensively studied in about 100 patients. The results will be a part of the doctoral thesis for PhD student Bjørn Neerland, *Department of Geriatrics,* to be defended in 2017.
Also in a study on the inflammatory state related to frailty, the results will be included in the doctoral thesis of Cand. Med. Benedicte Rønning, *Department of Geriatrics*, to be defended early 2017.

## Diabetes in children and atherosclerosis development

### Post.doc project (MD PhD Hanna Dis Margeirsdottir)

*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. Two PhD theses have been based on data from this study so far. 10-years follow-up will start early 2017.

## 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, Professor 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.

## Deleterious cardiac effects of long-time use of anabolic steroids evaluated by echo and biomarkers

### 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 of inflammation, coagulation and platelet activation are studied. The project is initiated from OUH Aker with all biochemical investigations being performed at 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.
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 reported in 2016, showing increased endothelial activation, but reduced inflammation and platelet activation during the work exposition (including α-quartz and diesel exhaust). The clinical significance remains to be elucidated.

## Microbial translocation as 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.*

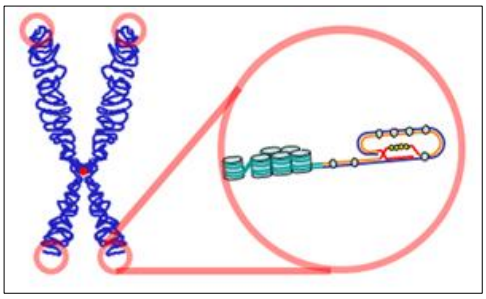
Microbial translocation has been suggested as a driving force of immune activation in several disease states as commented.
In chronic HIV-infected individuals the gastrointestinal mucosal barrier is distorted. Markers of microbial translocation have been shown to be independent predictors of future hypertension 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.

# Laboratory Methods

**has been further developed, 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)
- 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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  Uppsala University Hospital, Uppsala, Sweden

# Publications 2016

## Articles

1. Bliksøen M, Mariero LH, Torp MK, Baysa A, Ytrehus K, Haugen F, **Seljeflot I**, Vaage J, Valen G, Stensløkken KO. Extracellular mtDNA activates NF-κB via toll-like receptor 9 and induces cell death in cardiomyocytes. Basic Res Cardiol 2016; 111 (4), 42
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3. Chiva-Blanch G, **Bratseth V**, **Ritschel V**, Andersen GØ, Halvorsen S, Eritsland J, **Arnesen H**, Badimon L, **Seljeflot I**. Monocyte-derived circulating microparticles (CD14(+), CD14(+)/CD11b(+) and CD14(+)/CD142(+)) are related to long-term prognosis for cardiovascular mortality in STEMI patients. Int J Cardiol 2016; 227, 876-881.
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5. Haissman JM, Haugaard AK, Knudsen A, Kristoffersen US, **Seljeflot I**, Pedersen KK, Lebech AM, Hasbak P, Kjær A, Ostrowski SR, Gerstoft J, Trøseid M, Nielsen SD. Marker of Endothelial Dysfunction Asymmetric Dimethylarginine Is Elevated in HIV Infection but Not Associated With Subclinical Atherosclerosis. J Acquir Immune Defic Syndr 2016;, 73 (5), 507-513.
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10. **Njerve IU**, **Byrkjeland R**, **Arnesen H**, **Åkra S**, **Solheim S**, **Seljeflot I**. Effects of long-term exercise training on adipose tissue expression of fractalkine and MCP-1 in patients with type 2 diabetes and stable coronary artery disease: a substudy of a randomized controlled trial. Diabetes Metab Syndr Obes 2016; 9, 55-62

11. **Opstad TB**, **Arnesen H**, Pettersen AÅ, **Seljeflot I**. Combined Elevated Levels of the Proinflammatory Cytokines IL-18 and IL-12 Are Associated with Clinical Events in Patients with Coronary Artery Disease: An Observational Study. Metab Syndr Relat Disord 2016; 14 (5), 242-8
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## Abstracts

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5. Shetelig C, Limalanathan S, Eritsland J, Hoffmann P, Seljeflot I, Aukrust P, Ueland T, Andersen GØ. High osteoprotegerin levels are associated with adverse left ventricular remodelling in patients with ST-elevation myocardial infarction. Congress of the European Society of Cardiology 2016 Rome
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7. Cwikiel J, Seljeflot I, Bratseth V, Berge E, Flaa A. Pro-coagulant activity during exercise testing in patients with coronary artery disease. Congress of the European Society of Cardiology 2016 Rome
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10. Helseth R, Seljeflot I, Solheim S, Arnesen H, Opstad TB. Neutrophil extracellular traps (NETs) in acute myocardial infarction – a novel inflammatory pathway in atherothrombosis. 14th Center for Heart Failure Research Symposium 2016, Oslo
11. Warlo EMK, Seljeflot I, Arnesen H, Pettersen AÅR. Reduced levels of ADAMTS13 are associated with high on-aspirin residual platelet reactivity in patients with stable coronary artery disease. 14th Center for Heart Failure Research Symposium 2016, Oslo

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