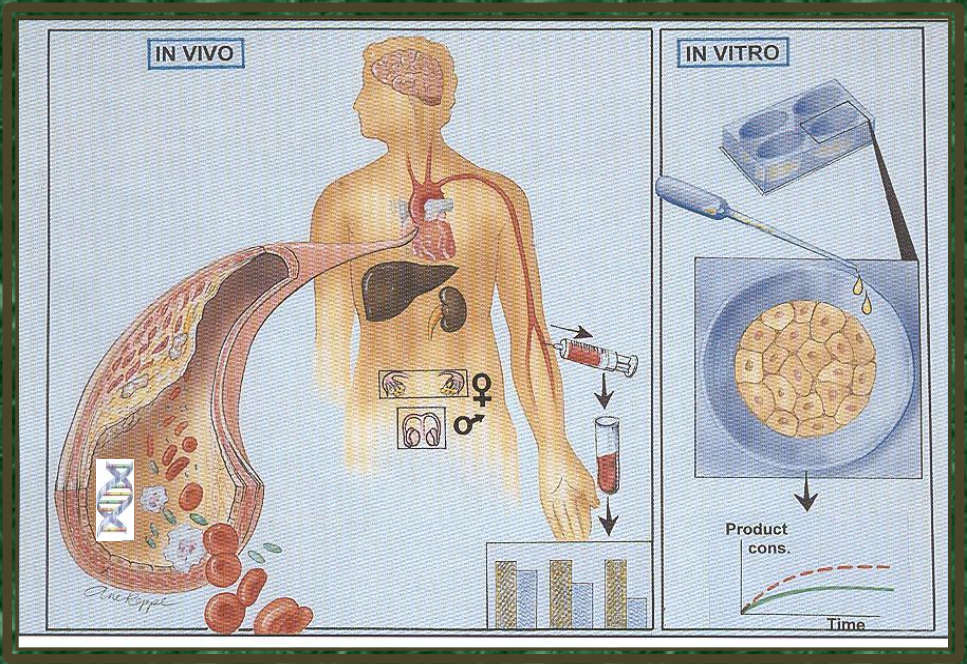
Annual Report 2022



Center for Clinical Heart Research (CCHR)

Department of Cardiology
Division of Medicine
Oslo University Hospital, Ullevål

http://research.no/clinicalheartresearch/

"Team building for individual excellence"

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Preface

Center for Clinical Heart Research (CCHR) is a research laboratory and a core center for research at Department of Cardiology, Oslo University Hospital Ullevål.
Organized within the department, located close to the patients is crucial for the scientific activities which mainly are
***Researcher - initiated clinical, randomized intervention trials; Translational studies on pathophysiological* mechanisms in cardiovascular disease states.**

The Center has close collaborations with research groups within the department, with other departments in Medical Division and other Divisions at OUH. Close collaborations have been developed especially to OUS Rikshospitalet, Oslo Diabetes Research Center, Asker & Bærum Hospital and Akershus University Hospital, by having common projects and PhD-students.

Also in 2022, focus has been to improve methodology related to the innate immune system, microbial translocation aspects, adipose tissue inflammation and the ageing process. The scientific activity has been high, despite still some side-effects/delays from the corona pandemic.
Three PhD thesis were defended and 24 internationally published papers, all original articles. This year some congresses have been ordinary/physically, and 19 abstracts have been presented, nationally and internationally. This is a very important activity for team-building, education of the PhD students and internationalization, in addition to our regularly internal research meetings that have been arranged traditionally this year.

The planned activities is on track, with one PhD candidate defended her thesis January 2023, and one is planned for April 2023, and additionally two are soon to ready to submit their thesis, of which one is a previous candidate from The Medical Research Student Program at the university, funded by the Norwegian Council of Research.
This year we have had the opportunity to lounge an Italian post.doc for 6 months, for international experience for her scientific carrier, bringing own money for salary. An important contributor, both scientifically and for international collaboration.
Our participation in the “Regional Research Network for Clinical Microbiota Science” and the “Norwegian Atrial Fibrillation Research Network”, financed from Health South East, are still very fruitful.

Professor emeritus Harald Arnesen has been exchanged by MD PhD Svein Solheim as our delegate in the Board for Stein Erik Hagens Foundation for Clinical Heart Research, and has now retired from his duties. Svein Solheim is also member of the steering committee at the Center. The research coordinator, Charlotte Holst Hansen, employed for administrative matters in 50% position has continued in 2022.

We are very pleased to give the annual report for 2022.

March 2023

Ingebjørg Seljeflot (sign)
Professor em dr. philos
Center Head

Strategy

- To perform research in line with the strategy for research in Department of Cardiology
- Clinical studies, including translational studies in cardiovascular medicine. Biochemical, cellular and genetic aspects related to the cardiovascular disease processes, focusing inflammation, remodeling, thrombosis, endothelial function and the ageing phenomenon.
    - Systematic researcher-initiated clinical heart research, based on validated research methodology along with the flow of patients in OUS
    - Projects related to acute myocardial infarction, chronic artery disease, diabetes, heart failure, atrial fibrillation and the elderly
    - Biobanking, standardized sampling and processing of blood and tissue
      About 90 % of all publications are based on biobanks
- To be an interdisciplinary composed research group, including researchers at post.doc level
- To collaborate in appropriate networks and with other research groups

Main Goals

The main goal is to develop novel treatment options in cardiovascular medicine

- to increase the understanding of disease mechanisms, pathogenic factors, and effects of interventions in patients with cardiovascular disease
- to design and carry out randomized clinical trials
- to further expand on translational research in light of new knowledge and by use of new technology in materials from extended biobanks

Other scientific goals

- 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 at a post doc level
- to strengthen collaboration with national and international research groups

Organization

The Center Head is responsible for administration and organization, in collaboration with a steering committee. Decisions on projects/scientific matters, and contracts for collaboration with other research groups are based on common scientific interests.
Our most important activity is the regular 2-hour-scientific meetings every 2-3 weeks with PhD fellows, post.docs, laboratory staff, professors and seniors, presentation and discussion on the progress in all projects. External experts on special relevant topics and co-workers from other groups and institutions are often invited. The PhD fellows are especially encouraged and trained to give presentations to prepare for international meetings.
Individual supervision of the PhD fellows is in addition undertaken, with a "supervisor-open-door-policy", and specific projects are separately discussed in smaller groups.

Personnel

Leadership: The Head is also the Head of the R&D Section at Department of Cardiology, 100% position, and professor em at University of Oslo (UiO). A cardiologist (MD PhD Svein Solheim) is medical responsible, and a research coordinator in 50% position for administrative matters.
Employees: 1 medical technologist with a Master of Science in Biomedicine, 2 scientists with PhD degree.
6 PhD fellows, 6 post.docs/seniors participate in the milieu and 1 student from the research program for medical students, funded by the Norwegian Research Council via UiO. In addition, the scientific milieu and the laboratory facilities are open for other PhD-fellows, mainly supervised in collaboration with other research groups at OUS Ullevål.

Finances

The Head is financed from the Department of Cardiology, OUS, Ullevål by a combined position for the Center and for being Head of the R&D section in the Department. Budgets for the single projects, including salary for PhD-fellows, technical personnel and running laboratory expenses are based on external funding from different sources. We strive for fundings by applications wherever we find it relevant. For 2022 we were happy to get grants from Health South East for funding of a PhD project.

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 activities also in 2022. The withdraw of additional funding from the Norwegian Council of Research, with retroactively effect, has been an extra economic challenge.

Scientific Activities

In addition to atherosclerosis, myocardial infarction, inflammation and remodeling in general, we also in 2022 had our methodological focus in the areas presented.

PhD-theses defended 2022

Cand Med Are Annesønn Kalstad

The role of n-3 fatty acids in cardiovascular diseases of ageing

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

This thesis is fully based on the OMEMI trial, further described (vide infra).
The main study results from the intervention with omega-3 fatty acid supplementation, showed no effects on clinical outcome (reinfarction, stroke, death, heart failure or unscheduled coronary intervention), whereas surprisingly, a tendency to increased frequency of new onset of atrial fibrillation.
The thesis further focused determinant important for the ageing phenomenon and processes per se i.e telomere length and sirtuins (vide infra), in cardiovascular disease. No significant association between telomeres and omega-3 fatty acids were found, but sirtuin-1 was associated with atrial fibrillation in the elderly.

Cand Med Miriam S. Langseth

Neutrophil extracellular traps (NETs) in coronary artery disease.

Prognostic value and roles in atherothrombosis in acute and stable coronary heart disease

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

In this project, markers of neutrophil extracellular traps (NETs) was studied in different stages of coronary artery disease, including cardiogenic chock following acute myocardial infarction, as related to hypercoagulability, myocardial injury and function and clinical endpoints.

The results showed the influence of NETs in all stages of the disease. Some of the markers were also to be useful as prognostic biomarkers, and double stranded DNA (ds DNA) seems to be a possible reliable target for therapy in patients with acute myocardial infarction.

Cand Med Sjur Hansen Tveit

Cardiac Troponin I and T: Comparison of the Diagnostic and Prognostic Performance in Coronary Artery Disease

Supervisors: Torbjørn Omland Professor, Peder Langeland Myhre MD PhD, Ingebjørg Seljeflot Professor

The candidate has been an important contributor to the OMEMI-study at AHUS, for patient inclusion and follow-up. In addition, his thesis with the overall aim to compare two different types and different laboratory methods of the troponins as cardiac biomarker in evaluation for the diagnosis of coronary artery disease (chronic coronary syndrome and acute coronary syndrome).
The results showed that both isoforms of troponin provide useful clinical information, but TnT seems to be a stronger prognostic marker, while TnI seems superior in diagnosing and ruling out coronary artery disease.

PhD-theses submitted

Gut microbial translocation in coronary artery disease. Emphasis on physical activity and cardiometabolic disturbances

Cand Med Susanne Kristine Aune PhD student

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

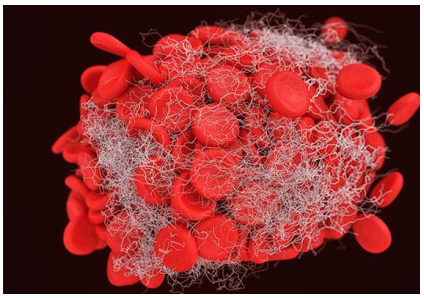
Based on existing biobank from the EXCADI study, a randomized controlled study in patients with combined type 2 diabetes and CAD on the effects of long-term exercise training on atherosclerosis, the effects on microbiota-related inflammation (gut leakage markers) have been investigated. In addition, any effect on acutely induced strenuous exercise in CAD patients, and on extreme exercise in participants from the Norseman race, were studied with regards to gut-leakage markers. The results show such markers to be strongly associated with physical fitness, and affected by short term acute exercise, extreme exercise, but not by regular exercise training.

Furthermore, from the OMEMI trial in which adipose tissue samples were available, the genetic regulation of these markers, important for the effect of lipopolysaccharides (LPS), showed to some degree an association with anthropometrics and dietary habits, but not with levels of long-chain fatty acids.

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

Cand Med Jostein Nordeng PhD Student

Supervisors: Ingebjørg Seljeflot Professor, Ragnhild Helseth MD, Bjørn Bendz Professor, Svein Solheim MD PhD



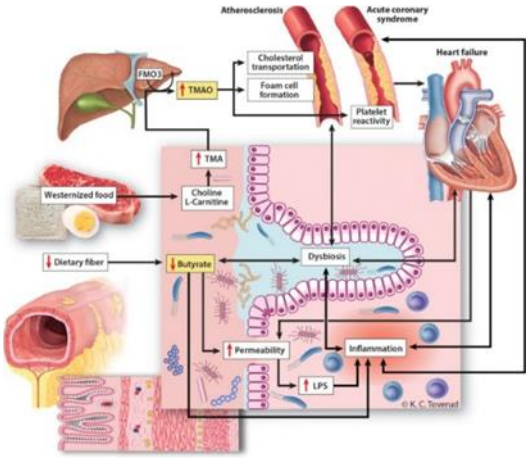
In this project thrombus content has been examined with morphological and immune-histochemical methods, as well as genetic regulation (mRNA) of selected signal molecules – all related to time from onset of symptoms to PCI, and to the degree of myocardial injury. Also peripheral venous blood samples were analyzed for signaling molecules and corresponding mRNA expression in circulating leukocytes.

The study has been in close collaboration with Department of Radiology and Department of Pathology, OUS Ullevål. There was some delay due to practical issues for collaborators and the corona situation. Results show that the NLRP3 inflammasome pathway, the remodeling phenomenon and fibrinolysis are highly regulated in the thrombus and related to infarct injury, thus underpinning some of these pathways to be target for anti-inflammatory therapy.

Scientific Activities; Ongoing Projects

Studies on Microbial Translocation

An altered gut microbiota has been linked to several chronic disease states, including obesity, type-2 diabetes and chronic heart failure. Translocation of products of the gut microbiota, and in particular endotoxins or LPS to the systemic circulation, is proposed to be early triggers 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.
In addition to the aforementioned work by Susanne Aune, other studies are ongoing.



Trøseid M et al EBioMed 2020

Microbial translocation and chronic heart failure

Based on the biobank from the GutHeart study, a study on patients with chronic heart failure, several mechanistic studies are underway to shed light on the gut-related inflammation in such patients. The microorganisms present in the gut consist of a diversity of families, including bacteria, viruses, fungi, archaea and protists. This study has focused mainly on the bacterial community in fecal samples, which serves as a surrogate for the total community.
These analyses are recourse demanding and as the data are huge, bioinformatics are needed. These analyses are ongoing and are related to the etiology of the disease, as well as to markers of gut-leakage, to sort out whether the focal content is mirrored in the gut-leakage inflammation. Also, peripheral blood mononuclear cells (PBMCs) have been isolated, and give possibility to in more depth, explore the inflammatory pathways involved; especially the TLR4 induced inflammation.

Gut microbiota Signatures in Acute Coronary Syndromes (GutACS)

Cand Med Andraz Nendl, PhD student
In collaboration with professor Marius Trøseid, Dept of Infectious Disease, OUH Rikshospitalet
Supervisors: Ayodeji Awoyemi MD, PhD, Marius Trøseid Professor, Ingebjørg Seljeflot Professor em, Sajan Raju MSc PhD

In this observational longitudinal study we want to define a signature of gut microbiota composition and related metabolites in patients with ST-elevation MI (STEMI), non-STEMI and chronic coronary syndrome (CCS) and relate such a signature to systemic inflammation,

troponin release and cardiac function assessed by echocardiography. The hypothesis is that they differ significantly and that AMI patients will normalize after 3 months. A huge biobank of stool and blood samples are prepared for mechanistic studies.
The inclusion of patients are very much delayed, firstly due to the corona situation, and second to a change of PhD student. The project is now running very satisfactory, and the inclusion soon to be finalized.

Microbial translocation in Acute heart failure. Effects of Levosimendan

Ayodeji Awoyemi MD PhD, Andraz Nendl PhD student, Geir Ø.Andersen MD PhD, Ingebjørg Seljeflot Professo emr, Marius Trøseid Professor em

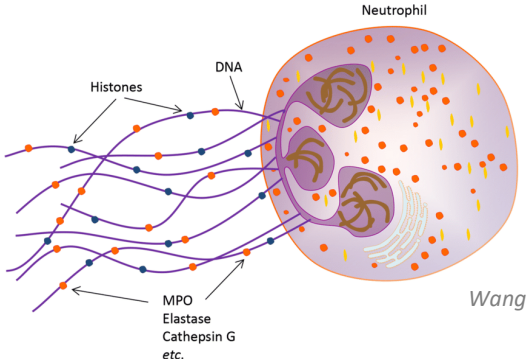
Sub-study of the LEAF (Safety and efficacy of Levosimendan in patients with Acute myocardial infarction complicated with symptomatic left ventricular Failure) study, initiated at CCU, Dept of Cardiology, OUH. The main study which was a randomized, placebo-controlled study to investigate the effect and safety of the levosimendan in patients with PCI-treated STEMI with complicating heart failure, was finalized in 2017. Infusion of levosimendan for 24 hours was compared to placebo, and a large biobank was conducted, based on serial sampling through the acute phase and further after 6 weeks, with additionally echocardiography for cardiac function testing. Studies on markers of gut-leakage as a sign of microbiota translocation and probably dysbiosis in this acute setting, are now undertaken.

Microbial translocation in long-standing type-1 diabetes

With diabetes, increased glucose levels will harm the gut-blood barrier, and as for type-2 diabetes, sign of microbial translocation may occur also with type-1 diabetes.
In the Dialong study (*vide infra),* a project on markers of gut-leakage in association with diabetes control, diabtes complications and degree of coronary artery disease is ongoing, i.e. to be a part of a PhD project on this specific population.

Studies on Neutrophil Extracellular Traps (NETs)

It has become 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), which are thought to induce thrombosis.



Wang Y. Med Inflam 2021

We have during 2018-2021 in patients with chronic coronary syndrome, STEMI and acute heart failure following STEMI, published on the relationship between the surrogate markers of NETs,

double-stranded deoxyribonucleic acid (dsDNA) and nucleosomes (DNA-histone complexes) and the thrombotic state, its importance for MI-complications and clinical outcome in these patients (vide supra – thesis of Miriam S. Langseth)

Neutrophil extracellular traps (NETs) in acute ST-segment elevation myocardial infarction: Roles in successful treatment and as a treatment target

Kristine Mørk Kindberg MD PhD student

Supervisors: Ragnhild Helseth MD PhD, Mathis Stokke Professor, Ingebjørg Seljeflot Professor em

This project is a combination of a clinical investigation and an animal model to sort out the potential for inhibiting dsDNA by the enzyme dNAse to reduce post myocardial reperfusion injury, especially in patients in which treatment with thrombolysis is unsuccessful. One part of the project is to explore whether levels of NETs can predict non-successful thrombolysis in STEMI-patients, and thus more rapid treatment with coronary intervention and stent implantation. Inclusion of thrombolysis treated patients is ongoing.
Another part of the project is based on the ASSAIL-MI trial (vide infra), in which NETs is investigated with regard to whether the beneficial effects seen can be related to less leukocyte activation and NETs formation. Results are under preparation.
The third part is a pig-model to sort out whether dNAse treatment will reduce post myocardial reperfusion injury. This sub-project is ongoing.

NETs as related to delirium

Vibeke Bratseth MSc PhD, Ragnhild Helseth MD PhD, Leiv Otto Vatne MD PhD (Dept of Geriatric)

A collaborative study with Department of Geriatrics. The hypotheses explored are whether innate immunity is important for the development of delirium and dementia and whether netosis can be used to distinguish between subtypes of dementia; whether patients with delirium have elevated NETs levels; whether NETs in cerebrospinal fluid (CSF) are comparable with serum levels. These studies were postponed due to the corona situation, but the results are now under consideration for international publication.
This topic has become very hot due to the theory of dementia diseases to have common features with cardiovascular diseases, especially related to inflammation, so-called neuro-inflammation. Indeed, we could show a distinct pattern in patients with delirium, dependent of having dementia or not, and all different from healthy controls.
This has lead us to continue in a larger project, with focus on Alzheimer disease (AD).

NETs in different dementia-related disorders

Ragnhild Helseth MD PhD, Vibeke Bratseth MSc PhD, Leiv Otto Vatne Professor, Anna-Brita Knapskog Professor (Department of Geriatric)

NETs has been found in the brain vasculature and in parenchyma of patients with AD, and higher circulating NETs levels are observed in AD patients compared to healthy controls. A hypothesis is that NETs contribute to the neurotoxicity and neurodegeneration in AD. As NETs can be degraded by DNAse, and inhibition of NETs formation is possible by NETose-inhibiting enzymes, NETs-related mediators could represent novel targets for therapy for AD and related disorders.
In this project, also is in collaboration with Department of Geriatrics, we will study NETosis in blood and CSF in AD and related disorders to sort out whether NETs products can be helpful for distinguishing between sub-types and whether NETs are related to cognitive functions also measure by imaging technology. A PhD student will be on this project during 2023.

NETs in association with gut-leakage

Vibeke Bratseth MSc PhD and Ayodejo Awoyemi MD PhD

It has been postulated an interaction between gut-related inflammation i.e. microbial translocation and the innate immunity in which NETs is of great importance.

In this study in patients with chronic heart failure (the GutHeart-study), we will explore such relationship and also any relationship between gut microbiota composition, diversity and NETs formation. NETs formation and cardiac function/ damage/ progression of heart failure, will further be investigated. This will likely increase our knowledge on the interaction between different inflammatory pathways that work in "conjunction", to sort out the most actual pathway for potential novel inhibitors for treatment.

Studies on Complement activation

The complex complement system, interacting with both inflammation and coagulation, is suggested to interplay with netosis and atherosclerosis. We investigate any relevance in patients with cardiovascular disease.

Complement activation in association with NETs

Karsten Kluge, Medical student in Research Program; Sverre Aukrust MD

Supervisors: Ragnhild Helseth, MD PhD and, Ingebjørg Seljeflot, Professor em

The first part, investigating the associations between complement activation, NETs and hypercoagulability and the role of complement activation on clinical outcome in patients with chronic coronary syndrome, was a part of a project in Medical School of Research. The results showed that total complement complex to some degree is associated with NETs and to future myocardial infarction. The work continued along with medical education for the candidate, studying this interplay in patients with acute myocardial infarction. These results were finalized and published in 2022.

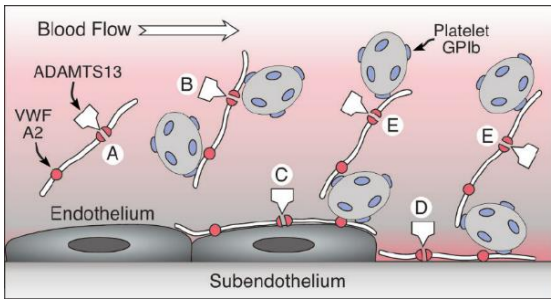
The importance of complement activation both type 1 and 2 diabetes has been limited explored. In an ongoing sub-study of the Dialong study, in collaboration with the Dialong team, we are now underway to the importance of complement activation for the development of the diabetes disease, and also for the development of coronary artery disease in such patients, which is frequent in diabetic patient in general. The connection between complement activation and **NETs formation** will further be explored to sort out whether an interplay is of importance.

Studies on Thrombogenicity

ADAMTS13 regulation of vWF in patients with CAD

MD Ellen M. K. Warlo PhD Student *(previous Medical Student in Research, University of Oslo)*
Supervisors: Vibeke Bratseth MSC PhD, Svein Solheim MD PhD, Pål Andre Holme Professor MD PhD and Ingebjørg Seljeflot Professor em

ADAMTS13 (a disintegrin and metalloprotease with thrombospondin 1 repeats) is a member of the ADAMTS family of metalloproteinases, responsible for the regulation of von Willebrand factor (vWF), which is a risk marker for coronary artery disease. vWF has pro-thrombotic properties and plays a central role in platelet activation upon vessel wall injury. In this project we have shown that reduced ADAMTS13 is of importance for clinical outcome after 2 years in patients with stable CAD, and also that some genetic polymorphisms in the gene coding for ADAMTS-13 are important for clinical outcome (Warlo E et al 2022). The candidate was off research to finalize for her diploma as a licensed doctor, but is now soon to finalize her PhD degree, including her last sub-projects, studying any relationship between these biomolecules and clinical outcome in patients with acute MI from the OMEMI biobank, with main focus on new onset of atrial fibrillation, as described.



Coronary thrombus and extracellular circulating microvesicles (cMVs)

Vibeke Bratseth MSc PhD, *Jostein Nordeng and the TASTI-group*
cMVs are phospholipid blebs of 0.2–1.0 µm in size shed from the membrane of 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.
cMVs 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. As occurring from the thesis of Jostein Nordeng, we have explored the relationship between the expression of cMVs and pro-thrombotic and pro-inflammatory signals in coronary thrombi, especially related to the NLRP3 inflammasome.

Studies on Omega-3 fatty acids

Steering Committee (re-established): *Harald Arnesen Professor em, Arnljot Tveit Professor, Svein Solheim MD PhD, MD PhD Peder Langeland Myhre, Professor, Ingebjørg Seljeflot Professor em.*
As mentioned for the doctoral thesis of Are AS. Kalstad, the main OMEMI trial was finalized in 2020, aimed 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 (≥70-82 years) after having experienced an acute MI. The study was neutral with regard to the clinical endpoints, and added to results from other studies in

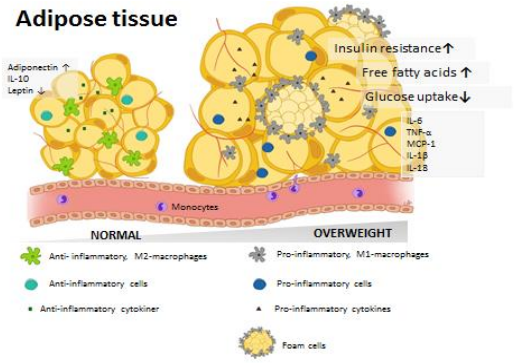
this field published in 2020/21. Special emphasis was paid on the incidence of atrial fibrillation in this elderly population, in which we could show a tendency to an unbeneficial effect. There are still several unanswered questions and a broad biobank for future research is established. There are several sub-studies ongoing, especially with regards to explore any importance of the different fatty acids.

***Topics addressed/Ongoing*:**

- The relationship between ***omega-3 fatty acids*** and the occurrence of atrial fibrillation, with special emphasis on micro atrial *fibrillation (Myhre PL et al. J Intern Med 2021; Berge T et al. Cardiology 2022)*
- ***Omega-3 fatty acids*** and dietary pattern as related to microbiota translocation and regulation in adipose tissue *(Aune S et al. Submitted)*
- Thrombogenicity assessed by vWF, ASDAMTS13 and thrompospondin1 (TSP1) ***in the elderly***, in prediction of clinical outcome in patients with acute MI, with main focus on new onset of atrial fibrillation *(Warlo E et al).*
- Studies on polymorphisms important for the effects of ***omega-3 fatty acids***, as well as related to ***ageing.***
- The prognostic utility of total bilirubin to clinical outcome ***in the elderly*** MI patients.

Studies on Adipose Tissue

We have for several years focused on inflammation and remodeling in adipose tissue, by studying genes expressed in different disease states, especially related to metabolic disorders, as visualized in several previous and ongoing projects. Differences in fat compartments are also focused.



Åkra L, Åkra S. 2020

Adipose tissue inflammation and remodelling in patients with CAD and type 2 diabetes - effects of exercise training

Cand Med Hani Zaidi PhD-student

Supervisors: Trine B. Opstad, MSc PhD, Rune Byrkjeland MD PhD, Ingebjørg Seljeflot Professor em

In this project on patients with CAD and Type-2 diabetes, combined, adipose tissue regulatory mechanisms related to glucose control, and to the effect of exercise training on i) the NLRP3 inflammasome pathway and ii) remodeling pathways (MMP-9/TIMP-1/EMMPRIN/axis) and iii) certain adipokines. The latter are further examined in a healthy cohort to explore such regulation in desease-free individuals in collaboration with *Section of Cardiovascular and Renal Research, OUS Ullevål,* based on a cross sectional study on middle-aged men undergoing glucose clamp for their status of insulin resistance, an in which data on the amount of adipose

tissue is available from CT-scans. The last results were published in 2022, and the project is soon to be finalized for PhD thesis.

Inflammatory activity in various compartments of adipose tissue 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 and analyses; **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 differences aspects of inflammation and remodeling by exploring specific genes expressed and protein secreted in various compartments of adipose tissue being exposed during open cardiac surgery on patients with CAD, and valvular disease for control.

- The first part examining the inflammatory ***NLRP3 pathway*** is finalized and published (*Åkra S, Seljeflot I et al 2022).*
- ***Monocyte/macrophage polarization***
  Based on this project, a collaboration with the University of Parma, Italy was established late 2021, in which an Italian post.doc. Bianca Papotti, was connected to our lab for 6 months, on the matter of monocyte/macrophage polarization, important for understanding new aspects of inflammation. The results are submitted for publication. Such international collaboration is of great importance for the milieu and for research in general.
- ***Sirtuin1***
  Sirtuins (SIRTs) are a family of NAD+ dependent protein deacetylases and SIRT1 is linked to longevity through several pathways of the ageing process, including protection from oxidative stress *(vide infra*). SIRT1 seems to inhibit inflammation, is linked to nutrition status and to have cardioprotective effects. Here, we have the possibility to study whether SIRT1 is differently expression in different AT compartments of the heart, and relate to anthropometry. The work is ongoing *(Trine B. Opstad MSc PhD).*

Gut-related endotoxemia-induced inflammation in adipose tissue. Impact of anthropometrics and dietary habits

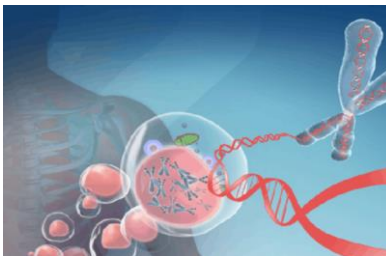
As mentioned for the doctoral thesis of Susanne K. Aune, adipose tissue samples from the OMEMI study are objected to study the relationship between genes regulating inflammatory markers of gut leakage in adipose tissue and diet and anthropometrics. It is well known that obese individuals have dysbiosis and increased release of endotoxemia (LPS) from the gut. Any relation to specific fatty acids thought to be of most importance is also assessed.

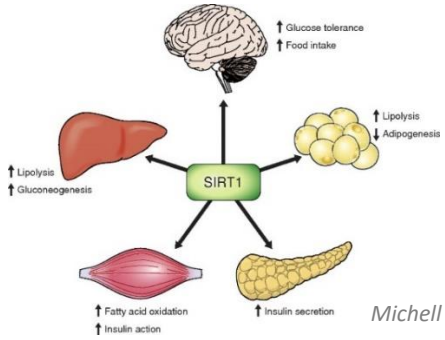
Studies on Telomere Length and Ageing

Trine B. Opstad MSc PhD, Are A. Kalstad MD PhD, and other

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 and lifestyle and environmental factors have been reported to influence the rate of telomere shortening. We have mainly focused on **leukocyte telomere length (LTL),** as it is easily available in blood samples.

As described, **Sirtuins (SIRTs)** are a family of NAD+ dependent protein deacetylases, and are highly conserved across species. Sirtuin-1 (SIRT1) is linked to longevity through several pathways of the ageing process, including protection from oxidative stress.





Michell S. Cell Resp 2014

CHIP (clonal hematopoiesis with indeterminate potential) is mainly affecting the elderly and suggested to be a novel link between inflammation and CVD. CHIP is caused by an age-dependent increased frequency of mutations in stem cells of the bone marrow. We are underway with a study to explore the influence of selected TET2 and TERT mutations, the latter been associated with telomere attrition, in a populations with CAD with regard to clinical status and outcome, telomere length and other ageing factors, and the degree of inflammation, known to be disturbed by age. The topic is given very much attention and interest internationally the last years, however, there is limited knowledge with regards to CVD.
We have the latest years addressed studies for understanding some mechanisms behind the ageing process in different populations, by measures of telomere length, SIRT1 and CHIP.

Previous

Telomere length *as related to myocardial injury and dysfunction in acute myocardial infarction* (from the OMEMI trial 2019)

Telomere length and Sirtuin-1 *as related to the presence of atrial fibrillation* (from the OMEMI trial) (2020).

Telomere length *in a population of patient with stable coronary artery disease*, we observed significantly shorter leukocyte telomere length in patient with previous myocardial infarction (2019).

Telomere length *related to other rejuvenating factors in patients with coronary artery disease.* We observed that higher levels of the growth differentiating factor GDF11 and SIRT1 associated with longer telomeres, accompanied by a reduced pro-inflammatory state (2019).

Telomere length *and rejuvenating factors in young and older healthy people*
In healthy young and elderly individuals, we explored the association between leukocyte telomere lengths and other longevity factors and pro-inflammatory markers and their

influence of life-style factors and presence of hereditary coronary heart disease, showing especially telomere length to be associated with cardiovascular heredity (2019).
Telomere length *and rejuvenating factor analyses in type- 1 diabetes* compared to healthy controls have been investigated based on the biobank from the Dialong study, showing telomere length and SIRT-1 to be lower in T1DM (2020).
SIRT-1 and lifestyle. Based on the link between longevity factors, lifestyle and oxidative stress, an intervention study on caloric restriction has been performed, in collaboration with Department of Medicine, OUS Ullevål, showing SIRT-1 to increase beneficially with caloric restriction for one year in obese individuals (2021).

Influence of selenium and Q10 on teleomere length and Sirtuin-1

In collaboration with Urban Alehagen, MD PhD Linkøping University, Sweden

Based on our experience in telomere and ageing research we have been participating in a project studying the effects of selenium and Q10 intervention in an elderly Swedish population, followed for 10 years. We have studied any effect on telomere attrition, in which the results, showing reduced LTL attrition during the intervention (*Opstad TB et al 2022*). Furthermore, we have explored any effects on SIRT-1, in which the results are in progress.

CHIP

In patients with stable CAD we could show that a mutation related to CHIP development (TERT mutation) associated with increased risk of clinical adverse events. Another mutation related to CHIP development (TET2 Ile1762Val missense mutation) associated with type 2 diabetes and Mets, along with dysregulated glucose metabolism, illustrating epigenetic regulation as a bridge between inherited and environmental causes in development of disease. We could also show the latter variation to be associated with shorter telomeres that may reflect their manifested CAD *(Opstad TB et al 2022)*.

Scientific Activities - Other

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

A Steering committee for BAMI has been re-established (Professor Sigrun Halvorsen, MD PhD, Geir Øystein Andersen MD PhD, Professor Ingebjørg Seljeflot (Chair))

This joint project between the Intensive Cardiac Care Unit, General Cardiology Section and CCHR in Department of Cardiology, is an extended biobank, mounted along with prospectively registered clinical data and are basis for studies on predictive biomarkers for later clinical events. A total of 2150 pts (1790 STEMI; 360 NSTEMI) are included. The biobank of selected biomarkers has been used in 2 defended PhD projects and in 2 ongoing.

Further projects are ongoing and genome wide association studies, with analyses performed at the Decode center at Iceland are now underway.

NORCAST (Norwegian Cardiac Arrest Survival Trial)

A project initiated by ***Professor Kjetil Sunde and Espen Rostrup Nakstad MD PhD,*** *Department of Anesthesia and Surgical Intensive Care Unit in close collaboration with the Intensive Coronary Care Unit by* ***MD PhD Geir Ø. Andersen*** *ao.*

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 collected 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 main study results were published 2019, and studies on complement activation have been performed and results published in 2021. Due to lack of manpower the biobank has been limited used, but during 2022 biomarker study on inflammation (Interleukins) that may impact future therapy has be undertaken and the results are in progress.

Diabetes in children and atherosclerosis development

Aida Simeunovic MD PhD-student

Supervisors: MD PhD Hanna Dis Margeirsdottir, MD PhD Martin Heier, 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. Initiated from Department of Pediatrics/Oslo Diabetes Center, 330 children/youth (aged 8-12 years) 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 and 10 years and the 15 year follow-up will be in 2023. All blood sampling/processing and facilities for biochemical translational research (biobanking and analyses) are undertaken at CCHR. The 4th PhD theses based on data from this study so far, is almost finalized.

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

Main responsible: Professor Tore Julsrud Berg

The hypothesis in this study was that patients with long-standing 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 study consists of 100 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. This is a unique population, and sub-studies based on the biobank is ongoing. It has so far been used for investigation of the ageing aspects and NETs aspects (vide supra), and the topic of microbial translocation is now ongoing.

ASSAIL-MI (ASSessing the effect of Anti-IL-6 treatment in Myocardial Infarction)

Main responsible: Professor Lars Gullestad OUS, Rikshospitalet, Professor Rune Wiseth, NTNU and MD PhD Geir Ø. Andersen, OUS Ullevål

The main study, aimed to examine whether a single administration of the IL-6 receptor antagonist tocilizumab can reduce myocardial injury in patients with acute ST-elevation myocardial infarction (STEMI) is finalized. This was a randomized, double blind, placebo-controlled trial conducted at three percutaneous coronary intervention (PCI) centers in Norway. Altogether, 200 patients with STEMI were randomized to receive tocilizumab or matching placebo prior to PCI. The patients were followed-up for 6 months. The results, showed a beneficial effect of the drug on heart function. A biobank is established, based on blood sampling at several time points during the acute phase and after 6 months. Studies on NETs are ongoing *(vide supra).*

CENS - Cardiovascular remodeling in living kidney donors with reduced glomerular filtration rate

Cand Med Kjersti Blom PhD-student

Supervisors: MD PhD Jon Arne Birkeland, Department of Nephrology and Professor Ivar Sjaastad, Institute of Experimental Medical Research, OUS

A collaboratory study between many departments.

Patients with advanced chronic kidney disease (CKD) are known to have a high risk of developing cardiovascular disease (CVD). However, little is known about the cardiovascular risk in patients with mildly reduced kidney function, affecting up to 10% of the general population; and importantly, also affecting living kidney donors. A recent Norwegian epidemiological study suggested that kidney donors have an increased risk of CVD. The main purpose of this project is to investigate the mechanisms underlying the development of cardiovascular remodelling induced by reduced kidney function. This is a prospective study including persons selected as living kidney donors according to the Norwegian donor criteria and accepted for surgery at Rikshospitalet, Norway and a control group. The project uses state of the art imaging combined with advanced molecular biology, to investigate cardiac, vascular and renal remodelling. The project has the potential to identify mechanisms linking reduced kidney function to CVD, identify predictors for adverse CV outcome, and recognize potential targets for risk lowering intervention. A huge biobank is established at CCHR. The project has been much delayed and influenced by the corona situation, but is ongoing with inclusions and follow-up.

PROACTIA PRediction and detection of Occult Atrial fibrillation in patients after acute Cryptogenic stroke and Transient Ischemic Attack (PROACTIA). Sub-study on biomarkers

The project is ongoing at Akershus university hospital by PhD student Loreta S. Strøm, supervised by MD PhD Harald Kjekshus and professor Kjetil Steine

The main aim of this project was to build and evaluate a novel composite scoring system to predict the occurrence of atrial fibrillation (AF) during follow-up in patients admitted for first time cryptogenic stroke or TIA. The scoring system is based on measurements performed during the initial hospitalization (age, CHA2DS2-VASc, echocardiography findings, biomarkers and Obstructive Sleep Apnea Screening (OSA) screening), and its purpose is to reliably asses

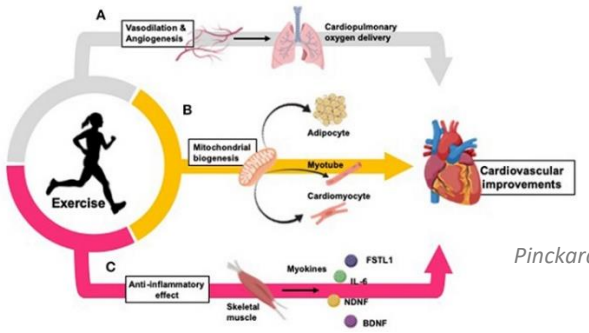
the risk of occult AF in each individual patient. 270 patients are included and followed for at least 1 year, and episodes of AF have been registered by implanted loop recorders. As AF is associated with left atrial remodelling and fibrosis, and several biomarkers of cardiac remodelling and fibrosis are studied as candidates to be of importance for AF, as well for left ventricular function and heart failure. Analyses of such candidates have been performed and the results are under publication.

Vascular function in Norseman athlets – ongoing at OUS Aker

Martin Bonnevie Svendsen MD PhD student

Supervisors: Jonny Hisdal Professor, Ingebjørg Seljeflot Professor em, Lars Øivind Høiseth MD PhD

While the benefits of regular exercise are widely accepted, the acute and chronic physiological adaptations arising from severe prolonged endurance exercise is not yet fully understood. This project aims to explore the physiological cardiovascular adaptations induced by such activity. More specifically, an extension of ongoing efforts to elucidate the behaviour of markers of endothelial function, cardiac strain and cardiac ischemia in athletes participating in an extreme endurance event, Norseman Xtreme Triathlon. The primary objective is to identify normative values of cardiovascular biomarkers in athletes participating in extreme endurance events. The work is ongoing



Pinckard K. Front Card Med 2019

Biomarker related to brain dysfunction in stroke patients

Collaborating study with Guri Hagberg MD PhD and coworkrs, The stroke unit at Department of Medicine

In this study patients with first-ever stroke or transient ischemic attack (TIA) have been classified exactly as to development of post-stroke cognitive impairments and vascular dementia. A biobank was conducted 7 years after, in parallel with clinical follow-up, to identify predictors for a favourable cognitive outcome. Neuro-inflammation and neuro-specific biomarkers are under investigation.

Biomarker related to maintained sinus rhythm after electrical cardioversion of atrial fibrillation – ongoing Bærum Hospital

Elizabeth Lyster Andersen MD PhD student

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

PRE-ELECTRIC is an ongoing prospective, observational study, including 200 patients with persistent atrial fibrillation. The main aim is to identify biomarkers, either functional (echo cardiography) or biochemically that can predict sinus rhythm maintenance after electrical cardioversion. A biobank with samples collected at several time points is established, and biomarker-analyses are ongoing at CCHR.

Laboratory Methods

- Method for telomere length
- Biomarkers of ageing; circulating and regulated
- Method for micro RNA, used as a tool for gene regulation of proteins as well as use as biomarkers
- Biomarker of gut-leakage, including LPS analysis
- Biomarkers of netosis
- Arrays for gene regulation
- 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 (”bedside” screening tests (PFA100, VerifyNow) Flowcytomtry (BD Accuri C6)
- Spectrophotometer for ELISA’s
- Fluoroscan
- PCR instruments and centrifuges for molecular biology
- ViiA7 RT-PCR (Applied Biosystems)
- Fume cupboard, moveable
- HPLC (Located at Institute for Experimental Medical Research, OUH Ullevål)

Cell-culture studies

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

Ultra freezers

Responsible for 12 ultra freezers for research in Department of Cardiology

Collaborators

We in depth thank all collaborators during the last year

- Geir Øystein Andersen MD, PhD, Department of Cardiology, OUS Ullevål, Oslo, Norway
- Jan Eritsland MD, PhD, Department of Cardiology, OUS Ullevål, Norway
- Arnljot Flaa MD, PhD, Department of Cardiology, OUS Ullevål, Oslo, Norway
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- Dennis WT Nielsen Professor, Stavanger University Hospital, Stavanger, Norway

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- Urban Alehagen, Linkøbing University, Sweden
- Franco Bernini Professor, Department of Pharmacy, University of Parma, Parma, Italy
- Carlos G. Santos Post doc. Mt. Sinai Hospital New York, USA

Networks

PhD candidates and other employees are members of NORHEART, which is a National PhD network for cardiovascular research. CCHR is a part of the Regional Microbiota Network, established in 2019, funded by the Norwegian Council of Research and Health South East, and the Norwegian Atrial Fibrillation Research Network, financed from Health South East. All contributing to fruitful meetings and collaborations.

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