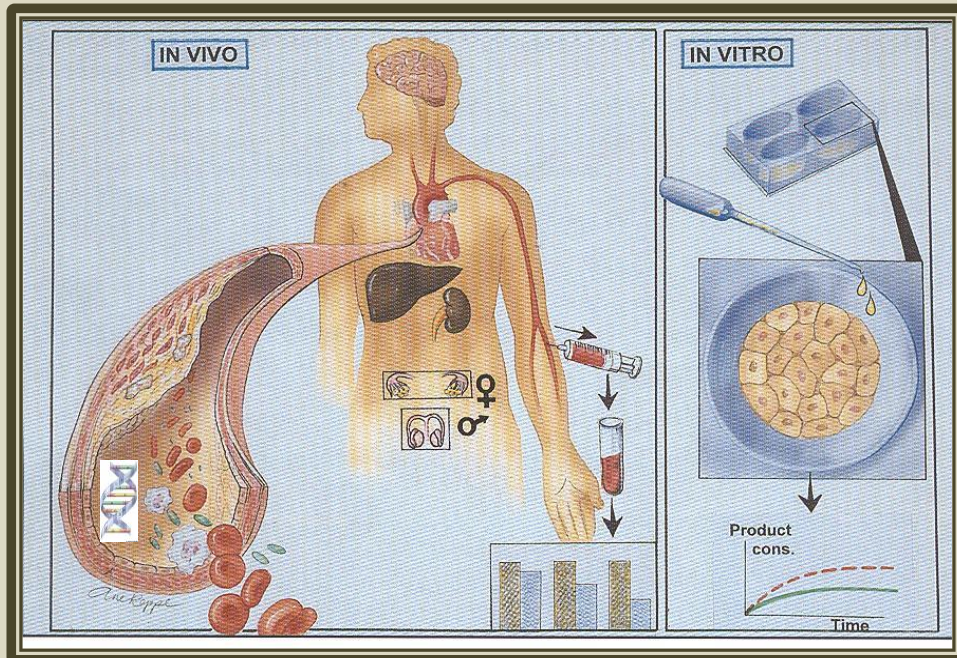


# Annual Report 2021



## Center for Clinical Heart Research (CCHR)

<http://research.no/clinicalheartresearch/>

Department of Cardiology  
Division of Medicine  
Oslo University Hospital, Ullevål

*"Team building for individual excellence"*

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## Preface

Center for Clinical Heart Research (CCHR) is a core center and laboratory 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 including translational studies on pathophysiological mechanisms in cardiovascular disease states.***

The Center has close collaborations with other milieus, especially with the research group at the ICCU within the department and with Asker & Bærum Hospital, Akershus University Hospital, OUH Rikshospitalet and the Oslo Diabetes Research Center, by having common projects and PhD-students.

Also in 2021, focus has been to improve methodology related to the innate immune system, microbial translocation aspects, adipose tissue inflammation and the ageing process. Due to the corona situation, several projects have been somewhat delayed. However, the scientific activity has been almost at the same level as previous years.

One PhD thesis defended and 22 internationally published papers, of which 21 are original articles. The number of abstract (16) was satisfactory taken into account that most congresses have been virtual. Although these virtual congresses/meetings have been available, the loss of integrative meetings has been challenging. That is also for our internal team-building meetings. Nevertheless, the scientific staff and PhD students have given a lot of effort into keeping a good working atmosphere and a high scientific spirit.

One PhD candidate defended his thesis January 2022, and 4 are preparing for submitting their thesis during 2022. Two of the young PhDs are now principal supervisors for new PhD candidates, which is an important philosophy for further education and growing.

We still had one candidate from The Medical Research Student Program at the university, funded by the Norwegian Council of Research this year. Also, one previous student candidate is now back performing her PhD work.

Our participation in the “Regional Research Network for clinical Microbiota Science” is of importance, with collaboration for two PhD projects in this novel field with regards to cardiovascular disease. Our participation in 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, but has stayed as “ex officio” member. Svein Solheim is also medical responsible at the center. The research coordinator, Charlotte Holst Hansen, employed for administrative matters in 50% position has continued in 2021.

We are very pleased to give the annual report for 2021.

March 2022

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

## Strategy

- Clinical studies, including studies on mechanisms/translational studies in cardiovascular medicine. Biochemical, cellular and genetic aspects especially related to the cardiovascular disease processes, focusing inflammation, remodeling, thrombosis, endothelial function and the ageing phenomenon.
  - Systematic researcher-initiated clinical heart research, based on accepted research methodology along with the flow of patients in OUS
  - Projects related to acute myocardial infarction, chronic artery disease, heart failure and atrial fibrillation
  - Especial 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
- To perform research in line with the strategy for research in Department of Cardiology
- To be an interdisciplinary composed research group, including researchers at post.doc level
- To collaborate in appropriate networks as well as at the research group and individual levels

## 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

Administration and organizational aspects are undertaken by the Center leader. Our most important activity is still 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 as lecturers. The PhD fellows are especially

encouraged to give presentations to prepare for international conferences. In 2021 these meetings have been conducted mainly digitally.

Individual supervision of the single PhD fellows is in addition undertaken, with a "supervisor-open-door-policy", and specific projects are separately discussed in smaller groups.

Decisions on projects/scientific matters, and contracts for collaboration with other research groups are based on common scientific interests.

### **Personnel**

*Leadership:* The leader is also the Head of the R&D Section at Department of Cardiology, 100% position, and professor em at University of Oslo (UiO). In addition, a cardiologist being medical responsible and the last year the Centers delegate in the Board for Stein Erik Hagens Foundation for Clinical Heart Research. One professor emeritus and a research coordinator in 50% position for administrative matters.

*Employees:* 1 medical technologist with a Master of Science in Biomedicine, 2 post.doc researchers (PhD).

8 PhD fellows, 5 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**

Budgets for the single projects, including salary for PhD-fellows, technical personnel and running laboratory expenses are based on external fundings from different sources.

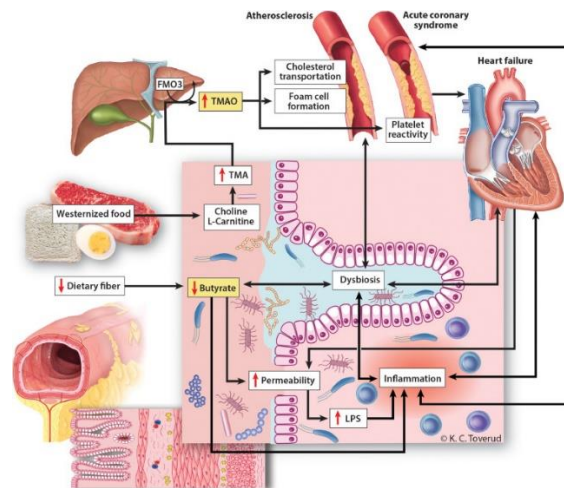
The Head is financed from the Department of Cardiology, OUS, Ullevål by a combined position for the Center and for being Head of the Research and Development Section in the Department. We strive for fundings by applications wherever we find it relevant. At the end of 2021 we succeeded in getting grants from Health South East for funding to 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 activity also in 2021. As for many other research institutions, the withdraw of fundings from the Norwegian Council of Research, has been an extra economic challenge.

## Scientific Activities

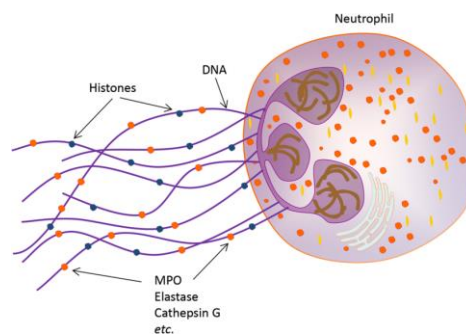
In addition to atherosclerosis, myocardial infarction, inflammation and remodeling in general, we also in 2021 had our methodological focus in the following areas, which has led to improved knowledge and several publications.

- **Microbial translocation**



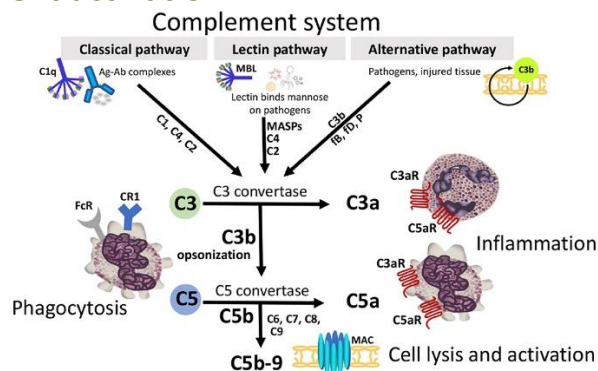
*Trøseid M et al EBioMed 2020*

- **Neutrophil extracellular traps**



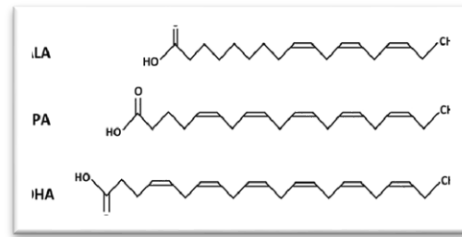
*Wang Y. Med Inflamm 2021*

- **Complement activation**

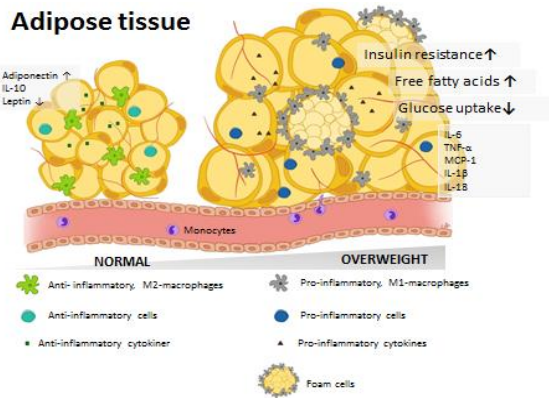


*Girardi et al. Front. Immunol 2020*

- Omega-3 fatty acids

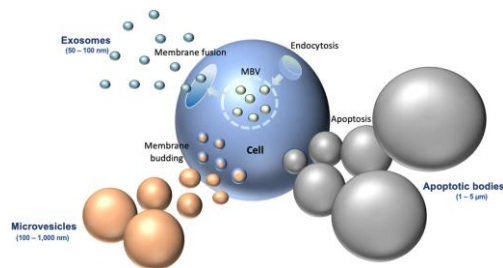


- Adipose tissue inflammation



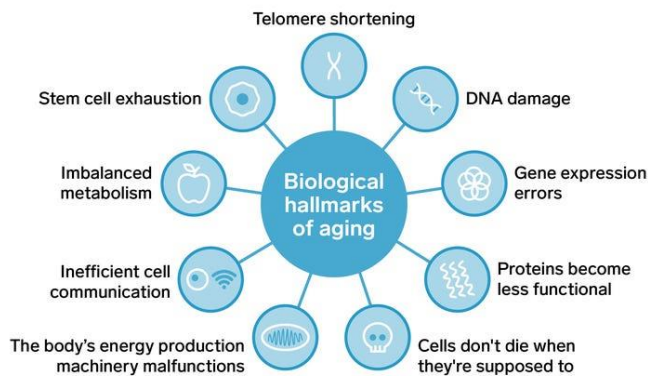
Åkra L, Åkra S. 2020

- Thrombogenicity and Microvesicles



Carnino et al, Respiratory Research, 2019

- Ageing



Source: Cell Journal

Insider inc.

# Scientific Activities

## Highlights 2021

The **OMEMI-trial**, which also was highlighted in 2020, has been ongoing from 2012 as a multicenter study, including 1027 elderly myocardial infarction patients from 3 different hospitals for the effect of omega-3 fatty acid supplement on clinical endpoints. The study was conducted at CCHR, which has been the study center throughout.

The main results were published in the well reputable cardiovascular journal *Circulation* in 2021, and the results, together with other similar internationally omega-3 fatty acid studies have been very much discussed and debated during 2021.

The study has several unanswered questions and a broad biobank for future research.

Four PhD students have worked on the project, whereof two have finalized their thesis, one finalized primo 2022 (vide infra), and one is in pipeline later in 2022.

The clinical study in collaboration with OUS Rikshospitalet, The **GutHeart study**, finalized in 2020, was a part of the thesis of Ajodeji Awoyemi, an intervention study with the goal to change the microbiota with subsequent improvement of heart function. Further substudies are ongoing.

Highlighted is also the increased collaboration with the Department of Vascular Surgery, Oslo University Hospital Aker, in which the influence of **exercise and extreme exercise** on cardiovascular endothelium, gut-leakage and cardiovascular risk factors are focused.

Also the extended collaboration with the Department of Geriatrics studying **the interplay between cardiovascular disease, dementia and delirium**, which is a growing field when people now are getting older, is highlighted.



## PhD-theses defended 2021

***Ayodeji Awoyemi MD PhD***

**Microbial translocation and cardiovascular disease states**

**Emphasis on chronic heart failure, diabetes and the metabolic syndrome**

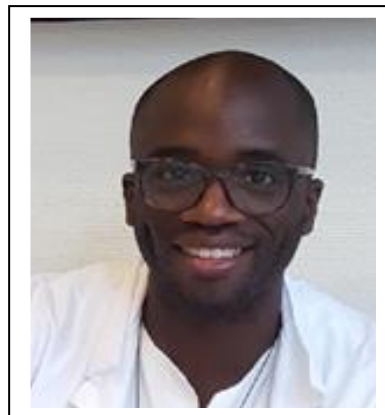
*Supervisors: Ingebjørg Seljeflot Professor, Svein Solheim MD PhD, Marius Trøseid Professor*

The first part of the project focused the potential role of microbial translocation and gut leakage in metabolic syndrome (MetS) and the prognostic importance for clinical endpoints.

Significant associations between LPS-binding protein (LPB), CD14 and obesity were found, and LPB was found to be significantly associated with clinical endpoints.

The second part was the abovementioned intervention study on the effect of treatment with antibiotics and/or probiotics on heart function (ejection fraction).

The intervention did not show any significant effects on the outcome variables, probably due to the well-treated population included. Four papers were included in the thesis, defended February 2021.



## PhD-theses defended primo 2022

***Cand Med Are Annesønn Kalstad, PhD student***

**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, commented as Highlight, and 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.



## PhD-theses submitted for evaluation

*Cand Med Miriam S. Langseth, PhD student*

### **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 the importance of markers of neutrophil extracellular traps (NETs) (vide infra) was explored in

- i) stable coronary artery disease as related to hypercoagulability and clinical endpoints;
- ii) patients with ST-elevation myocardial infarction undergoing coronary angiography with percutaneous coronary intervention (PCI) and the relation to myocardial injury and left ventricular function (from the BAMBI-biobank (vide infra)
- iii) exploring NETosis in patients with post-MI heart failure and cardiogenic shock.

The work is the main content in the thesis submitted for evaluation in 2021, in which one of the most cited and reputed international professor in this field has agreed to judge the work.

*Cand Med Sjur Hansen Tveit, PhD student (at AUH)*

### **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, he has worked on 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 CADENCE-population (vide infra) is one of the populations studied. The thesis was submitted for evaluation in 2021.

# Scientific Activities

## Ongoing Projects

### Studies on Microbial Translocation

An altered gut microbiota has lately 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 lipopolysaccharides (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 Ayodeji Awoyemi, other studies are ongoing.

#### ***Microbial translocation and chronic heart failure***

Based on the biobank from the GutHeart study, several mechanistic studies are underway to shed light on the gut-related inflammation in chronic heart failure 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 now ongoing and will be 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.

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.

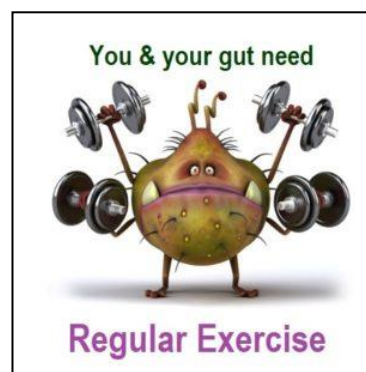
#### ***Microbial translocation and lifestyle factors***

##### ***Cand Med Susanne Kristine Aune PhD student***

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

Based on existing biobank from the EXCAD1 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 effect on microbiota-related inflammation (gut leakage markers) is investigated.

This first part is finalized, showing markers of gut leakage to be strongly associated with physical fitness, submitted for publication. The second part, a sub-study of the CADENCE study, aimed to explore any effect of acutely induced strenuous exercise on gut-leakage inflammation. This part is finalized and showed significant increase in gut-leakage, however, without any difference between patients with manifest CAD compared



to those without. These results lead to the interest in investigating subjects running extreme exercise, and an available biobank from the Norseman race was used for the investigation. This work is underway.

Furthermore, from the OMEMI trial in which adipose tissue samples are available, TLR4 regulation, as well as regulation of the LBP and CD14, important for the effect of LPS, will be explored and related to anthropometrics, dietary habits and levels of long-chain fatty acids.

### ***Microbial translocation in HIV. Effects of probiota treatment***

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

Patients with HIV-infection who do not respond to antiviral treatment, so-called immunological non-responders (INR) have an increased low-grade inflammation and systemic immune activation. The hypothesis is that these patients have reduced mucosal barrier, and thus an increased leakage from the gut. We investigated such patients in comparison with responders to antiviral treatment as well as the effect of probiota treatment for 8 weeks. The results were published in 2020 and 2021, and the allocated PhD student has delivered her thesis on this topic.

### ***Gut microbiota Signatures in Acute Coronary Syndromes (GutACS)***

***Cand Med Andraz Nend, 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 an 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 will be prepared.

The inclusion of patients has been very much delayed due to the corona situation, and another PhD student continues the work, which now is running very satisfactory. The candidate will, in addition, work of the aforementioned sub-study of the GurHeart study.

### ***Microbial translocation in Acute heart failure. Effects of Levosimendan***

***Ayodeji Awoyemi MD PhD, Geir Ø.Andersen MD PhD, Ingebjørg Seljeflot Professor, 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 was finalized in 2017.

This 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. 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.

## 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 is thought to induce thrombosis. We have during 2018-2020 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.

In addition to these aforementioned studies by Miriam S. Langseth, other studies on NETosis are ongoing.

### - **NETs in coronary thrombi from STEMI patients**

**Jostein Nordeng and Miriam Langseth PhD-students**

In the TASTI-study (vide infra) we aim to explore cell types and content, in addition to the genetic profile in aspirated coronary thrombus. The presence and localization of NETs markers are under examination with morphological and immunohistochemical methods, however, methodological challenges have made it difficult. In addition, the corona situation has contributed to further delay, but we still hope to manage. The results are planned to be related to time from onset of symptoms to PCI, as well as to the degree of myocardial necrosis.

### - **NETs in type-1 diabetes**

**Sverre Aukrust MD**

*Supervisors: Ragnhild Helseth MD, PhD, Ingebjørg Seljeflot Professor*

Based on the findings of netosis to potentially be glucose dependent, the Dialong biobank (vide infra) are used to explore any differences in NETs markers between individuals with long-standing type-1 diabetes and age-matched healthy controls, and potential differences in the diabetics who have developed coronary artery disease vs those who have not. The project was delayed due to the corona situation, but was finalized late 2021, published primo 2022.

### - **NETs as related to dementia**

**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 are comparable with serum levels. These studies were postponed due to the corona situation, but have continued in 2021. Results are under evaluation.

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.

### - **NETs as related to covid-19 vaccination thrombosis**

**In Collaboration with OUS Rikshospitalet**

Based on our research and experience in NETs research, we were invited to participate in the mechanistic study to sort out whether NETs could be an explanation of the serious thrombotic situation for some Astra Zeneca vaccinated people, in addition to several other

pathways that were explored. We could show that netosis indeed was an important player. The results were published in 2021 as part of a huge collaborating project.

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

This protocol for this project, initiated by young post doc researcher MD PhD Ragnhild Helseth and Professor Mathis Stokke, carried out during 2021. The 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. The project will be started primo 2022, with grants from Health South East.

## **Studies on Complement activation**

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

### ***Complement activation in association with NETs***

***Karsten Kluge, Medical student in Research Program***

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

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. Finalized and published in 2020 showing total complement complex to some degree to be associated with NETs and to future myocardial infarction. The work continues along with medical education for the candidate, studying this interplay in patients with acute myocardial infarction. These results were finalized in 2021, awaiting to be published.

The importance of complement activation in diabetes both type 1 and 2 has been discussed, however, as there is limited knowledge in this field we plan for such study in collaboration with the Dialong team (*vide infra*).

## **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.***

As mentioned in the Highlights, the main OMEMI trial was finalized in 2020. The main aim was 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 ( $\geq 70$ -82 years) after having experienced an acute MI. The study was quite 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. The

study has generated important new knowledge about the elderly with CAD. The study was a randomized, placebo-controlled, double blind multicenter study with study center at CCHR. The main results was a part of the thesis of Are A. Kalstad (vide supra), including three papers from the OMEMI cohort.

There are several sub-studies ongoing, especially with regards to explore any importance of the different fatty acids.

#### **Topics previously addressed:**

***Omega-3 fatty Acids*** as related to traditional CVD risk factors and co-morbidities in elderly patients with myocardial infarction, and ***Omega-3 Fatty Acids*** and the importance for myocardial function and cardiac remodeling, both part of the thesis by Kristian Laake (2017).

***Nordic Diet and Omega-3 Fatty Acids*** and reduced platelet activation assessed by circulating microvesicles (Chiva-Blanche G et al. 2019)

***Diet and Omega-3 Fatty Acids*** according to “Leukocyte Telomere Length”, a suggested marker of longevity as well as proneness for CVD (Kalstad A et al. 2019).

***Markers of Ageing / Senescence*** (telomere length, sirtuins) (vide infra), as related to the presence of atrial fibrillation in the elderly (Kalstad A et al. 2020)

***The importance of EPA/DHA serum*** concentration on clinical outcome (Myhre PM et al 2021)

The importance of ***n-6 fatty acid*** concentration on clinical outcome (Nilsen DWT et al 2021)

***The importance of omega-3 fatty acid supplementation on*** prothrombotic microvesicles in elderly subjects after suffering a myocardial infarction (Chiva-Blanch G et al 2021).

#### **Ongoing:**

- Further studies on the relationship between omega-3 fatty acids and the occurrence of atrial fibrillation, with special emphasis on micro atrial fibrillation
- Omega-3 and dietary pattern as related to microbiota translocation and regulation in adipose tissue
- Studies on polymorphisms important for the effects of omega-3 fatty acids, as well as related to ageing

## **Studies on Adipose Tissue Inflammation**

We have for several years focused on inflammation and remodeling in the metabolic to genetic expression of inflammatory and remodeling mediators, visualized in several previous and ongoing projects. Furthermore, differences in fat compartments are focused.

### ***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, Senior Scientist, Ingebjørg Seljeflot Professor, Rune Byrkjeland MD PhD*

In this project on patients with CAD and Type-2 diabetes, combined, the first parts of the project are finalized; 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 disease-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, in which data on the amount of adipose tissue is available from CT-scans.

### ***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 drafting manuscript

**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 in inflammatory genes expressed and protein secretion in various compartments of adipose tissue being exposed during open cardiac surgery on patients with CAD, and valvular disease for control. Different pathways are investigated, and the first part examining the NLRP3 pathway were finalized in 2021, and is under publication.

Based on this project, the biobank with available adipose tissue samples, a collaboration with the university of Parma, Italy was established late 2021, in which an Italian post.doc will work for 6 months in our lab, on the matter of monocyte/macrophage polarization, important for understanding new aspects of inflammation. Such international collaboration is of great importance for the milieu and for research in general.

### ***Regulation of gut-related endotoxemia induced inflammation in adipose tissue Impact of anthropometrics and dietary habits***

As mentioned, adipose tissue samples are available from the OMEMI study, and the objective is 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 will also be assessed. The study is ongoing.

## **Studies on Thrombogenicity**

### ***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 is 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 are analyzed for signaling molecules and corresponding mRNA expression in circulating leukocytes. The study is in close collaboration with Department of Radiology and Department of Pathology, OUS Ullevål. There have been some delay due to practical issues for collaborators and the corona situation. Results from the NLRP3 inflammasome pathway were published in 2021, showing this to be highly regulated in the thrombus and related to infarct injury, thus underpinning this pathway to be target for anti-inflammatory therapy. Results on the remodeling phenomenon were published primo 2022, also showing especially the metalloproteinase inhibitors to be important for myocardial injury. The work on fibrinolysis is ongoing.



### ***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. From the above mentioned TASTI project, we have explored the relationship between the expression of cMVs and pro-thrombotic and pro-inflammatory signals in coronary thrombi, especially related to the presence of NETs.

Flow-cytometry with a renewed and more advanced method that better distinguish the cMVs and their origin cells has been used. The results are submitted for publication.

### ***The importance of ADAMTS13 on vWF regulation 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. Genetic polymorphisms in the gene coding for ADAMTS-13 is further investigated for the impact on ADAMTS-13 levels as well as on clinical events. The candidate has been off research to finalize for her diploma as a licensed doctor, but will now continue for the PhD degree. This imply to further study any relationship between vWF, ADAMTS13 and also thrombospondin1 (TSP1) that is important for the regulation of ADAMTS13, and clinical outcome in patients with acute MI. The OMEMI biobank is available for this study, in which a main focus will be on the new onset of atrial fibrillation (AF), as there has been a theory that there may be a link between vWF and AF.

### ***Exercise induced changes in pro-thrombotic and cardiac biomarkers in CAD patients***

***Charlotte Holst Hansen, Study Nurse***

Patients from the CADENCE study which were tested with exercise ECG for the diagnosis of CAD, showed a hypercoagulable state after exercise. Some of these patients were re-examined after successful revascularization to explore whether they still had a tendency to be hypercoagulable, and also whether they still induced release of cardiac biomarkers. The study was finalized in 2021, being under review for publication.

## 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.



**Sirtuins (SIRT)** are a family of NAD<sup>+</sup> 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.

We have addressed studies for understanding some mechanisms behind the ageing process in different populations.

### **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 (Published 2021).

### **Influence of selenium and Q10 on telomere length and Sirtuin-1**

***In collaboration with Urban Alehagen, MD PhD Linköping University, Sweden***

Based on our experience in telomere and ageing research we have been invited to participate in a project studying the effects of intervention with selenium and Q10 in an elderly Swedish population, followed for 10 years. We have studied any effect on telomere attrition, in which the results were finalized in 2021 and is submitted for publication. Furthermore, we have explored any effects on SIRT-1, in which the results will be available in 2022

**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.

## 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. Consecutive patients with STEMI and NSTEMI were included after consent. 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 planned, including genome wide association studies, with analyses performed at the Decode center at Iceland.

### ***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 patients are followed for three years, the last patient during 2018. 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, and later also due to corona, the biobank has been limited used, but other biomarker studies are under planning.

### ***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 years and 10 years and will be further followed every fifth year. All blood sampling/processing and facilities for biochemical translational research (biobanking and analyses) are undertaken at CCHR. Three PhD theses have been based on data from this study so far, and one is ongoing. Planning now for the 15 yrs follow-up.

### ***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 cheirography 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, cheirography, levels of AGE's in collagen from the shoulder region, inflammatory biomarkers, glycemic control as well as genetic factors. The main study was finalized in 2019, with thesis defended. This is a unique population, and sub-studies based on the biobank is still ongoing. It has so far been used for investigation of the ageing aspects and NETs aspects (vide supra), but other topics are planned.

### ***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*

As mentioned, this main study was finalized and main results presented.

The 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). A randomized, double blind, placebo-controlled trial conducted at three high-volume percutaneous coronary intervention (PCI) centers in Norway. Altogether, 200 patients with first-time STEMI were randomized to receive tocilizumab or matching placebo prior to PCI. The patients were followed-up for 6 months. The results, showing a beneficial effect of the drug, were presented at the European congress of cardiology (digital) august 2020, and published early 2021). A biobank is established based on blood sampling at several time points during the acute phase and after 6 months. Studies on mechanisms are ongoing.

### ***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 collaborative study between many departments, initiated by the supervisors.*

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 longitudinal parallel group 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 will use 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 of blood, urine and stool samples are established at CCHR. The project has been much delayed and influenced by the corona situation, but is ongoing with inclusions.

### ***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 assess 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.

***To improve blood flow in patients with peripheral artery disease; by intermittent negative pressure (INP) – ongoing at OUS Aker***

***Cand Med Henrik Hoel PhD student***

*Supervisors; Jonny Hisdal Professor, Gunnar Sandbæk MD PhD, Iacob Mathiesen PhD*

The main goal of the project was to evaluate a novel method for improving blood flow in patients with reduced peripheral arterial circulation (PAD-patients), and to identify and optimize the level of negative pressure to improve blood flow in patients with varying degrees of PAD. A double blinded randomized placebo-controlled trial. All patients receive standard medical treatment; randomized to either INP treatment with pressure level of -10 mmHg (placebo group), or to INP treatment with pressure level of -40 mmHg (Intervention), for 12 weeks. A biobank, focusing endothelial activation/function is established and analyses performed at CCHR. Results showed beneficial clinical effect of the treatment, and also improved endothelial function. The results were included in thesis defended January 2022.

***Vascular function in Norwegian female elite runners – ongoing at OUS Aker***

***Karoline Kyte, Medical student in Research Program***

*Supervisors: Jonny Hisdal Professor, Ingebjørg Seljeflot, Professor*

Increased aerobic capacity and regular aerobic exercise are well known to have a positive impact on the cardiovascular system. It has, however, been claimed that in healthy young women, the effect of high amounts of endurance training may not be that obvious. The aim in this study is to investigate especially vascular function, including the endothelial function, in female elite runners compared to inactive women. Special emphasis is given to menstrual state which may be of importance. The results are under publication.

***Biomarker related to brain dysfunction in stroke patients***

*Collaborating study with Guri Hagberg MD PhD and coworkers, 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.

# Laboratory Methods

have been further established according to recent knowledge

- 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

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## 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.



# Publications 2021

## Articles

1. Saeed M, Tapia G, Ariansen I, Stene LC, Seljeflot I, Tell GS, Skriverhaug T, Joner G. Serum galectin-3 and subsequent risk of coronary heart disease in subjects with childhood-onset type 1 diabetes. A cohort study. *Diabetes Care* 2021; doi.org/10.2337/dc20-1712
2. Kalstad, AA, Myhre PL, Laake K, Opstad TB, Tveit A, Solheim S, Arnesen H, Seljeflot I. Biomarkers of ageing and cardiac remodeling are associated with atrial fibrillation. *Scand Cardiovasc J* 2021; doi.org/10.1080/14017431.2021.1889653
3. Aune SK, Byrkjeland R, Solheim S, Arnesen H, Trøseid M, Awoyemi A, Seljeflot I, Helseth R. Gut-related inflammation and cardiorespiratory fitness in patients with CAD and type 2 diabetes: A randomized controlled study on exercise training. *Diabetol Metab Syndr* 2021; 13:36 Doi.org/10.1186/s13098-021-00655-2
4. Broch K, Anstensrud AK, Woxholt S, Sharma K, Tøllefsen IM, Bendz B, Aakhus S, Ueland T, Amundsen BH, Damås JK, Berg ES, Bjørkelund ES, Bendz C, Hopp E, Kleveland O, Stensæth KH, Opdahl A, Kløw NE, Seljeflot I, Andersen GØ, Wiseth R, Aukrust P, Gullestad L. Interleukin-6 receptor inhibition in acute ST-segment elevation myocardial infarction: A randomized placebo-controlled trial. Brief title: ASSAIL-MI. *J Am Coll Cardiol* 2021; 77:1845-55. Doi.org/10.1016/j.jacc.2021.02.049
5. Myhre PL, Seljeflot I, Arnesen H. Omega-3 tilskudd har liten plass i forebygging av hjertesykdom. *Tidsskrift for Norske Legeforening* 2021; doi:10.4045/tidsskr.21.0033
6. Opstad TB, Sundfør T, Tonstad S, Seljeflot I. Effect of intermittent and continuous caloric restriction on Sirtuin1 concentration depends on sex and body mass index. *Nutr Metab Cardiovasc Dis* 2021;31:1871-1878. doi.org/10.1016/j.numecd.2021.03.005
7. Hoel H, Pettersen EM, Høiseth LØ, Mathiesen I, Seternes A, Seljeflot I, Hisdal J. Effects of intermittent negative pressure treatment on circulating vascular biomarkers in patients with intermittent claudication. *Vasc Med* 2021; doi:10.1177/1358863X211007933
8. Helseth R, Kleveland O, Ueland T, Wiseth R, Damås JK, Broch K, Michelsen A, Bendz B, Gullestad L, Aukrust P, Seljeflot I. The interleukin-6 receptor antagonist tocilizumab increases markers of neutrophil extracellular traps in patients with non ST segment elevation myocardial infarction. *The Heart* 2021; doi:10.1136/openhrt-2020-001492
9. Nordeng J, Schandiz H, Solheim S, Åkra S, Hoffman P, Roald B, Bendz B, Arnesen H, Helseth R, Seljeflot I. Inflammasome signaling in coronary thrombi from STEMI patients. *Med Inflamm* 2021; doi.org/10.1155/2021/5525917
10. Skaarud KJ, Hov JR, Hansen SH, Kummen M, Valeur J, Seljeflot I, Bye A, Paulsen V, Lundin KEA, Trøseid M, Tjønnfjord GE, Iversen PO. Microbial diversity and mortality after allogeneic haematopoietic stem cell transplantation: secondary analysis of a randomized nutritional intervention trial. *Sci Rep* 2021; 11:11593. doi: 10.1038/s41598-021-90976-z
11. Pischke S, Chaban V, Nakstad ER, Stær-Jensen H, Schjalm C, Seljeflot I, Vaage J, Lundqvist C, Benth JS, Sunde K, Mollnes TM, Andersen GØ. Complement Activation is Associated With Poor

Outcome After Out-of-Hospital Cardiac Arrest. Resuscitation 2021; doi.org/10.1016/j.resuscitation.2021.05.038

12. Nyborg C, Melsom HS, Seljeflot I, Hisdal J. Transient reduction of FMD-response and L-arginine accompanied by increased levels of E-Selectin, VCAM, and ICAM after prolonged strenuous exercise. *Sports* 2021; doi.org/10.3390/sports9060086
13. Awoyemi A, Mayerhofer C, Felix AX, Hov JR, Moscovitch SD, Lappegård TK, Hovland A, Halvorsen S, Halvorsen B, Gregersen I, Svardal A, Berge RK, Hansen SH, Götz A, Aukrust P, Åkra S, Seljeflot I, Solheim S, Lorenzo A, Gullestad L, Trøseid M, Broch K. Rifaximin or *Saccharomyces Boulardii* in heart failure with reduced ejection fraction: Results from the randomized GutHeart trial. *EBioMed* 2021; doi.org/10.1016/j.ebiom.2021.103511
14. Holm S, Kared H, Michelsen AE, Kong XY, Dahl TB, Schultz NH, Nyman T, Fladeby C, Seljeflot I, Ueland T, Stensland M, Mjaaland S, Løvik GG, Nissen-Meyer LS, Aukrust P, Ryeng Skagen K, Gregersen I, Skjelland M, Holme PA, Munthe LA, Halvorsen B. Immune complexes, innate immunity and NETosis in ChAdOx1-vaccine induced thrombocytopenia. *Eur Heart J*. 2021;42(39):4064-4072.
15. Aune SK, Cwikiel J, Flaa A, Arnesen H, Solheim S, Awoyemi A, Trøseid M, Seljeflot I, Helseth R. Gut leakage markers in response to strenuous exercise in patients with suspected coronary artery disease. *Cells* 2021: 10,2193 doi.org/10.3390/cells10092193
16. Nyborg C, Bonnevie-Svendsen M, Melsom HS, Melau J, Seljeflot I, Hisdal J. Reduced L-Arginine and L-Arginine-ADMA-ratio, and increased SDMA after Norseman Xtreme triathlon. *Sports* 2021; doi.org/10.3390/sports9090120
17. Nilsen DVT\*, Myhre PL\*, Kalstad A, Schmidt EB, Arnesen H, Seljeflot I. Serum levels of dihomo-gamma ( $\gamma$ )-linolenic acid (DGLA) are inversely associated with linoleic acid and total death in elderly patients with a recent myocardial infarction. *Nutrition* 2021; 13,3475 doi.org/10.3390/nu13103475
18. Chiva-Blanca G, Bratseth V, Laake K, Arnesen H, Solheim S, Schmidt EB, Badimon L, Seljeflot I. One year of omega-3 polyunsaturated fatty acid supplementation does not reduce circulating prothrombotic microvesicles in elderly subjects after suffering a myocardial infarction. *Clin Nutr* 2021; 40: 5674-5677.
19. Alehagen U, Opstad TB, Alexander J, Larsson A, Aaseth J. Impact of Selenium on Biomarkers and Clinical Aspects Related to Ageing. *Biomolecules* 2021; Oct 7;11(10):1478. doi: 10.3390/biom11101478. *Review*
20. Zaidi H, Byrkjeland R, Njerve IU, Åkra S, Solheim S, Arnesen H, Seljeflot I, Opstad TB. Association between improved cardiorespiratory fitness assessed by VO<sub>2</sub> peak levels, and circulating adiponectin in exercise-intervened patients with CAD and Type 2 diabetes – an EXCADI sub-study. *Adipocyte* 2021; 10: 612-620
21. Tøllefsen IM, Shetelig C, Seljeflot I, Eritsland J, Limalanathan S, Hoffmann P, Andersen GØ. The role of IL-6 receptor trans-signalling in ischemia-reperfusion injury, infarct healing and future adverse events in patients with ST-Elevation Myocardial Infarction. *Open Heart* 2021;8:e001869. doi:10.1136/openhrt-2021-001869

22. Omland T, Prebensen C, Jonassen JM, Svensson M, Berdal JE, Seljeflot I, Myhre PL. Soluble ST2 concentrations Associate with In-Hospital Mortality and Need for Mechanical Ventilation in Unselected Patients with COVID-19. *Open Heart* 2021; doi:10.1136/openhrt-2021-001884

## Abstracts

1. Zaidi H, Byrkjeland R, Njerve IU, Åkra S, Solheim S, Arnesen H, Seljeflot I, Opstad TB. Adiponectin associates with VO<sub>2</sub>peak after exercise in patients with CAD and Type 2 diabetes. [Eur Atheroscler Soc Helsinki 2021 Virt](#)
2. Opstad TB, Sundfør T, Tonstad S, Seljeflot I. Effect of intermittent and continuous caloric restriction on Sirtuin1 concentration depends on sex and body mass index. [Eur Atheroscler Soc Helsinki 2021 Virt](#)
3. Åkra S, [Solheim S](#), Tønnesen T, Braathen B, Hansen CH, Arnesen H, Seljeflot I. Inflammasome activation in epicardial, pericardial and subcutaneous adipose tissue in patients with coronary heart disease. [Eur Soc Cardiology Virt 2021, Oral](#)
4. Kluge KE, Langseth MS, Andersen GØ, Halvorsen S, Eritsland J, Hansen CH, Arnesen H, Tønnesen T, Seljeflot I, Helseth R. Complement activation is linked to neutrophil extracellular traps and associated with death in ST-elevation myocardial infarction. [Eur Soc Cardiology Virt 2021](#)
5. Aune SK, Cwikiel J, Flaa A, Arnesen H, Solheim S, Awoyemi A, Trøseid M, Seljeflot I, Helseth R. Gut leakage markers in response to strenuous exercise in patients with suspected coronary artery disease. [Eur Soc Cardiology Virt 2021](#)
6. Hansen CH, Cwikiel J, Bratseth V, Arnesen H, Flaa A, Seljeflot I. Effect of revascularization on exercise-induced changes in cardiac and pro-thrombotic biomarkers in patients with coronary artery disease. [Eur Soc Cardiology Virt 2021](#)
7. Myhre PL, Schmidt EB, Kalstad AA, Tveit SH, Laake K, Smith P, Nilsen DWT, Tveit A, Solheim S, Arnesen H, Seljeflot I. Changes in EPA and DHA During Supplementation with Omega-3 Fatty Acids and Incident Cardiovascular Events: Secondary analysis from the OMEMI trial. [Eur Soc Cardiology Virt 2021. Oral](#)
8. Nilsen DWT, Myhre PL, Kalstad AA, Schmidt EB, Arnesen H, Seljeflot I. Low levels of dihomo-gamma ( $\gamma$ )-linolenic acid are associated with all-cause death in elderly patients with a recent myocardial infarction. [Eur Soc Cardiology Virt 2021](#)
9. Tøllefsen IM, Shetelig C, Seljeflot I, Eritsland JE, Hoffmann P, Andersen GØ. The role of IL-6 receptor trans-signalling in ischemia-reperfusion injury, infarct healing and future [major] adverse] clinical events in patients with ST-Elevation Myocardial Infarction. [Eur Soc Cardiology Virt 2021](#)
10. Nordeng J, Solheim S, Åkra S, Hoffman P, Schandiz H, Roald B, Bendz B, Arnesen H, Helseth R, Seljeflot I. Plaque and remodeling markers in coronary thrombi. [Eur Soc Cardiology Virt 2021](#)

11. Nilsen DWT, Myhre PL, Kalstad AA, Schmidt EB, Arnesen H, Seljeflot I. Reduced delta-desaturase activity may be associated with major adverse cardiac events during 2 years follow-up in elderly patients with a recent myocardial infarction. Am Heart Ass Virt 2021 Oral
12. Nilsen DWT, Myhre PL, Kalstad AA, Schmidt EB, Arnesen H, Seljeflot I. The relationship between linoleic acid (LA) and dihomo-gamma-linolenic acid (DGLA) as indicator of delta-6-desaturase activity. Am Heart Ass Virt 2021
13. Aune SK, Cwikiel J, Flaa A, Arnesen H, Solheim S, Awoyemi A, Trøseid M, Seljeflot I, Helseth R. Gut leakage markers in response to strenuous exercise in patients with suspected coronary artery disease. Oslo Symposium on Heart Research, Soria Moria 2021
14. Bratseth V, Nordeng J, Helseth R, Solheim S, Åkra S, Chiva-Blanch G, Seljeflot I. Microvesicles, the NLRP3-inflammasome- and IL-6 gene expression in coronary thrombi from STEMI patients. Oslo Symposium on Heart Research, Soria Moria 2021
15. Nordeng J, Helseth R, Åkra S, Hoffman P, Schandiz H, Roald B, Bendz B, Arnesen H, Solheim S, Seljeflot S. Plaque and remodeling markers in coronary thrombi. Oslo Symposium on Heart Research, Soria Moria 2021
16. Aune SK, Cwikiel J, Flaa A, Arnesen H, Solheim S, Awoyemi A, Trøseid M, Seljeflot I, Helseth R. Gut leakage markers in response to strenuous exercise in patients with suspected coronary artery disease. National Microbiota Symposium, Oslo 2021