Danish Cardiovascular Academy

Abstract Book

DCACADEMY SUMMER MEETING 2023

15-17 June 2023
Storebælt Sinatur Hotel & Konference
Nyborg

DCAcademy is supported by

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HJERTE FORENINGEN

PROGRAMME

Thursday 15TH of June 2023

YOUNG INVESTIGATOR DAY

09:30 - 10:00	**Arrival and coffee**
10:00 - 10:30	Welcome and Meet & Greet
10:30 - 11:00	**Opening Speech**
11:00 - 12:30	**Session 1: SCIENTIFIC ENTREPRENEURSHIP/INNOVATION**
11:00 - 11:30	Changing the Beat: How to develop Innovative Medical Devices for Cardiology
11:30 - 12:00	My personal journey into personalized medicine
12:00 - 12:30	Panel debate
12:30 - 13:30	**Lunch**
13:30 - 15:30	**Session 2: SCIENTIFIC CRAFTMANSHIP**
13:30 -14:00	Designing research studies
14:00 -14:30	Design of preclinical studies
14:30 -15:00	Evidence and Guidelines
15:00 - 15:30	**Break / check-in / change for activities**
15:30 - 17:00	**Outdoor activities**
	Arrival of PI's & senior researchers
17:00 - 17:30	**Snacks**
17:30 - 18:30	**Meet the professor**
18:30 - 19:00	**Refreshment and networking**
19:00 - 20:30	**Dinner**
20:30 - 21:15	**EVENING SESSION**
20:30 - 21:15	Pragmatic clinical trials/Leveraging electronic health records to streamline the conduct of cardiovascular clinical trials
21:15	**Networking and games** (downstairs, at Østerø)

Friday 16TH of June 2023

7:00-8:30	**Breakfast, optional morning run, ocean dip**
8:30 - 10:00	**Session 3: HEART FAILURE**
08:30 - 08:40	Intro + SGLT-2
08:40 - 09:00	Pathofysiology, hemodynamics
09:00 - 09:20	Advanced HF and transplantation
09:20 - 09:40	New facets of the calcitonin signalling in the heart
09:40 - 10:00	Novo-projekt
10:00 - 10:30	**Break & energizer**

10:30 - 12:00	**Session 4: Parallel session – HEART FAILURE AND ATHEROSCLEROSIS**		
10:30 - 12:00	BASIC CARDIOLOGY	CLINICAL HEART FAILURE	BASIC ATHEROSCLEROSIS
12:00 - 13:00	**Lunch**		
13:00 - 15:15	**Session 5: REHABILITATION / PREVENTION**		
13:00 - 13:20	Cardiac rehabilitation and palliative care – status 2023		
13:20 - 13:40	Cardiac rehabilitation in ischemic heart disease		
13:40 - 14:00	Prevention and Rehabilitation focusing on sportscardiology		
14:00 - 14:10	**Break**		
14:10 - 14:30	Atrial Fibrillation and Cardiac Rehabilitation and Prevention- evaluation of a family-focused intervention for patients with atrial fibrillation		
14:30 - 14:50	Telemonitoring /Fibri-check and lifestyle interventions in AF		
14.50 - 15:00	Labor market participation in patients with a CRT-System		
15:00 - 15:15	**Coffee**		
15:15 - 17:00	**Session 6: POSTER SESSION**		
16:30 - 17:00	Mechanosensitive Channels, Stretch and Fibrosis – A Pathophysiological Role in Atrial Fibrillation?		
17:00 - 18:15	**Session 7: WHAT WILL BE THE BIG CARDIOVASCULAR CHALLENGES IN 2040?**		
18:15 - 18:30	**Refreshment & networking**		
18:30 - 18:50	Award ceremony: 2023 DCAcademy Lifetime Achievement Award		
19:00 - 21:00	**Barbecue**		
21:00 - -	**Networking on the terrace, bonfire, music and games**		
22:00 --	**Games & networking** (at Østerø)		

Saturday 17TH of June 2023

7:30 - 8:30	**Breakfast, optional morning run, ocean dip**		
8:30 - 9:50	**Session 8: BIG DATA AND DATA SCIENCE**		
08:30 - 08:50	Why Is it so Difficult to Realise Medical AI?		
08:50 - 09:10	Target Trial Emulation using Danish Registries		
09:10 - 09:30	What we are learning from Applied Machine Learning		
09:50 - 10:20	**Break**		
10:20 - 11:40	**Session 9: Parallel session – BIG DATA AND DATA SCIENCE**		
	Modellering og AI	Novel development in cardiac devices – a Danish perspective	Microvascular function
12:00 - 12:45	**Lunch**		
12:45 - 13:30	**Keynote speech**		
12:45 - 13:30	The renal microcirculation		
13:30 - 13:45	**Closing remarks & Award ceremony**		
14:00 - 14:30	DCAcademy business meeting (optional – everybody is invited)		

POSTER SESSIONS

P1: Clinical cardiology 1	
Chairs:	**Johannes Grand** **Olav Wendelboe Nielsen**
P1-1	Caroline Damsgaard Jensen
P1-2	Eva Havers-Borgersen
P1-3	Lasse Hubertus Tiroke
P1-4	Nadia Iraqi
P1-5	Nigopan Gopalasingam
P1-6	Peter Fruergaard Andersen
P1-7	Sarah Holle
P1-8	Selma Hasific
P1-9	Sissel Johanne Godtfredsen
P1-10	Caroline Elnegaard

P2: Clinical cardiology 2	
Chairs:	**Laust Dupont Rasmussen** **Morten Bøttcher**
P2-1	Anders Lehmann Dahl Pedersen
P2-2	Anne Mohr Drewes
P2-3	Edina Hadziselimovic
P2-4	Jonas Schaarup
P2-5	Joseph Bonner
P2-6	Louise Aas Holm
P2-7	Manijeh Noori
P2-8	Niels Jespersen
P2-9	Yan Zhou

P3: Epidemiology	
Chairs:	**Arnela Saljic** **Gunnar Gislason**
P3-1	Anna Meta Dyrvig Kristensen
P3-2	Henrik Laurits Bjerre
P3-3	Jan Walter Dhillon Shanmuganathan
P3-4	Nadja Albertsen
P3-5	Peter Engel Thomas
P3-6	Rasmus Bo Lindhardt
P3-7	Signe Wolthers
P3-8	Sofie Dannesbo
P3-9	Tobias Skjelbred
P3-10	Anne Storgaard Nørskov
P3-11	Anton Mariager
P3-12	Filip Gnesin

P4: Basic cellular cardiology	
Chairs:	**Carolin Sailer** **Niels Thue Olsen**
P4-1	Danielle Medina-Hernandez
P4-2	Helena Magnusson
P4-3	Karina Poulsdóttir Debes
P4-4	Kristine Kyle De Leon
P4-5	Louise Bjerregaard
P4-6	Lucas Xing
P4-7	Nicolai Palstrøm
P4-8	Sara Enevoldsen
P4-9	Sergio D'Anna
P4-10	Helena Bogdanovic

P5: Translational cardiology	
Chairs:	**Lisa Amalie Gottlieb** **Dominik Linz**
P5-1	Alisha Niskala
P5-2	Kezia Jerltorp
P5-3	Luca Soattin
P5-4	Melodie Schneider
P5-5	Mette Wørmer Poulsen
P5-6	Sarah Torp Yttergren
P5-7	Sebastian Buhl Rasmussen
P5-8	Simon Haugaard
P5-9	Simone Juel Dragsbæk
P5-10	Diana Sofia Usai
P5-11	Josephine Kanta

P6: Data Science & Exercise	
Chairs:	**Jonas L. Isaksen** **Jørgen Kanters**
P6-1	Adrian Atienza
P6-2	Gouthamaan Manimaran
P6-3	Gregory Wood
P6-4	Jacob Valentin Hansen
P6-5	Jakob Jensen
P6-6	Mads Fischer
P6-7	Mulham Ali
P6-8	Sheyla Barrado Ballestero
P6-9	Alexandra Amalie Uglebjerg

P7: Basic vasculature	
Chairs:	**Manan Pareek** **Thomas Jepps**
P7-1	Andrietta Grentzmann
P7-2	Gustavo Luis Tripodi
P7-3	Cancelled
P7-4	Jennifer van Der Horst
P7-5	Joakim A. Bastrup
P7-6	Karen C. Yang
P7-7	Kathrine Væver Jokumsen
P7-8	Salomé Rognant
P7-9	Samuel Baldwin
P7-10	Asli Bahar Topaktas

Inter active poster
Maya Elena Ramirez Schambye
Mathilde Løk

O-1

Computed Tomography or Chest X-ray to Diagnose Acute Heart Failure with Pulmonary Congestion in Dyspnoeic Patients

Kristina Miger*[1,2], Anne Sophie Overgaard Olesen[1], Johannes Grand[3], Andreas Fabricius-Bjerre[1], Ahmad Sajadieh[1], Nis Høst[1], Nanna Køber[1], Annemette Abild[4], Lars Pedersen[5], Hans Henrik Lawaetz Schultz[5], Christian Torp-Pedersen[6,7], Mikael Ploug Boesen[4], Jens Jakob Thune[1,2], Olav W. Nielsen[1,2]

Lead presenter: kristina.cecilia.miger@regionh.dk
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[2]*Faculty of Health and Medical Sciences, Copenhagen University, Denmark*
[3]*Department of cardiology, Amager-Hvidovre Hospital, Denmark*
[4]*Department of Radiology, Bispebjerg and Frederiksberg Hospital, Denmark*
[5]*Department of Pulmonary Medicine and Infectious Diseases, Bispebjerg and Frederiksberg Hospital, Denmark*
[6]*Department of Cardiology, Nordsjaellands Hospital, Denmark*
[7]*Department of Cardiology, Aalborg University Hospital, Denmark*

Background
Pulmonary congestion, a key feature in acute heart failure (AHF), can be diagnosed by radiography. It is unknown whether chest computed tomography (CT) or chest X-ray (CXR) is superior for diagnosing AHF in consecutive dyspnoeic patients. The aim was to determine if chest CT is more associated with AHF compared to CXR in adult dyspnoeic patients in the emergency department.

Methods
We conducted an observational, prospective study, including adult dyspnoeic patients from the emergency department. Patients underwent concurrent clinical examination, NT-proBNP, echocardiography, CXR and low-dose non-contrast CT. Radiographic pulmonary congestion required agreement between two radiologists. The primary outcome, adjudicated AHF, was ascertained by comprehensive expert consensus. The secondary outcome, echo-bnp AHF, was based on objective echocardiographic cardiac dysfunction, elevated cardiac filling pressure, loop diuretic administration and NT-proBNP>300 pg/ml.

Results
Of 228 included patients, 64 patients had adjudicated AHF, and 79 patients had echo-bnp AHF. CT outdid CXR using conditional odds ratio (cOR) for the

association with adjudicated AHF (cOR:3.89) and echo-bnp AHF (cOR:2.52), Figure 1. CT resulted in better model performance for the primary outcome with e.g., higher univariate OR (CT:79.0 versus CXR:20.3, Table 1) and higher interrater agreement (kappa CT:0.88 versus CXR:0.73). Similar results were demonstrated for echo-bnp AHF. Examination of 12.5 patients with CT instead of CXR will find one additional AHF and, in 20 patients, prevent one false positive congestion.

Conclusion

Chest CT was significantly better than CXR in diagnosing AHF with pulmonary congestion in consecutive dyspnoeic patients admitted to the emergency department.

Figure 1: *Diagnostic odds ratios of pulmonary congestion evaluated on the chest X-ray versus chest CT for the association with AHF.*

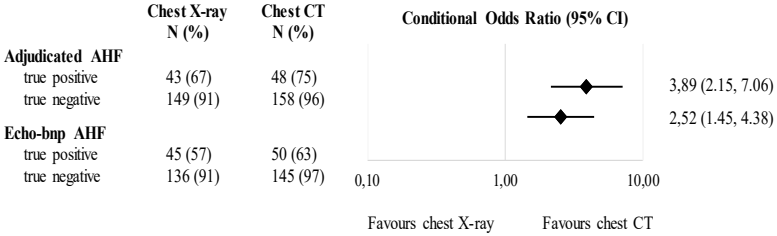

Table 1: *Diagnostic accuracy calculated from 2x2 tables by chest X-ray and chest CT to detect the two types of AHF.*

	Adjudicated AHF		Echo-BNP AHF	
Parameters	**Chest CT**	**Chest X-ray**	**Chest CT**	**Chest X-ray**
Sensitivity (%)	75	67	63	57
Lower limit 95% CI	63	54	52	45
Upper limit 95% CI	85	78	74	68
Specificity (%)	96	91	97	91
Lower limit 95% CI	92	85	93	86
Upper limit 95% CI	99	95	99	95
PPV (%)	89	74	92	78
Lower limit 95% CI	77	61	82	65
Upper limit 95% CI	96	85	98	87
NPV (%)	90	88	83	80
Lower limit 95% CI	85	82	76	73
Upper limit 95% CI	94	92	88	86
PLR	20.07	7.35	23.10	6.53
Lower limit 95% CI	9.03	4.40	8.65	3.75
Upper limit 95% CI	44.63	12.26	61.68	11.36
NLR	0.28	0.36	0.39	0.47
Lower limit 95% CI	0.18	0.25	0.29	0.36
Upper limit 95% CI	0.41	0.51	0.52	0.61
Odds ratio	79.0	20.3	65.5	13.8
Lower limit 95% CI	31.3	9.9	23.3	6.9
Upper limit 95% CI	233.5	44.1	219.0	244.5
AIC	153.1*	197.5	192.8*	235.9
BIC	159.9*	204.3	199.6*	242.7

O-2

Proteomic characterization of microfibrillar-associated protein 4 – deficient atherosclerotic lesions

[1]Christensen KB., [1]Ünsal S.*, [1]Steffensen LB., [2]Beck HC., [1]Dubik M., [1]Pilecki B., [1]Schlosser A., [1]Sørensen GL. *sunsal@health.sdu.dk

**Lead presenter*
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[2]Department of Clinical Biochemistry, Odense University Hospital, Odense, Denmark

Background: Atherosclerosis is progressive inflammatory disease characterized by lipid accumulation in the arteries. Microfibrillar-associated protein 4 (MFAP4) is an extracellular matrix protein, highly expressed by arterial contractile vascular smooth muscle cells, and binds integrin αVβ3 ligand. This integrin evokes angiogenesis and is highly expressed on endothelial cells in atherosclerosis.

Aim
Here we investigated the role of MFAP4 in atherosclerosis.

Methods: *ApoE-/-* high-fat diet (HFD) atherosclerosis mouse model used for two independent studies for 24 weeks. In the first study, *ApoE-/- Mfap4+/+* or *ApoE-/- Mfap4-/-* double deficient mice were used to assess the effect of genotypical loss of MFAP4. In the second study, *ApoE-/- Mfap4+/+* mice were injected intraperitoneally with 10 mg/kg of recombinant humanized anti-MFAP4 or human IgG1 isotype control antibody twice a week between week 14-24.

Results: *Mfap4*-deficient mice exhibited a significantly lowered lesion area and proteomic analysis of plaques showed that *Mfap4*-deficiency is associated with decreased mitochondrial translation, endothelial cell migration and angiogenesis, while increased intracellular translation and macromolecule transport was observed. CD31 stainings supported that intraplaque neovessel formation is reduced in knockout mice and endothelial cell migration is increased when cells are exposed to MFAP4 *in vitro.* Intraplaque necrosis was tendentially decreased in *Mfap4*-deficiency and significantly decreased by anti-MFAP4 treatment in support of more efficient macromolecule homeostasis with MFAP4 inhibition in atherosclerosis.

Conclusion: Our study suggests that MFAP4 is an aggravator of atherosclerosis, and that the main effects of its depletion or pharmacological blocking are reduction of intraplaque angiogenesis and protection of necrosis.

O-3

Tomoelastography: A possible new way to quantify Diastolic Dysfunction

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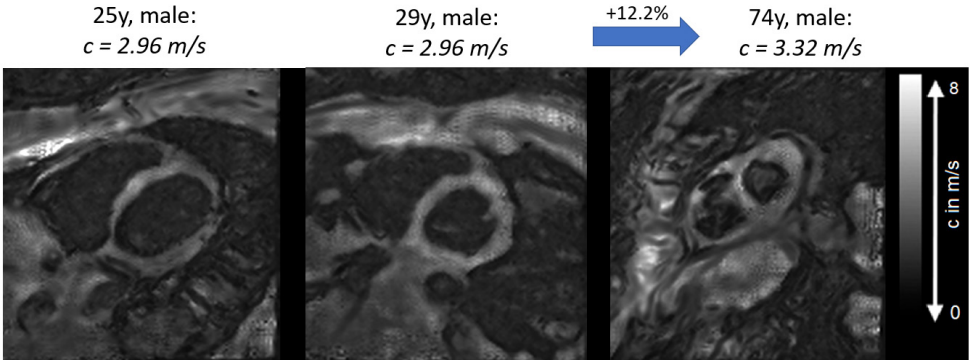
[3]Department of Nuclear Medicine & Molecular Imaging, University Medical Center Groningen, University of Groningen, the Netherlands

Background
The heart is the motor of blood circulation. The periodic increase and decrease of the myocardial shear modulus over the cardiac cycle drives blood through the systemic and pulmonary circulatory systems. Therefore, determining the myocardial shear modulus is of high clinical relevance for assessing cardiac function. One of the most promising and emerging applications to noninvasively quantify the myocardial shear modulus is using Tomoelastography (TMRE), employing mechanical wave fields with multiple frequencies. The resulting metrics like stiffness and viscosity have the potential to assess myocardial remodeling.

Aim
We aimed to optimize our TMRE setup to overcome technical challenges and demonstrate its feasibility in quantifying myocardial diastolic stiffness.

Methods
We acquired diastolic shear wave speed (SWS) maps of three healthy subjects (two young and one elderly male) using a single-shot spin-echo EPI and driving frequencies from 100 to 150Hz. In addition, manual ROI segmentation of the left ventricle (LV) has been performed on the TMRE magnitude images.

Results
Resulting SWS maps – a surrogate for stiffness –showed an increase in LV myocardial diastolic stiffness of 12.2%, as seen in the figure below. Determined stiffness increase accounts for the physiological aging of the myocardium due to cellular remodeling.



Conclusion

Our results demonstrated the feasibility of measuring LV myocardial diastolic stiffness using TMRE. Furthermore, our cardiac TMRE might pave a novel way to characterize myocardial abnormalities and heart dysfunctions. Consequently, future studies should validate our preliminary results and verify the repeatability of our setup.

O-4

Beneficial APD/QT prolongation by L-carnitine in transgenic SQT1 rabbit models

Tibor Hornyik[1,2,3,4], Konstantin Michaelides[2,3], Lea Mettke[2,3], Ilona Bodi[2,3,4], Stefanie Perez-Feliz[2,3], Michael Brunner[2,5], Manfred Zehender[2], Katja E. Odening[2,3,4]

[1]Department of Pharmacology and Pharmacotherapy, University of Szeged Albert Szent-Györgyi Medical School, [2]Department of Cardiology and Angiology I, Heart Center University of Freiburg, Medical Faculty, Freiburg, Germany; [3]Institute of Experimental Cardiovascular Medicine, Heart Center University of Freiburg, Medical Faculty, Freiburg, Germany; [4]Translational Cardiology, Department of Cardiology, Inselspital, Bern University Hospital, and Institute of Physiology, University of Bern, Bern, Switzerland, [5]Department of Cardiology and Medical Intensive Care, St. Josefskrankenhaus, Freiburg, Germany

Background: Short QT syndrome type-1 (SQT1) is a genetic cardiac channelopathy caused by gain-of-function in HERG/I_{Kr}, leading to QT-shortening, atrial/ventricular arrhythmias, and sudden cardiac death. Data on efficient pharmacotherapy is limited. In patients with primary L-carnitine-deficiency, acquired-SQTS has been described, indicating that L-carnitine might affect cardiac repolarization.

Aim: We hypothesize that L-carnitine may exert beneficial (prolonging) effects on cardiac repolarization in genetic SQT1.

Methods: Effects of L-carnitine on cardiac repolarisation were assessed in adult wildtype (WT) and transgenic SQT1 rabbits (KCNH2-N588K) using *in vivo* ECG and *ex vivo* Langendorff-perfused whole-heart or isolated ventricular cardiomyocyte action potential (AP) recordings. Effects on ion currents were assessed by whole-cell patch-clamping.

Results: *In vivo,* the heart-rate corrected QT index (QTi) was prolonged by L-carnitine in SQT1 (QTi, % baseline, 94.8 ± 7.4 vs. carnitine, 99.5 ± 8.2, p<0.0001, n=13) and WT. *Ex vivo*, whole-heart monophasic and cellular APs were also prolonged by L-carnitine in WT and SQT1 (change in monophasic APD_{75}, ms, WT +13.9±4.4, SQT1 +9.9±7.0; change in cellular APD_{90}, %, WT +10.4%, SQT1 +10.4%, all p<0.05). Underlying mechanisms are: i) reduction of I_{Kr}-steady, which is pathologically increased in SQT1 (WT: -23% , SQT1: -16%), ii) acceleration of the deactivation kinetics of I_{Kr} and iii) decrease of I_{Ks}-steady by L-carnitine both in SQT1 and WT.

Conclusion: L-carnitine prolongs/normalizes QT&APD in transgenic SQT1 rabbits by acutely decreasing the pathologically increased I_{Kr}-steady and also I_{Ks}-steady. L-carnitine may serve as potential QT-normalizing/anti-arrhythmic therapy in SQT1.

O-5

Evaluation of different heatmap methods for deep learning-based ECG analysis

[1,2]Storås, A.M*.

*Lead presenter
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[2]Oslo Metropolitan University, Norway

Background: Machine learning (ML) is defined as giving machines ability to solve tasks directly from data. Artificial deep neural networks make up a branch of ML where the models are loosely inspired by the human brain architecture. Because of impressive performance, deep neural networks have become popular for analyzing medical data. However, deep neural networks sometimes fail to capture medically relevant features and instead focus on features related to artifacts. Moreover, the models might fail drastically when analyzing new data that lacks these artifacts. This problem can be avoided by applying explanation techniques, such as heatmap methods.

Aim: This study aims to evaluate heatmap methods explaining neural networks trained to predict either amplitudes or intervals in 12-leads electrocardiograms (ECGs).

Methods: Several heatmap methods are applied to several neural networks analyzing ECGs. The explanations are evaluated qualitatively by domain experts and objectively by applying a perturbation-based method.

Results: Our results show that there is no explanation method that performs best in all use-cases. According to the domain experts, none of the investigated techniques highlighted clinically relevant features in the ECGs in a satisfactory way.

Conclusion: To conclude, existing explanation methods are not appropriate to explain deep neural networks for ECG analysis. Improved techniques that are tailored for medical data analyses are required. To ensure high quality explanations that cover the needs of healthcare personnel, medical experts should be highly involved in development of the explanation techniques.

O-6

A Hybrid Approach to Full-scale Reconstruction of Renal Arterial Network

Peidi Xu[1]*, Niels-Henrik Holstein-Rathlou[2], Stinne Byrholdt Søgaard[2], Carsten Gundlach[3], Charlotte Mehlin Sørensen[2], Kenny Erleben[1], Olga Sosnovtseva[2] & Sune Darkner[1]

*Lead presenter
[1] Department of Computer Science, University of Copenhagen, Denmark
[2] Department of Biomedical Sciences, University of Copenhagen, Denmark
[3] Department of Physics, Technical University of Denmark, Denmark

Background
The renal vasculature, acting as a resource distribution network, plays an important role in both the physiology and pathophysiology of the kidney. However, no imaging techniques allow an assessment of the structure and function of the renal vasculature due to limited spatial and temporal resolution. To develop realistic computer simulations of renal function, and to develop new image-based diagnostic methods based on artificial intelligence, it is necessary to have a realistic full-scale model of the renal vasculature.

Aim
To reconstruct a realistic model of the full-scale renal vasculature of a rat kidney, which begins at the renal artery and ends in the afferent arterioles and can be used in advanced mathematical models of renal function.

Methods
We propose a hybrid framework by using semi-automated segmentation of large arteries and estimation of cortex area from a micro-CT scan as a starting point, and by adopting physiologically based optimization for generating smaller vessels.

Results
Our constructed renal arterial tree shows close agreement with existing anatomical data obtained from a rat kidney with respect to morphometric and hemodynamic parameters.

Conclusion
We reconstruct a full-scale arterial vascular network that reaches afferent arterioles and matches anatomical data. With a full-scale tree structure, the next goal is to model pathological changes in the kidney, e.g., by modifying the radii of certain vessels while simulating the resulting changes in pressures and flow to mimic renal artery stenosis.

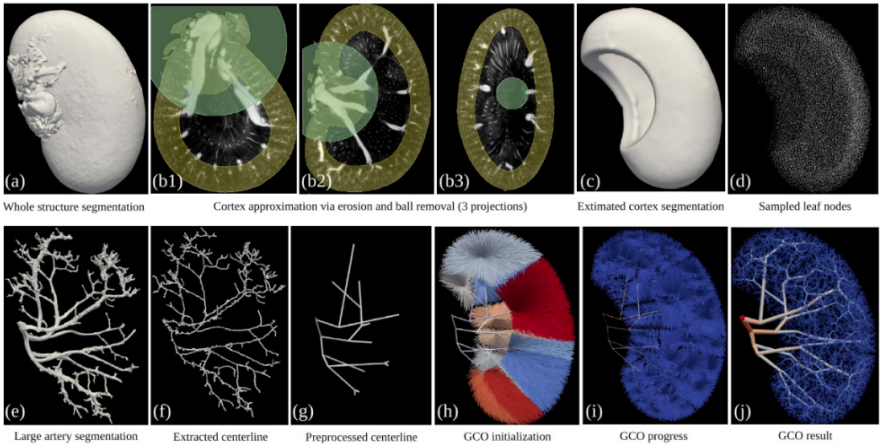

Figure 1. GCO Pipeline, visualized by 3D Slicer[27] and ParaView[28]. The initial micro-CT scan is used to extract whole structure segmentation (**a**) and large artery segmentation (**e**). Top row: renal cortex (**c**) is approximated by a subtraction of erosion followed by a ball removal (**b**), where the leaf nodes (**d**) are sampled using Poisson disk sampling. Bottom row: extracted centerline (**f**) is pre-processed to pre-build a renal arterial tree consisting of only the first few large arteries (**g**). In GCO initialization (**h**), all the sampled leaf nodes (**d**) are connected to the nearest node in the pre-built tree (**g**) with color indicating the group of leaf nodes that are connected to the same node. Colors in the GCO progress and result (**i**,**j**) indicate the radius of each vessel: from 300 μm in renal artery to 10 μm in afferent arterioles (AA).

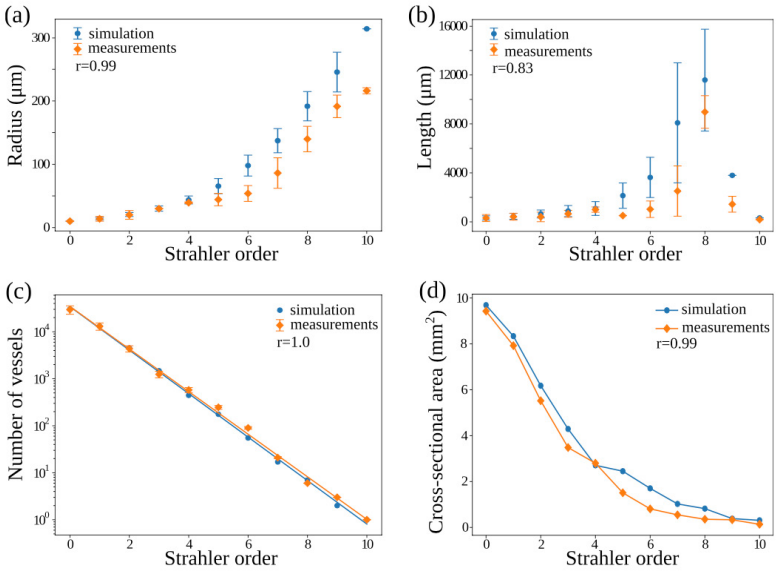

Figure 2. Morphometric features of the generated renal vascular arterial network (simulation) and the experimental data reported in the literature (measurements). In each subfigure, *r* indicates the Pearson correlation coefficient of the mean values with respect to Strahler order. (**a**) Vessel radius vs Strahler order. (**b**) Vessel length vs Strahler order. (**c**) Number of vessels (in log scale) of a particular Strahler order. (**d**) Total cross-sectional area vs Strahler order.

O-7

Biventricular Human Heart Model for Designing Self-powered Intra-leadless Pacemaker

[1]Hasani, Milad*., [1]Rezaniakolaei, Alireza & [2]Riahi, Sam

**Lead presenter: miha@energy.aau.dk*
[1] Department of AAU Energy - Aalborg University, Aalborg, Denmark,
[2] Department of Cardiology - Aalborg University Hospital and Department of Clinical Medicine - Aalborg University, Aalborg, Denmark

Background

Pacemaker devices must be replaced after some years due to limited battery life. The energy harvesting methods can tackle this limitation.

Aim

This project aims to provide an endocardial energy harvester design to convert the kinetic energy of the human heart motion to electrical power for pacemaker devices. The optimized design of this energy harvester depends on individual heart's movement. Thus, a preliminary patient-specific biventricular heart model was conducted to study endocardial heart motion leading to better energy conversion performance.

Methods

A 3D solid model was prepared through an available point clouds[1] dataset measured from an actual human heart (Fig. 1). The muscle fibers wrapped around the heart were considered by associated PDEs[2], as shown in Fig. 2.

Results

The preliminary model without blood flow can mimic electric potential distribution and heart motion during the systole stage, as illustrated in Fig. 3. Furthermore, the sequential DICOM images of MRI scans are evaluated by artificial intelligence-based software to derive valves' volumetric flow to improve this model.

1 A discrete set of data points in space
2 Partial Differential Equations (PDEs)

Conclusion

The model integrated with the blood flow can simulate the 6-dimensional motion of the endocardium. This significant advancement opened possibilities to find the best implanting location and improve the design of patient-specified energy harvesters. Moreover, a finite element analysis (including solid mechanics and electrophysiology physics) was conducted to study the heart's dynamic.

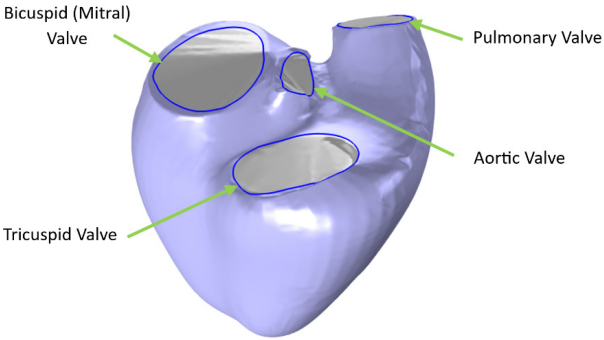

Figure 1. *The 3D solid model of the heart.*

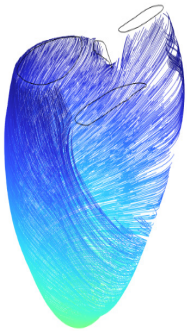

Figure 2. *The cross-section of heart's muscle fiber distribution.*

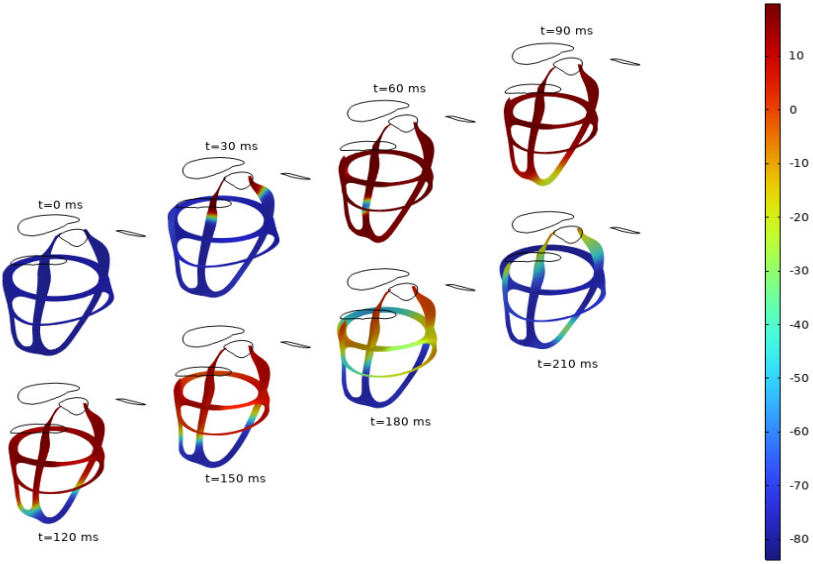

Figure 3. *The heart's electrical potential heart at different times within systole.*

O-8

Right ventricular lead position is not associated with clinical outcome in cardiac resynchronization therapy

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Background: Cardiac resynchronization therapy (CRT) is a guideline-directed therapy for selected heart failure (HF) patients. While the impact of left ventricular (LV) lead positioning has extensively been studied, far less is known about the optimal right ventricular (RV) lead position. Previous studies all applied two-dimensional fluoroscopy and chest radiography to assess the lead position, which is inaccurate and modestly reproducible as compared with three-dimensional cardiac computed tomography (CT).

Aim: To evaluate the association between different RV lead positions as assessed by cardiac CT and clinical long-term outcomes in patients receiving CRT.

Methods: We reviewed patient records of 278 patients for the occurrence of the pre-defined primary composite endpoint of HF hospitalization or all-cause death during long-term follow-up after CRT implantation. The endpoint was compared between RV lead positions (non-apical vs. apical and free-wall vs. septal RV) using adjusted Cox regression analysis.

Results: During a median (interquartile range) follow-up of 4.7 (2.9–7.1) years, 130 (47%) patients met the endpoint. The risk of meeting the endpoint was not significantly different between patients with non-apical vs. apical RV lead position (adjusted hazard ratio [HR] 0.78, 95% confidence interval [CI] 0.54–1.12, p=0.17) and free-wall vs. septal RV lead position (adjusted HR 1.03, 95% CI 0.72–1.47, p=0.86).

Conclusion: In patients receiving CRT, the risk of HF hospitalization or all-cause death during long-term follow-up is not significantly associated with certain anatomical RV lead positions as assessed by cardiac CT.

O-9

CCN2 deficiency leads to severe atherosclerosis through smooth muscle cell lipid accumulation

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Background

Cellular Communication Network Factor 2 (CCN2/CTGF) is matricellular protein and an established promoter of fibrotic disease. Recent findings imply a protective effect during vascular diseases, but its role in atherosclerosis remains to be investigated.

Aim

We hypothesize that CCN2 is crucial in SMC phenotype maintenance and thereby athero-protection. We aim to investigate the effect of CCN2 deficiency *in vivo* and *in vitro* on atherosclerosis and related parameters.

Methods
Ccn2 were investigated *in vivo* in global and SMC-specific knockout mouse model under normo- and hyperlipidemia. Hyperlipidemia was induced through rAAV8-De77y-mPCSK9 IV injection followed by western type diet. Furthermore, the effect of CCN2 silencing were studied *in vitro* on human aortic smooth muscle cells, HAoSMCs. Flow cytometry was used to study DiI-oxLDL uptake.

Results
This study identifies CCN2 as one of the top-ranking transcribed genes in healthy artery tissue from humans and mice in SMCs.

Ccn2 deficiency led to abnormal SMC de-differentiation and medial growth in baseline mice in both mouse models. Hyperlipidemia resulted in severe atherosclerosis throughout the whole aorta. *In vitro* knockdown of CCN2 led to a decrease of MYOCD transcription. Flowcytometry showed an increase in DiI-oxLDL uptake following *in vitro* CCN2 knockdown.

Conclusions
Our results establish CCN2 as a critical governor of normal aorta morphometry via its impact on SMC phenotype, and a critical determinant for smooth muscle investment in atherosclerosis development and highlight the proteins as a potent factor for SMC fate. The results counterargue the use of systemic anti-CCN2 therapy.

O-10

What can we learn about Angiotensin II Type 1 Receptor in mammalian cells by using Superresolution microscopy?

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Plasma membrane receptors and their interactions are major drug targets because of their central roles in regulating cellular signal transduction. Despite this, knowledge about membrane receptors remains limited due to the limitations of the techniques available allowing us to study them in their native context. Deepening of the understanding of membrane receptors has been accelerated by current advances in super-resolution fluorescence microscopy techniques, which allowed visualization and quantification of cellular processes with high temporal and spatial resolution in living cells. Specifically, the mechanism by Angiotensin II type 1 Receptors (AT1Rs) are organized and diffused in the plasma membrane (PM) remains unclear despite its crucial role in the homeostasis of salts and fluids, Cardiac adaptation, and Blood pressure in the cell.

In this study, we used newly- developed bioimaging methods that allowed the visualization of AT1Rs in renal cells; as well as, obtaining information on the dynamics and organization of the AT1Rs and their corresponding receptor-ligand complexes. This was achieved by using Photoactivated Localization Microscopy combined with Spatial-temporal Correlation Image Analysis and Expansion microscopy. This study showed 1) an increase in the lateral diffusion of AT1Rs after Angiotensin II (AngII) treatment. 2)The receptor diffusion was found transiently confined in the PM. 3) Clustering of AT1Rs in the PM followed by decreased cluster size after AngII treatment. This study opens up a path into a new level of understanding regarding the mechanism which regulates AT1Rs.

P1-1

The effects of BMP10 and palovarotene in pressure overload induced right ventricular failure

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Background
Right ventricular (RV) failure is the predominant cause of death in patients with pulmonary hypertension (PH) leaving an unmet need for new treatment strategies to support the failing RV. Bone morphogenetic protein (BMP) signaling is disturbed in patients with PH, but the direct effects on the RV remain unknown.

Aim
To investigate whether administration of exogenous BMP10 or increasing endogenous BMP10 by administration of palovarotene can attenuate development of RV failure in an animal model of isolated RV failure.

Methods
Wistar rats (n=36) underwent pulmonary trunk banding (PTB) surgery and were randomized to three groups one week after surgery. Two groups received treatment for four weeks: one with BMP10 and one with palovarotene. The third group served as a control. Five weeks after surgery, RV function was evaluated by echocardiography, MRI and invasive pressure-volume measurements. The hemodynamic as well as histological and molecular analyses on cardiac tissue are ongoing.

Results
After five weeks, all PTB rats had increased RV systolic pressure (PTB rat: 74.5±17.5 mmHg vs. healthy rat: 24.9±3.0 mmHg) and signs of RV dysfunction evident by reduced TAPSE and cardiac output.

Conclusion
PTB caused RV dysfunction in all rats. The ongoing analyses will help elucidate if administration of exogenous BMP10 or palovarotene can attenuate RV failure in an animal model of isolated RV failure, and thereby BMP10's potential role as a new treatment target for RV failure in patients with PH.

P1-2

Association between Preeclampsia and Long-Term Risk of Venous Thromboembolism

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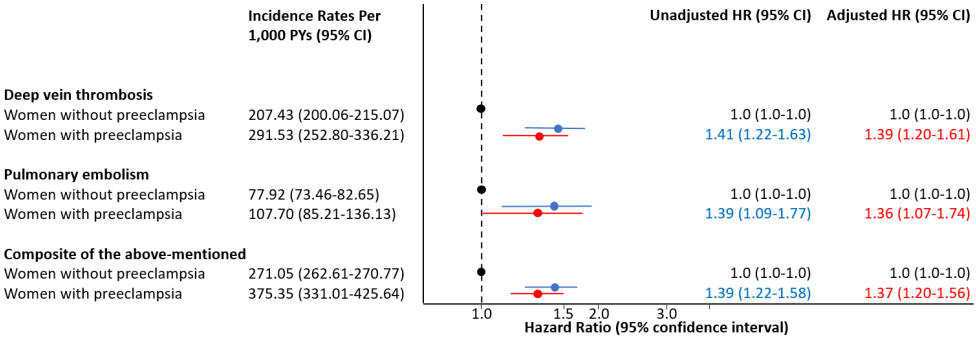
Background: As venous thromboembolism (VTE) remains one of the leading causes of maternal mortality, identifying women at increased risk is of great importance. Preeclampsia is a pregnancy-induced hypertensive disorder with generalized endothelial dysfunction. Some studies suggest that preeclampsia is associated with an increased risk of VTE, but much controversy exists.

Methods: In this observational cohort study, we identified all primiparous women who gave birth in Denmark from 1997 to 2016 using Danish nationwide registries. The women were followed from primiparous pregnancy to incident VTE, emigration, death, or end of study (December 31, 2018). The risk of VTE among women with vs without preeclampsia in their primiparous pregnancy was compared in cause-specific Cox regression analyses adjusted for thrombogenic risk factors.

Results: A total of 522,545 primiparous women with a median age of 28 years (IQR 25-31 years) were included and 23,330 (4.5%) were diagnosed with preeclampsia. Women with vs without preeclampsia were of similar age but had a higher burden of comorbidities. During a median follow-up of 10.2 years (IQR 5.2-15.4), preeclampsia was associated with a higher incidence of VTE (1.04% vs 0.77%, respectively) corresponding to an unadjusted HR of 1.39 (95%CI 1.22-1.58) and an adjusted HR of 1.37 (95%CI 1.20-1.56, **Figure**). These findings held true in landmark analyses during pregnancy, during the puerperium, and following the puerperium.

Conclusion: Preeclamptic women were associated with a significantly increased risk of VTE during pregnancy, during the puerperium, and following the puerperium – even after thorough adjustment.

Figure


Incidence Rates Per 1,000 PYs (95% CI)
Unadjusted HR (95% CI)
Adjusted HR (95% CI)
Deep vein thrombosis
Women without preeclampsia
207.43 (200.06-215.07)
1.0 (1.0-1.0)
1.0 (1.0-1.0)
Women with preeclampsia
291.53 (252.80-336.21)
1.41 (1.22-1.63)
1.39 (1.20-1.61)
Pulmonary embolism
Women without preeclampsia
77.92 (73.46-82.65)
1.0 (1.0-1.0)
1.0 (1.0-1.0)
Women with preeclampsia
107.70 (85.21-136.13)
1.39 (1.09-1.77)
1.36 (1.07-1.74)
Composite of the above-mentioned
Women without preeclampsia
271.05 (262.61-270.77)
1.0 (1.0-1.0)
1.0 (1.0-1.0)
Women with preeclampsia
375.35 (331.01-425.64)
1.39 (1.22-1.58)
1.37 (1.20-1.56)
1.0
1.5
2.0
3.0
Hazard Ratio (95% confidence interval)

P1-3

A cardiac CT study on long-term safety after left atrial appendage occlusion

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Background: Left atrial appendage occlusion is a non-inferior treatment in atrial fibrillation patients unsuited for anticoagulant treatment. However, long-term imaging studies are scarce.

Methods: A prospective cohort study including 52 patients implanted with the Amplatzer Amulet device (Abbott, Chicago, Illinois) at Aarhus University Hospital, Denmark with 4+ year follow-up time. All patients had a 2-month follow-up scan, 27/52 had a 12-month follow-up scan available, allowing for temporal comparisons with the 4+ year CT-scan. The primary outcome was left atrial appendage (LAA) sealing based on distal LAA contrast patency and peridevice leak (PDL) stratified into complete occlusion and grade 1-3 leakage. Secondary outcomes were low-grade and high-grade hypoattenuated thickening (HAT), and device integrity evaluated by device compression and possible frame fractures.

Results: At two-month, 12-month and latest follow-up CT, complete occlusion was observed in 17/52(33%), 10/27(37%), and 18/52(35%) patients. Grade 3 leak (PDL at disc, lobe, and contrast patency) was observed in 1/52(2%), 2/27(7%), and 6/52(12%) patients at two-, 12-month, and late follow-up. Low-grade HAT was observed in 6/52(12%), 10/27(37%) and 21/52(40%) patients. No high-grade HAT was seen. The structural device integrity was preserved and device compression virtually unchanged from 2 months to latest follow-up CT.

Conclusion: This study indicates a stable LAA sealing status throughout the follow-up period. Few patients had PDL progression emphasizing the importance of optimal procedural results to avoid PDL. There were no cases of device-related thrombosis and device integrity was maintained.

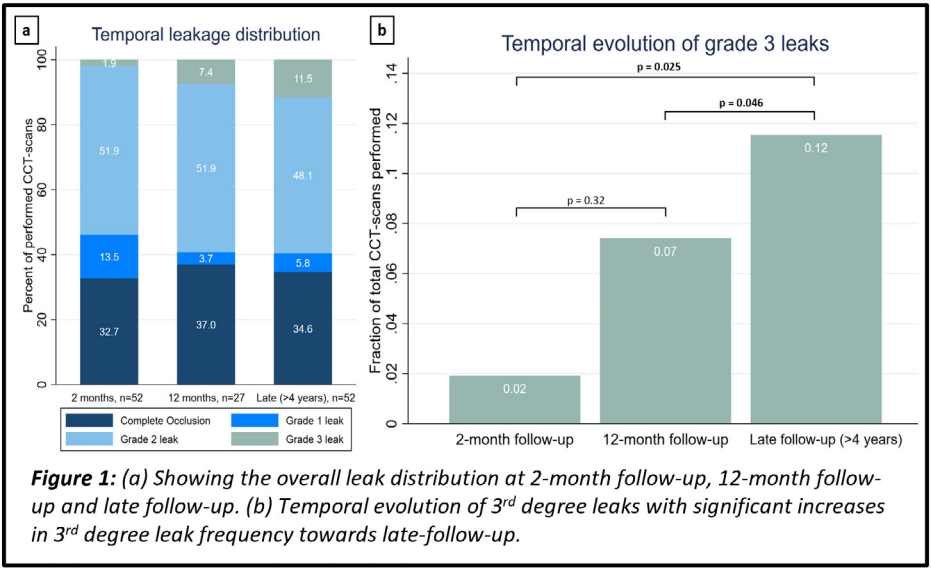

Figure 1: *(a) Showing the overall leak distribution at 2-month follow-up, 12-month follow-up and late follow-up. (b) Temporal evolution of 3rd degree leaks with significant increases in 3rd degree leak frequency towards late-follow-up.*

P1-4

The effect of intensive lipid lowering with statins and ezetimibe on FFRCT in patients with stable chest pain – FLOWPROMOTE

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Background: Lipid lowering by statins is the cornerstone for preventive care in patients with coronary artery disease (CAD). Studies have shown that statins reduce coronary plaque volume, particularly low-density plaque (LDP) and this regression may be dose dependent. Additionally, studies have shown a correlation between the volume of LDP and ischemia, irrespective of degree of luminal stenosis.

Aims: This study aims to investigate if intensive lipid lowering treatment improves coronary flow through plaque regression, and whether this effect depends on the degree of LDL-lowering.

Methods: FLOW-PROMOTE is a prospective randomized "proof-of-concept" study consisting of patients referred for coronary CT angiography and FFRCT. In the presence of ≥1 lesion with ≥50% stenosis and FFRCT ≤0.8 patients were randomized to usual care with atorvastatin or intensive regimen with rosuvastatin and ezetimibe. Patients are followed for 18 months, with repeated biochemical analysis, CTA scans and FFRCT at 9 and 18 months.

Results: A total of 109 patient are included. All follow-up scans were completed in 54 patients (49.5%) and 9-month follow-up scans have been performed in 94 patients (86.2%). The first results will be presented when all 9 months follow-up data is available.

Conclusion
This study will potentially contribute to a better understanding of coronary pathophysiology, especially whether coronary flow can be modulated through changes in plaque morphology. In addition, it emphasizes the importance of lipid lowering treatment in patients with CAD.

P1-5

Hydroxycarboxylic acid receptor 2 stimulation with ketone body 3-hydroxybutyrate and niacin in patients with heart failure

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Background
The ketone body 3-hydroxybutyrate (3-OHB) increases cardiac output (CO) in patients with heart failure (HFrEF) through unknown mechanisms. 3-OHB activates the hydroxycarboxylic acid receptor 2 (HCA_2), which increases prostaglandins and suppresses circulating free fatty acids (FFAs). We investigated if the cardiovascular effects of 3-OHB involved HCA_2 activation and if the potent HCA_2-stimulator niacin may increase CO.

Methods
Twelve patients with HFrEF were included in a randomized crossover study and examined by right heart catheterization, echocardiography, and blood sampling on two separate days. On study day one, patients received aspirin to block the HCA2 downstream cyclooxygenase enzyme, followed by 3-OHB and placebo infusions. We compared the results with a previous study in which patients received no aspirin. On study day two, patients received niacin and placebo. The primary endpoint was CO.

Results
3-OHB increased CO (2.3 L/min, $p<0.01$) and stroke volume (19 mL, $p<0.01$) with preceding aspirin. 3-OHB did not change prostaglandin levels, neither in the ketone/placebo group receiving aspirin or the previous study cohort. Aspirin did not block 3-OHB-induced changes in CO. 3-OHB decreased FFAs by

58% (p=0.01). Niacin increased prostaglandin D2 levels by 330% (p<0.02) and reduced FFAs by 75% (p<0.01) but did not affect CO.

Conclusions

The acute increase in CO during 3-OHB infusion was not modified by aspirin and niacin had no hemodynamic effects. These findings show that HCA2 receptor-mediated effects were not involved in the hemodynamic response to 3-OHB.

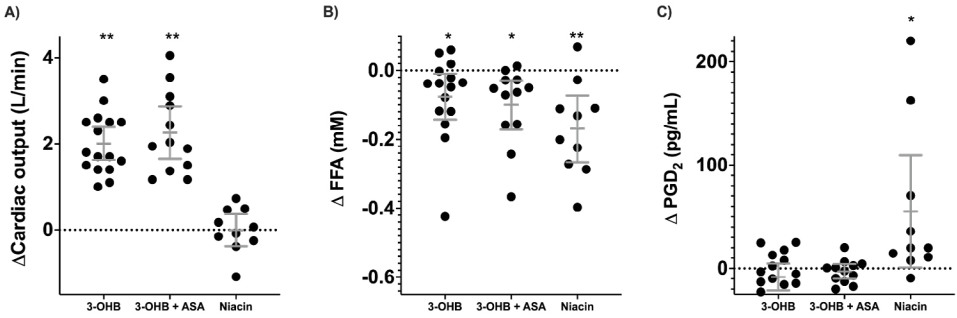

Figure : *Changes in Cardiac output, Free Fatty Acids and Prostaglandin D_2*

Figure: ΔCardiac output (A), ΔFFA (free fatty acids) (B) and ΔPGD_2 (prostaglandin D_2) (C) changes recorded during the intervention period as compared with the placebo period. 3-OHB: 3-hydroxybutyrate, ASA: aspirin. *p<0.05 ** p<0.01

3-OHB: HCA_2 receptors are activated; 3-OHB+ASA: HCA_2 receptors are activated, whereas the downstream COX enzyme is inhibited with aspirin (ASA); Niacin: HCA_2 receptors are activated by an even stronger HCA_2 agonist than 3-OHB.

P1-6

Blood pressure lowering properties of glycosylized ANP

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Background: Reducing blood pressure (BP) to an acceptable, cardio-protective level by means of marketed antihypertensive drugs, represents a challenge in some individuals with arterial hypertension. Therefore, an obvious incentive exists for exploring novel molecular mechanisms and alternative targets with the purpose of expanding the space for future drug development. Recently a proteoform of Atrial Natriuretic Peptide (ANP) with a trisaccharide-glycan attached was discovered (gANP), where presence of the glycan instigated a limitation of proteolytic activity and activation of natriuretic peptide receptor A (NPR-A).

Aim: The aim of this study was to characterize the properties of gANP in terms of natriuretic effect as well as BP lowering capability.

Methods: This study was conducted as a double-blinded crossover RCT and included ten healthy subjects for three separate trial days, consisting of a two-hour infusion of either gANP, ANP or isotonic saline followed by two hours observation. BP was measured every 10 minutes and blood was sampled every 20 minutes. Urine was collected after completion of infusion and again after observation. Immunohistochemical quantification of cGMP, the second messenger following stimulation of the NPR-A, as well as biomarkers related to metabolism and vascular tonus, was performed in all blood- and urine samples.

Results: Physiological measurements insinuate a reduction in BP during as well as shortly after infusion of both ANP and gANP. Analysis of biomarkers is still in progress.

Conclusion: Preliminary results suggest the hypothesis of BP lowering characteristics in gANP to be true.

P1-7

Sex differences after targeting MAP and oxygenation in comatose patients after out-of-hospital cardiac arrest

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Background
Previous studies have found lower survival rate for women with out-of-hospital cardiac arrest (OHCA). Evidence concerning sex differences in outcome after different oxygenation and mean arterial blood-pressures (MAP) in OHCA patients is limited.

Aim
To investigate whether female sex in comatose OHCA patients was associated with higher one-year mortality after similar treatment with oxygenation and MAP – and the effect of the treatment in both sex.

Methods
Comatose OHCA patients (age ≥18 years) were included in a dual-center, double-blind, randomized trial. Patients were allocated into a MAP target of 63mmHg or 77mmHg and arterial oxygen concentration of 9–10kPa or 13–14kPa. The primary outcome was all causes of death within a year.

Results
Of the 789 included patients, 152 (19%) were women. Mean age of women and men were similar, 61±14 years and 63±13 years, respectively. Comorbidities and characteristics of the cardiac arrest were comparable between sexes except for ischemic heart disease (12% women, 24% men) and pulseless electrical activity (8% women, 4% men). Women had a higher, but non-significant one-year mortality (42% vs. 35%), Figure 1. In univariate Cox regression model, the difference in all-cause mortality was non-significant (HR:1.25, CI:0.95-1.63), but showed significance after adjustment for age (HR:1.31, CI:1.004-1.72).

Conclusion

Men and women in comatose after OHCA had similar one-year mortality when treated in the same manner with oxygenation and MAP and had similar effect of the treatment.

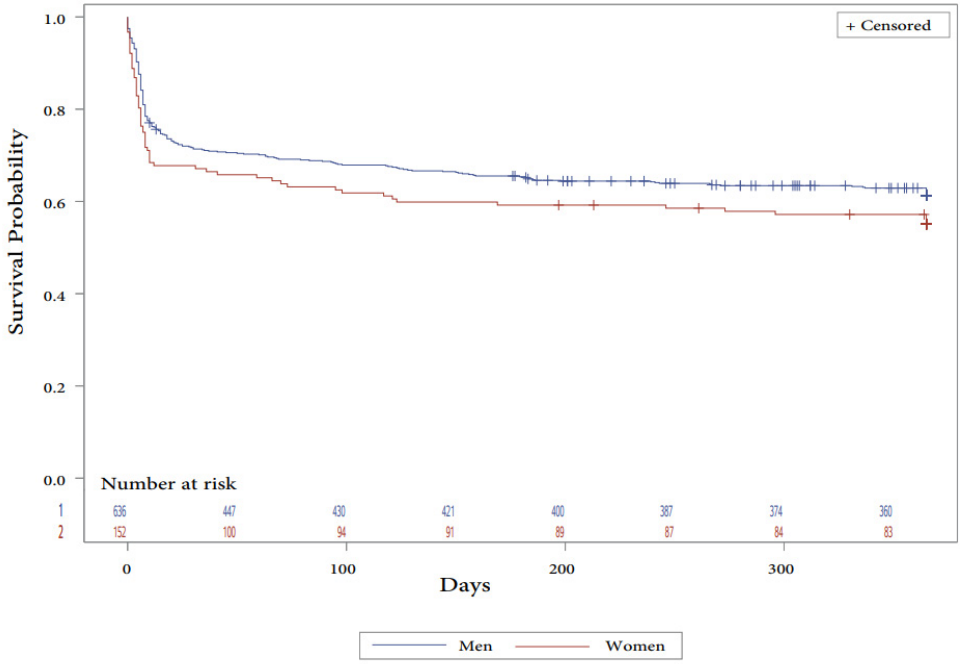

Figure 1. *Survival curve stratified by sex.*

P1-8

The effects of vitamin K2 and D3 supplementation in patients with severe coronary calcifications: protocol for a RCT

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Background
Progression of coronary artery calcification (CAC) is a strong predictor of acute myocardial infarction and cardiovascular mortality. Supplementation with vitamin K2 and D3 has been suggested to have a protective role in CAC progression. In this study, we will examine the effect of vitamin K2 and D in men and women with severe CAC.

Aim
We hypothesize that supplementation with vitamin K2 and D3 will slow down the calcification process.

Methods
In this multicenter double-blinded placebo-controlled study, 400 men and women with CAC score≥ 400 are randomized to treatment with vitamin K2 (720 µg/day) and vitamin D (25 µg/day) or placebo treatment for two years. Among exclusion criteria are treatment with vitamin K antagonist, coagulation disorders and prior coronary artery disease. To evaluate progression in coronary plaque, a cardiac CT-scan is performed at baseline and repeated after 12 and 24 months of follow-up.

Results
Primary outcome is CAC score progression from baseline to follow-up at two years. Among secondary outcomes are coronary plaque composition and cardiac events.

Conclusion
The protocol is approved by the Regional Scientific Ethical Committee for Southern Denmark and the Data Protection Agency. It will be conducted in accordance with the Declaration of Helsinki. Positive as well as negative findings will be reported. If positive effects are shown, a new treatment option may be available to prevent not only progression of CAC, but also ischemic heart disease.

P1-9

Ticagrelor or prasugrel versus clopidogrel in patients with AF undergoing PCI for myocardial infarction

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Background: The efficacy and safety of ticagrelor or prasugrel versus clopidogrel in patients with atrial fibrillation (AF) on oral anticoagulation (OAC) undergoing percutaneous coronary intervention (PCI) for myocardial infarction are unclear.

Methods: Nationwide cohort study of patients on an OAC for AF who underwent PCI for myocardial infarction from 2011 through 2019 and were prescribed a $P2Y_{12}$ inhibitor at discharge. The efficacy outcome was major adverse cardiovascular events (MACE), a composite of death from any cause, stroke, recurrent myocardial infarction, or repeat revascularization. The safety outcome was bleeding requiring hospitalization. Absolute and relative risks for outcomes at 1 year were calculated through multivariable logistic regression with average treatment effect modeling. Outcomes were standardized for the components of CHA_2DS_2-VASc and HAS-BLED scores as well as type of OAC, aspirin, and proton pump inhibitor use.

Results: We included 2259 patients of whom 1918 (84.9%) were prescribed clopidogrel and 341 (15.1%) ticagrelor or prasugrel. The risk of MACE was significantly lower in the ticagrelor or prasugrel group compared with clopidogrel group (standardized absolute risk, 15.8% vs. 19.6%; relative risk, 0.82, 95% CI, 0.68 to 0.93; P=0.009), while the risk of bleeding did not differ (standardized absolute risk, 5.2% vs. 5.2%; relative risk, 1.00, 95% CI, 0.69 to 1.32; P=1.00).

Conclusion: In patients with AF on OAC who underwent PCI, ticagrelor or prasugrel versus clopidogrel was associated with reduced ischemic risk, without a concomitantly increased bleeding risk.

P1-10

Municipal prevention and rehabilitation for people with atrial fibrillation. Results from a pilot study

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Background: Atrial fibrillation (AF) influences life with symptoms like palpitations, dyspnoea, fatigue, fear and anxiety. Guidelines suggest people with AF benefit from prevention and rehabilitation (PR); however, evidence is scars and hospital-based. It is unknown whether this is transferable to municipal setting. In 2019, a Danish municipality and the cardiac department at the local hospital completed a multidimensional PR intervention for people with AF.

Aim: To investigate quality of life (QoL), anxiety and depression before and after participation in multidimensional municipality-based PR.

Methods: This study is a prospective cohort study. Inclusion was at the hospitals' AF-clinic referring to municipal PR. PR consisted of risk factor management, patient education, physical activity and MediYoga. Outcomes were QoL measured by HeartQoL, and anxiety and depression measured by the Hospital Anxiety and Depression Scale (HADS). Data was collected before PR, at end of PR, and at two-months follow-up. Data is analysed descriptively, and Minimal Important Difference (MID) is used to evaluate clinical important differences.

Results: 43 people with AF completed the PR intervention. 23 (53.5%) were female and mean age was 66.5 years (SD: 7.6, range: 52-81 years). Table 1 shows QoL increased by 0.3, anxiety and depression decreased by 2.4 and 2.0, and these results lasted after two months.

Conclusion: QoL increased and symptoms of anxiety and depression decreased clinically significant among people with AF participating in municipality-based multidimensional PR. Future large randomized controlled trial must confirm these results.

Table 1. *Quality of life, anxiety and depression in people with AF participating in municipality-based prevention and rehabilitation*

	Before intervention n = 43	After intervention n = 43	Two-months follow-up n = 34
Quality of life, HeartQoL*	*Mean (sd) [range]*	*Mean (sd) [range]*	*Mean (sd) [range]*
Global scale	1.9 (0.7) [0,4;2,9]	2.2 (0.7) [0.6;3]	2.2 (0.7) [0.6;3]
Physical scale	1.8 (0.8) [0;3]	2.1 (0.8) [0.3;3]	2.2 (0.8) [0.2;3]
Emotional scale	2.1 (0.8) [0;3]	2.5 (0.6) [0.8;3]	2.4 (0.7) [0.8;3]
Hospital Anxiety and Depression Scale, HADS#	*Mean (sd) [range]*	*Mean (sd) [range]*	*Mean (sd) [range]*
Anxiety, HADS-A	6.8 (4.0) [0;15]	4.4 (3.9) [0;14]	4.7 (3.9) [0;16]
Depression, HADS-D	4.9 (3.7) [0;13]	2.9 (3.2) [0;13]	3.1 (3.4) [0;12]

*MID HeartQoL: 0.3
#MID HADS: 1.5

P2-1

Prognostic value of myocardial work indices in aortic stenosis

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Background. Evaluation of left ventricle (LV) systolic function in patients with aortic stenosis (AS) undergoing transcatheter aortic valve replacement (TAVR) is challenging, as LV ejection fraction (LVEF) and global longitudinal strain (LVGLS) does not take afterload into account. Myocardial global work indices (GWI) estimate the work of the LV assessing contractility with strain analysis and afterload with blood pressure and aortic valve mean gradient.

Aim. To evaluate the serial changes of GWI in subgroups of AS patients from before TAVR to 12-months after TAVR, and to assess the prognostic value of LV GWI.

Methods. We included 486 patients undergoing TAVR. GWI was estimated using speckle tracking strain imaging and by adding the aortic valve mean gradient to the systolic blood pressure, as a non-invasive estimate of LV pressure. The primary event was all-cause mortality.

Results. Patients with preserved LVEF (>50%) decreased in GWI from preoperative assessment to 12-months follow-up across all subgroups as seen in figure 1. For patients with reduced LVEF (<50%) GWI increased in all subgroups of AS. In multivariate analysis (table 1) each 100 mmHg% increase in GWI was associated with improved prognosis (hazard ratio 0.95 [95%CI: 0.91-0.99], p=0.014).

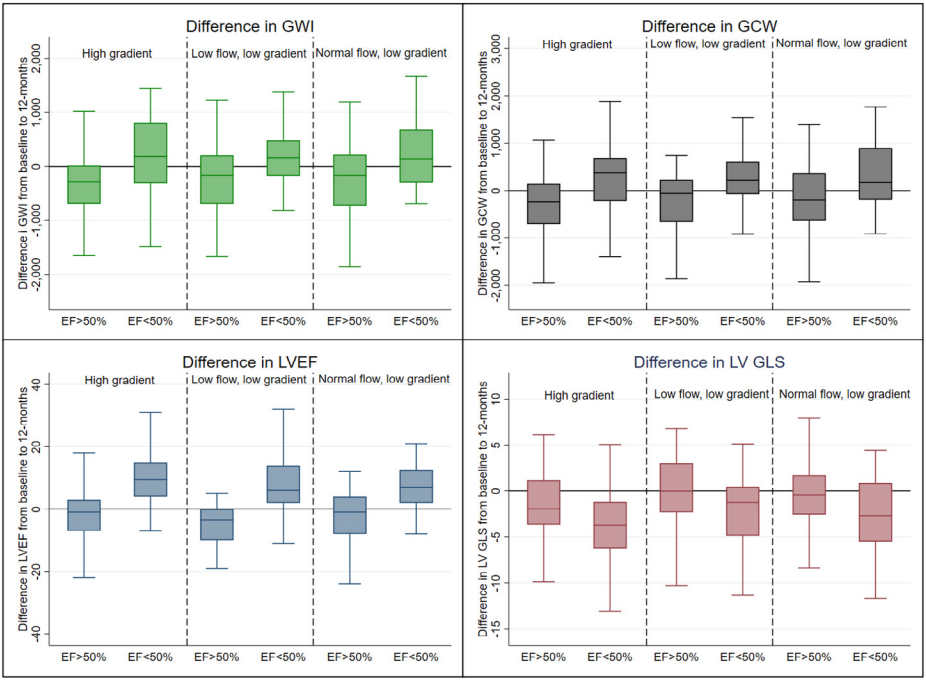
Conclusions. LV GWI increases in patients with preoperative reduced LVEF across subgroups of AS patients due to increased contractility whereas LV GWI decreases in patients with preserved LVEF due to stationary contractility and decreased afterload after TAVR. Preoperative assessment of GWI offers additional prognostic implications beyond LVEF and LVGLS.

Table 1 *Uni- and multivariate analysis*

	Univariate		Multivariate	
Variable	HR [95% CI]	P-value	HR [95% CI]	P-value
Age, years	1.04 [1.01-1.06]	0.015	1.04 [1.00-1.07]	0.021
Sex, female	0.93 [0.66-1.31]	0.668	0.91 [0.64-1.28]	0.597
Hypertension	1.01 [0.68-1.50]	0.950	1.08 [0.71-1.63]	0.728
Diabetes	0.78 [0.50-1.22]	0.280	0.77 [0.48-1.23]	0.244
IHD	1.54 [1.08-2.18]	0.016	1.50 [1.05-2.15]	0.031
BMI	0.98 [0.94-1.02]	0.286	0.99 [0.95-1.04]	0.700
LV EF < 50%	1.57 [1.12-2.22]	0.010	1.25 [0.79-1.98]	0.330
LV GLS < 14 %	1.17 [0.82-1.65]	0.392	0.97 [0.94-1.00]	0.060
GWI/100	0.96 [0.94-0.99]	0.003	0.95 [0.91-0.99]	0.014

BMI, body mass index; GWI, global work index; IHD, ischemic heart disease; LV EF, left ventricular ejection fraction; LV GLS, left ventricular global longitudinal strain.

Figure 1 *Boxplots of differences from baseline to 12-months after TAVR*



GCW, global constructive work; GWI, global work index; LVEF, left ventricular ejection fraction, LV GLS, left ventricular global longitudinal strain.

P2-2

Cardiovascular risks of non-steroidal anti-inflammatory drugs in patients with coronary artery disease

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Background: Non-steroidal anti-inflammatory drugs (NSAID) use increases the risk of major adverse cardiovascular events (acute myocardial infarction, ischemic stroke, congestive heart failure, atrial fibrillation or flutter, or cardiovascular death). Since 2002, the use of NSAIDs has declined in patients with cardiovascular disease, but use remains common at 10–15% within one year after the cardiovascular event. There are few studies on the cardiovascular risks of NSAID use in patients with imaging and angiography-confirmed coronary artery disease. Also, no studies have examined the cardiovascular risks of NSAID use in patients undergoing coronary artery bypass graft in Denmark, despite the high demand for pain relief after surgery in these patients.

Aim: The aim of this PhD project is to examine NSAID-associated cardiovascular risks according to both severity (graded by cardiac computerized tomography, myocardial scintigraphy, and coronary angiography), type of treatment (percutaneous coronary intervention or coronary artery bypass graft), and comorbidity.

Methods: The PhD project is designed as a series of population-based cohort studies using Danish health registries (2008-2022). We will follow the patients until the first major adverse cardiovascular event, emigration, death, or October 2022. We will use Cox proportional-hazards regression to compute hazard ratios with 95% confidence intervals for the study outcomes stratified by the degree of coronary obstruction and the Agatston calcium score (continuous and categorical). Dose-response and sensitivity analyses to further address confounding and misclassification will be included.

P2-3

ASGARD risk score for safe monitoring of asymptomatic aortic stenosis: development and validation

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BACKGROUND: Standard monitoring for non-severe aortic valve stenosis (AS) involves routine-echocardiography at 1-2 year intervals. Since these costly routine-echocardiograms often lack clinical consequences during extended watchful-waiting, we propose their substitution with a risk stratification approach.

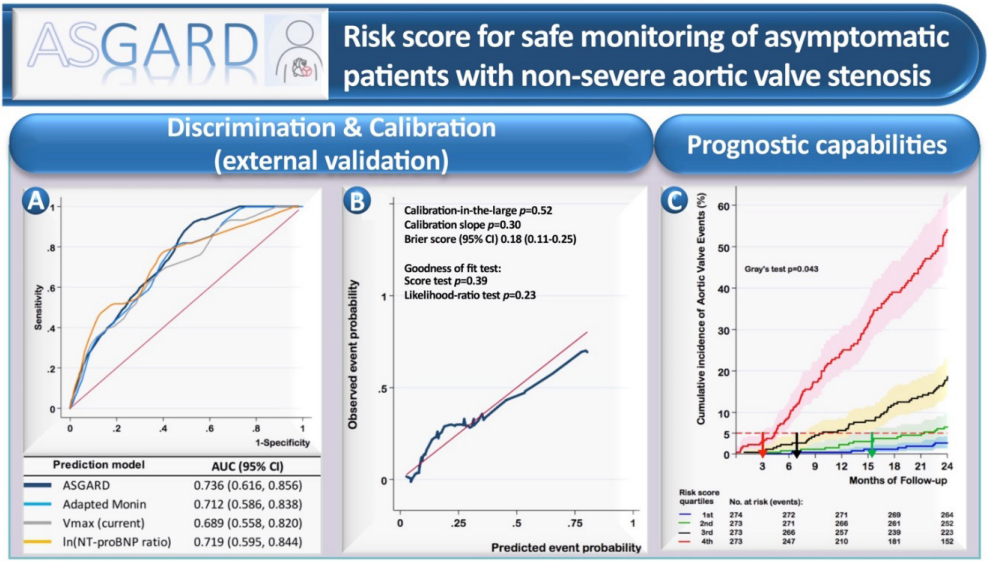
Aim: To develop and validate a clinical risk score to identify low-risk AS-patients who can postpone routine-echocardiography for a safe estimated interval.

Methods: The development cohort comprised of 1093/1579 (69%) asymptomatic patients with mild-to-moderate AS who remained event-free one year after inclusion in the randomized, multicenter SEAS trial. Cox regression landmark analyses, starting at year-1with a 2-year follow-up, estimated the best prognostic model for AS-related composite outcome (heart failure hospitalization, aortic valve replacement, and cardiovascular death) with non-cardiovascular death as a competing risk. Final model included heart rate, age- and sex-adjusted N-terminal pro-brain natriuretic peptide, and transaortic maximal velocity (Vmax) measured at baseline. We internally validated the model in 486 patients (31% hold-out from SEAS-population) and externally in

71 asymptomatic out-clinic patients with Vmax ≤4 m/s from six Copenhagen hospitals.

Results: The model performed consistently across the validation cohorts (external validation: area under the curve: 0.74 [95% CI, 0.62-0.86]; calibration-in-the-large, p=0.52; calibration slope, p=0.30; Brier score, 0.18) comparable with a new Vmax measurement (Figure 1A-1B). The ASGARD score <50% was associated with annual AS-related event-rates ≤5% for minimum 15 months (Figure 1C).

Conclusion: The ASGARD risk score show promise for individualized surveillance of low-risk patients with non-severe AS without requiring new echocardiography.



Abbreviations: AUC, area under the curve; NT-proBNP, N-terminal pro-brain natriuretic peptide; Vmax, transaortic maximal velocity.

Figure 1. *Panel A*: The ASGARD prediction model compared to a new Vmax and the Monin risk score for aortic valve stenosis (AS) related primary composite outcome (heart failure hospitalization, aortic valve replacement, and cardiovascular death) during a 2-year follow-up. The graphs show AUC (95% CI) for prediction models tested in the external validation cohort. *Panel B*: The calibration plot of the ASGARD prediction model plotted for external validation shows acceptable overall agreement between predicted and observed event probability. *Panel C*: Nelson-Aalen cumulative incidence curves plotted for derivation cohort, where the red dashed line demarcates the 95th percentile for risk of AS-related outcomes due to the AS-progression to ASGARD risk score quartiles. The downward pointing arrows demarcate the optimal follow-up interval for quartiles with a risk of ≤5%.

P2-4

Cardiovascular risk factors associations with long-term weekly heart rate variability in prediabetes

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Introduction
Autonomic dysfunction is seen throughout the diabetic continuum including prediabetes. Lifestyle and cardiometabolic risk factors are associated with autonomic function, demonstrated in changes in short-term heart rate variability (HRV). Studies of week-long HRV indices including free-living daily activity are scarce. We aimed to investigate the cross-sectional associations between cardiovascular risk factors and week-long HRV.

Methods
Data were obtained from 1,230 participants with a high risk of diabetes in the Danish ADDITION-PRO study 2009-2011. Cardiometabolic markers were assessed by anthropometric measures, blood samples and blood pressure measurements. Lifestyle factors of smoking and alcohol consumption were self-reported and physical activity was measured by a combined heart rate monitor/accelerometer. HRV index standard deviation of normal-to-normal heartbeat intervals (SDNN) was estimated from 48 hours and up to seven days of continuous HR monitor, based on mean inter-beat intervals for 30-second epochs. We used linear regression to quantify the univariate association between each exposure and SDNN as crude estimates and after adjustment for age and sex.

Results
Mean (SD) age was 66 years (7), and 52 % were men. The population had a mean (SD) SDNN of 11.6 ms (4.1). Age, sex (being women), smoking, HbA1c, triglycerides, body mass index, waist circumference, fat percentage, and diastolic blood pressure were associated with lower SDNN (Table 1). Associations did not change materially upon adjustment for age and sex.

Conclusion

Higher age, smoking, overweight and higher markers of glucose, and triglycerides were linked with autonomic dysfunction based on novel long-term measurement of HRV.

Table 1: *Cardiovascular risk factors associations with SDNN*

	Univariate		Adjusted*	
CVD Risk factor	**Beta**	**95% CI**	**Beta**	**95% CI**
Age (year)	-0.03	(-0.07, 0.00)		
Sex (male vs female)	1.19	(0.74, 1.66)		
Alcohol consumption (units per week)	0.00	(-0.02, 0.03)	-0.02	(-0.04, 0.01)
PAEE (KJ / kg / day)	0.00	(-0.01, 0.01)	0.00	(-0.01, 0.01)
Smoking (smoker vs non-smoker)	-0.68	(-1.31, -0.04)	-0.83	(-1.46, -0.20)
BMI (kg/m^2)	-0.09	(-0.14, -0.04)	-0.10	(-0.15, -0.05)
Waist circumference (cm)	-0.02	(-0.04, -0.01)	-0.05	(-0.07, -0.03)
Fat percentage (%)	-0.10	(-0.12, -0.07)	-0.09	(-0.12, -0.05)
HbA1c (%)	-1.12	(-1.56, -0.67)	-1.12	(-1.56, -0.68)
Triglycerides (mmol/L)	-0.73	(-1.10, -0.36)	-0.82	(-1.18, -0.45)
HDL cholesterol (mmol/L)	-0.29	(-0.81, 0.24)	0.26	(-0.30, 0.81)
LDL cholesterol (mmol/L)	0.07	(-0.16, 0.31)	0.08	(-0.15, 0.32)
Total cholesterol (mmol/L)	-0.10	(-0.32, 0.11)	-0.02	(-0.23, 0.20)
Systolic blood pressure (mm hg)	0.00	(-0.02, 0.01)	-0.01	(-0.02, 0.01)
Diastolic blood pressure (mm hg)	-0.03	(-0.05, -0.01)	-0.04	(-0.06, -0.02)

CI = Confidence Interval

Beta = SDNN per unit change in exposure

*Adjusted for age and sex

P2-5

The Effect Of Adiposity On Vascular Markers Of A Diverse Group Of Pre-Menopausal Women

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Background: Adiposity (BF) and visceral adipose tissue (VAT) contribute to proinflammation which can increase chronic disease risk. Racial groups have demonstrated differences in adiposity and vascular markers of cardiac risk.

Aim: To understand the relationship between vascular markers of cardiac risk, BF, and VAT among pre-menopausal women of different races.

Methods: 61 participants from South Florida were recruited (White, N = 29, Black = 8, Hispanic = 24). Height (cm), weight (kg), BF%, and VAT (liters) were recorded. Adiposity was measured via the SECA MBCA 515 unit. Carotid-femoral artery pulse wave velocity (PWV), augmentation index (cAIX) and mean arterial pressure (MAP) were measured via the Sphygmocor XCeL unit. Pearson correlations and ANOVA tests were conducted with SPSS version 27.

Results: For the entire sample, positive associations were found between PWV and BF ($p<.001$), PWV and VAT ($p = .034$), cAIX and BF ($p<.001$), cAIX and VAT ($p<.001$), and MAP and BF ($p = .002$). When analyzed by race, White women had lower BF than Black Women ($p = .048$), lower VAT than Hispanic women ($p < .001$), and lower BF than Hispanic women (.007). Black women also had lower VAT than Hispanic women ($p = .004$). Hispanic women additionally had higher cAIX than non-Hispanic white women ($p = .008$).

Conclusion: Positive correlations exist between adiposity and vascular markers of cardiac risk in this sample. Furthermore, there were differences when analyzing by race. It would be beneficial to include a larger and more racially diverse sample.

P2-6

Adiposity Indices and Cardiometabolic Risk Factors in Children and Adolescents

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Background
Cardiometabolic disease risk is a heterogenous trait among children/adolescents with excess adiposity. More accurate and regional adiposity measures may improve evaluation of such risk.

Aim
To investigate associations between anthropometric and dual-energy X-ray absorptiometry (DXA)-based indices of adiposity and cardiometabolic risk factors in children/adolescents.

Methods
We included 1,029 boys and girls, age 6-17 years, from The HOLBAEK Study, who underwent anthropometric and blood pressure measurements, fasting blood sampling, a DXA-scan, and a magnetic resonance spectroscopy scan for liver fat content (N=336). We measured markers of glucose, liver, and lipid metabolism, inflammation, proglucagon-derived hormones, and adipokines, then calculated standard deviation scores (SDS) for BMI, waist circumference, body fat % (BF%), and blood pressure. We applied Spearman correlation on adiposity indices and linear regression of adiposity indices on cardiometabolic risk factors adjusted for age and sex (significance level $p<0.001$).

Results
The correlation between BMI SDS and other adiposity measures are moderate to poor (r=0.30-0.77, figure 1). BMI SDS and BF% SDS associate with several cardiometabolic risk factors (figure 2). Strong associations are seen

between all adiposity indices, especially truncal and android fat, hs-CRP, and leptin ($p<0.001$). Interestingly, the android/gynoid- and trunk/leg-ratio have stronger associations to ALT, AST, GGT, glucagon, insulin, triglycerides, liver fat%, and total GLP-1, and inverse associations to adiponectin, AST/ALT-ratio, and HDL-C than other indices ($p < 0.001$).

Conclusion

Adiposity indices intercorrelate in varying degrees and associate to several cardiometabolic risk factors in children and adolescents. Integration of regional adiposity may improve cardiometabolic disease risk evaluation.

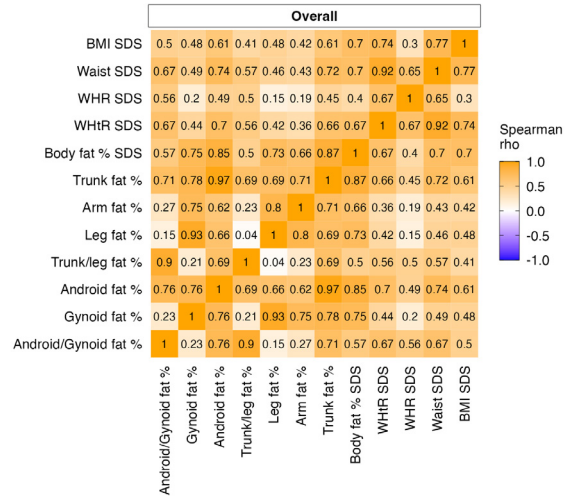

Figure 1. *Correlation between anthropometric and DXA-derived indices of total, central, and peripheral adiposity.*

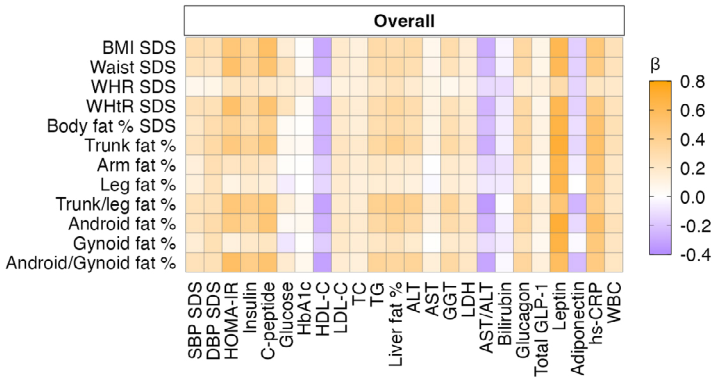

Figure 2. *Association between adiposity indices and cardiometabolic risk factors.*

P2-7

Near-Infrared Spectroscopy Guided Percutaneous Coronary Intervention in Patients with Myocardial Infarction

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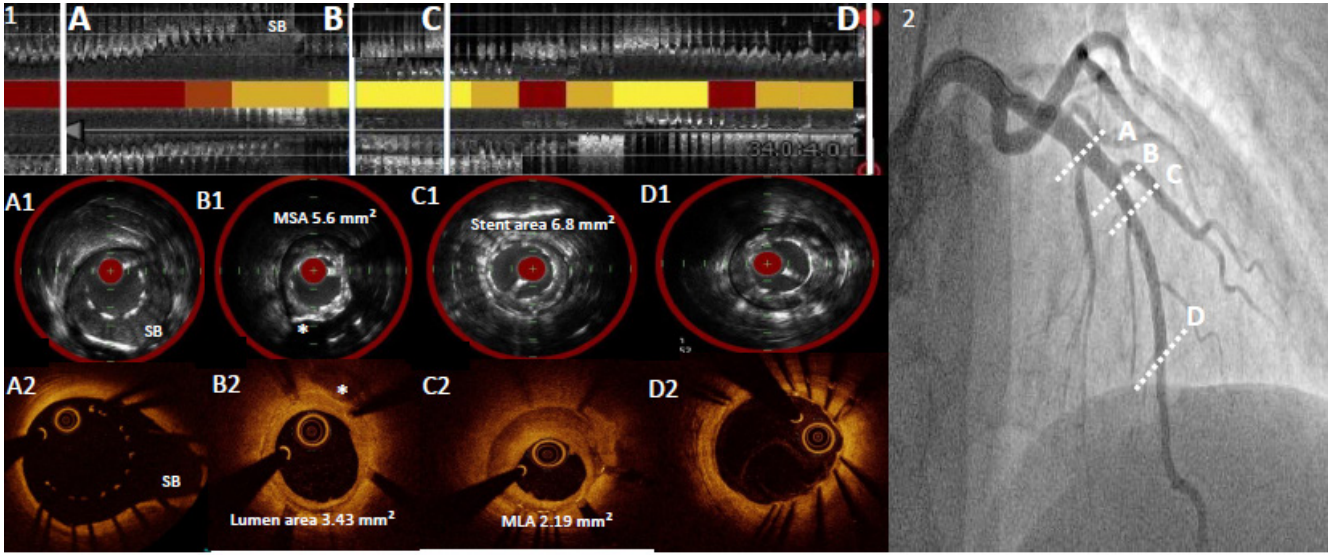
Background: Lesions in patients with acute coronary syndromes are more frequently composed of lipid-rich plaques (LRP) compared to lesions in patients with stable angina. Near-infrared spectroscopy (NIRS) can identify LRP. The impact of LRP on stent struts coverage is unclear.

Aim: We investigated whether NIRS-guided percutaneous coronary intervention in patients with acute myocardial infarction (MI) provides improved stent strut coverage at 6 months compared to standard angiography-guided alone, and further to assess if LRP influenced struts coverage.

Methods: The randomized controlled trial was conducted at a University Hospital including 104 patients with acute MI and de novo lesion, where percutaneous coronary intervention (PCI) with implantation of drug-eluting stent was indicated. Patients were randomly assigned to either NIRS-guided PCI or angio-guided PCI. Intravascular ultrasound (IVUS) and NIRS was performed in both groups before stent implantation. In the NIRS-guided group, the LRP was identified and lesion length measured in order to find the optimal stent length and diameter. In the angio-guided group, the PCI operator was blinded to the IVUS/NIRS data. A final pullback with Optical Coherence Tomography (OCT) was performed at baseline and at 6 months in both groups to assess stent strut coverage.

Results: Primary endpoint was percentage of covered stent struts at 6-month follow up estimated by OCT. Secondary endpoints: uncovered stent struts, acute/late acquired stent malapposition and maximal neointimal growth.

Conclusion: Will provide information how NIRS-guided PCI of LRP have an impact on sent strut coverage.



Near-infrared spectroscopy, intravascular ultrasound (1) at baseline (A1-D1) and optical coherence tomography at 6-month follow up (A2-D2) of Left anterior descending artery with stent implantation of DES 3.5 x 38 mm in a patient with non-ST segment myocardial infarction from angiography-guided group. Longitudinal view with chemogram shows yellow blocks indicating a lipidrich lesion. (1) Proximal stent edge next to a side branch with acute stent malapposition at baseline (A1) and at 6-month follow up (A2). Stent underexpansion in a calcified area (*) with minimum stent area (MSA) 5.6 mm² (B1), and additional lumen reduction at follow up (B2). Stent embedded in a lipidrich area (C1) shows neointimal hyperplasia with minimum lumen area (MLA) 2.19 at follow up (C2). Distal stent edge in a relatively healthy segment shows stent coverage without lumen loss (D1 and D2).

P2-8

Hyperpolarized MRSI in Ischemic Heart Disease: Metabolic Profiling of the Myocardium

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Background

Assessing myocardial viability plays a critical role in guiding therapeutic decisions for patients with ischemic heart disease and determining their prognosis. Currently, conventional imaging techniques, such as [^{18}F]fluoro-deoxyglucose (FDG) / [^{15}O]H_2O positron emission tomography (PET), are commonly employed for evaluating myocardial viability. However, studies indicate that these conventional viability PET scans demonstrate limited prognostic value. In recent years, hyperpolarized magnetic resonance spectroscopic imaging (MRSI) has emerged as a promising non-invasive technique for assessing tissue viability and metabolic processes in real-time. With less than 50 patients with heart disease studied worldwide, this novel technique awaits further investigation.

Methods

This study aims to investigate myocardial metabolism using hyperpolarized MRSI, with the objective of visualizing metabolic changes in the myocardium associated with ischemic heart disease. A cohort of n=15 patients with varying degrees of ischemic heart disease will be recruited for this study. Endpoints will be presented as quantitative numerical data, given as metabolite ratios. These ratios will enable the identification and characterization of variation within the myocardium of individual patients. Further, hyperpolarized [1-^{13}C]-pyruvate cardiac MRI will be compared to cardiac MRI, late gadolinium MRI (LGE-MRI), and [^{18}F]fluoro-deoxyglucose (FDG) / [^{15}O]H_2O positron emission tomography (PET).

Perspectives

Findings of this study have the potential to enhance our understanding of myocardial metabolism in patients with ischemic heart disease. Ultimately, this area of research carries the potential to offer clinicians a valuable means for guiding treatment decisions.

P2-9

The role of VEGF family in STEMI patients after PCI

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Background: The vascular endothelial growth factor (VEGF) family can regulate inflammation, angiogenesis, lymphangiogenesis, oxidative stress and lipid metabolism, presenting its potential therapeutic and prognostic value for people with ST-segment elevated myocardial infarction (STEMI). However, there is no clinical study about its potential role in these patients. Cardiac magnetic resonance (CMR) as a practical clinical examination to assess the recovery of myocardium after STEMI is also seldom applied as outcomes in clinical studies.

Aim: We therefore aim to characterize the levels of VEGF family and CMR data in STEMI patients after percutaneous coronary intervention (PCI). We subsequently aim to find out the relationship between the serial changes in VEGF family with the CMR outcome.

Methods: One hundred STEMI patients undergoing PCI will be included in the study. We will test the plasma levels of VEGF family with ELISA and measure CMR data at baseline and three-month follow up. CMR data at three months will be the outcome variables.

(**Results&Conclusion:** My PhD project just starts from this February, so the study is still ongoing.)

P3-1

Non-adherence to long-term aspirin therapy following myocardial infarction and cardiovascular risk

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Background. Aspirin is mandatory immediately after myocardial infarction (MI); however, its long-term efficacy is less well established.

Aim: To investigate the effectiveness of long-term aspirin therapy.

Methods: Using Danish nationwide registries, we included patients ≥40 years with MI from 2004-2017, who were alive, not on anticoagulant therapy, and had stayed adherent to aspirin at one year after index-MI (Figure 1). Adherence to aspirin (proportion of days covered (PDC): ≤80% versus >80%) was evaluated at four landmarks (2,4,6, and 8 years after MI). At each landmark, patients were excluded if they had suffered a recurrent MI, stroke, died, emigrated or were on anticoagulant/$P2Y_{12}$-inhibitor therapy. The standardized absolute and relative risks of a composite of death, recurrent MI, or stroke at 2 years from each landmark were calculated through multivariable logistic regression analysis with average treatment effect modelling. Non-cardiovascular death was used as neutral comparator.

Results: A total of 40,114 individuals were included. The standardized relative risk (RR) was significantly higher for patients with PDC≤80% at all landmarks (Figure 2). A trend towards a diminished protective effect of aspirin appeared from 4 years after index-MI and onwards (landmark 2, RR: 1.40 (95% confidence interval [CI]: 1.26-1.53); landmark 4, RR: 1.20 (95%CI: 1.04-1.35). The RR of non-CV death did not differ between PDC-groups.

Conclusion: Non-adherence to long-term aspirin therapy following MI was associated with an increased risk of recurrent MI, stroke, or death, but the risk appeared to decrease slightly over time.

Figure 1: *Study flow diagram.*

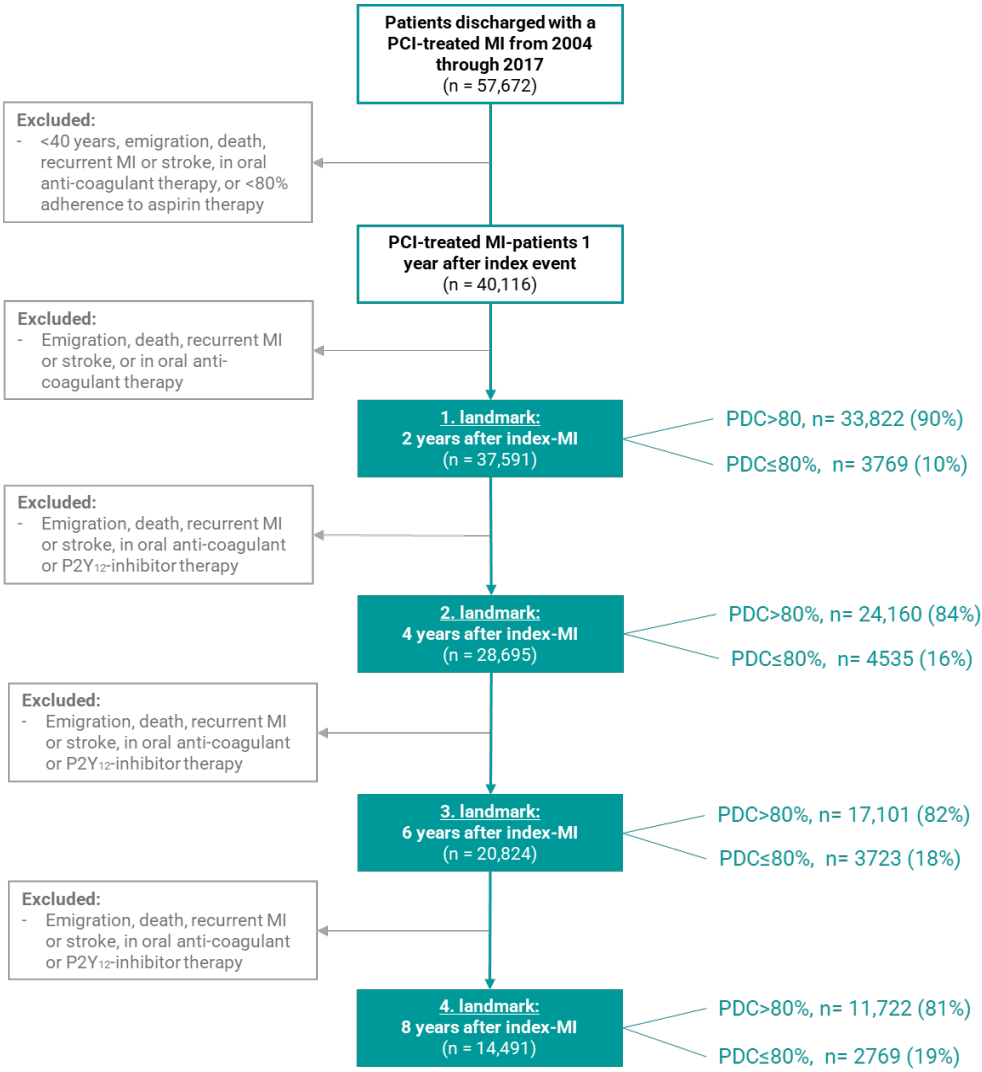
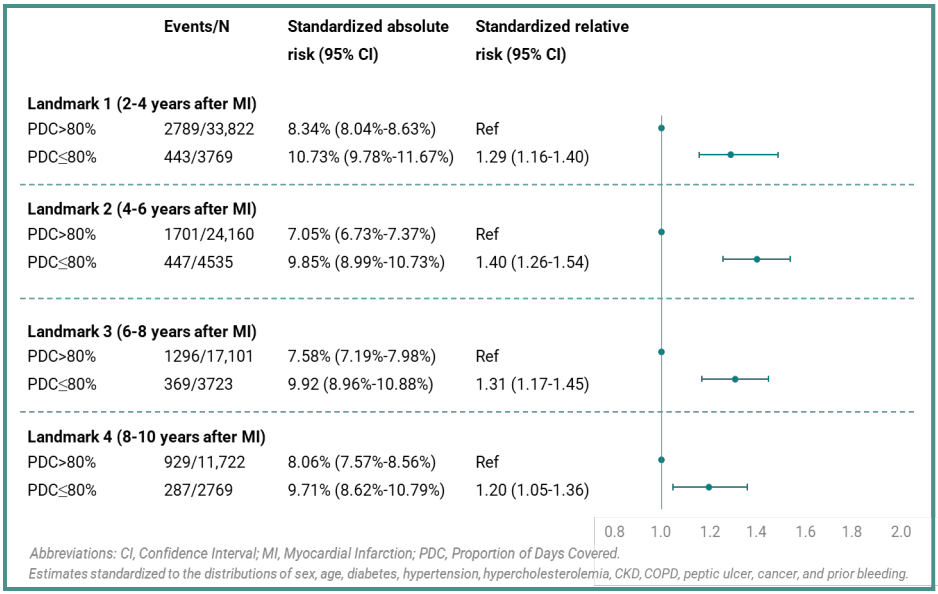


Figure 2: *Standardized absolute and relative risks of recurrent myocardial infarction, stroke, or death at four landmarks after myocardial infarction stratified by adherence status.*



P3-2

Long-term outcomes after CRT de novo implantations and upgrade to CRT – a Danish nationwide cohort study

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Background: Patients with an implanted pacemaker (PM) or implantable cardioverter defibrillator (ICD) who develop heart failure (HF) or frequent right ventricular pacing, may be upgraded to Cardiac Resynchronization Therapy (CRT) device. Such upgrades constitute approximately 25% of CRT implantations.

Purpose: We aimed to investigate long-term outcomes in patients undergoing upgrade to CRT after previous PM or ICD implantation and patients undergoing CRT de novo implantation.

Methods: This was a nationwide register-based cohort study. The patient cohort was identified via the Danish Pacemaker and ICD Registry and comprised consecutive Danish patients undergoing CRT-implantation from 2000-2018. The primary endpoint was total mortality. Secondary endpoints were cardiovascular death and HF-hospitalization.

Results: We identified 8,880 patients: 6,685 (75.3%) with de novo implantation and 2,195 (24.7%) with an upgrade procedure. At baseline, patients who underwent upgrade to CRT were older and had more comorbidities. Upgrade implantations were associated with a higher unadjusted total mortality (HR 1.29, [95% CI 1.20;1.38]) compared to de novo implantations, but there was no difference in the multiple adjusted analysis (HR 1.03, [95% CI 0.96;1.10], p=0.46). Likewise, we found no difference in the secondary endpoints.

Conclusion: When adjusting for differences in comorbidities, we found no difference in total mortality, cardiovascular death, and HF-hospitalization among patients undergoing upgrade to CRT and patients undergoing CRT de novo implantation. This suggests that CRT is equally beneficial in both de novo and upgrade implantations.

Figure 1: *all-cause mortality*

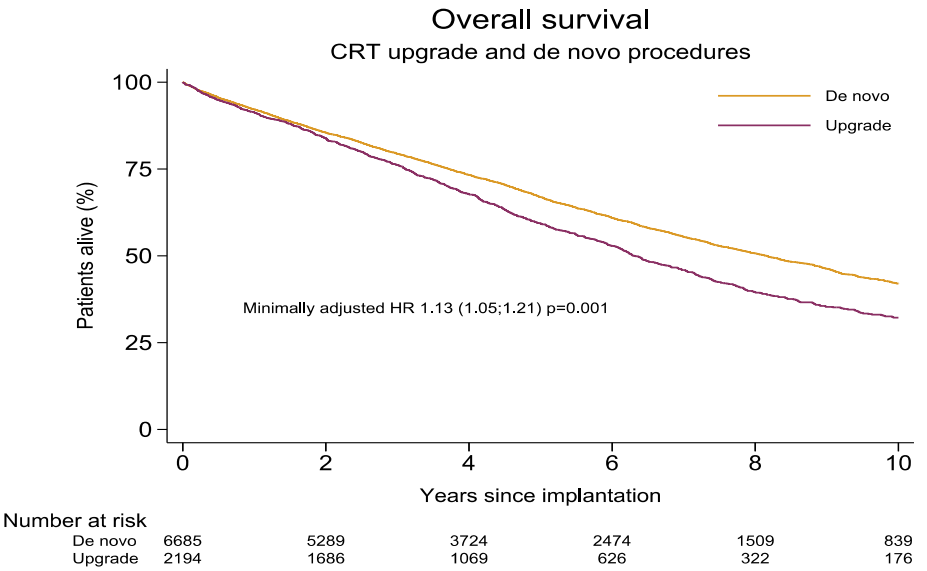

Table 1: *baseline characteristics*

	Upgrade	De novo
Age, median years (25-75 percentile)	71.9 (64.7-77.5)	69.3 (61.2-75.8)
Female sex, n (%)	348 (15.9)	1,677 (25.1)
Co-morbidities, n (%)		
Hypertension	1,067 (48.6)	2,770 (41.4)
Diabetes	535 (24.4)	1,511 (22.6)
Ischemic heart disease	1,449 (66.0)	3,748 (56.1)
High-grade AV-block	960 (43.8)	1,001 (15.0)
Atrial fibrillation or atrial flutter	1,248 (56.9)	2,192 (32.8)
Chronic obstructive pulmonary disease	300 (13.7)	909 (13.6)
Chronic kidney disease	217 (9.9)	465 (7.0)
Device type: CRT-D, n (%)	1,376 (62.7)	3,581 (53.6)

P3-3

Risk of Myocardial Infarction Following Capecitabine Treatment in Patients With Gastrointestinal Cancer – A Nationwide Registry-Based Study

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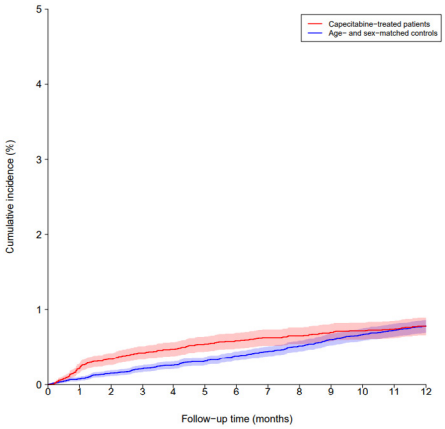
Background: Myocardial infarction is a cardiac adverse event associated with fluoropyrimidines such as 5-fluorouracil and its orally available prodrug capecitabine.

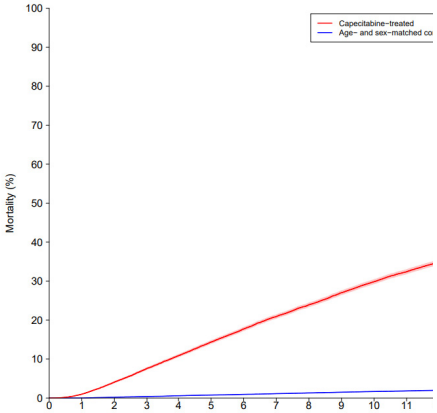
Aim: To examine the risk of myocardial infarction in patients with gastrointestinal (GI) cancer treated with capecitabine compared with age- and sex-matched population control subjects without cancer.

Methods: Patients with GI cancer treated with capecitabine between 2004-2016 were identified within the Danish National Patient Registry. Those with a history of ischemic heart disease were excluded. Absolute and relative risks of myocardial infarction at 6 months and 1 year were derived from multivariable Cox regression with average treatment effect modeling.

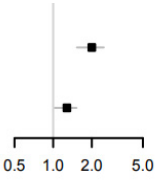
Results: A total of 71,460 patients were included in the final analysis of whom 23,820 had GI cancer treated with capecitabine, and 47,640 were population control subjects without cancer. The 6-month absolute risk (AR) of myocardial infarction was significantly higher for capecitabine-treated patients at 0.6% [95% confidence interval (CI): 0.5%-0.7%] versus 0.3% [95% CI: 0.2%-0.3%] in population control subjects, corresponding to a relative risk (RR) of 2.00 [95% CI 1.53-2.48; P <0.001]. The corresponding 1-year ARs were 0.7% [95% CI: 0.6%-0.9%] versus 0.6% [95% CI: 0.5%-0.6%]; RR 1.28 [95% CI 1.03-1.52; P= 0.03]. Six-month and one-year all-cause mortality ARs for patients treated with capecitabine versus controls were 15.2% vs. 0.7% and 29.7% vs. 1.6% respectively.

Conclusion: The risk of myocardial infarction of capecitabine-treated patients both 6- and 12-month risks were higher compared with population controls.





	RR	Low 95%	High 95%	P-value
Standardized 180-day risk	2.00	1.53	2.48	<0.001
Standardized 1-year risk	1.28	1.03	1.52	0.026



P3-4

Atrial fibrillation among ischemic stroke patients in Greenland

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Background
After a standardized examination regime for ischemic stroke patients in Greenland was implemented, a study from 2013 indicated a prevalence of atrial fibrillation (AF) of 30% among patients discharged with a diagnosis of ischemic stroke.

Aim
The study aims to give an update on the current prevalence of AF among ischemic stroke patients in Greenland.

Methods
Patients discharged from Queen Ingrid's Hospital in Nuuk between 2016 and 2021 with an ICD-10 diagnose of ischemic stroke or stroke without specification were included. Data on Holter analyses, age, gender, medical treatment with a DOAC or VKA, and ICD-10 and ICPC codes for AF were extracted for each patient.

Results
470 ischemic stroke patients were identified, of which 26% were younger than 55 years. Sixty-eight patients (14.5%) had AF either according to the Holter analysis, diagnose code or medication (figure 1).

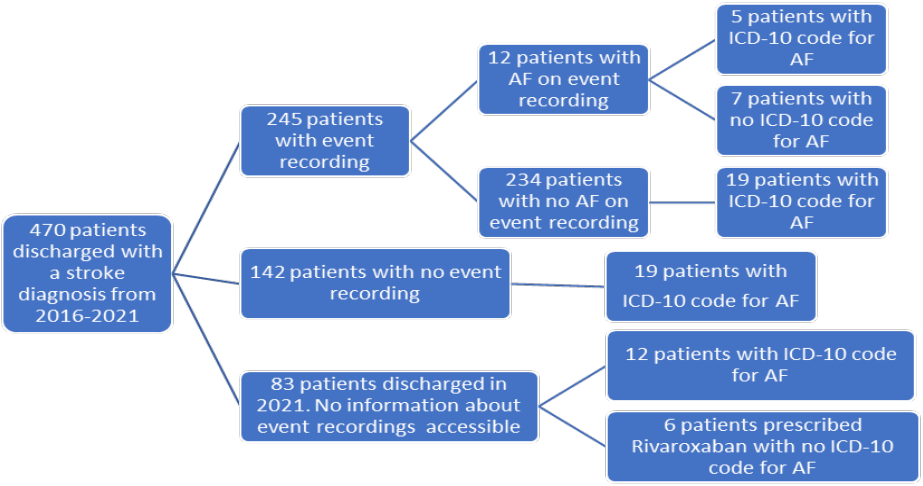

Figure 1. *AF among patients with ischemic stroke.There was no difference between the ratio of men and women with AF, but the number of patients with AF increased after the age of 65 years.*

Conclusion:

The prevalence of ischemic strokes in Greenland is unchanged since 2012, but many patients are young. Additionally, a significantly lower number of stroke patients were diagnosed with AF upon hospital discharge. Part of the drop may be explained by better preventive care with Rivaroxaban, but many patients seemingly lack sufficient continuous ECG monitoring, and AF may therefore be underdiagnosed. Strategies for improving diagnostics should be considered (94).

P3-5

Lipoprotein(a) is linked to atherothrombosis and aortic valve stenosis independent of C-reactive protein

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Background: Recent evidence suggest that the lipoprotein(a)-associated risk of atherosclerotic cardiovascular disease (ASCVD) may be observed only in individuals with low-grade systemic inflammation.

Aims: We hypothesized that high lipoprotein(a) is a main driver for risk of ASCVD, myocardial infarction, and aortic valve stenosis irrespective of C-reactive protein levels.

Methods: We included 68,090 individuals from the Copenhagen General Population Study. During a median of 8.1 years of follow-up, 5,104 developed ASCVD, 2,432 myocardial infarction, and 1,220 developed aortic valve stenosis.

Results: The risk of ASCVD, myocardial infarction, and aortic valve stenosis increased with higher values of both lipoprotein(a) and C-reactive protein. For individuals with lipoprotein(a) in the 91st-100th percentiles (≥69mg/dL,≥147nmol/L) versus 1st-33rd percentiles (≤6mg/dL,≤9nmol/L), the multivariable adjusted hazard ratio for ASCVD was 1.61(95% CI:1.43-1.81) for those with C-reactive protein <2 mg/L and 1.57(1.36-1.82) for those with C-reactive protein ≥2 mg/L (P for interaction 0.87). Corresponding values were 2.08(1.76-2.45) and 1.65(1.34-2.04) for myocardial infarction, and 2.01(1.59-2.55) and 1.73(1.31-2.27) for aortic valve stenosis, respectively (P for interaction 0.15 and 0.18). The highest absolute 10-year risks were in men aged 70-79 with lipoprotein(a) levels in the 91st-100th percentiles and C-reactive protein ≥2mg/L, with 34% for ASCVD, 19% for myocardial infarction, and 13% for aortic valve stenosis. Corresponding values in women were 20%, 10%, and 8%, respectively.

Conclusion: High lipoprotein(a) was a main driver for risk of ASCVD, myocardial infarction, and aortic valve stenosis at both high and low C-reactive protein level.

P3-6

Acute kidney injury to chronic kidney disease transition after cardiac surgery:

A systematic review

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Background
Acute kidney injury (AKI) is a common and serious complication after cardiac surgery, affecting approximately 1/3 of patients. Recent evidence suggest that an episode of AKI significantly increases the risk of transition to chronic kidney disease (CKD) within few years.

Aims
We aim to determine the impact of AKI, as a postoperative complication, for transition to incident CKD after cardiac surgery.

Methods
A systematic literature search in Medline and Embase identified 4329 studies. Of these, 86 were independently assessed for full-text review. Twelve studies were included and underwent analysis. Studies were extracted for data on AKI- and CKD frequencies. A random-effects model was utilized to compute pooled odds ratio using RStudio (metafor package). Analysis included heterogeneity statistics and risk of bias assessment.

Results
Mean AKI occurrence across studies was 16% (min-max: 8 – 50), while mean occurrence of CKD was 14% (min-max: 0.1 – 35), with high variability depending on CKD definitions and follow-up time.

AKI was associated with an increased risk of CKD in all individual studies (Figure 1). The pooled OR across studies was 5.67 (95% CI: 3.34 – 9.64, $p < 0.0001$). The studies included demonstrated considerable heterogeneity; however, risk of bias was low.

Conclusion

AKI as a complication after cardiac surgery entails an increased risk of transition to CKD within few years.

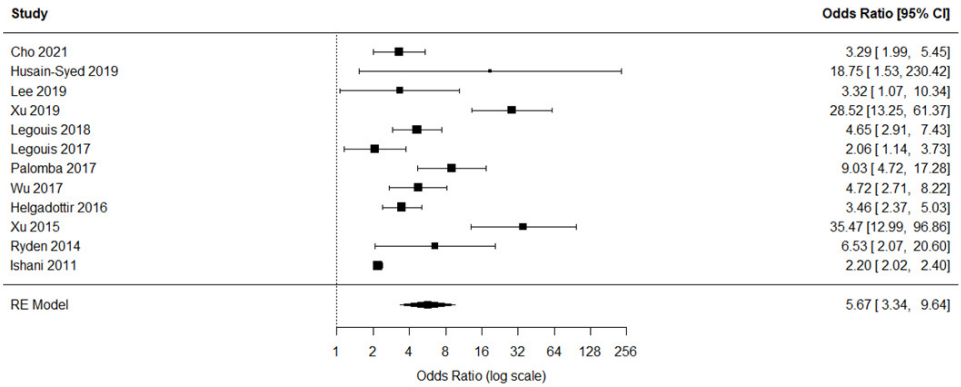

Figure 1: *Meta-analysis on AKI to CKD transition. I2 = 92.6% (95% CI: 83.1 – 97.7). Q(11) = 110.3, p < 0.0001.*

P3-7

A validation study of the new variable AED in the Danish Cardiac Arrest Registry

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[2] Prehospital Center, Region Zealand, Denmark

Background: The Danish cardiac arrest registry is based on nationwide data on all out-of-hospital cardiac arrest patients with resuscitative attempts.

Aim: This study aimed to introduce the automated external defibrillator (AED)-variable into the Danish cardiac arrest registry. The purpose of this novel variable was to address the challenges of reporting out-of-hospital cardiac arrest.

Methods: This validation study examined all Danish out-of-hospital cardiac arrest patients from 2016 to 2019. Their medical records were reviewed, and all patients with an AED applied were included for comparative analyses. The primary and secondary outcome was 30-day survival and the return of spontaneous circulation, respectively.

Results: A total of 1576 cases were included; 747 cases had an AED applied and received a shock. Most defibrillated patients were witnessed by bystanders (72%). They presented a higher return of spontaneous circulation rate (57%) and higher 30-day survival rate (35,2%) compared to patients who were not defibrillated. Comparing the AED-present group with the non-AED-present group, the former was more likely to be witnessed and to receive bystander cardiopulmonary resuscitation. 30-day survival rate was 20% in the AED-present group compared to 14% in the non-AED-present group, OR 1.14 (95% CI 1.20 –1.66).

Conclusion: This study highlights the differences between receiving defibrillation and not receiving defibrillation after AED placement. These differences emphasise the need for uniform reporting of out-of-hospital cardiac arrest. This study showed improvement in the completeness of the registration by implementing the AED-variable.

P3-8

Patency of neonatally identified interatrial communications in preschool children.

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Background
Atrial septal defect (ASD) of the secundum type is a common congenital heart defect. It is challenging to distinguish ASDs from physiological interatrial communications (IACs) within the oval fossa, i.e. patency of the oval foramen (PFO). On this basis, we recently developed an algorithm for classification of neonatal IACs identified by transthoracic echocardiography.

Aim
We aim to investigate the patency of neonatal IACs categorized as ASDs or PFOs in preschool children.

Methods
Children participating in a large, multicenter, prospective population study, with an IAC detected during the first 30 days after birth, were enrolled for a follow-up echocardiogram. We aim to include 600 children with a PFO and 600 with an ASD according to the algorithm. The follow-up echocardiograms were assessed for patency of IAC by a single operator blinded to the neonatal IAC subtype. A patent IAC was defined as the presence of a color Doppler flow crossing the atrial septum in combination with either a visual defect on the transsectional image or flow acceleration in the color Doppler signal.

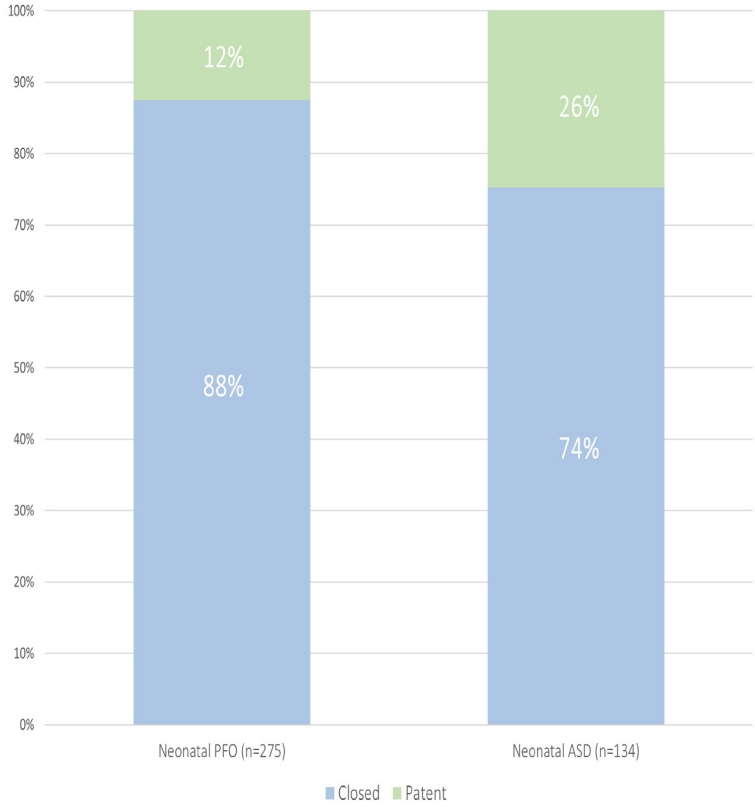
Results
Currently, 409 children (median age 5.1 [4.9-5.4] years, 59% female) have been examined. Neonatally, the IACs were classified as ASDs in 134 and PFOs

in 275 newborns. The follow-up echocardiograms showed patency of the IAC in 35 of the children with an ASD (26%) and in 32 with PFO (12%), (p=0.0002).

Conclusions

Preliminary findings showed a significantly higher patency of neonatal ASDs versus PFOs in preschool children. The findings support the value of the novel diagnostic algorithm.

Figure: The prevalence of patency of the oval foramens (PFOs) and atrial septal defects (ASDs) in 409 preschool children, showing patency of the IAC in 35 of the children with an ASD (65%) and in 32 of the children with PFO (12%), (p=0.0002).



P3-9

Sudden cardiac death in persons without a history of cardiovascular disease – a nationwide study of 54,028 deaths

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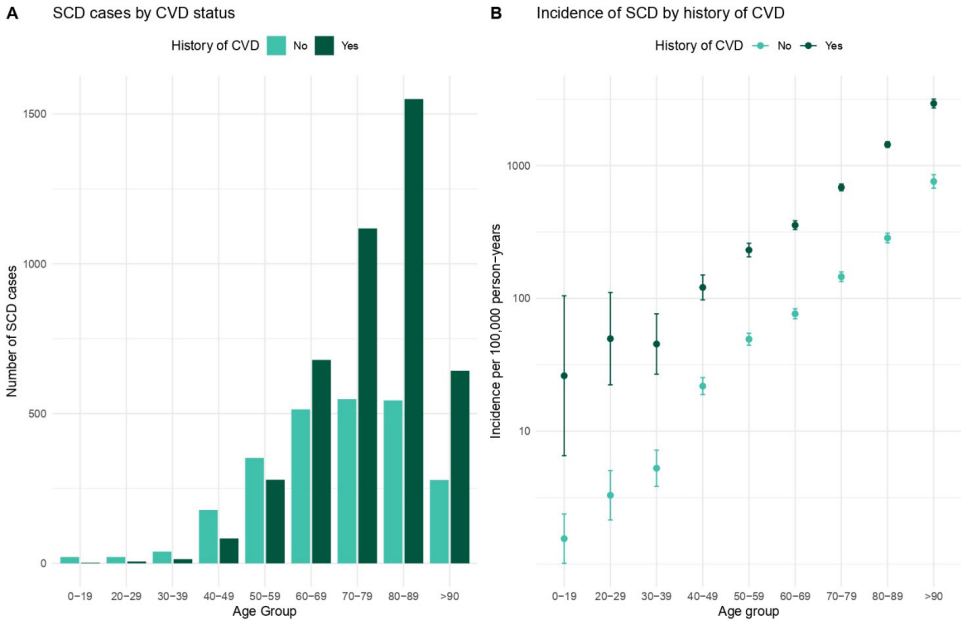
Background and aim: Sudden cardiac death (SCD) is a leading cause of death and previous studies have shown that approximately half of all cases have no known history of cardiovascular disease (CVD). Epidemiological studies of SCD cases of all ages are sparse. The aim of this study was to examine differences in incidence rates, clinical characteristics, comorbidities between SCD cases with and without known history of CVD.

Methods: All deaths in Denmark in 2010 (54,028) were reviewed. Autopsy reports, death certificates, discharge summaries and nationwide health registries were reviewed to identify cases of SCD. Based on the available information in nationwide registries, cases were separated based on whether they had a history of cardiovascular disease or not.

Results: A total of 6,867 SCD cases were identified, of which 2,495 (36.3 %) had no history of cardiovascular disease and 4,373 (63.7 %) had a history of CVD. Incidence rates of SCD increased with age and were higher in cases of SCD with a history of CVD across all age groups. The difference in incidence of SCD between persons with and without history of CVD decreased with increasing age with incidence rate ratios ranging from 16.84 (95 % CI: 3.95 – 71.82) to 3.86 (95 % CI: 3.35 - 4.44). After adjusting for age, persons with a CVD diagnosis had significantly more comorbidities, and females were significantly less likely to have a CVD prior to SCD.

Conclusion: This is the first nationwide study of SCD victims with and without history of cardiovascular disease across all ages. SCD is more common in the populations of persons with a history of cardiovascular disease, but the difference narrows with increasing age.


A
SCD cases by CVD status
History of CVD
No
Yes
Number of SCD cases
1500
1000
500
0
0–19
20–29
30–39
40–49
50–59
60–69
70–79
80–89
>90
Age Group
B
Incidence of SCD by history of CVD
History of CVD
No
Yes
Incidence per 100,000 person–years
1000
100
10
0–19
20–29
30–39
40–49
50–59
60–69
70–79
80–89
>90
Age group

P3-10

Severe mental illness and symptoms of acute coronary syndrome

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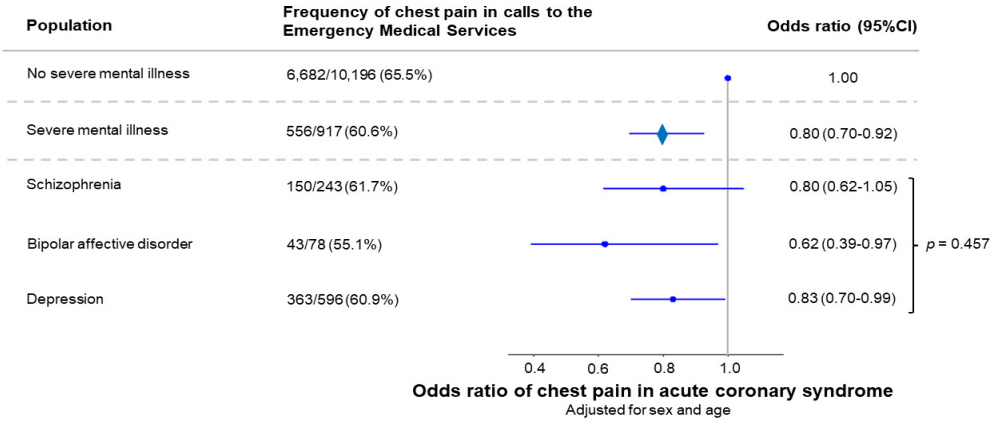
Background: It can be lifesaving to act fast when acute life-threatening diseases occur. This is, however, challenging in some patients with severe mental illness (SMI) as they sometimes experience symptoms differently than patients without SMI. This may affect the patients' chances of receiving adequate help, as these patients are already stigmatized even by healthcare personnel.

Aim: We aimed to determine whether patients with SMI experienced different symptoms of acute coronary syndrome (ACS) than patients without SMI.

Methods: In this registry-based study, we analyzed symptoms of ACS in calls from 2014 to 2018 to the Copenhagen Emergency Medical Services, including the Emergency Number (1-1-2) and the Medical Helpline (1813). The study population comprised patients with SMI (defined by schizophrenia, bipolar affective disorder, and depression) and a control group of patients without SMI.

Results: In total, 11,113 calls were included; 917 were from patients with SMI (45.4% were female, average age was 64.6 years), and 10,196 were from patients without SMI (35.3% were female, average age was 67.7 years). SMI was associated with less frequent chest pain in ACS (OR: 0.80, 95%CI: 0.70-0.92). The mean time difference from the call to hospitalization was 17 minutes longer for patients with SMI (1 hour 21 minutes vs. 1 hour 4 minutes, p=0.002)

Conclusion: Patients with SMI presented less frequent chest pain in ACS in calls to the Emergency Medical Services than patients without SMI and had increased time to hospitalization.


Population
Frequency of chest pain in calls to the Emergency Medical Services
Odds ratio (95%CI)
No severe mental illness
6,682/10,196 (65.5%)
1.00
Severe mental illness
556/917 (60.6%)
0.80 (0.70-0.92)
Schizophrenia
150/243 (61.7%)
0.80 (0.62-1.05)
Bipolar affective disorder
43/78 (55.1%)
0.62 (0.39-0.97)
Depression
363/596 (60.9%)
0.83 (0.70-0.99)
p = 0.457
0.4
0.6
0.8
1.0
Odds ratio of chest pain in acute coronary syndrome
Adjusted for sex and age

P3-11

Age-related prevalence of open ductus arteriosus in full-term newborns

Anton Friis Mariager, MD[1,2]*, Alberte Hammeken, MD[3], Mikkel Malham, MD, PhD[1], Anna Axelsson Raja MD, PhD [3,8] Anna Sellmer, MD, PhD[4,5], Signe Levring Skjellerup, MD[6], Raheel Altaf Raja MD, PhD[7], Johan Navne MD[8], Anne-Sophie Sillesen MD, PhD[2,3], Niels Vejlstrup, MD, PhD[9], Henning Bundgaard, prof, MD[3,10], Kasper Iversen, prof, MD[2,3], Ester Garne MD[11], Dorthe Lisbeth Jeppesen, MD, PhD[1,3]

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Background

The ductus arteriosus (DA) is part of the fetal circulation. Normally the DA close shortly after birth, but for some neonates the closure is delayed. Little is known about the prevalence and timing of spontaneous DA closure in term born children.

Aim

The aim of this study was to evaluate the daily prevalence of open DA in term born neonates within the first 28 days after birth.

Method

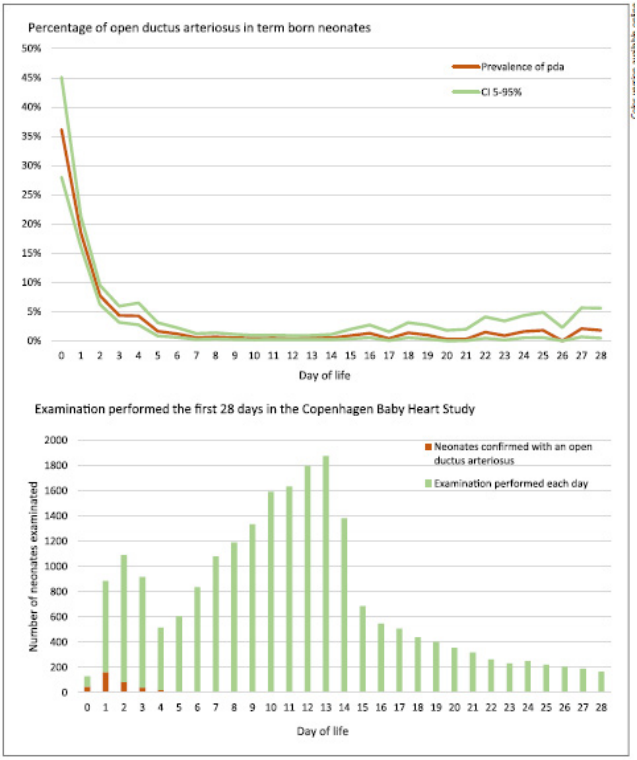
Echocardiograms were collected in the Copenhagen Baby Heart Study with 25.000 examination in the database. The present study included term born neonates with an echocardiogram performed in the neonatal period, defined as day 0-28 after birth. Neonates with findings of other congenital heart defects than atrial septal defects were excluded. All echocardiograms were analyzed to diagnose an open DA.

Results

A total of 21,649 neonates were included in this study. The median age at examination was 11 days (IQR=4-18). In 485 neonates, an open DA (2.3%) were identified. In those examined at day zero (n=130), day two (n=1090), and seven (n=1080), an open DA were found in 36%, 8% and 0.6%, respectively. After day seven the prevalence of an open DA was stable around 0.6%.

Conclusion

This large-scale echocardiography study in healthy neonates showed a high prevalence of open DA on the first day of life, with a rapid decline to a prevalence of less than 1% at day seven remaining stable around 0.6% hereafter.



P3-12

Dyspnoea as reason for calling emergency medical services – cardiac and non-cardiac causes

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Background
Dyspnoea, a frequent prehospital complaint to emergency medical services (EMS), is related to high mortality and necessitates further investigation.

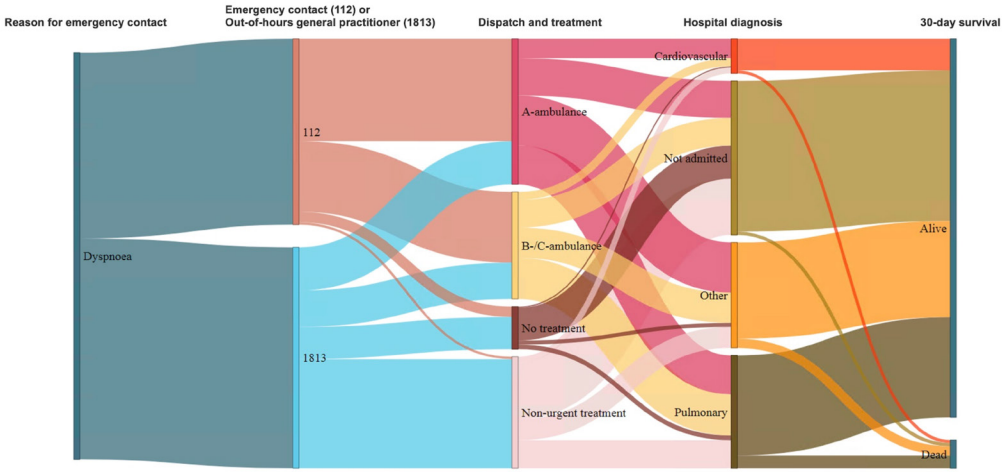
Aim
To investigate the prognosis of patients reporting prehospital dyspnoea

Methods
We included patients aged >18 years reporting dyspnoea to Copenhagen EMS between 2014 through 2018. We linked data pertaining to these patients to nationwide registries and databases on demographics, emergency response, hospital admissions, and mortality status. We included only the first call per patient and excluded out-of-hospital cardiac arrest cases.

Results
We included 45,404 patients with prehospital dyspnoea (54% female, median age 65 years). Among these, 46% (20,736/45,404) called using the emergency number (“1-1-2”), 64% using the out-of-hours general practitioner contact (“1813”), 36% received an emergency dispatch (“A-ambulance”), 62% were admitted to a hospital within a week of their call, and 7% died within 30 days (Fig. 1). Among admitted patients, 45% (12,583/28,193) received a pulmonary diagnosis, 12% received a cardiovascular one, and 36% received other diagnoses. Among patients that died within 30 days of their call, 88% (2,760/3,143) had been admitted to a hospital within a week of their call. Among all deaths, the most common causes were due to malignancy (26% (802/3,143)), chronic lower respiratory disease (15%), and cardiovascular disease (11%), and causes of death were similar between admitted and non-admitted patients.

Conclusion

Among patients reporting prehospital dyspnoea, approximately half of patients were admitted with a pulmonary diagnosis and 12% with a cardiovascular one. 7% died within 30 days of their call, most often due to malignancy.



P4-1

Effect of SGLT2i empagliflozin on left ventricular and mitochondrial function in a porcine model of anthracycline-induced cardiotoxicity

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Background: Cancer therapies have significantly improved the survival of cancer patients, however, more than 35% of cancer survivors treated with anthracyclines will develop cardiotoxicity. Cancer patients with diabetes receiving anthracyclines and treated with sodium-glucose co-transporter-2 inhibitors (SGLT2i) have been found to have lower rates of cardiac events.

Aim: To evaluate the ability of SGLT2i empagliflozin (EMPA) to mitigate left ventricular (LV) dysfunction and mitochondrial dysfunction.

Methods: Female large-white pigs (n= 16) were randomized to receive either an oral EMPA dose (10 mg/day) or no treatment (see Figure 1). All pigs received 6 doses of doxorubicin (DOX) by an intravenous infusion (25 mg/m2/ every 3 weeks). LV function was assessed with CMR obtained prior each DOX infusion and 3 and 6 weeks after the last infusion. At week 21, the pigs were sacrificed and the LV was collected for OROBOROS assessment of mitochondrial respiration.

Results: The pigs treated with EMPA (n=8) had a higher LVEF (49.5 % vs 44.5%; p = 0.09) and LV mass (95.7 g/m2 vs 82.8 g/m2) compared to the untreated pigs (n=8). Mitochondria isolated from the LV presented more oxidative phosphorylation capacity in the treated pigs (n=8) compared to the untreated pigs (n=7) (5250 pmol·s-1·x-1 vs 4200 pmol·s-1·x-1). The maximum capacity of the electron transport chain was also higher in mitochondria isolated from the treated pigs (5430 pmol·s-1·x-1 vs 4430 pmol·s-1·x-1).

Conclusion: Our findings suggest that EMPA may have a cardioprotective effect against DOX-induced cardiotoxicity.

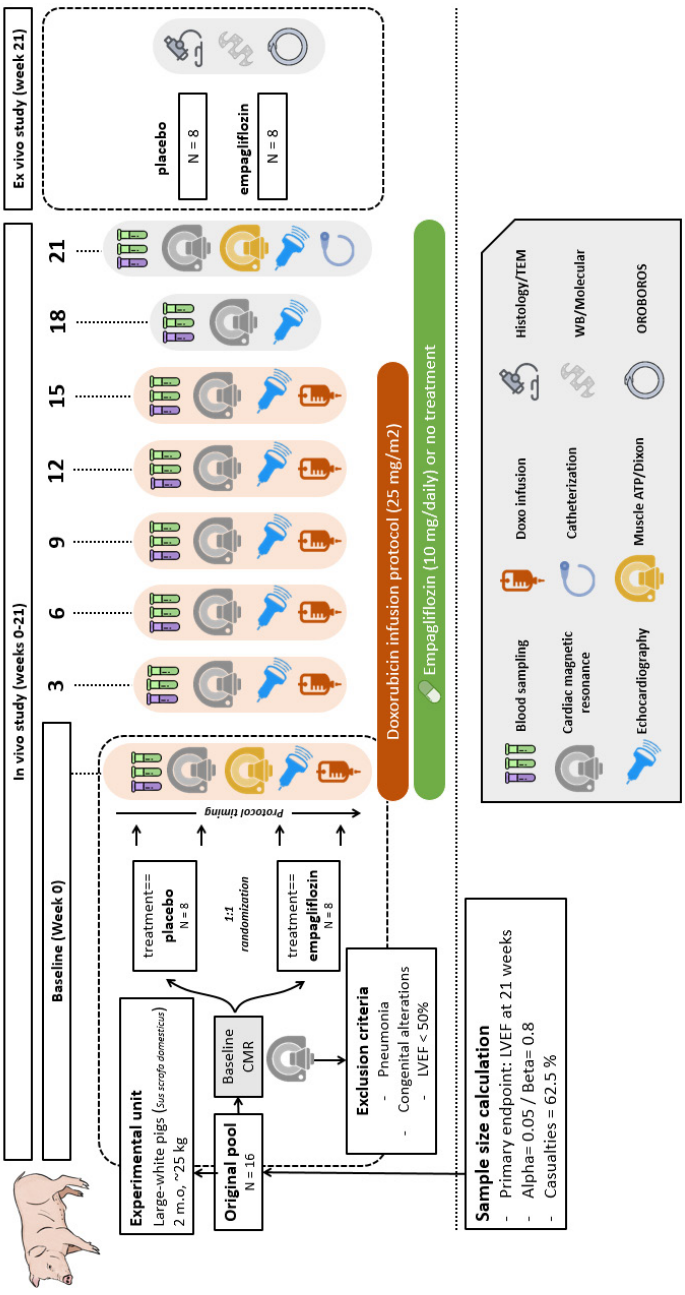
In vivo study (weeks 0-21)
Baseline (Week 0)
3
6
9
12
15
18
21
Ex vivo study (week 21)
placebo
N = 8
empagliflozin
N = 8
Experimental unit
Large-white pigs (Sus scrofa domesticus)
2 m.o, ~25 kg
Original pool
N = 16
Baseline
CMR
Exclusion criteria
- Pneumonia
- Congenital alterations
- LVEF < 50%
1:1
randomization
treatment== placebo
N = 8
treatment== empagliflozin
N = 8
Protocol timing
Doxorubicin infusion protocol (25 mg/m2)
Empagliflozin (10 mg/daily) or no treatment
Sample size calculation
- Primary endpoint: LVEF at 21 weeks
- Alpha= 0.05 / Beta= 0.8
- Casualties = 62.5 %
Blood sampling
Doxo infusion
Histology/TEM
Cardiac magnetic resonance
Catheterization
WB/Molecular
Echocardiography
Muscle ATP/Dixon
OROBOROS

Figure 1.

P4-2

The Nav1.5 variant G213D found in MEPPC syndrome patients is associated with increased window and gating pore current

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[3] Department of Health Technology, University of Copenhagen, Denmark
[4] Department of Cardiology, Aarhus University Hospital, Denmark

Background: Genetic variants in the SCN5A gene have been linked to the multifocal ectopic Purkinje-related premature contractions (MEPPC) syndrome, characterized by frequent premature contractions and linked to dilated cardiomyopathy (DCM). The link between MEPPC and SCN5A variants is not fully understood but an increased sodium current, either through increased window current or a gating pore current appear to be central.

Aim: Electrophysiological characterization of the $Na_v1.5$_G213D variant.

Materials and Methods: A large Danish family was identified where an MEPPC-like phenotype co-segregated with the genetic variant c.638G>A in SCN5A resulting in p.Gly213Asp (G213D). Patch clamp recordings were carried out on CHO-K cells and Xenopus laevis oocytes expressing either wildtype $hNa_v1.5$ or $hNa_v1.5$_G213D. Action potential recordings were also made from human induced pluripotent stem cell-derived cardiomyocytes (hiPSC-CMs), comparing a wildtype (WT) cell line with the same cell line with G213D inserted using CRISPR/Cas9 gene editing.

Results: The half-maximal of the activation of $hNa_v1.5$_G213D was significantly more negative compared to wildtype, while the half-maximal of steady-state inactivation was significantly shifted towards more positive potentials. Both findings suggest a gain-of-function variant, where the channel activates at lower voltages and is released from inactivation at less negative voltages compared to wildtype. In Xenopus laevis oocytes, a gating pore current was found.

Conclusion: $Na_v1.5$_G213D is a gain-of-function variant associated with the MEPPC syndrome. It leads to an increased window current and induces a gating pore current.

P4-3

Mitochondrial respiration in porcine models of acute and chronic myocardial infarction

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**Lead presenter*
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Background: Ischemic heart disease has been linked to reduced mitochondrial respiratory capacity. A better understanding of the myocardial pathophysiological mechanisms are needed.

Aim: The aim of the study was to measure myocardial mitochondrial respiratory capacity in the infarct zone (IZ), the infarct border zone (BZ) and the remote zone (RZ) in an acute and chronic porcine model of myocardial infarction (MI).

Methods: Female Landrace pigs underwent MI by balloon occlusion of the left anterior coronary descending artery. Pigs were euthanized after 120 minutes of reperfusion (acute MI, n=7) or after 4 weeks (chronic MI, n=11). Transmural myocardial tissue samples were collected from IZ, BZ and RZ. Mitochondrial respiratory capacity was measured using high-resolution respirometry. Citrate synthase (CS) activity was measured as surrogate of number of mitochondria in tissue.

Results: Complex I mitochondrial respiratory capacity was significantly reduced in IZ after acute (P=0.047) and chronic MI (P=0.023), compared to RZ. Complex I+II respiratory capacity (P=0.012), and CS activity (P=0.0060) in IZ were reduced after chronic MI, but not after acute MI (Complex I+II respiratory capacity: P=0.89, CS activity: P= 0.94), compared to RZ. When mitochondrial respiratory capacity was adjusted for CS activity, differences between zones were not significant.

Conclusion: Myocardial mitochondrial respiratory capacity was affected in acute and chronic pig models of MI. Differences in respiratory capacity could be related to number of mitochondria in tissue. The study is limited by low sample size, different occlusion times, and lack of randomization.

P4-4

The role of micro RNAs in the obese adipose vascular niche

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**Lead presenter*
[1]University of Southern Denmark, Denmark
[2] Stockholm University, Sweden

Background: Obesity is a prevailing health concern intimately linked to adipose tissue (AT) dysfunction, characterized by hypertrophied adipocytes (AC) that contribute to lipid overflow into vital organs. Adipose endothelial cells (adEC) are crucial for maintaining AT function and undergo changes in response to altered AC adipokine secretion during obesity, suggesting the importance of AC-adEC interaction for AT and metabolic health.

MicroRNAs (miRNA) are regulatory molecules that can be secreted and exchanged from the AT via extracellular vesicles (EVs), influencing gene expression in recipient cells. Obesity influences the secretion and expression of miRNAs in AT. However, the specific miRNAs that control crosstalk between AC and adEC and their significance in the obese vascular niche has not been addressed to date.

Preliminary research in my host laboratory has demonstrated abundant expression of miR-149 in mature AC upon high fat diet feeding, whereas miR-149 has been shown in another study to be repressed in obese adEC. This suggests a potential exchange of miR-149 between AC and adEC in metabolic disease.

Aim: This project aims to investigate the EV-mediated exchange of obesity-associated miRNAs between AC and adEC.

To achieve this, we will (1) integrate data from various omics datasets and single-cell databases to map obesity-related changes of miRNA:mRNA gene networks in adipose vasculature and identify potential miRNA candidates for further analysis, and (2) study the miRNA exchange in EV-mediated adEC-AC communication with genetically modified 'ExoRep' mice expressing CD9-eGFP^{+} EVs exclusively in AC and adEC.

P4-5

Treatment effects of Bisoprolol and Verapamil in non-obstructive hypertrophic cardiomyopathy

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Background: Hypertrophic cardiomyopathy (HCM) is the most common hereditary heart disease with a prevalence of 1:500. The clinical manifestations range from asymptomatic to severe functional limitations at early age. Medical treatment plays an important role when managing symptoms and preventing arrhythmia and sudden cardiac death. Nevertheless, the guideline-recommended medical treatments with non-dilating beta blockers (BB) or cardio-specific calcium channel blockers (CCB) for symptomatic HCM patients has never been systematically evaluated.

Aim: To compare the treatment effects of Bisoprolol and Verapamil in non-obstructive HCM. The clinical aim is to reduce the symptomatic burden and arrhythmic complications in HCM.

Method: The study is designed as a multicenter double-blinded randomized placebo- controlled cross-over trial. Patients are randomized into three 35-day treatment periods of Bisoprolol, Verapamil and Placebo. Each treatment period consists of 7-day up-titration period, 21-day target dose period and 7-day down-titration period. Endpoints will be evaluated by echocardiography, cardiopulmonary exercise test, 7-day Holter monitoring, biomarkers, and Kansas City Cardiomyopathy Questionnaire at day 21. A subgroup of patients will be evaluated by cardiac MRI.

Results: Results are not available as the study is still recruiting. The study will be the so far largest randomized trial on the effects of BB and CCB in HCM and the only study making a head-to-head comparison between the two guideline-recommended treatments of HCM.

Conclusion: The study has the potential to form the basis of the future recommended treatment of non-obstructive HCM.

P4-6

Effects of Systematic Atrial Fibrillation Screening according to N-Terminal Pro-B-Type Natriuretic Peptide:

A Secondary Analysis of the randomized LOOP Study

Primary author: Lucas Xing

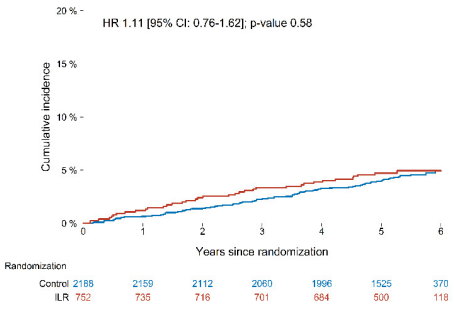
Background: An evidence-based approach for risk-stratifying and selecting individuals for atrial fibrillation (AF) screening is lacking. This study aimed to assess N-terminal pro-B-type natriuretic peptide (NT-proBNP) as a potential marker to identify those who would benefit from AF screening.

Methods: In the LOOP Study, 6004 AF-naïve individuals aged 70-90 years with additional stroke risk factors were randomized 1:3 to either continuous screening with implantable loop recorder (ILR) and anticoagulation initiation upon AF detection, or usual care (Control). This secondary analysis included the study participants with available NT-proBNP measurement at baseline.

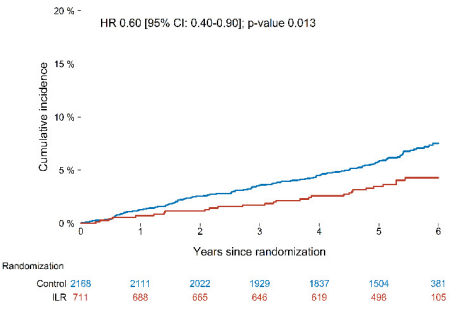
Results: A total of 5819 participants were included (mean age 74.7 years (standard deviation, 4.1), 47.5% females). The median NT-proBNP level was 15 pmol/L [interquartile range: 9-28]. Participants with NT-proBNP above median were at higher risk of stroke or systemic embolism (SE) than those with lower levels (HR 1.21 [95% CI: 0.96-1.54]). Compared with usual care, ILR screening was associated with a significant reduction in stroke/SE among participants with NT-proBNP above median (HR 0.60 [95% CI: 0.40-0.90]), but not among those with lower levels (HR 1.11 [95% CI: 0.76-1.62]); pinteraction=0.029. Analyzing NT-proBNP as a continuous variable yielded similar findings.

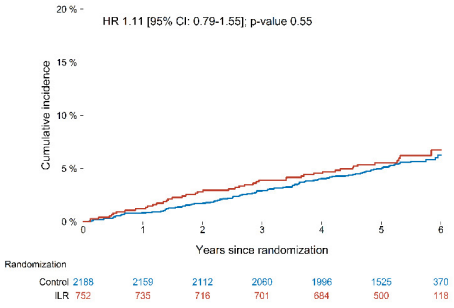
Conclusion: In an elderly population with additional stroke risk factors, ILR screening for AF was associated with a significant stroke reduction among individuals with higher NT-proBNP levels, but not among those with lower levels.

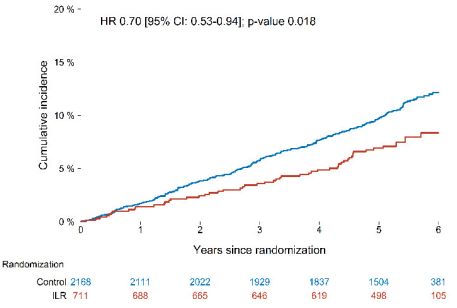
A) NT-proBNP ≤ 15 pmol/L

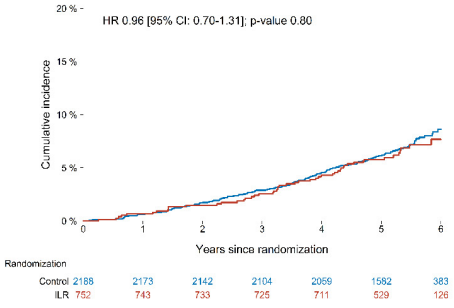


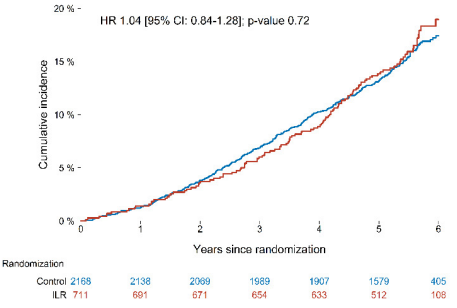
B) NT-proBNP > 15 pmol/L











P4-7

Spectral Library Assisted Discovery of Potential Diagnostic Biomarkers for Abdominal Aortic Aneurysms

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Background: Abdominal aortic aneurysms (AAA) pose a life-threatening risk due to unexpected rupture of the aortic wall, but current methods often fail to identify asymptomatic cases. Simple blood tests for detection outside hospital settings are urgently needed.

Plasma proteomics faces challenges in protein identifications due to the complexity of plasma. Laborious sample preparation are commonly employed to improve the number of protein identifications.

Aim: To address the need for improved identifications of potential AAA biomarkers, we propose that a tailored spectral library for plasma proteomics will increase protein identifications without the use of laborious and time-consuming pre-analytical procedures.

Methods: Mass spectrometry analysis was performed on human plasma, human cell lysates, and artery tissue. A spectral library was created and utilized in combination with sequence database searching. Individual plasma samples from two patient cohorts were analyzed: a discovery cohort for training a Random Forest classification model for diagnosis of AAA patients, and a validation cohort used for model optimization and unbiased evaluation.

Results: Spectral library searching increased the number of identified proteins by 25% across human plasma sets. A panel of 18 proteins showed significant regulation in both discovery and validation cohorts. The Random Forest classification model achieved an AUC of 0.82 on an independent test dataset.

Conclusion: We demonstrated the promising use of spectral libraries for clinical proteomics. By eliminating the need for extensive pre-analytical procedures, this approach can simplify and improve detection of potential plasma protein biomarkers.

P4-8

Challenges in establishing animal induced pluripotent stem cells

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Background
Induced pluripotent stem cell (iPSC)-derived cardiomyocytes offer a promising *in vitro* tool for preclinical drug development and screening of pro-arrhythmic effects. Most iPSC-derived cardiac models are based on human iPSCs. However, the limited access to native human cardiac tissue and data challenges model validation.

To support model validation, we aim at generating iPSC-based cardiac models of the major animal models within cardiac safety pharmacology: Pig and dog where available *in vivo* data exist. Human iPSCs are routinely generated from patient skin biopsies or less invasively from blood samples. Here we present our initial work at optimizing a human blood reprogramming protocol to obtain canine and porcine iPSCs.

Methods
Peripheral blood mononuclear cells (PBMCs) were isolated from canine and porcine blood samples. PBMCs were cultured in suspension before being nucleofected with episomal plasmids containing human reprogramming factors and plated for colony formation. Variations in pre-transfection culture length, plasmid combination, nucleofection setup, and culture condition were tested.

Results
Cell attachment was achieved for transfected canine and porcine PBMCs with varying degrees. However, it did not result in colonies with compacted morphology characteristic of iPSCs.

Conclusion
Reprogramming canine and porcine PBMCs using a human protocol were in our hands unsuccessful, suggesting that human-based protocols cannot directly be applied in an animal context. Whether this insufficiency is due to the combination of reprogramming factors, media composition, or both is unclear. Undetermined species-specific differences in pluripotency are a remaining challenge in animal iPSC establishment.

P4-9

Proteome coverage of low-input formalin-fixed paraffin-embedded human heart tissue

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Background
Cardiovascular diseases are the leading causes of death globally, making heart pathophysiology investigation crucial. Over the past 20 years, proteomics approaches have contributed to disease phenotyping by discovering protein biomarkers and potential therapeutic targets for cardiovascular conditions. As diseases can determine region-specific proteome alterations, the field is now approaching spatial resolution as opposed to bulk approaches that evaluate biological samples in their entirety. Here, we test a method for low-input spatial proteomics on formalin-fixed paraffin-embedded (FFPE) human heart tissue, which could potentially retain the spatial tissue context.

Aim
Analyze the proteome coverage of FFPE human heart tissue for different sample quantities and tissue microenvironments.

Methods
Laser capture microdissection (LCM) was employed to collect regions of 50.000µm^2 of FFPE cardiac tissue following Van Gieson's staining. Proteins were then solubilized, de-crosslinked, and quantified subsequently by liquid chromatography-tandem mass spectrometry (LC-MS/MS) using a data-independent acquisition (DIA) methodology.

Results
The proteomic profile of single 50.000µm^2 regions varied when measured from different human heart microenvironments, namely myocardium, blood vessels, and adipose tissue. In addition, increasing the tissue quantity led to higher proteome coverage, especially for proteins typically low-abundant in heart tissue.

Conclusion
Even with our lowest input samples, a difference in the proteomic profile of the tested cardiac tissue microenvironments could be captured.

P4-10

Altered Myosin Function In Patients With Hypertrophic Cardiomyopathy And Type 2 Diabetes

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Background
The combination of hypertrophic cardiomyopathy (HCM) and type 2 diabetes mellitus (T2D) leads to heart failure and excessively high mortality rates. The mechanisms of such damaging combination (T2D-HCM) remain unexplored.

Aim
Based on recent works highlighting the pathogenic role of myosin in T2D-related cardiomyopathy alone, here, I aimed to explore whether and how myosin relaxed conformation and related ATP consumption are altered in T2D-HCM patients.

Methods
To achieve this aim, I isolated and permeabilized thin cardiac strips from HCM patients (n=6, serving as controls) and T2D-HCM patients (n=6). I then ran a Mant-ATP chase protocol allowing the measurement of myosin super-relaxed (SRX) and disordered-relaxed (DRX) states, as well as their respective ATP consumption. The data was fitted to a double exponential decay equation, from which the proportions of SRX and DRX myosins as well as their ATP turnover times were determined.

Results
I observed that the proportion of DRX myosins was greater, while the proportion of SRX myosins was lower in T2D-HCM patients compared to the HCM patients. No differences in the ATP turnover lifetime for SRX and DRX myosins were found between the two groups of patients.

Conclusion
My findings suggest that in HCM patients, T2D specifically disrupts myosin function by increasing the proportion of myosin heads in the DRX state, further enhancing their ATP consumption. These findings may have metabolic consequences and give us valuable insights into the pathogenesis of T2D-HCM.

P5-1

The role of colchicine on early activators of inflammation in a porcine model of chronic atrial fibrillation

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Background: Affecting 37.5 million people worldwide, atrial fibrillation (AF) is the most common cardiac arrhythmia. An enhanced inflammatory response is commonly observed in patients with AF linked to structural remodeling and activation of the NRLP3 inflammsome.

Aim: To evaluate the role of colchicine, an NLRP3 inflammasome inhibitor, on fibrosis and early activators of inflammation in the pathogenesis of AF.

Methods: AF was induced in 12 pigs by atrial tachypacing at 7 Hz. The pigs were divided into two study groups; Colchicine (0.5 mg bidaily, n=6) and placebo (calcium tablets bidaily, n=6). The pigs were euthanized after 7 weeks and the hearts were excised. Whole tissue lysates from the pig's right atrium were collected and analyzed through Western Blot.

Results: The colchicine treated group demonstrated downregulated relative protein levels for NLRP3 (**, p=0.0058) with no effect of colchicine on downstream inflammasome component ASC (p=0.3451) and pro-caspase 1 (p=0.7052). Colchicine indicates a trend in downregulating early fibroblast activation with cross talk from macrophages as observed through decreased protein levels of fibroblast activators and macrophage markers; vimentin (p=0.0531), αSMA (p=0.2381), periostin (p=0.1205), TLR4 (*, p=0.0409), and TGF-β (p= 0.2296).

Conclusion: Colchicine demonstrates a trend in downregulation of priming signals of the NLRP3 inflammasome and early activation of fibroblasts with cross talk signaling from macrophages and subsequent release of pro inflammatory cytokines.

P5-2

Electrophysiological Characterisation of Indomethacin in a Porcine Model of Obstructive Sleep Apnea

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Background: Non-steroidal anti-inflammatory drugs are used daily by more than 30 million people worldwide to treat inflammatory pain. Cardiovascular diseases (CVD) are the leading cause of death worldwide and are highly associated with obstructive sleep apnea (OSA), which moreover shows a strong association with other CVDs.

Aim: The aim was to investigate the effect of indomethacin on cardiac electrophysiology and arrhythmia susceptibility and whether it intensifies the arrhythmogenic substrate during obstructive events simulated by intermittent negative upper airway pressure (INAP).

Methods: The study population consisted of 12 sedated (4.2% alpha-chloralose), spontaneously breathing LYD-pigs (8 indomethacin, four vehicles). INAP was applied four times for 75 seconds. Utilising a pacing protocol, indomethacin's effect on the sinus node recovery time and the refractoriness of the atria (AERP) and the atrioventricular node were investigated. Furthermore, the electromechanical window (EMW), the QTc-interval and the occurrence of brady-/tachyarrhythmia and extra-systoles, were measured.

Results: The pigs showed a tendency in AERP shortening (10 min: -17%±9%, 20 min: -17%±9%) and a significant shortening of the QTc-interval (10 min: -20.50±4.30 ms, 20 min: -15.88±3.70 ms) within the first 20 minutes post indomethacin. Furthermore, the occurrence of 2. Degree AV-blocks correlated with a high indomethacin plasma concentration. INAP-induced electrophysiological changes, such as AERP and EMW, did not worsen in the presence of indomethacin.
Conclusion: The effect of indomethacin was most pronounced in the ventricles. However, indomethacin did not worsen the arrhythmogenic substrate during INAP. Further research is needed to elucidate potential ion channel involvement in indomethacin-induced electrophysiological changes.

P5-3

Electrophysiological remodelling of pulmonary veins in a dog model of endurance training-induced atrial fibrillation

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Background: Atrial fibrillation (AF) incidence increases in endurance-athletes. However, the associated mechanism is still unclear.

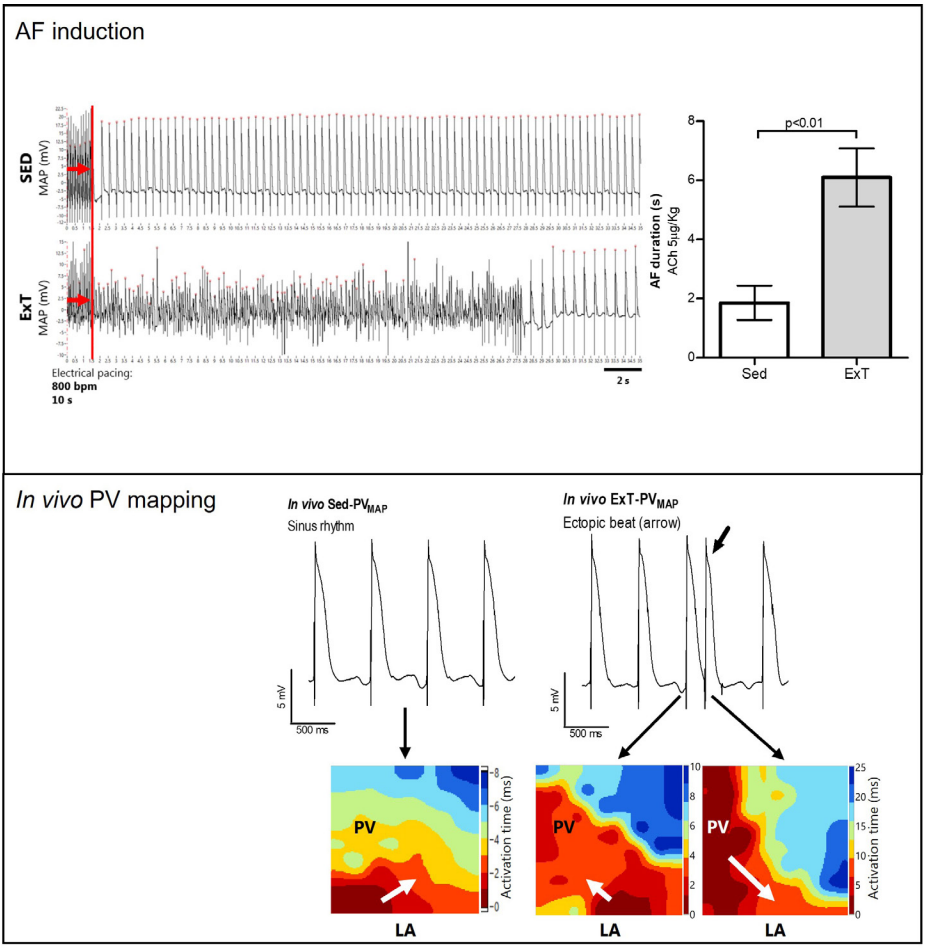
Aim: We investigated the involvement of electrophysiological pulmonary vein-myocardium (PV) remodelling in a dog-model of high-intensity exercise.

Methods: Adult Beagle dogs were randomised into sedentary (Sed, n=9) or exercise trained (ExT, n=7) groups. ExT-dogs underwent treadmill-training (16 weeks, 5 days/week, 280 min/day). At termination, epicardial stimulation, burst pacing, and concomitant PV-monophasic action-potential (AP) recordings were performed during open-chest surgery.

Results: ExT-dogs were more prone to induced-AF (Sed, 23±7%; ExT, 57±13%;p=0.05). Burst-pacing combined with 5µg/kg acetylcholine intravenous *bolus* evoked longer AF events in ExT-dogs (Sed, 1.9±0.6s; ExT, 6.1±0.9s;p<0.01). Differences in PV-AP duration were not detected between groups. Multielectrode-array mapping of the left atrial (LA)-PV junction demonstrated that the radial propagation of conducted-APs differed significantly in ExT-dogs (Sed, 96±14°; ExT, 162±24°;p<0.05). In *ex vivo* LA-PV preparations paced at 2Hz, ExT PVs conducted more APs than Sed-PVs (Sed, 33.4%; ExT, 100%;p<0.05). Following 10Hz pacing +1µM isoproterenol exposure, ExT-PVs generated more spontaneous APs (67%) than Sed-PVs (14%). These spontaneous bursts were significantly longer (Sed, 0.3±0.3s; ExT,

39.6±21.3s;p<0.05) and faster (Sed, 10.3±10.3 beats/min; ExT, 111.8±40.5 beats/min;p<0.05) in ExT-PVs than in Sed-PVs.

Conclusion: This is the first demonstration of training-induced electrophysiological remodelling of PVs in a large animal model that provides insight into the electro-anatomical PV-substrate predisposing athletes to AF.



P5-4

Exploring cardiac innervation by 3D light sheet imaging in horses with atrial fibrillation

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Background: Local hyperinnervation plays a pivotal role in the initiation and maintenance of atrial fibrillation (AF). To gain insights into the intricate neural network dynamics involved in cardiac arrhythmia, non-destructive imaging techniques capable of visualizing large tissue samples are crucial. Here, we explore the potential of whole-mount immunohistochemistry and 3D light sheet fluorescence microscopy (LSFM), for visualization of fluorescently-labelled cells within entire cleared tissue samples at high optical resolution.

Aim: This study aims to investigate the feasibility of 3D LSFM in equine atrial tissue and characterize the autonomic cardiac remodeling in a horse model of experimentally induced chronic AF.

Methods: Biopsies from the anterior descending ganglionated plexus are harvested from horses after 4-months of induced AF (n =13) and healthy control horses (n = 3). Two neuronal markers (Tyrosine hydroxylase and Choline Acetyltransferase) are stained in parallel with a vascular marker (Lectin) to determine the local density of nerves and vasculature. Whole-mount immunohistochemistry and clearing is optimized for equine heart samples by testing different depigmentation, permeabilization and imaging protocols.

Results: We demonstrate the feasibility of LSFM in equine tissue samples and show the impact of different tissue transparentization protocols for visualizing cardiac innervation.

Conclusion: 3D LSFM has the potential of offering novel insights into the role of autonomic remodeling in AF. Here we optimized 3D LSFM for equine tissue samples. The successful implementation of this imaging technique could advance our understanding of the pathophysiological mechanisms underlying AF.

P5-5

Effects of oxygen therapy on pulmonary perfusion in a porcine model of acute pulmonary embolism

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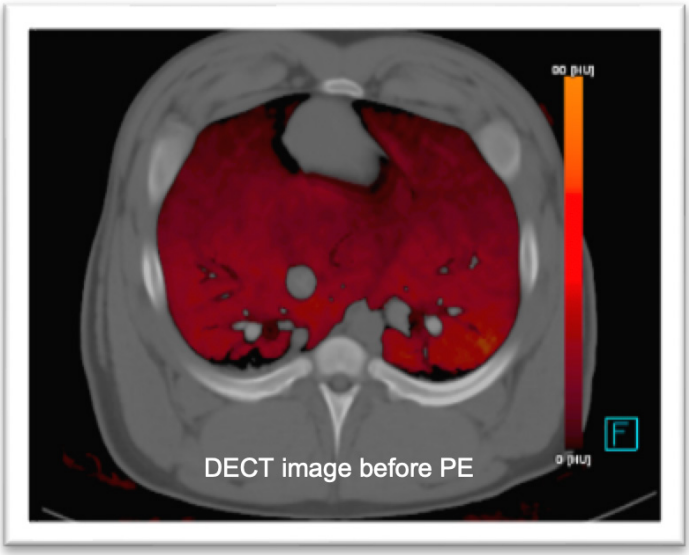
Background
Every year 300.000 people die of acute pulmonary embolism (PE) in Europe. Oxygen is key element of acute PE treatment, although knowledge about the exact mechanism is sparse. Dual Energy CT (DECT) is a new, valuable tool in assessing lung perfusion. It offers both quantitative values for perfusion and images as traditional CT pulmonary angiogram.

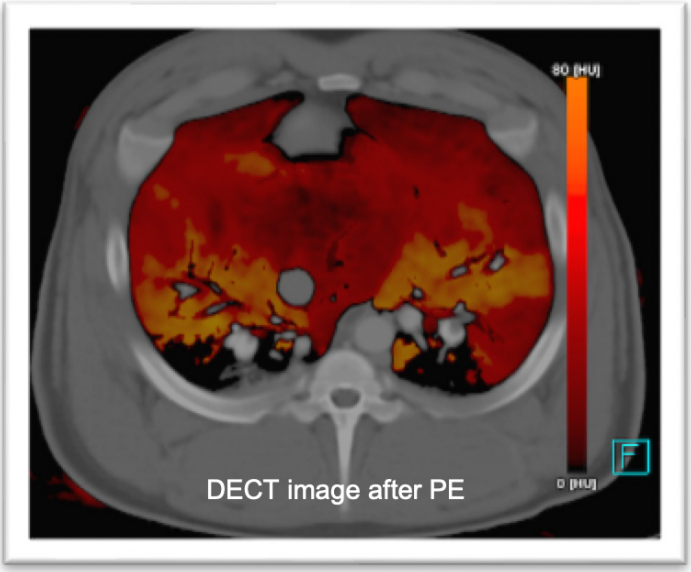
Aim
To evaluate pulmonary perfusion changes at different fractions of inhaled O2 (FiO2) in acute PE by utilizing novel software for DECT technology.

Methods
Female pigs (n=10) underwent DECT-scans at four different levels of FiO2, before and after acute PE. Images were uploaded into machine-learning based software for quantitative analyses of perfusion. The results from these analyses were compared to blood pressures obtained at the same timepoints.

Results
Imaging analysis has been initiated but is still in progress (May 2023). We have included 10 pigs and preliminary results will be presented at the conference if available.

Conclusion
This study will explore the effects of oxygen on pulmonary perfusion in acute pulmonary embolism and will help evaluate the clinical usefulness of machine-learning based software for quantification of pulmonary perfusion.


DECT image before PE


DECT image after PE

P5-6

Investigation of cardiac dysfunction in the db/db reninAAV Unx mouse model

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Background: Cardiovascular complications are now leading cause of diabetes-related morbidity and mortality, and diabetes alone increases the risk of heart failure even after controlling for other risk factors such as hypertension. The pathogenesis of diabetes-associated cardiomyopathy is not fully understood, and lack of preclinical models combining multiple risk factors has hindered the development of novel pharmaceuticals specifically targeting the heart.

Aim: The present study aimed to develop a state-of-the-art mouse model of cardiomyopathy in the setting of type 2 diabetes, kidney disease and hypertension.

Methods: Adeno-associated virus (AAV)-mediated renin overexpression was established in the uninephrectomized diabetic (db/db UNx-ReninAAV) mouse. Echocardiography and speckle-tracking were used to evaluate cardiac function 16 weeks post-AAV injection.

Results: Compared to db/+ controls the db/db UNx-ReninAAV model demonstrated an increase in body weight, hyperglycemia and albuminurea. Diastolic dysfunction was evident by a reduction in reverse peak longitudinal strain rate (RPLSR) and elevated mitral E/e' ratio. Global longitudinal strain (GLS) was reduced despite preserved ejection fraction indicative of early systolic dysfunction. Increased LV-mass and LV-diameter indicated myocardial hypertrophy. Comparison of speckle-tracking strain analysis and conventional echocardiographic parameters indicated superiority of strain analyses for detection of cardiac dysfunction.

Conclusion: The db/db UNx-ReninAAV mouse model recapitulates multiple key risk factors for development of diabetic cardiomyopathy with hallmarks of cardiac dysfunction in the setting of preserved ejection fraction. Collectively, this supports utility of the db/db UNx-ReninAAV mouse model for profiling novel drugs with potential therapeutic effects in diabetic cardiomyopathy.

P5-7

Ex vivo kidney perfusion – a model for kidney injury during cardiac surgery

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Background
Cardiac surgery involving cardiopulmonary bypass carries a high risk for development of acute kidney injury (AKI). It is difficult to investigate specific causes for AKI with in vivo studies due to the complex and multifactorial etiology. There is a need for a proof-of-concept-model to evaluate potential renoprotective treatments under standardized hemodynamic conditions.

Methods
Pigs of ~45 kg are anesthetized followed by retrieval of the kidney with viable parts. The kidney is then perfused for 2.5 hours with a combination of heparinized whole blood and Ringer's Acetate. Temperature is kept at 37˚C using a heater unit. A gasmixer is used to maintain a PaO_2 above 100 mmHg and a $PaCO_2$ at ~40 mmHg. Perfusion pressure is measured as a side-pressure on the arterial cannula and targeted 80 mmHg. Blood flow is monitored using a flow probe. We have, specifically for pigs, developed our own assays for NGAL in plasma and urine and primers for NGAL at mRNA level.

Results
We have successfully performed perfusion on 7 porcine kidneys. PaO_2 and $PaCO_2$ was kept within targets. The flow gradually increased to a mean (± SD) of 121 ± 19 mL/min within first 30 minutes. Mean pH, hemoglobin and lactate was 4.39 (± 0.1), 4.7 (± 0.4) mmol/L and 2.1 (± 0.6) mmol/L, respectively. Mean urine output was 13.7 (± 8.7) mL/h.

Conclusion
We have developed an experimental *ex vivo* animal model using porcine kidneys to evaluate potential renoprotective treatments.

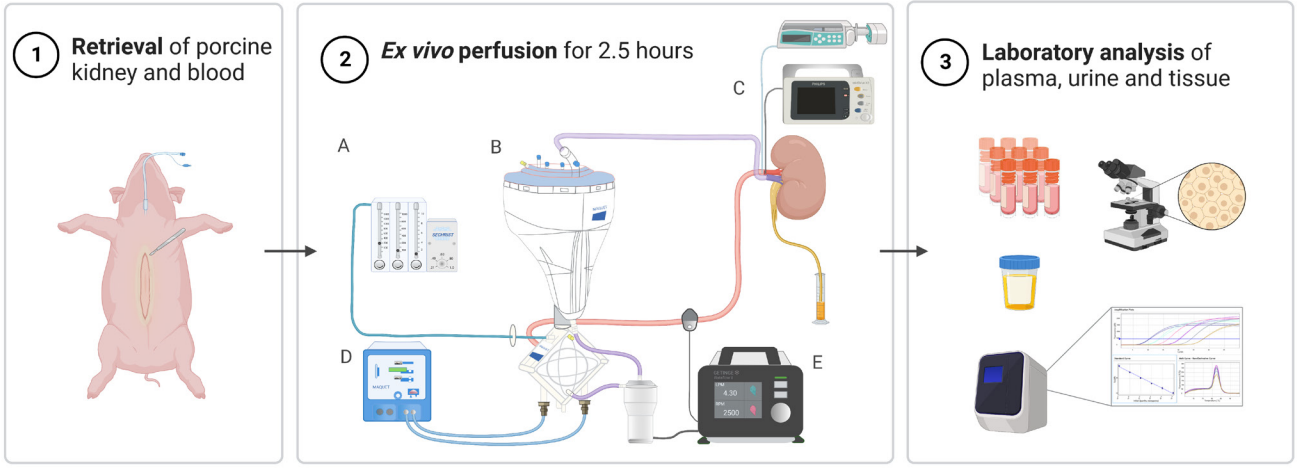

Figure 1: Schematic presentation of the *ex vivo* perfusion model. A) gas mixer with adjustment of CO_2, O_2 and air, B) hard-shell reservoir with neonatal oxygenator, C) invasive pressure module and infusion line with vasodilator, D) heater-cooler unit, E) extracorporeal life support system with centrifugeal pump and ultrasonic flow probe. (created with BioRender.com).

P5-8

Metformin Reduces Atrial Fibrillation Inducibility in Horses

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Background: Atrial fibrillation (AF) is perpetuated by electrical remodelling of the atria, characterized by a decrease in atrial effective refractory period (aERP) and an increase in AF inducibility.

Aim: This study investigates the potential of metformin, an antidiabetic drug, in preventing cardiac remodelling during chronic AF.

Methods: Twenty retired Standardbred racehorses underwent continuous right atrial tachypacing for two weeks to induce AF. Ten horses were treated with 30mg/kg metformin orally twice daily and ten served as controls. After two weeks of tachypacing, heart rhythm was evaluated and, if needed, additional tachypacing was initiated to reinduce AF. After four months of AF, the aERPs were recorded by incremental S1-S2 epicardial pacing under general anaesthesia.

Results: A significant higher proportion of metformin-treated horses (6/10) required additional tachypacing to develop self-sustained AF compared to control horses (1/10) ($p = 0.02$). Preliminary data indicate that metformin-treated horses ($n = 7$) have longer right atrial ERPs after 4 months of AF compared to controls ($n = 8$) (mean right atrial ERP ±SD 1000ms = 177+26 vs 143±26ms ($p = 0.03$) and mean right atrial ERP 500ms = 226±52 vs 189±32 ms ($p = 0.11$)).

Conclusion: These preliminary findings suggest that metformin treatment reduces AF inducibility and may protect against the AF-induced aERP shortening. This ongoing longitudinal in vivo study will provide novel insights into the atrial arrhythmogenic remodelling during AF and may shed light on anti-remodelling mechanisms of metformin.

P5-9

A Porcine Model of Human-like Chronic Thromboembolic Pulmonary Disease

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Background: Chronic Thromboembolic Pulmonary Disease (CTEPD) is a long-term complication after acute pulmonary embolism (PE). Untreated, CTEPD can lead to right sided heart failure. The pathophysiology is unknown but is believed to be multifactorial.

Aim: We aimed to develop a porcine model of chronic thromboembolic lesions that was comparable with CTEPD patients.

Methods: Twelve pigs were randomized (1:1) into: PE group and SHAM. PE group received infusion of autologous blood clots while SHAM received saline infusion. After one month, the pigs were evaluated with hemodynamics, Computed Tomography Pulmonary Angiography (CTPA), pressure volume recordings, and samples of the pulmonary arteries were collected. The samples from PE group were compared with samples from CTEPD patients who underwent pulmonary endarterectomy.

Results: One month after intervention, pulmonary arterial pressure (PAP) had decreased in both groups compared to baseline (PE group: 19.3±3.1 mmHg vs. 12.7±0.52 mmHg, p=0.03, SHAM: 17.8±3.4 mmHg vs. 12.3±2.1 mmHg, p=0.009). Right ventricular (RV) ejection fraction (EF) and RV-PA coupling had normalized in PE group (RV EF: 72±7 % vs. 78±11 %, p=0.2, RV-PA coupling: 1.4±0.5 vs. 2.0±1.1, p=0.1) while SHAM was unaltered (RV EF: 75±8 % vs. 82±5 %, p=0.2, RV-PA coupling: 2.3±1.6 vs. 2.3±0.8, p=0.98). PE group had visible clots on CTPA after one month. Histological samples from PE group showed organized thrombus with fibrotic tissue, macrophages, neointima formation and recanalization comparable to CTEPD patients.

Conclusion: Induction of large autologous PE in pigs induced chronic thromboembolic human-like lesions without pulmonary hypertension.

P5-10

Evaluation of a multi-hit mouse model of Heart Failure with Preserved Ejection Fraction

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Background
Underlying causes for heart failure with preserved ejection fraction (HFpEF) are not fully understood due to the complex pathophysiology of the disease. The patients often have several chronic co-morbidities such as hypertension, diabetes and obesity. There is no effective treatment for the patient with HFpEF, possibly because we do not understand the disease mechanism. We need a translational animal model that accurately mimics the cardiovascular phenotype of HFpEF to study the pathological mechanisms and test new potential treatments.

Aim
The aim of this study is to develop and validate a mouse model of HFpEF.

Methods
In order to develop a multi-hit model, male C57Bl/6 mice at 8 weeks of age were divided into two groups. The first two hits were introduced by feeding both groups a high fat diet (60% fat) and dissolving L-NAME (NO-synthase antagonist; 1 g/L) in the drinking water, to induce obesity and hypertension, respectively. 1 group was introduced to an additional third hit by receiving 1% NaCl in their drinking water. The treatment groups were compared to an untreated age-matched control group. Cardiac performance was evaluated in vivo by echocardiography before study start and every 4 weeks. After 16 weeks, preload dependency was tested ex vivo in isolated hearts.

Results and Conclusion
Preliminary results will be presented.

P5-11

Medium chain fatty acids as dietary tool to improve cardiac metabolism and function in heart failure

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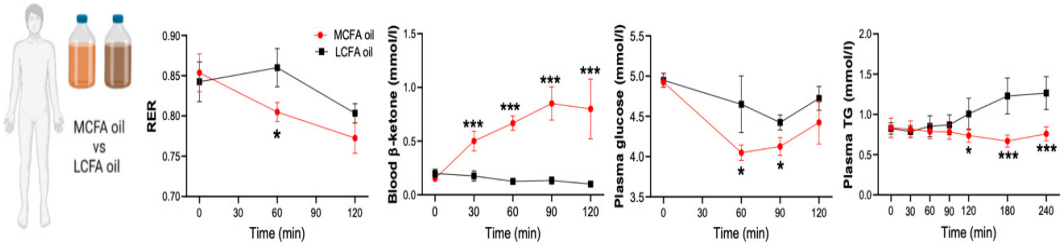
Background

Myocardial metabolic remodeling constitutes an inherent part of heart failure (HF) progression, with reduced cardiomyocyte fat oxidation (FAOX) and an increased reliance on ketone bodies (KB). Accordingly, increased KB availability is suggested to improve cardiac function in HF. Medium-chain fatty acids (MCFAs) have the ability to increase whole-body FAOX, induce ketogenesis, and mediate several cardio-metabolic health benefits.

Our preliminary observations in healthy individuals demonstrate that acute intake of 35g MCFAs increases circulating KB levels, whole-body FAOX, and lowers postprandial plasma glucose and triacylglycerol levels compared with LCFA.

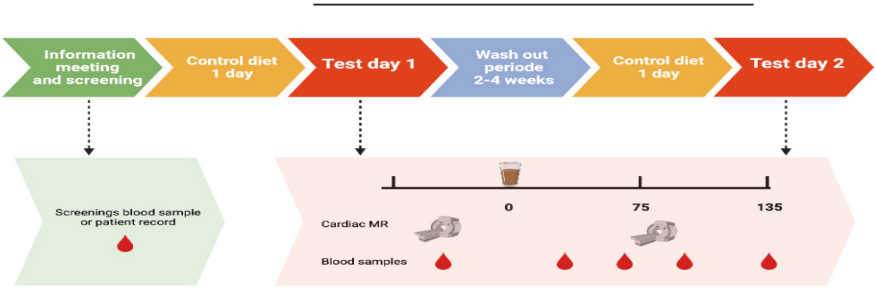


We hypothesize that MCFA consumption will improve cardiac function, by improving and KB availability, hence restore the cardiac metabolic dysfunction, and might elicit effects on cardiovascular-relevant blood parameters.

The aim is to investigate the effect of MCFA intake on heart function in patients with HF and molecular mechanisms in mouse models.

Methods

Participants with HF and matched healthy individuals will be included in a block-randomized cross-over study. il. Heart function will be assessed by cardiac magnetic resonance imaging before and following acute intake of 45 g of either MCFA or long-chain fatty acid (LCFA) oils. and whole-body substrate metabolism will be investigated.



Furthermore, in rodents HF or impaired cardiac FAOX will be induced to investigate whether MCFA intake can improve cardiac function, metabolism. Potential molecular mechanisms will be studied.

Future perspectives

We expect that MCFA consumption will improve cardiac function by improving fat oxidation and ketone availability. This project will clarify the therapeutic potential of MCFA intake for HF patients and elucidate potential underlying mechanisms.

P6-1

Addressing Challenges in Implantable Cardioverter Defibrillators through Self-Supervised Learning Techniques

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Implantable cardioverter defibrillators (ICDs) play a crucial role in managing cardiovascular diseases, including atrial fibrillation (AFib) episodes. However, three primary challenges have been recognized associated in relation to this device: (i) improving patient selection, (ii) optimizing the initial programmable parameter configuration, and (iii) enhancing AFib episode forecasting. Compounding these challenges is the difficulty in accurately annotating the vast amounts of data associated with ICDs.

To tackle these issues, this research proposes the utilization of Self-Supervised Learning (SSL) techniques. So far, a novel SSL procedure has been developed, tailored specifically for electrocardiogram (ECG) signals. This approach has demonstrated significant advancements. (i) It has achieved a 10% increase, compared to other existing SSL methods, in the identification of AFib across various patients and databases, with the utilization of only a few labeled instances. (ii) It also captures subject-specific characteristics present in the temporal data, as demonstrated by the formation of subject-based clusters when a Principal Component Analysis (PCA) is performed on the learned representations.

Overall, this research explores the potential of Self-Supervised Learning as a powerful technique in addressing challenges related to ICDs. The developed SSL procedure exhibits promising results in learning representations that contain valuable information. These representations enable us to comprehend the information embedded within the physiological signals of the heart and employ it to better patient outcomes through enhanced ICDs devices.

P6-2

Identification of Digital Biomarkers for Heart Failure

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**Lead presenter*
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[2] Bispebjerg-Frederiksberg Hospital, Denmark

Background
Digital biomarkers are becoming more prevalent today due to their non-invasive qualities and suitability for long-term monitoring. These biomarkers can vary across a wide spectrum from ambient temperature sensors, voice, ECG Holter monitoring, etc. Such devices are also scalable for screening large populations for certain diseases. In this work, we try to identify and quantify such digital biomarkers for predicting Incidence of Heart Failure (HF) or HF Worsening.

Aim
Our aim is to first build a platform to collect real-time data from various sensors in a patient's ambulatory living conditions. Once we have the technology to enable further data analysis, we plan on using deep learning algorithms to find anomalies in ECG and other sensors in a patient's normal environment.

Methods
We identify existing digital biomarkers through a thorough literature review and try to include and enable collection of all or most of these into our mobile platform. To have longitudinal data, we also plan on conducting a technical study to collect data (N=50) over a year to find signs of HF worsening. With the available data, we can find the differences however minute between a healthy and a worsening heart.

Results
Research is still in early stages to have conclusive results.

Conclusion
We hope to be able to device a Risk Score based on available data that is accurate in identifying incident HF or HF worsening.

P6-3

Automated Detection of Cardiac Rest Period for Trigger Delay Calculation in Coronary MR Angiography

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Background

Accurate determination of the trigger delay to place the acquisition window within the quiescent part of the cardiac cycle is critical to reduce cardiac motion in Coronary Magnetic Resonance Angiography (CMRA). This is currently reliant on operator-led decision making, which can negatively affect consistency of scan acquisition. Novel deep learning (DL) derived software may overcome these issues by automation of cardiac rest period detection.

Aim

To determine if novel DL software can accurately calculate the optimal trigger delay for use in CMRA.

Methods

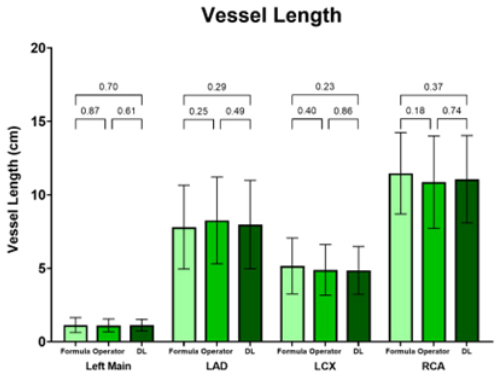
Twenty individuals (female = 9) were investigated using a 0.9 mm^3 image-navigator (iNAV)-based motion-corrected CMRA sequence. Each individual was scanned three times utilising different strategies for determination of the optimal trigger delay: 1) the novel DL software, 2) an experienced operator decision, and 3) a standardised formula. Methodologies were compared using custom-made analysis software to assess visible coronary vessel length and coronary vessel sharpness.

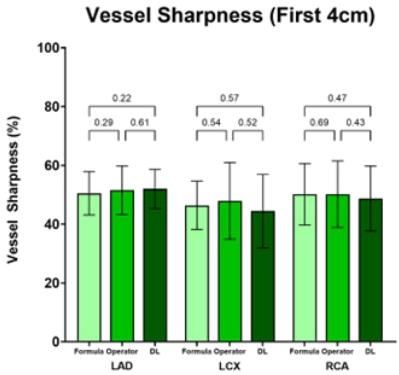
Results

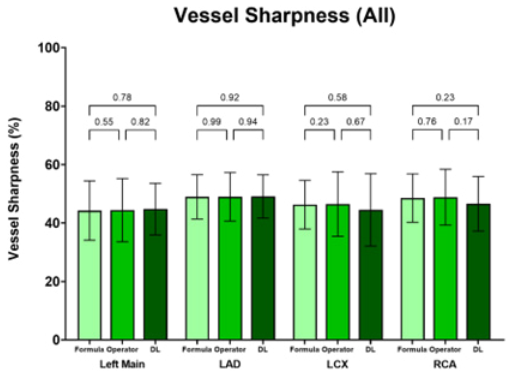
There was no difference in image quality between each method to determine trigger delay, as assessed by visible coronary vessel length and coronary vessel sharpness for both the entire vessel and the first 4 cm of each vessel. Calculation of trigger delay did not differ between the 3 methodologies, however the operator-led method calculated a significantly shorter trigger delay compared to the formula (669.2 ± 130.5 vs 719.0 ± 81.6ms, p = 0.017).

Conclusion

Novel deep-learning derived automated software can effectively determine the optimal trigger delay for acquisition of CMRA and thus may simplify workflow and improve reproducibility.







P6-4

Quantitative pulmonary perfusion in chronic thromboembolic pulmonary hypertension and acute pulmonary embolism

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Background
Guidelines on severity assessment of chronic thromboembolic pulmonary hypertension (CTEPH) and acute pulmonary embolism (PE) rely on hemodynamic and clinical parameters, imaging, and laboratory findings. Pulmonary perfusion is not widely considered, as no reliable and quick evaluation methods for quantification of perfusion have been validated. Dual-energy computed tomography pulmonary angiography (DE-CTPA) can provide fully automated, user- independent, quantification of pulmonary perfusion concurrent with traditional CTPA images for diagnosis of the diseases.

Aim
To investigate the differences in quantitative lung and lobar perfusion metrics between CTEPH and PE patients.

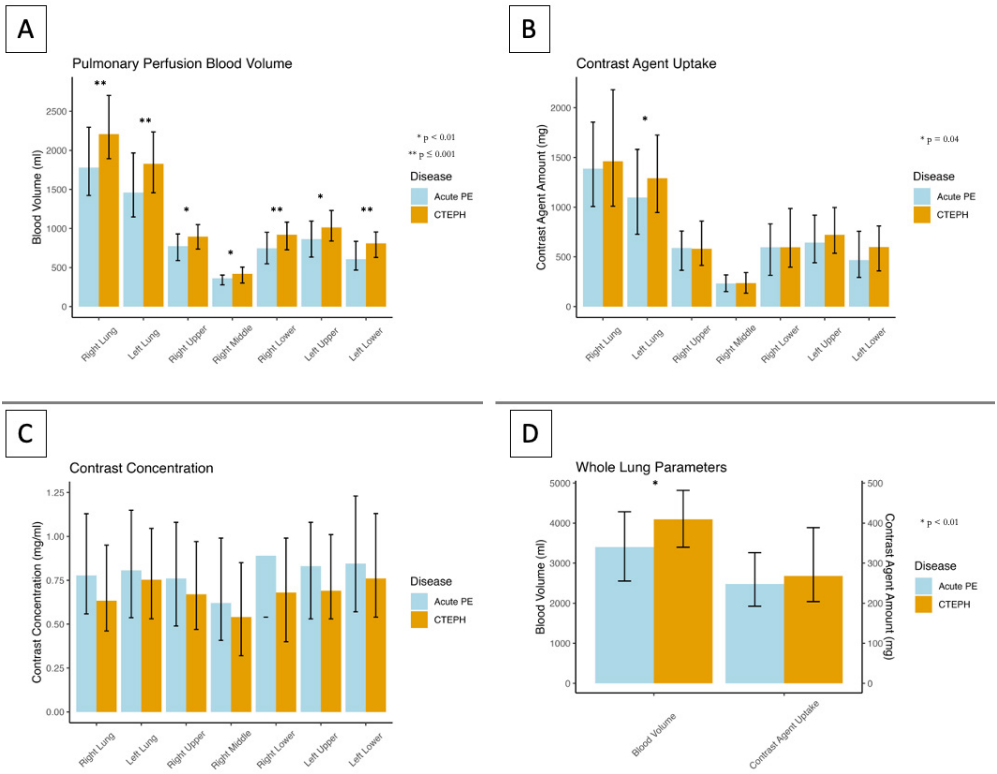
Methods
We included patients (n=162) diagnosed with acute PE or CTEPH and scanned using DE-CTPA between 2019 and 2023. We processed DE-CTPA images from 81 PE patients (median age 69 years [60; 76]) and 81 CTEPH patients (median age 71 [61; 78]) using the automated, machine-learning based eXamine software to obtain quantitative lung and lobar perfusion data.

Results
Whole lung blood volume was lower ($p<0.001$) in PE patients (median 3399 mL [2554, 4284]) than in CTEPH patients (median 4094 mL [3397, 4818]). The same was observed at single lung and lobar level (figure 1A). Multivariate comparison encompassing all perfusion variables (figure 1A-D) showed a difference between the two groups ($F=6.15$, $Pr>(F)=0.004$). We found poor correlation ($r<0.3$) between perfusion parameters and clinical parameters.

Conclusion

Lung and lobar perfusion are lower in patients with acute PE than patients with CTEPH as highlighted by differences in DECT-derived pulmonary blood volume parameters.

Figure 1



P6-5

Elevated systolic exercise blood pressure is associated with elevated 24-hour mean systolic blood pressure already in the young

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Background: Increased exercise blood pressure (BP) is an emerging independent risk factor for cardiovascular disease. The regulation of blood pressure during exercise may, already in young adults, depict who are at immediate risk of conventionally determined 24h hypertension.

Aim: To investigate the relationship between exercise and 24h BP in young adults (15-17-years) still unaffected by age-related stiffening of the conductance arteries.

Methods: As part of the CARMA-ART study investigating cardiovascular regulation in 300 young adults conceived after natural or artificial conception. Participants underwent incremental exercise testing and 24h BP measurement. Exaggerated exercise BP was systolic BP>210mmHg in males and >190mmHg in females. Hypertension on 24h BP was systolic BP >130 mmHg.

Results: 80 participants were included (43 female). Mean 24h systolic BP was 125mmHg 95%CI:[114;135] in participants with exaggerated exercise BP (n=20) compared to 118mmHg 95%CI:[109;125] in participants with normal exercise BP ($p<0.001$ adjusted for sex, conception method, maximal workload, and physical activity). A linear relationship was established between 24h BP and maximum systolic exercise BP (mean 24h BP = 97mmHg + 0.138 x maximal exercise BP, $p=0.01$). More participants with exaggerated exercise BP had hypertension by 24h BP(7/20) compared to other participants(2/60); risk ratio:10.5, 95%CI:[2.4;46.5].

Conclusion: Exaggerated exercise BP may represent a fundamental pathophysiological BP regulation that precedes or even reveals sustained BP elevation and hypertension in young seemingly normotensive adults, and a technique for early identification of future cardiovascular risk.

P6-6

Physical activity levels are not reflected in cardiac dimensions and function at rest in postmenopausal women

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Background In women, the risk of cardiovascular disease increases significantly after the onset of menopause.

Aim We aimed to describe the impact of more than two decades of differentiated physical activity on cardiac morphology and function in (late) postmenopausal women.

Methods The study design was cross-sectional with age-matched non-smoking, non-medicated healthy late postmenopausal women divided in to three groups based on their self-reported physical activity level with regards to intensity and volume over the past decade. Thirty-one women were included in the study (age of 61 ± 1 years; 11 ± 2 postmenopausal years; body mass index 23 ± 3 kg/m2) and divided into three groups based on activity levels categorized as sedentary (SED; ≤1 h exercise weekly; n=9); moderately active (MOD; ≥2 ≤6h exercise weekly; n=11) and highly active (HIGH; <4 h exercise weekly; n=14). Cardiac function and dimensions were assessed at rest with transthoracic echocardiography.

Results Maximum oxygen uptake levels differed significantly ($p<0.05$) between the three groups (24.9 ± 5.8; 30.5 ± 5.8; 38.4 ± 4.4 ml O2/kg/min respective, for SED, MOD and HIGH). There were no differences ($p > 0.05$) between the three groups in left ventricular morphology, systolic function, diastolic function, and right ventricular function.

Conclusion These data show that significant differences in activity level and maximal oxygen consumption do not appear to be reflected in any conventional echocardiographic measures of cardiac diastolic or systolic function.

P6-7

Non-benign Hemodynamic Response to Exercise in Patients with Asymptomatic Moderate Aortic Stenosis and Preserved Left Ventricular Ejection Fraction – An Invasive Exercise Hemodynamic Study

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Background: Left ventricular (LV) diastolic dysfunction (DD) in moderate aortic stenosis (AS) with preserved LV ejection fraction (LVEF ≥50%) is associated with a higher mortality rate and aortic valve replacement (AVR). Exercise pulmonary hypertension (PH) and elevated pulmonary capillary wedge pressure (PCWP) under exercise are hallmarks of LV DD, and are highly prevalent in asymptomatic severe AS. However, the hemodynamic exercise response in patients with moderate AS is unknown.

Aim: To characterize the hemodynamic response to exercise in moderate AS with preserved LVEF by estimating the prevalence of:

1. Postcapillary pulmonary hypertension (pcPH) at rest
2. Exercise pcPH
3. Elevated PCWP at rest and under exercise

Methods: A cross-sectional descriptive study in patients with asymptomatic moderate AS (aortic valve peak jet velocity (AV Vmax) ≥2.5<4m/sec) and preserved LVEF underwent right heart catheterization (RHC) at rest and under cycle ergometer exercise.

Results: In 42 patients with median age 74 (69-78) years, 76% males, mean LVEF 58±4%, mean AV Vmax 3.1±0.4m/s, AV mean peakgradient 24±7mmHg, AV max peakgradient 40±10mmHg, and an aortic valve area of 1.2±0,3 cm^2. The prevalence of pcPH was 31.0%, exercise pcPH 47.6%, elevated rest-PCWP 42.8% and exercise-PCWP 66.7%. The RHC was safe with no complications.

Conclusion: Exercise RHC unmasked a high prevalence of pcPH and elevated PCWP in asymptomatic moderate AS with preserved LVEF, a potentially non-benign stage that might benefit from early AVR.

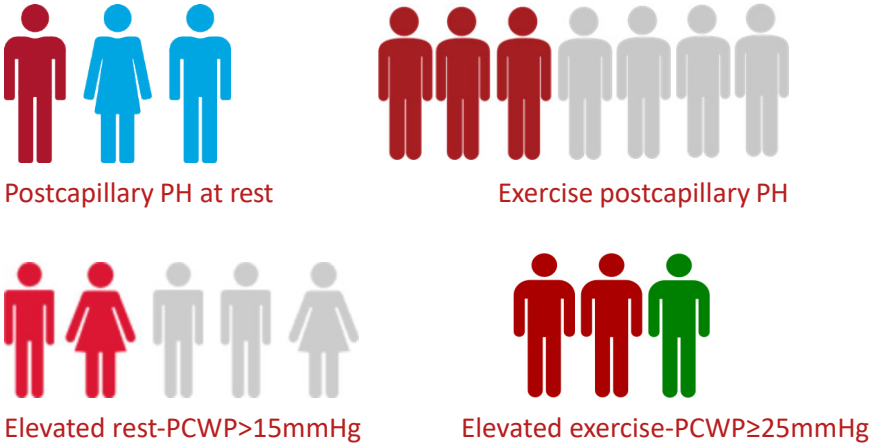

Figure 1 *– Prevalence of PH and elevated PCWP in moderate AS patients PH: pulmonary hypertension; PCWP: pulmonary capillary wedge pressure; AS: aortic stenosis.*

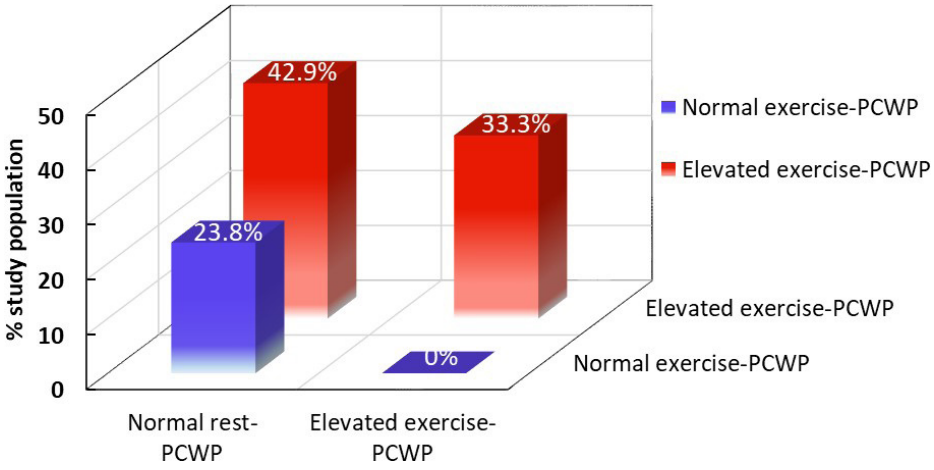

Figure 2 *– PCWP at rest and during peak cycle exercise in moderate AS patients PCWP: pulmonary capillary wedge pressure; AS: aortic stenosis.*

P6-8

Automated image analysis for preclinical speckle-tracking echocardiography

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Background: Echocardiography (ECG) is a well-established imaging modality for assessing cardiac function and morphology in both clinical and preclinical research. However, ECG analysis is time-consuming and involves significant operant bias which limits output and accuracy in ECG outcome studies.

Aim: The aim of the current study was to design and implement an unbiased and fully automated machine-learning based pipeline for in-depth characterization of preclinical ECG data, including cardiac strain, in mouse models of heart failure.

Methods: A sequential block of three neural networks (NN) was employed to, (1) classify ECG views, (2) segment and extract cardiac parameters from the parasternal long axis (PLAX) and parasternal short axis (PSAX) views, and (3) evaluate cardiac strain. The machine-learning based pipeline was tested and validated in a standard mouse model of heart failure.

Results: Our AI-model successfully classifies the Digital Imaging and Communications in Medicine (DICOM) images and redirects them to their corresponding NN. Resulting AI-based ECG data were highly correlated with corresponding parameters calculated manually using the VevoLAB software.

Conclusion: Collectively, our machine-learning based pipeline markedly increased preclinical ECG data throughput, thus being highly applicable in preclinical drug discovery for heart failure.

P6-9

Detection of high-risk coronary atherosclerotic plaques using Magnetic Resonance Imaging

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Background:Assessment of coronary plaque composition in addition to traditional luminal stenosis detection is central for predicting and preventing acute coronary events in patients with coronary artery disease (CAD). A high burden of lipid-rich plaques has consistently been linked to increased risk of coronary events and mortality. Coronary Magnetic Resonance Angiography (CMRA) allows visualization of the coronary arteries without the use of ionizing radiation or contrast agents. State-of-the-art CMRA utilizing T1-weighted imaging has emerged as an approach for detecting high-risk plaques with significant lipid content visualized as high-intensity plaques.

Aim: The objective is to establish a correlation between plaque characteristics observed on T1-weighted CMRA and those visualized on coronary CT angiography (CCTA).

Methods: In an observational study, 120 patients with ≥1 proximal coronary low-attenuation plaque will be recruited. CMRA, CCTA and blood samples will be performed at inclusion and repeated 12 months later. The primary endpoint is plaque progression at 12-month follow-up in patients with high-intensity coronary plaques detected by CMRA versus patients without. Plaque quantification will be performed manually for CMRA images and semi-automatically using dedicated software for CCTA images.

Results: Data collection is ongoing. Preliminary results including a comparison of high-intensity plaques on CMRA and corresponding plaque features on CCTA from 43 patients will be presented.

Conclusion: CMRA represents a future option for CAD diagnosis. If T1-weighted CMRA can identify plaques with high-risk features, it has the potential to enhance risk stratification and optimize treatment of patients with CAD.

P7-1

The Role of Pyruvate Dehydrogenase Kinase-1 in cardiovascular diseases

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Introduction

Atherosclerosis is a chronic inflammatory disease driven by maladaptive immune responses. Novel insights into the regulation of immune processes have revealed that changes in intracellular metabolism can strongly affect inflammation. Pyruvate dehydrogenase kinase-1 (PDK1) has been identified as a major metabolic enzyme regulating immune cell activation. Preliminary data suggest that PDK1 expression is associated with symptomatic atherosclerotic disease in humans, and that pyruvate dehydrogenase (PDH) activity could be a major metabolic step regulating inflammation. Whether the PDK/PDH axis play a role in vascular inflammation and atherosclerotic cardiovascular disease remains unclear and will be explored in this project.

Aims and Methods

The project aims at investigating PDK1-driven inflammatory mechanisms and evaluating the potential of targeting PDK1 to modulate experimental atherosclerosis, as well as investigating its potential as a biomarker for disease progression and/or complications. To achieve our goals, we will combine cell culture systems, genetically modified animal models of disease, and unique human peripheral blood samples, as well as perform deep molecular profiling using FACS, immunostaining techniques, qPCR, Seahorse Bioscience technology, and mass spectrometry that will pinpoint the role of PDK1 in modulating vascular and immune cell responses.

Conclusion

Better understanding of the molecular mechanisms driving atherosclerosis will help accelerate the development of new diagnostic modalities, as well as new therapies against major life-threatening diseases, including myocardial infarction and stroke, which are the major cause of death worldwide.

P7-2

Targeting the kynurenine pathway of tryptophan degradation to combat abdominal aortic aneurysm

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**Lead presenter:*
Institute of Molecular Medicine, University of Southern Denmark, Odense

Generally asymptomatic, rupture of abdominal aortic aneurysms (AAA) leads to lethal bleeding and death in 65-85% of cases. While treatment relies almost exclusively on surgical intervention, proven drugs to prevent AAA remain absent. Strong evidence indicates that targeting the inflammatory process driving AAA pathogenesis could be a suitable approach against this disease. Our group has shown that modulating the kynurenine pathway (KP) of tryptophan degradation halts vascular inflammation and atherosclerosis. Whether targeting of the KP can protect against AAA remains unclear. This project will characterize in depth the KP in AAA and explore new potential therapeutic and diagnostic targets against it. In this context, we will i) access and analyze KP enzymes and metabolites on unique human AAA samples, ii) investigate and detail molecular process in cell culture systems, and iii) test lead KP candidate targets in animal models of AAA. This work carries the potential to reveal whether the KP enzymes and metabolites can regulate major inflammatory components in the vascular wall, including activation of the NFκB and the inflammasome on macrophages, antigen presentation and T cell expansion, and the deleterious dedifferentiation of vascular SMCs.

P7-3

Characterization of Angiotensin-(1-5) as a biologically active component of the Renin-Angiotensin system

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**Lead presenter*
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Background: Angiotensin-(1-5) has been considered a biologically inert peptide within the Renin-Angiotensin System (RAS). It is cleaved from Angiotensin-(1-7) by angiotensin-converting enzyme (ACE) and its plasma levels increase in response to recombinant human ACE2.

Aim: We propose that Angiotensin-(1-5) is a biologically active peptide within the protective arm of the RAS.

Methods: Nitric oxide (NO) release was measured in human aortic endothelial cells (HAEC) or Chinese hamster ovary cells transfected with the AT_2-receptor (AT_2R-CHO) or non-transfected (CHO-NT) by DAF-FM diacetate fluorescence staining. Ang-(1-5) signaling patterns were evaluated by mass spectrometry-based phosphoproteomics in HAEC treated with Ang-(1-5) (1µM) for 1, 3, 5 or 20 minutes.

Results: Ang-(1-5) (1µM) significantly increased NO production in HAEC and AT_2R-CHO. This response was AT_2R-specific since no effect was observed in HAEC treated with PD123319 (AT_2R antagonist) or in CHO-NT. Induction of NO generation by Ang-(1-5) in AT_2R-CHO cells was concentration-dependent [E_{max}= 50.8%, EC_{50}= 45nM]. Treatment of HAEC with Ang-(1-5) (1µM) significantly modified the phosphorylation status of 831 proteins at 1799 residues. The majority of residues (1079 out of 1799) was dephosphorylated, and most changes occurred after 20 minutes. Functional bioinformatic analysis revealed a cluster of proteins involved in the regulation of cell cycle and cell division.

Conclusion: Angiotensin-(1-5) is an endogenous, high-efficacy AT_2R agonist. The early signaling phosphorylation patterns resemble those of other protective RAS agonists, such as C21 and Angiotensin-(1-7).

P7-4

Oral Dosing Hypertensive Rats with Anti-Inflammatory Agent Colchicine Gives Vascular Function Recovery

Jennifer van der Horst[1], Samuel Baldwin[1], Joakim Bastrup[1], Olga Kudryavtseva[1], Salomé Rognant[1], Johs Dannesboe[1], Anthony Mozzicato[1], Morten Thomsen[1] & Thomas A Jepps[1]

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[1] University of Copenhagen, Denmark

Abstract Format (Obligatory):
Developing novel therapies to prevent and treat hypertension is crucial, as both resistant and controlled hypertension are associated with increased all-cause mortality and cardiovascular disease risk. Recently, we demonstrated the potential of colchicine, an anti-inflammatory agent, to restore vascular function in *ex vivo* arteries from hypertensive rats, although its long-term effects in hypertension remain unclear.

This study aimed to investigate the impact of colchicine on blood pressure, vascular function, vascular remodeling, and proteomic changes in normotensive (WKY) and hypertensive (SHR) rats.

Eleven-week-old WKY and SHR were used for all experiments. *In vivo*, animals were orally administered placebo or colchicine (0.05mg/kg) once daily for four weeks, with continuous blood pressure monitoring. *Ex vivo* isometric tension recordings of third-order mesenteric arteries assessed vascular function, while Sirius red staining and electron microscopy evaluated vascular remodeling. Mass spectrometry was performed on isolated arteries to investigate proteomic changes.

Four weeks of colchicine treatment in SHRs resulted in reduced blood pressure compared to placebo, with no acute effect on blood pressure. Colchicine treatment enhanced responsiveness to SNP, isoprenaline, and ML213 in *ex vivo* arteries of SHRs. Vascular remodeling analysis revealed a reduced media-to-lumen ratio in colchicine-treated SHRs.

In conclusion, long-term colchicine treatment effectively reduced blood pressure in SHRs, potentially through improved vascular responsiveness and reduced remodeling. These findings position colchicine as a promising novel therapeutic candidate for the treatment of hypertension.

P7-5

Proteomic mapping reveals dysregulated angiogenesis in the cerebral arteries of rats with early-onset hypertension

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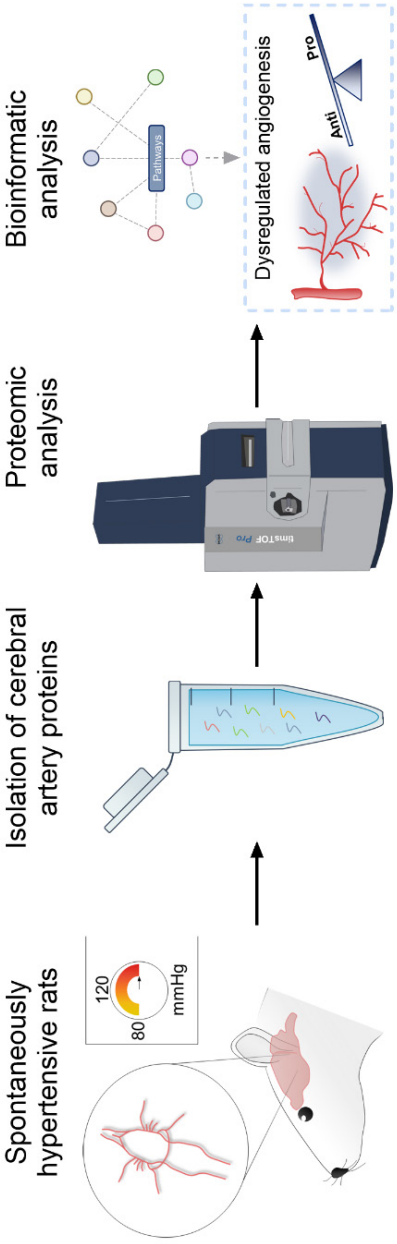
Background: Hypertension is associated with presence of vascular abnormalities, such as remodeling and rarefaction. These processes play an important role in cerebrovascular disease development, however, the mechanistic changes leading to these diseases are not well characterized.

Methods: Using data-independent acquisition-based mass spectrometry analysis, we determined the protein changes in cerebral arteries in pre- and early-onset hypertension from the spontaneously hypertensive rat (SHR), a model that resembles essential hypertension.

Results: Our analysis identified 125 proteins with expression levels that were significantly up- or downregulated in 12-week old SHRs compared to normotensive Wistar Kyoto rats. Using an angiogenesis enrichment analysis, we identified a critical imbalance in angiogenic proteins, promoting an anti-angiogenic profile in cerebral arteries at the early-onset of hypertension. In a comparison to previously published data, we demonstrate that this angiogenic imbalance is not present in mesenteric and renal arteries from age-matched SHRs. Finally, we identified two proteins (Fbln5 and Cdh13), whose expression levels were critically altered in cerebral arteries compared to the other arterial beds.

Conclusion: The observation of an angiogenic imbalance in cerebral arteries from the SHR reveals critical protein changes in the cerebrovasculature at the early-onset of hypertension and provides novel insight into the early pathology of cerebrovascular disease.

Graphical abstract:


Spontaneously hypertensive rats
120
80
mmHg
Isolation of cerebral artery proteins
Proteomic analysis
timsTOF Pro
Bioinformatic analysis
Pathways
Dysregulated angiogenesis
Pro
Anti

P7-6

Human atherosclerotic plaques contain oxidant-modified extracellular matrix proteins

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Compared to stable atherosclerotic plaques, unstable rupture-prone plaques contain higher levels of activated inflammatory cells that release the enzyme myeloperoxidase (MPO). MPO generates potent oxidants, including hypochlorous acid (HOCl), which may damage extracellular matrix (ECM) proteins in the plaques, potentially causing destabilization and rupture.

The aim of this study is to investigate whether human carotid artery atherosclerotic lesions, obtained from endarterectomy surgery, contains oxidant-modified ECM-proteins, and whether these changes correlate with, and determine plaque stability.

Proteins were extracted from human carotid artery plaques, digested with proteolytic enzymes, then subject to high pH reverse-phase fractionation. Fractions were subjected to liquid-chromatography mass spectrometry (LC-MS) to identify parent peptides and oxidation products. In vitro studies were carried out by immunoblotting, ELISA and LC-MS to validate the in vivo data.

9542 proteins were identified from plaques. Multiple proteins were shown to contain oxidative modifications. The ECM glycoprotein fibronectin (FN) was amongst the most abundant and heavily modified proteins, with 21 specific sites in FN detected as chlorinated or nitrated species. Purified human plasma FN exposed to increasing doses of HOCl, or an MPO-enzymatic system, underwent similar chemical and structural changes, with formation of oxidation-derived species. These products increased in a concentration dependent manner with increasing HOCl doses.

Our data indicate that human carotid artery atherosclerotic plaques contain oxidant-modified ECM proteins. These oxidative modifications alter protein structure, as indicated by the purified FN studies, which may perturb protein function and weaken plaque structure.

P7-7

Iodide as a potential therapeutic in atherosclerosis

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Background
Myeloperoxidase (MPO) is an enzyme released at sites of inflammation which generates powerful oxidants. It is strongly associated with atherosclerosis with both MPO and its reaction products being present in human atherosclerotic plaques. Inhibition of oxidant formation by MPO may therefore have therapeutic potential in preventing atherosclerosis. MPO generates the oxidant hypochlorous acid from chloride, but it can also use the alternative substrates iodide (I-) and thiocyanate (SCN-) to form less damaging species. We hypothesize that I-, alone or in combination with SCN-, might reduce atherosclerotic plaque development by decreasing oxidative damage and inflammation.

Methods
Apolipoprotein E deficient mice were fed a western-type diet for 16 weeks with concomitant supplementation with I- (18 µM) and/or SCN- (10 mM) in the drinking water. Plaque burden was examined in the aortic arch by en face analysis. In the aortic valves, plaque size and composition were evaluated by histological staining.

Results
Treatment with I- decreased atherosclerotic plaque burden in the aortic arch but not the aortic valves. I-, alone and in combination with SCN-, reduced plasma cholesterol levels. Measurements of thyroid hormone levels and body weight indicated that treatment did not affect basic metabolism.

Conclusion
I- appears to have positive effects in reducing atherosclerosis. Whether the reduction in plaque burden observed with I- is due to changes in lipid metabolism or decreased MPO-derived oxidative damage remains to be clarified. However, I- supplementation has potential as a cheap, safe, and readily available primary prevention of atherosclerosis.

P7-8

Acute, pro-contractile effects of prorenin on rat mesenteric arteries

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Background: Prorenin and the prorenin receptor ((P)RR) are new key players in the renin-angiotensin-aldosterone system. The ((P)RR) is broadly expressed through the body, including the vasculature but its role is not fully understood.

Aim: Elucidate the direct effect of prorenin on arterial contractility.

Methods: Within rat mesenteric arteries, immunostaining and proximity ligation assays were used to determine the interacting partners of (P)RR in freshly isolated vascular smooth muscle cells (VSMCs). Wire myography was used to examine the functional effect of prorenin. Simultaneous changes in $[Ca^{2+}]_i$ and force were recorded in arteries loaded with Fura-2AM. Spontaneously transient outward currents were recorded via whole cell patch clamp configuration in freshly isolated VSMCs.

Results: We found that the (P)RR co-localizes with the V-ATPase, caveolin-1, ryanodine receptors and large conductance Ca^{2+} activated K^+ channels (BK_{Ca}) in VSMCs. $[Ca^{2+}]_i$ imaging and isometric tension recordings indicate that 1 nM prorenin is able to enhance α1-adrenoreceptor-mediated contraction. This was associated with an increase in the number of Ca^{2+} waves, independent of voltage-gated Ca^{2+} channels activation. Incubation of VSMCs with 1 nM prorenin decreased the amplitude and frequency of spontaneously transient outward currents and attenuated BK_{Ca}-mediated relaxation. Inhibition of the V-ATPase with 100 nM bafilomycin prevented prorenin-mediated inhibition of BK_{Ca}-derived relaxation.

Conclusion: Prorenin enhances arterial contractility by increasing store-operated Ca^{2+} release and inhibition of BK_{Ca}. It is likely that this effect is mediated through a local shift in pH upon activation of the (P)RR and stimulation of the V-ATPase.

P7-9

Metabolomics as a novel candidate for the pathogenesis of hypertension

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The current pharmacopeia of hypertensive fails to ameliorate hypertension in many patients, highlighting the need for new treatment strategies for hypertension. This exploratory investigation aimed to determine novel candidates for the pathogenesis of hypertension in mesenteric arteries (MAs) from spontaneously hypertensive rats (SHRs) and normotensive (WKY) control rats.

In light of previously observed dysregulation of proteins associated with metabolomics, we focused on lipidomic and mitochondrial function changes in MAs via thin layer chromatography (TLC), radiolabeled free fatty acid uptake/incorporation, electron microscopy and high-resolution respirometry via oxygraph.

Triglyceride content was significantly reduced within MAs, but not renal nor aortic lysates from SHRs compared to WKY. Further, no change in content of free fatty acids nor free cholesterol was observed. Overnight incubation of MAs from WKYs with agonists of the following receptors, AT_{II}, α_1-AR and β-AR had no effect on lipid content. Radiolabeled free fatty acid uptake and incorporation assay indicates a trend towards reduced incorporation of fat into MAs from SHRs when compared to WKY. O_2 flux rate (pmol-s^{-1}-mg^{-1}) when uncoupling electron transport via FCCP revealed an increase in total electron transport capacity, independent of a change in the gross structure of mitochondria, between MAs of SHRs compared to SHRs.

In conclusion, vascular tissue from hypertensive animals are in a state of metabolic distress as demonstrated by an increase in triglyceride metabolism, reduced fat incorporation and enhanced electron transport. Though the underlying mechanism remain unclear, it merits further investigation.

P7-10

Exploring the role of LRP2 O-glycosylation in maintaining renal and cardiovascular homeostasis

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Background
The risk of developing cardiovascular disease (CVD), a leading cause of death worldwide, is significantly increased by chronic kidney disease (CKD). The fundamental mechanisms behind the relationship between CVD and CKD are yet unknown. The low-density lipoprotein receptor related protein 2 (LRP2) is a large multi-ligand endocytic receptor highly expressed in renal proximal tubule cells. LRP2 malfunction and genetic deficits cause CKD and GaLNT11-mediated o-glycosylation is involved in the reabsorption and clearance of several ligands from the tubular fluid.

Preliminary Results
We recently discovered that LRP2 is glycosylated in the extracellular ligand-binding domain and that loss of LRP2 glycosylation result in kidney disease in animal models. Additionally, genome-wide association studies link the glycosylating enzyme (GALNT11) to CKD in humans.

Aim
To correlate the level of LRP2 O-glycosylation to human kidney disease and cardiovascular homeostasis and explore the functional consequences of LRP2 glycosylation in cell and animal models.

Methods
We will employ a parallel reaction monitoring (PRM)-based targeted mass spectrometry to evaluate and quantify LRP2-derived peptides and glycopeptides in urine samples from a large CKD cohort. We will examine the roles

of GALNT11 in LRP2 function in established Caco2 cell lines and validate our findings in vivo by visualizations of the uptake of fluorescently conjugated ligands in conditional Galnt11-deficient mice using intravital microscopy.

Perspectives

We expect to provide light on the basic biology of renal LRP2 and mechanisms behind cardiorenal syndrome and to identify new therapeutic intervention targets.

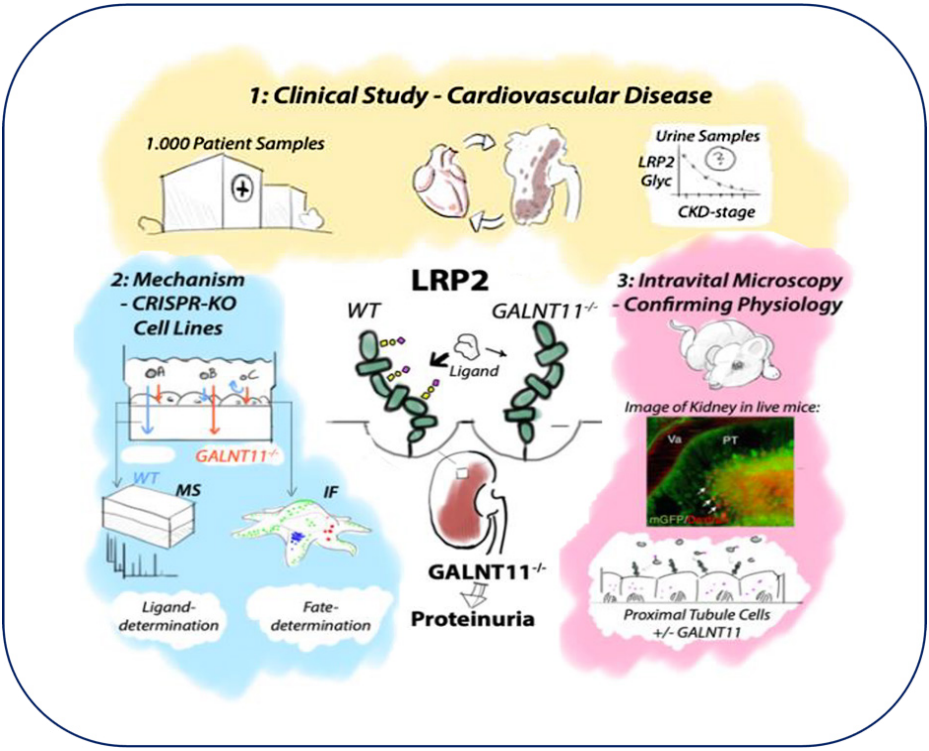

Figure: *An overview of the proposed project in 3 parts: Clinical, Mechanistic and Intravital*

Inter active poster

Equal Access – advanced frontline cardiovascular diagnostics independent of geographical location

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Large inequalities in health exist in Denmark. The difference in morbidity and mortality might be amplified by regional differences in diagnostic approach. For instance, advanced cardiovascular diagnostics are centralized at few locations, why the access to golden standard diagnostic tools currently depends on the patient's graphical location.

A cardiac MRI is a precise and versatile imaging tool that plays an increasingly significant role in diagnosing patients with acute and chronic cardiovascular diseases. Physicians can confirm or exclude the presence of a long list of cardiovascular diseases by using standardized cardiac MRI protocols. However, the necessary expertise to perform and analyze cardiac MRI scans is limited. Furthermore, we experience a general shortage of radiographers in Denmark. Thus, patients must be transported to highly specialized centers often after long periods on waiting lists. Additionally, the cardiac MRI examination may be preceded by other, potentially, unnecessary procedures.

Equal Access is an ambitious pilot project aimed at increasing access to cardiac MRI scans independent of the patients' place of residence. Using new technology that connects MRI machines and scanning stations remotely, patients are scanned at their local hospital by a radiographer at a different facility. An increased accessibility to cardiac MRI scans for radiology departments, researchers, and physicians allows quicker diagnosis and thus effective treatment of patients, ultimately transporting patient data between hospitals, rather than the patients themselves.

We look forward to providing a status and preliminary results at the DCA summer meeting on this important ongoing project.

Danish
Cardiovascular
Academy