

32nd Annual Scandinavian Atherosclerosis Conference
March 18-21, 2026 at Krogerup Højskole, Humlebæk, Denmark



2026 Program

SCIENTIFIC COMMITTEE

Ida Gregersen (Norway)
Michael Davies (Denmark)
Sofie Taageby Nielsen (Denmark)
Camilla Huse (Norway)
Uwe Tietge (Sweden)
Monique Mulder (The Netherlands)
Lærke Kyhl (Denmark)
Anna-Kaisa Ruotsalainen (Finland)

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Organized by**SCANDINAVIAN SOCIETY
FOR ATHEROSCLEROSIS
RESEARCH**

Kirsten B. Holven (Chairman)
Liv Tybjærg Nordestgaard (Social Media, Temporary treasurer)
Jacob J. Christensen (Social Media)
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Monique Mulder (Secretary)
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WEBSITE

www.ssar.dk (Matteo Pedrelli, Webmaster)

Wednesday, March 18, 2026

16.00 – 18.00	Arrival, registration, and coffee (dining room until 17.45)
18.00 – 19.30	Dinner
19.30 – 19.35	Welcome Kirsten B. Holven (Norway)
THE NIKKILÄ MEMORIAL LECTURE	
19.35 – 19.40	Introduction of the 2026 Nikkilä Lecturer Anna-Kaisa Ruotsalainen (Finland)
19.40 – 20.25	<u>2026 Nikkilä Lecture</u> <i>Behind and between lipoproteins</i> Kjetil Retterstøl (Norway)
20.25 – 20.45	Discussion
20.45 –	Pub will be open

Thursday, March 19, 2026

07.30 – 08.30	Breakfast
SESSION I	INFLAMMATION AND VASCULAR BIOLOGY Chaired by Ida Gregersen (Norway) and Michael Davies (Denmark)
08.30 – 09.00	<i>Invited speaker</i> <i>Humoral immunity as modulator of atherosclerosis</i> Christoph Binder (Austria)
09.00 – 09.15	Proteomic analysis of murine atherosclerotic plaques and healthy aorta provides evidence for location-specific differences in protein abundances Kathrine Væver Jokumsen (Denmark) - YIA
09.15 – 09.30	IgE ⁺ CD63 ⁺ mast cells positively associate with neovascularization in advanced human atherosclerosis Anish A. Kanhai (The Netherlands)
09.30 – 09.45	Proteomic analysis of oxidative modifications on metabolic proteins in human atherosclerotic plaques and control arteries Michael Davies (Denmark)
09.45 – 10.00	Endothelial STING-IFN-I signaling drives atherogenic inflammation and disrupts cholesterol homeostasis Cong Liu (Denmark) - YIA
10.00 – 10.45	Poster Walk (Session I) Coffee and tea
10.45 – 11.15	<i>Invited speaker</i> <i>Vascular repair: a failing key process in diabetes-associated atherosclerotic events</i> Andreas Edsfeldt (Sweden)
11.15 – 11.30	Sex-dependent immune signatures associate with site-specific plaque progression in gasdermin-deficient ApoE ^{-/-} mice Michelle Zurek (Belgium) - YIA
11.30 – 11.45	Circular RNA as novel, promising mediators in the immunopathogenesis of cardiovascular diseases Tuva Dahl (Norway)
11.45 – 12.00	Lineage tracing uncovers endothelial origin of mesenchymal-like cells in progeroid atheromas Magda R Hamczyk (Denmark)
12.00 – 13.00	Lunch

SESSION II

CARDIOVASCULAR DISEASE

Chaired by **Sofie Taageby Nielsen** (Denmark) and **Camilla Huse** (Norway)

13.00 – 13.30

Invited speaker

Mast cell subsets in cardiovascular atherosclerotic disease

Ilze Bot (The Netherlands)

13.30 – 13.45

Lipoprotein(a) lowering and risk of cardiovascular disease in primary and secondary prevention

Peter E. Thomas (Denmark) - YIA

13.45 – 14.00

In familial hypercholesterolaemia, remnant cholesterol above 1 mmol/L implies 50% higher lifetime risk of coronary artery disease

Florian Mourre (Denmark)

14.00 – 14.15

Forcing myocardin expression in smooth muscle cells reduces atherosclerosis and lowers systemic fat deposition in mice

Julian Albarran-Juarez (Denmark)

14.15 – 14.30

Patient preferences in the design of cardiovascular pharmacotherapy trials: a discrete choice experiment focusing on women

Marte F. van der Bijl (The Netherlands) - YIA

14.30 – 15.30

General meeting of the Scandinavian Society for Atherosclerosis Research

Open for all participants

Afternoon free for the Louisiana Museum of Modern Art (5 min walk), beach (5 min walk), Kronborg, the castle of Hamlet (12 min by train) or downtown Copenhagen (50 min by train)

16.00 – 17.00

Traditional soccer match between countries

Remember to bring sports clothing and suitable footwear

18.00 – 19.00

Dinner

SESSION II

CARDIOVASCULAR DISEASE – continued

Chaired by **Sofie Taageby Nielsen** (Denmark) and **Camilla Huse** (Norway)

19.00 – 19.30

Invited speaker

Preeclampsia and later development of cardiovascular disease in mothers and their children

Heather Boyd (Denmark)

19.30 – 20.30

Poster Walk (Session II)

Coffee and tea

20.30 – 20.45

Association between a healthy lifestyle and risk of cardiovascular disease in patients with familial hypercholesterolemia

Tone Svilaas (Norway)

20.45 – 21.00

Cardioprotective glucose-lowering drugs, statins, and secondary major adverse cardiovascular events

Tummas Ternhamar (Denmark) - YIA

21.00 – 21.15

Elevated remnant cholesterol explains a substantial part of the excess risk of myocardial infarction and atherosclerotic cardiovascular disease in the metabolic syndrome

Karen Hvid (Denmark) - YIA

21.15 – 21.30

Lipid-lowering treatment in familial hypercholesterolaemia from 1996 through 2021: a nationwide Study

Jacob Reeh (Denmark) - YIA

21.30 –

Pub will be open

Friday, March 20, 2026

07.30 – 08.30	Breakfast
SESSION III	LIPOPROTEINS AND LIPID TRANSPORT Chaired by Uwe Tietge (Sweden) and Monique Mulder (The Netherlands)
08.30 – 09.00	<i>Invited speaker</i> <i>Connecting atherosclerosis and thrombosis through lipoproteins</i> Ze Zheng (USA)
09.00 – 09.15	High lipoprotein(a) confers highest absolute risk of atherosclerotic cardiovascular disease in individuals aged 70-100 years Janeni Jeevanathan (Norway) - YIA
09.15 – 09.30	Inhibition of nicotinamide N-methyltransferase reverses dyslipidemia and protects against atherosclerosis in APOE*3-Leiden.CETP mice Jing Miao (The Netherlands) - YIA
09.30 – 09.45	Long-acting glucagon receptor agonism increases circulating triglyceride levels in diet-induced obese mice Jamie I. van der Vaart (The Netherlands) - YIA
09.45 – 10.00	Bempezoic acid: real-world data and sex-specific analysis from an Italian cohort Elisa Acitelli (Italy)
10.00 – 11.00	Poster Walk (Session III) Coffee and tea
11.00 – 11.30	<i>Invited speaker</i> <i>HDL in age-related macular degeneration</i> Magda Smoor (The Netherlands)
11.30 – 11.45	Cardiovascular disease and age-related macular degeneration in the general population Aniq Shamin (Denmark) - YIA
11.45 – 12.00	Lipoprotein(a), age and sex-specific absolute and relative hazards of atherosclerotic cardiovascular disease: new insights from 16-year follow-up of the Norwegian HUNT study Youssef Khalil (Norway) - YIA
12.00 – 12.15	Elevated plasma triglycerides in incidence of atherosclerotic cardiovascular disease versus acute pancreatitis in women and men: prospective and nationwide cohort studies Børge G. Nordestgaard (Denmark)
12.15 – 13.15	Lunch

SESSION IV

OTHER TOPICS

Chaired by **Lærke Kyhl** (Denmark) and **Anna-Kaisa Ruotsalainen** (Finland)

13.15 – 13.45

Invited speaker

Lipoprotein retention, atherosclerosis and liver disease

Stefano Romeo (Sweden)

13.45 – 14.00

Cardiometabolic risk factors, dietary habits and pharmacological treatment in Norwegian adults with severe mental illness

Madeleine E. Angelsen (Norway) - YIA

14.00 – 14.15

Mast cell activation induced eosinophilia in pulmonary inflammation and atherosclerosis.

Iris J. van Wissen (The Netherlands) - YIA

14.15 – 14.30

Many women with familial hypercholesterolemia do not receive lipid-lowering therapy and are diagnosed too late: results of a survey of women with FH across the world

Marianne Klevmoen (Norway) - YIA

14.30 – 14.45

Pregnancy complications and risk of chronic kidney disease

Rikke Mohr Lytsen (Denmark) - YIA

14.45 – 15.45

Poster Walk (Session IV)

Coffee and tea

15.45 – 16.15

Invited speaker

Decoding steatotic liver disease: a multiomics approach to pathogenesis

Stefan Stender (Denmark)

16.15 – 16.30

The impact of menstrual cycle on lipid levels in healthy premenopausal women: a systematic review and meta-analysis

Eirin B. Løvheim (Norway) - YIA

16.30 – 16.45

Characteristics of females and males with familial hypercholesterolemia and self-perceived side effects to lipid-lowering drugs

Amara Synøve Ø Uduma (Norway) - YIA

16.45 – 17.00

Cetoleic acid in adipose tissue is inversely associated to the risk of atherosclerotic Cardiovascular disease: a case-cohort study

Iselin Schjelle Holen (Norway) - YIA

17.00 – 17.15

Midlife metabolic syndrome and rare functional GLP-1R variants and risk of late-life dementia

Ida Juul Rasmussen (Denmark)

17.15 - 17.20

Concluding remarks

Kirsten B. Holven (Norway)

18.30 – 19.00

Cocktail

19.00 –

Banquet and dancing

Saturday, March 21, 2026

08.30 – 10.00

Breakfast and departure

Safe travels and see you next year!

32nd Annual Scandinavian Atherosclerosis Conference
March 18-21, 2026 at Krogerup Højskole, Humlebæk, Denmark



2026 Posters

Thursday, March 19, 2026

Posters are displayed upstairs in “Lille Sal”. Posters should be in place before 9.00 on the board with the corresponding number, and removed after the last poster session of the day. You should be present at your poster during all poster sessions of the day.

SESSION I

INFLAMMATION AND VASCULAR BIOLOGY

- No. 01** Temporal dynamics of systemic immune responses and exploratory molecular imaging in early experimental atherosclerosis
Maria del Pilar Murillo Angarita (Norway)
- No. 02** Effect of high intensity statin medication on circulating foamy monocytes in healthy individuals
Siina Pamilo (Finland)
- No. 03** Modulation of histone-induced cellular dysfunction from NETs in atherosclerosis..
Clare L. Hawkins (Denmark)
- YIA Poster walk I**
10.00 – 10.45
- Selected abstracts (3 min presentation + 2 min discussion)**
- No. 04** New insights into apolipoprotein B-100 degradation by proteases in vivo and ex vivo
Nicoline W. Thorsen (Denmark) - YIA
- No. 05** Age-associated B-cells serve as key precursors of antibody-secreting cells in atherosclerosis
Anna Witteveen (The Netherlands) - YIA
- No. 06** Integrative analysis of single-cell transcriptomics data reveals three distinct mast cell subpopulations in human atherosclerotic lesions
Pier P. Lindenbergh (The Netherlands) - YIA
- No. 07** Halofuginone enhances collagen remodeling during diet-induced atherosclerosis regression by beneficially impacting the systemic inflammatory status
Andisyah Putri Sekar (The Netherlands) - YIA
- No. 08** Organ-specific translomic insights of vascular endothelial cells and their association to human metabolic traits
Peter Stenzel (Germany) - YIA
- No. 09** Characterisation of the protein composition and histone modification in neutrophil and eosinophil extracellular traps
Helen Hemmling (Denmark) - YIA

SESSION II

CARDIOVASCULAR DISEASE

- No. 10** Platelet inhibiting effects by the novel nitric oxide-donor nitrosooxypropanol (PDNO)
Madelene Lindkvist (Sweden)
- No. 11** The AhR/P38 MAPK pathway mediates kynurenine-induced cardiomyocyte damage: the dual role of resveratrol in apoptosis and autophagy
Sara Mohiti (Denmark)
- No 12** Hypoxia drives a pro-atherogenic extracellular matrix that promotes myeloperoxidase retention and tissue damage that can be attenuated by heparin mimetics
Christine Y. Chuang (Denmark)
- No 13** Age-associated CD8+GZMK+ T-cells clonally expand and preferentially home to the atherosclerotic plaque in mice
Danxia Zhao (The Netherlands)
- No 14** Cardiometabolic impact of Ramadan fasting in adolescents with MASLD
Gabriele Mocciaro (Denmark)
- No 15** LAGOM trial (Longitudinal Approach to Generate positive cardiometabolic health Outcomes in severe Mental illness)
Hemen Najar (Sweden)
- No 16** Real-world use of bempedoic acid in patients with heterozygous familial hypercholesterolemia, an Italian experience.
Chiara Iurato (Italy)

YIA Poster walk II 19.30 – 20.30

Selected abstracts (3 min presentation + 2 min discussion)

- No. 17** The anti-ischemic activity of cardioprotective 6-piperazinyl-purine analogues bearing nitrate esters is determined by the length of the carbon side chain
Marianne Haug (Sweden) - YIA
- No. 18** Role of endothelial autophagy in atherosclerotic plaque development and composition
Eline Roeyen (Belgium) - YIA
- No. 19** Activated age-associated B cells accumulate in human atherosclerotic plaques
Kauthar Parker (The Netherlands) - YIA
- No. 20** N=1-studies in statin-intolerance; objectifying nocebo effects (NISON): a protocol for a randomized controlled trial assessing the implementability of N=1-studies to promote the use of statins
Ruben J.M. Mijster (The Netherlands) - YIA
- No. 21** True statin-associated muscle symptoms that can be attributed to statin-therapy as determined by N=1 trials and cross-over randomized controlled trials: a systematic review and meta-analysis
Ruben J.M. Mijster (The Netherlands) - YIA

Friday, March 20, 2026

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SESSION III

LIPOPROTEINS AND LIPID TRANSPORT

- | | |
|---------------|---|
| No. 22 | Intra-individual variability in lipoprotein(a) in a large primary care dataset: predominantly analytical or biological variation?
Sigrid M. Blom (Norway) |
| No. 23 | Lack of perilipin 2 is not critical for lipid deposition in the aortic root and the aortic arch
Johanne Kristofina Mikkelsen (Norway) |
| No. 24 | A human-like bile acid composition attenuates atherogenesis in female Ldlr ^{-/-} mice by reducing cholesterol absorption
Folkert Kuipers (The Netherlands) |
| No. 25 | Atherogenic lipid profiles and the association with historical malnutrition in Tanzanian and Zambian Cohorts: a cross-sectional study.
Nicolai Sandau (Denmark) |
| No 26 | PROSS-design and synthesis of thermostable LPL for treatment of familial chylomicronemia syndrome
Louise Laursen (Denmark) |
| No 27 | The role of apolipoprotein M in intestinal lipid metabolism
Pernille M. Christensen (Denmark) |

YIA Poster walk III
10.00 – 11.00

Selected abstracts (3 min presentation + 2 min discussion)

- No. 28** Variant effect predictions identify novel functional impact of APOE based on whole genome sequencing
Lucía Sánchez Schneider (Denmark) - YIA
- No 29** Cholesterol metabolism-linked regulators of brown adipose thermogenesis: Dhcr24 and 4931406C07Rik as novel modulators of UCP1-dependent respiration
Marita Klich (Germany) - YIA
- No 30** ApoC3/non-LDL TG ratio as a potential novel predictor of reduced liver steatosis risk
Lorenzo Luciani (Italy) - YIA
- No 31** All-trans retinoic acid increases fatty acid oxidation in human myotubes in part through altered mitochondrial activity
Ulrik N. Mjaaseth (Norway) - YIA
- No 32** Overeating polyunsaturated fat increases the HDL anti-inflammatory activity compared with saturated fat
Ana Vankova (Sweden) - YIA
- No 33** From silent plaque to clinical events: mass-spectrometry-based sphingolipid profiling to link subclinical carotid atherosclerosis with overt cardiovascular disease
Lukas Cudlman (Sweden) - YIA

SESSION IV

OTHER TOPICS

No. 34 The SGLT2 inhibitor empagliflozin promotes increased fatty acid oxidation in skeletal muscle cells

Arild C. Rustan (Norway)

No. 35 Harnessing neural signals to resolve hepatic immuno-metabolic dysfunction

Osman Ahmed (Sweden)

No. 36 Impact of the rare TM6SF2 L156P variant and its interaction with E167K on liver disease and plasma lipids: a large-scale population study

Lærke Kristine Kyhl (Denmark)

No. 37 Role for the liver X receptor agonist 22-ketositosterol in preventing disease progression in an Alzheimer's disease mouse model

Monique T. Mulder (The Netherlands)

YIA Poster walk IV
14.45 – 15.45

Selected abstracts (3 min presentation + 2 min discussion)

No. 38 Using loss-of-function variation in PNPLA3 to elucidate the mechanism of PNPLA3 I148M

Tobias Vegge Andersen (Denmark) - YIA

No. 39 Eleven clinical risk factors for age-related macular degeneration identified using 600,000 individuals from two prospective cohorts

Sabina O. Beheshti (Denmark) - YIA

No. 40 MumCare: a postpartum digital health companion for women following hypertensive disorders of pregnancy or gestational diabetes mellitus: preliminary retainment rate data

Miriam K.C. Sollie-Hoel (Norway) - YIA

No 41 *Flavonifractor plautii* mediates the decrease of visceral fat during dietary interventions in metabolic syndrome through regulating bile acid metabolism

Mingqian He (The Netherlands) - YIA

No 42 Fructose-induced liver steatosis model to study the inter-organ crosstalk on the liver-heart axis.

Joanna Konieczny (Norway)- YIA



**Oral Presentations – Abstracts –
Inflammation and Vascular Biology**

SESSION I

Proteomic analysis of murine atherosclerotic plaques and healthy aorta provides evidence for location-specific differences in protein abundances

Kathrine Væver Jokumsen [ORCID iD](#)¹, Christina Christoffersen^{1,2}, Michael Jonathan Davies¹, Luke Francis Gamon^{1,3}

¹Department of Biomedical Sciences, University of Copenhagen, Copenhagen, Denmark. ²Department of Clinical Biochemistry, Rigshospitalet, University of Copenhagen, Copenhagen, Denmark. ³Department of Clinical Sciences Malmö, Lund University, Malmö, Sweden

Abstract

Introduction: Atherosclerotic plaques develop at specific vascular sites exposed to disturbed blood flow, yet the protein changes underlying this site-specific susceptibility remain unclear. Mouse models are widely used to study atherosclerosis but yield limited tissue, previously restricting proteomic studies. Advances in mass spectrometry now enable proteomic analysis of very small tissue samples. We hypothesized that this would allow detection of site-specific protein changes in aortic regions prone or resistant to plaque formation.

Methods: Aortic arches from ApoE^{-/-} mice fed a Western diet or chow for 16 weeks were dissected into plaques and adjacent visibly healthy regions. Proteins were extracted, enzymatically digested, and analysed by liquid chromatography tandem mass spectrometry.

Results: Despite samples consisting of < 1 mg tissue, we detected > 4000 proteins per sample. Principal component analysis showed clustering of samples according to disease status and anatomical location within the aortic arch, indicating distinct proteomes. Proteins known to drive atherosclerosis – including vascular cell adhesion molecule 1 (Vcam1), apolipoprotein B (ApoB), lipoprotein lipase (Lpl) and galectin 3 (Lgals3) – were most abundant in advanced plaques and decreased gradually across anatomical regions, reaching their lowest levels in the healthy region furthest from the plaques. We also observed significant differences in protein expression between aortas from mice fed a Western diet versus chow, reflecting different stages of atherosclerosis. Enrichment analysis revealed that proteins involved in the immune response, cell adhesion and extracellular matrix were enriched with atherosclerosis progression.

Conclusion: Our findings demonstrate the feasibility of location-specific proteomics in individual murine aortas and provide new molecular insight into the site-specific nature of atherosclerotic plaque development.

IgE⁺CD63⁺ mast cells positively associate with neovascularization in advanced human atherosclerosis

Anish A. Kanhai¹, Esmeralda Hemme¹, Janne Lepage¹, Marie A.C. Depuydt¹, Margreet R. de Vries², Kayleigh van Dijk², Anouk Wezel³, Harm Smeets³, Paul H.A. Quax², Ilze Bot¹

¹Division of Biotherapeutics, Leiden Academic Centre for Drug Research, Leiden University, Leiden, The Netherlands. ²Department of Surgery, Leiden University Medical Center, Leiden, The Netherlands. ³Department of Surgery, HMC Westeinde, The Hague, The Netherlands

Abstract

Introduction: Mast cells (MCs) contribute to atherosclerotic plaque progression and destabilization. In human plaques, MC numbers correlate with plaque neovascularization and cardiovascular events. Here, we used flow cytometry to characterize MC activation in human carotid atherosclerotic plaques and correlate these findings to plaque stability measures. We also aimed to identify mediators involved in MC-induced neovascularization and plaque instability.

Methods: Human carotid artery (HCA) plaques (n=85) were analyzed for histological characteristics and with flow cytometry to identify MCs (CD117⁺FcεRI⁺) and their activation (CD63⁺;IgE⁺) status. Associations between plaque stability, MC frequencies and activation were also studied. Ligand-receptor pairs involved in MC-endothelial cell (EC) communication in HCA plaques were analyzed using CellChat and then studied with *ex vivo* and *in vitro* experiments.

Results: MCs comprised 1.0±0.1% of all intraplaque CD45⁺ cells, of which 79.0±2.7% were CD63⁺. Most activated MCs (43.7±3.0%) were IgE⁺, a known mast cell activator. A positive association was found between IgE⁺CD63⁺ MCs and neovessel score (lowest tertile:34.1±4.4% vs. highest tertile:54.8±6.6%, p=0.04). IgE-activated MC supernatant stimulated aortic sprouting vs. controls (6.2±3.7 vs. 11.9±4.3, p=0.03). CellChat identified multiple ligand-receptor pairs involved in intraplaque MC-EC communication, in particular the cathepsin G (CTSG)-proteinase-activated receptor 1 pair. 2.5 µg/mL CTSG induced mouse EC activation vs. controls, measured by % VCAM1⁺ (3.6±1.5% vs. 6.7±0.9%, p=0.04) and ICAM1⁺ (6.8±0.3% vs 13.4±1.6%, p=0.002) ECs.

Conclusion: We here show that IgE⁺CD63⁺ intraplaque MCs are positively associated with plaque neovascularization. This was confirmed *in vitro* via increased sprout formation by IgE-activated MC supernatant, potentially mediated by CTSG. Our data reinforces that IgE-mediated MC activation contributes to plaque destabilization and may lead to novel therapeutic strategies to inhibit this.

Proteomic analysis of oxidative modifications on metabolic proteins in human atherosclerotic plaques and control arteries

Karen C. Yang-Jensen¹, Lasse G. Lorentzen^{1,2}, Karin Yeung², Camilo Lopez-Alarcon³, Jonas P. Eiberg^{2,1,4}, Michael J. Davies¹

¹University of Copenhagen, Copenhagen, Denmark. ²Department of Vascular Surgery, Heart Center, University Hospital Copenhagen - Rigshospitalet, Copenhagen, Denmark. ³Departamento de Química Física, Facultad de Química y de Farmacia, Pontificia Universidad Católica de Chile, Santiago, Chile. ⁴Copenhagen Academy for Medical Education and Simulation (CAMES), Copenhagen, Denmark

Abstract

Introduction: Cardiovascular disease is a major cause of worldwide mortality and morbidity. A prime underlying cause is atherosclerosis and the formation of plaques at specific locations throughout the arterial tree. Considerable evidence links plaques with chronic inflammation and leukocyte activation, with this potentially resulting in enhanced oxidative damage to proteins. We hypothesized that higher levels of oxidative post-translational modifications (PTMs) would be present on proteins from plaques compared to control arteries, be more abundant in unstable (presence of ulceration, intraplaque hemorrhage, soft consistency) versus stable plaques, and present on key metabolic proteins.

Methods: Symptomatic human carotid artery plaques and control (superior thyroid) tissue were analyzed by LC-MS/MS proteomics for multiple PTMs.

Results: Of the 7150 proteins detected across all samples, 2724 were detected carrying at least one PTM, with these including mono- and di-oxidation at methionine, tryptophan, histidine and tyrosine, conversion of cysteine to cysteic acid, and chlorination and nitration of tyrosine and tryptophan. Higher levels of PTMs were detected on proteins from plaques compared to control artery tissue, but similar types of modification were detected. Higher levels of PTMs were detected in plaques classified as unstable compared to stable, consistent with PTMs being associated with plaque instability. These PTMs may arise from reactions of species generated by the heme protein myeloperoxidase, but causality has not been established except for chlorination. Large numbers of PTMs were detected on key cellular proteins including those involved in glycolysis/gluconeogenesis, the pentose phosphate pathway, the citric acid (TCA) cycle and oxidative phosphorylation. Particularly high levels were detected on glycolytic enzymes including glyceraldehyde-3-phosphate dehydrogenase (GAPDH), and on Complex V subunits, consistent with perturbations to cellular metabolism in atherosclerotic plaques.

Endothelial STING-IFN-I signaling drives atherogenic inflammation and disrupts cholesterol homeostasis

Cong Liu¹, Julie N. Christensen¹, Lolita Dokshokova¹, Ibrahim AlZaim^{1,2}, Bettina Hansen¹, Jacob F. Bentzon^{3,4}, Joanna M. Kalucka^{1,2}

¹Department of Biomedicine, Aarhus University, Aarhus, Denmark. ²Steno Diabetes Centre Aarhus, Aarhus University Hospital, Aarhus, Denmark. ³Department of Cardiology, Aarhus University Hospital, Aarhus, Denmark. ⁴Institute of Clinical Medicine, Aarhus, Denmark

Abstract

Introduction: Lipid-lowering therapies have reduced the incidence of atherosclerotic cardiovascular disease (ASCVD). However, substantial residual risk persists, driven largely by unresolved inflammation. The endothelium is a central regulator of this inflammatory process, yet remains an underexplored target. Although the cytosolic DNA sensor STING is known to drive inflammation in immune cells, its specific role within endothelial cells (ECs) during atherosclerosis remains unknown. This study aimed to define the impact of endothelial-intrinsic STING signalling on vascular health and to assess its potential as a novel therapeutic target for ASCVD.

Methods and Results: scRNA-seq analysis revealed a potent STING-dependent induction of a IFN-I signature in ECs. This was confirmed in vitro, where stimulation of ECs with the STING agonist cGAMP robustly activated the IFN-I pathway, as demonstrated by the upregulation of interferon-stimulated genes (e.g., *ISG15*). Furthermore, STING activation promoted a pro-inflammatory EC phenotype, characterized by increased expression of adhesion molecules and secretion of CXCL10. scRNA-seq further indicated that EC STING activation disrupted cholesterol homeostasis and enhanced LDL transcytosis pathways. Consistently, STING–IFN-I signaling impaired vascular barrier integrity, evidenced by reduced levels and disorganization of junctional proteins. All these effects were abolished by genetic knockout of key STING–IFN-I axis mediators in vitro. Notably, these findings translated to an in vivo setting, as EC-specific STING knockout mice were protected from cGAMP-induced vascular inflammation and barrier dysfunction.

Conclusion: Endothelial STING activation drives a potent IFN-I response, leading to a pro-inflammatory, metabolically dysregulated, and barrier-disrupting endothelial phenotype. This establishes endothelial STING as a novel mediator of vascular inflammation in atherogenesis, positioning its inhibition as a promising therapeutic strategy to mitigate ASCVD.

Sex-dependent immune signatures associate with site-specific plaque progression in gasdermin-deficient ApoE^{-/-} mice

Michelle Zurek [ORCID iD](#)₁, Jasper Ott, Melissa Van Praet, Lynn Roth, Guido R.Y. De Meyer, Wim Martinet

University of Antwerp, Wiriijk, Antwerpen, Belgium

Abstract

Introduction: Cell death is a hallmark of advanced atherosclerotic lesions and directly contributes to plaque progression through multiple regulated necrotic pathways, among which gasdermins (GSDMs) function as inflammatory pore-forming executors. Although GSDM-mediated necrosis is well defined in acute inflammation, its contribution to plaque phenotype and associated immune signaling in atherosclerosis is poorly understood. To address this gap, we investigated atherosclerotic plaque characteristics and plasma immune profiles in ApoE^{-/-} mice lacking GSDMD and/or GSDME, the two gasdermins most strongly implicated in inflammatory cell death.

Methods: Male and female ApoE^{-/-} (n = 9/genotype/sex) lacking GSDMD, GSDME, or both were fed a Western-type diet for 16 weeks. Body weight was monitored weekly throughout the study. Plasma was collected for lipid profiling and cytokine analysis using the Olink Target 48 Mouse Cytokine panel. Global aortic plaque burden was quantified by en face Oil Red O staining, while advanced lesions in the brachiocephalic artery were assessed by hematoxylin and eosin staining.

Results: Body weight, plasma lipid levels, and full aorta *en face* Oil Red O staining did not differ between genotypes, indicating comparable systemic metabolic burden and global lesion load. In contrast, brachiocephalic plaque area was significantly reduced in ApoE^{-/-}GSDMD^{-/-} mice, with effects predominantly observed in females, while GSDME deficiency alone or combined did not confer protection. Plaque composition analyses revealed sex-specific trends toward altered necrotic core content, most evident in females. Plasma profiling identified sex-dependent differences in PDCD1LG2 and CXCL1 and genotype-dependent changes in HGF and IL-1 α , linking gasdermin deficiency to distinct immune signatures associated with site-specific plaque progression.

Conclusion: These data identify GSDMD and GSDME as modulators of advanced plaque biology and reveal sex-dependent immune signatures associated with altered plaque phenotype. Together, our findings suggest that gasdermin-mediated inflammatory cell death pathways may represent context- and sex-specific regulators of atherosclerotic plaque biology.

Circular RNA as novel, promising mediators in the immunopathogenesis of cardiovascular diseases

Tuva B. Dahl PhD [ORCID iD](#)¹, Alba Kaci PhD [ORCID iD](#)², Camilla Huse PhD [ORCID iD](#)^{1,3}, Fredric A. Holme [ORCID iD](#)^{1,3}, Azhar Abbas PhD, MD⁴, Bente Halvorsen PhD [ORCID iD](#)^{1,3}

¹Research Institute for Internal Medicine, Oslo University Hospital (OUH) Rikshospitalet, Oslo, Norway. ²Center for Laboratory Medicine, Østfold Hospital Trust, Grålum, Norway. ³Institute of Clinical Medicine, University of Oslo, Oslo, Norway. ⁴Østfold Hospital Trust, Kanes, Fredrikstad, Norway



Tuva B. Dahl

Abstract

Background: Circular RNAs (circRNAs) are non-coding RNAs where the 3' and 5' ends have been joined in a covalently closed loop. CircRNAs are highly conserved and are believed to have important roles in regulating a correct immune response. Molecular functions include transcriptional and translational regulation by acting as a microRNA sponge, binding and transporting RNA-binding proteins, and competing with the linear RNA counterpart. circRNAs are stable and measurable in the bloodstream and therefore hold the promise as biomarkers in disease. In addition, we believe that circRNA level and structure can be manipulated and hence also have the potential as novel targets for treatment. Although circRNAs have been studied in various disorders like cancer, data on circRNAs in atherosclerosis and cardiovascular diseases (CVD) are scarce. To investigate the potential as a treatment target, it is of major importance to understand the molecular role of circRNA in immunopathogenesis.

Methods: We have previously studied the circRNA profile in atherogenic mouse models and identified 867 circRNAs from immune cells that differed between atherogenic and WT mice. To investigate the human counterparts, in a human CVD setting, we have developed ddPCR assays for the most promising circRNA identified in the murine atherogenic model. We have investigated the profiles of circEZH2, circANKRD4, circKIF21A, circTUBGCP3, circRRPH1, and circHIPK3 in plasma obtained from patients with ischemic stroke (n=233) compared to age and gender matched healthy controls (n=57). Further, the individual circRNAs were related to different aetiologies of the ischemic stroke and clinical outcome. Finally, we have investigated the expression of various relevant cells and atherogenic stimuli as sources of the investigated circRNAs.

Lineage tracing uncovers endothelial origin of mesenchymal-like cells in progeroid atheromas

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Abstract

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Oral Presentations – Abstracts –

Cardiovascular Disease

SESSION II

Lipoprotein(a) lowering and risk of cardiovascular disease in primary and secondary prevention

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Abstract

Introduction: High lipoprotein(a) [Lp(a)] is a causal risk factor for atherosclerotic cardiovascular disease. Therapies that reduce Lp(a) by 80–98% are in phase 3 trials, but their cardiovascular benefit remains uncertain. We estimated the effect of Lp(a) lowering on major adverse cardiovascular events (MACE) in ongoing secondary prevention trials and hypothetical primary prevention trials.

Methods: Trial emulation was performed using 522,494 individuals from UK Biobank and Copenhagen General Population Study. Sub-cohorts mirrored inclusion criteria from Lp(a)HORIZON, ACCLAIM-Lp(a), OCEAN(a), and hypothetical primary prevention trials stratified by baseline cardiovascular risk factors and Lp(a) thresholds. The outcome was 5-year risk of MACE (myocardial infarction, ischemic stroke, coronary revascularization, or coronary death).

Results: In secondary prevention, 5-year absolute risk reductions for Lp(a) lowering vs high levels were 2.3% (95% CI: -0.5–5.1, p=0.16) in Lp(a)HORIZON, 3.4% (1.0–5.9, p=0.0003) in ACCLAIM-Lp(a), and 3.7% (1.0–6.5, p=0.008) in OCEAN(a). Corresponding hazard ratios (HRs) were 0.86 (0.69–1.07), 0.74 (0.63–0.87), and 0.76 (0.61–0.93). In primary prevention, 5-year risk reductions ranged from 1.1–4.2%, increasing with baseline risk and intensity of Lp(a) lowering. HRs ranged from 0.53–0.71 for 80% lowering and 0.43–0.57 for 98%.

Conclusion: In this trial emulation study, lipoprotein(a) lowering was associated with clinically meaningful reductions in MACE across secondary and primary prevention settings. These findings support the therapeutic potential of ongoing lipoprotein(a)-lowering trials, identify cardiovascular risk subgroups most likely to benefit, and offer a framework for selecting optimal inclusion criteria for primary prevention trials.

In familial hypercholesterolaemia, remnant cholesterol above 1 mmol/L implies 50% higher lifetime risk of coronary artery disease

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Abstract

Introduction: Familial hypercholesterolaemia (FH) leads to lifelong elevated low-density lipoprotein (LDL) cholesterol and increased risk of coronary artery disease. However, whether elevated remnant cholesterol additionally increases cardiovascular events in FH is unknown. We tested the hypothesis that elevated remnant cholesterol is associated with higher lifetime risk of coronary artery disease in individuals with FH.

Methods: In the Copenhagen General Population Study (CGPS) and UK Biobank, 108,751 and 428,625 individuals were classified as with or without FH according to clinical scores and genetic mutations. In the two cohorts, 7,708 and 50,997 experienced lifetime coronary artery disease, respectively.

Results: In the CGPS and UK Biobank, remnant cholesterol ≥ 1 mmol/L (39 mg/dL) was observed in 12% and 11% of individuals without FH (N=104,226 and 403,172), in 33% and 40% with Simon Broome FH (N=3,923 and 23,860), in 44% and 78% with MEDPED FH (N=1,005 and 2,465), in 33% and 34% with DLCN FH (N=744 and 1,207), and in 12% and 21% of individuals with genetic FH (N=188 and 875). Likewise in the CGPS and UK Biobank, the multivariable adjusted hazard ratios for lifetime coronary artery disease by remnant cholesterol ≥ 1 vs. < 1 mmol/L (39 mg/dL) were 1.49 (95% CI: 1.39-1.59) and 1.47 (1.43-1.52) in individuals without FH, 1.59 (1.31-1.93) and 1.18 (1.10-1.27) in Simon Broome FH, 1.50 (1.08-2.08) and 1.14 (0.89-1.45) in MEDPED FH, 1.60 (1.17-2.21) and 1.59 (1.20-2.09) in DLCN FH, and 1.48 (0.59-3.69) and 1.39 (0.88-2.19) in genetic FH.

Conclusion: In familial hypercholesterolaemia, remnant cholesterol ≥ 1.0 mmol/L (39 mg/dL) vs below implies 50% higher risk of coronary artery disease, that is, above the already high risk due to lifelong genetically elevated LDL cholesterol.

Forcing myocardin expression in smooth muscle cells reduces atherosclerosis and lowers systemic fat deposition in mice

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Julian Albarran-Juarez

Abstract

Introduction: Atherosclerosis drives vascular smooth muscle cells (SMCs) to lose their contractile identity and adopt diverse phenotypes. Myocardin (Myocd), a transcriptional coactivator, is a key regulator of the contractile program. We investigated how myocardin overexpression in SMCs influences their phenotype and atherosclerosis development in mice.

Methods: To assess direct cellular effects, we generated doxycycline-inducible SMCs overexpressing myocardin. *In vitro* Myocd induction enhanced actin cytoskeleton organization, increased contractility, and reduced proliferation. Transcriptomic profiling revealed upregulation of smooth muscle contractile genes (*Myh11*, *Cnn1*) and cardiac markers (*Actc1*, *Casq2*). For *in vivo* analysis, we created Cre-inducible, smooth muscle-specific myocardin transgenic mice (SMC-Myocd-TG) under the *Myh11* promoter, crossed with a tdTomato reporter line to trace SMC-derived cells in AAV-PCSK9-induced atherosclerosis during a 20-week high-fat diet.

Results: SMC-Myocd-TG mice exhibited lower total and ApoB-associated plasma cholesterol, smaller aortic root plaques, and reduced *en face* Oil Red O-positive area in aortas compared to controls. Single-cell RNA sequencing revealed high plaque SMC heterogeneity with six subclusters. Notably, chondromyocytes were markedly reduced in SMC-Myocd-TG plaques, while “supercontractile” SMCs expressing smooth muscle and cardiac markers (*Myh11*, *Actg2*, *Tnnt2*, *Casq2*) appeared exclusively in transgenic mice. Immunofluorescence confirmed fewer SOX9⁺ chondromyocytes and preserved ACTA2⁺ contractile cells in SMC-Myocd-TG lesions. Interestingly, SMC-Myocd-TG mice gained less body weight and adipose mass and showed reduced hepatic steatosis despite higher food and water intake compared to control littermates.

Conclusion: Overall, myocardin overexpression preserves SMC contractile phenotype, attenuates atherosclerosis, and limits systemic fat accumulation, highlighting myocardin as a potential therapeutic target in vascular and metabolic disease.

Patient preferences in the design of cardiovascular pharmacotherapy trials: a discrete choice experiment focusing on women

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Abstract

Introduction: Randomized controlled trials (RCTs) are the gold standard for evaluating new therapies, yet women remain underrepresented in cardiovascular disease (CVD) trials. This limits external validity and raises concerns about equity and trust. Using a discrete choice experiment (DCE), we quantify patient benefit–risk preferences and identify trial design features influencing participation.

Methods: Patients with established CVD, including atherosclerotic CVD, were recruited from Dutch outpatient clinics and online patient platforms, including a women-focused CVD patient organization and the Dutch Heart Foundation. From November 2025 onwards, patients completed a web-based anonymous DCE survey. Both women and men were invited. Participants compared 12 pairs of hypothetical RCTs varying in side-effect risk, trial duration, number and length of visits, probability of receiving placebo, and availability of an open-label extension, with the option to choose neither trial. Responses were analyzed using a conditional logit model.

Results: This interim analysis included 150 respondents (95% women, mean age: 58 years). The most influential attributes on willingness to participate were side-effect risk, chance of receiving placebo, and availability of early access to the study drug. Side-effect risk was the dominant driver, with higher risks showing steep declines in participation likelihood, reaching reductions of up to 50%. Trial duration, number of hospital visits, and visit duration had comparatively modest effects. Model predictions indicated a 92% participation likelihood for an ideal RCT profile with 6-month duration, 30-minute monthly visits, early access available, 0% placebo probability, and 1% side-effect risk.

Conclusion: These early findings identify side-effect risk as the strongest factor influencing women's willingness to participate in a CVD trial. Continued data collection will help identify preference heterogeneity and guide more inclusive trial design.

Association between a healthy lifestyle and risk of cardiovascular disease in patients with familial hypercholesterolemia

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Abstract

Introduction: Familial hypercholesterolemia (FH) is a genetic risk factor for cardiovascular disease (CVD). Adults with FH are advised to use lipid lowering therapy (LLT) and to adopt a healthy lifestyle, including a heart-healthy diet adhering to dietary guidelines, regular physical activity, no smoking, and a normal weight. The aim of this study was to investigate whether a healthy lifestyle influences the risk of CVD in adults with FH.

Methods: The study was a registry-based cohort study on patients being treated for FH at the Lipid Clinic at Oslo University Hospital. Participants were above the age of 18 years, without registered CVD at the first visit. Information was obtained from visits to the clinic and medical journals. A lifestyle score was developed based on information on diet, physical activity, smoking, and obesity. The score classified the participants into having a favourable, intermediate, or unfavourable lifestyle. The effect of the lifestyle score on CVD risk was assessed by a logistic regression analysis.

Results: In total, 1,413 FH patients were included in the study. The median age was 38.7 (25-75 percentile: 28.8,48.1) years at baseline and 50.1 (40.3,60.5) years at the last visit, reflecting a follow-up of 11.3 years. The population's lifestyle score improved over the follow-up period. By the last visit, 97 (6.4%) patients had experienced CVD. A higher lifestyle score was associated with reduced CVD risk, OR 0.70 (95% CI:0.52-0.94, p=0.02). This effect seemed largely driven by a higher level of physical activity, which showed reduced risk, OR 0.70 (95% CI:0.53-0.94, p=0.02).

Conclusion: A healthy lifestyle, characterized by a heart-healthy diet, physical activity, no smoking, and a normal weight, was associated with a reduced risk of CVD in FH patients. Lifestyle counselling should be emphasized as an important tool for health professionals in addition to LLT also in individuals with FH.

Cardioprotective glucose-lowering drugs, statins, and secondary major adverse cardiovascular events

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Abstract

Introduction: In type 2 diabetes, cardioprotective glucose-lowering drugs, including sodium-glucose cotransporter-2 inhibitors and glucagon-like peptide-1 receptor agonists, and statins reduce the risk of secondary major adverse cardiovascular events (MACE). No trials examined the combination of these drugs. We tested the hypothesis that cardioprotective glucose-lowering drug and statin combined is associated with lower risk of secondary MACE than either drug alone.

Methods: Individuals with type 2 diabetes and established cardiovascular disease from December 2012 through 2021 were identified via national Danish health registers. First, in an active comparator cohort, 15,404 individuals were followed from treatment intensification with cardioprotective glucose-lowering drug or dipeptidyl peptidase-4 inhibitor. Second, in a time-varying cohort, 76,853 individuals were followed with yearly updated treatment and covariate status. The primary outcome was MACE (myocardial infarction, stroke, or cardiovascular death).

Results: During mean 2.7 and 4.7 years of follow-up, 1,843 and 23,051 had MACE in the active comparator and time-varying cohorts. In the active comparator cohort, when compared to nonusers of cardioprotective glucose-lowering drug or statin, multivariable adjusted hazard ratios of secondary MACE were 0.82 (95% confidence interval: 0.66–1.01) for cardioprotective glucose-lowering drug, 0.84 (0.74–0.97) for statin, and 0.71 (0.60–0.83) for cardioprotective glucose-lowering drug and statin combined. Corresponding hazard ratios in the time-varying cohort were 0.76 (0.68–0.85), 0.73 (0.70–0.75), and 0.57 (0.54–0.60).

Conclusion: In individuals with type 2 diabetes and established cardiovascular disease, treatment with a cardioprotective glucose-lowering drug and statin in combination was associated with lower risk of secondary MACE than using either drug alone. This is important given the persistently suboptimal uptake of both drug classes in real-world practice.

Elevated remnant cholesterol explains a substantial part of the excess risk of myocardial infarction and atherosclerotic cardiovascular disease in the metabolic syndrome

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Abstract

Requested not to publish.

Lipid-lowering treatment in familial hypercholesterolaemia from 1996 through 2021: a nationwide study

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Abstract

Requested not to publish.



**Oral Presentations – Abstracts –
Lipoproteins and Lipid Transport**

SESSION III

High lipoprotein(a) confers highest absolute risk of atherosclerotic cardiovascular disease in individuals aged 70-100 years

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Abstract

Introduction: High lipoprotein(a) is considered a causal risk factor for atherosclerotic cardiovascular diseases; however, whether lipoprotein(a) is also a strong risk factor in individuals aged 70-100 is unclear. We tested the hypothesis that individuals aged 70-100 with high lipoprotein(a) have the highest absolute risk of atherosclerotic cardiovascular disease.

Methods: We included 59,325 women and 48,597 men aged 20-100 years from the Copenhagen General Population Study, of which 20,723 were aged 70-100. Age- and sex-stratified incidences rates and hazard ratios for atherosclerotic cardiovascular disease were estimated.

Results: During a median follow-up of 12.5 years (maximum 19.1), 9,091 individuals were diagnosed with atherosclerotic cardiovascular disease. Incidence rate differences per 50 mg/dL (105 nmol/L) higher lipoprotein(a) were 0.3 (95% confidence interval 0.2-0.4) for age 20-49, 0.8(0.6-0.9) for age 50-59, 1.5(1.2-1.7) for age 60-69, 2.7(2.2-3.2) for age 70-79, and 4.5(3.7-5.4) for age 80-100. For lipoprotein(a) of 70-89 mg/dL(148-190 nmol/L) such incidence rates were 2.7 for age 20-49, 7.1 for age 50-59, 13.3 for age 60-69, 24.4 for age 70-79, and 40.9 for age 80-100. Corresponding values for lipoprotein(a) of 90-426 mg/dL(191-924 nmol/L) were 3.2, 8.3, 15.6, 28.7, and 48, respectively. The above results were similar in women and men, but with the highest incidences in men. Hazard ratios per 50 mg/dL higher lipoprotein(a) were similar across all age groups and sexes ranging from 1.12-1.18 (p for interaction: by age=0.48; by sex=0.74).

Conclusion: In a contemporary primary prevention cohort, individuals aged 70-100 with high lipoprotein(a) had the highest absolute risk of atherosclerotic cardiovascular disease.

Inhibition of nicotinamide N-methyltransferase reverses dyslipidemia and protects against atherosclerosis in APOE*3-Leiden.CETP mice

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Abstract

Requested not to publish.

Long-acting glucagon receptor agonism increases circulating triglyceride levels in diet-induced obese mice

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Jamie I. van der Vaart

Abstract

Introduction: Glucagon receptor agonists, including glucagon receptor-based co-agonists, are in development for obesity and associated diseases, such as atherosclerotic cardiovascular disease. While glucagon is well studied for its effects on glucose metabolism, its actions on lipid metabolism are less defined. Emerging evidence suggests glucagon promotes hepatic fatty acid oxidation. Therefore, this study explored how glucagon receptor agonism modulates plasma lipid levels, lipid fluxes, and lipoprotein dynamics in diet-induced obese mice.

Methods: Diet-induced obese male C57BL/6N mice were fed a Western diet (40% fat, 40% sucrose) and treated daily with a long-acting glucagon receptor agonist (GFA-015; 10 nmol/kg) or vehicle for 2 weeks, during which body weight, body composition, and energy expenditure were monitored. In a second experiment, mice were treated every three days for 2 weeks, after which 4 h-fasted plasma triglyceride (TG) levels, VLDL production, and VLDL catabolism were assessed.

Results: Compared to vehicle, daily treatment with the glucagon receptor agonist reduced fat mass (-31%), lean mass (-16%) and food intake (-15%), while increasing energy expenditure (+8%). Interestingly, while reducing hepatic TG levels (-47%) the agonist increased plasma TG levels (+64%). Mechanistically, the glucagon receptor agonist increased enhanced VLDL particle production (+51%) rather than affecting VLDL clearance.

Conclusion: In diet-induced obese mice, long-acting glucagon receptor agonism reduced fat mass and increased energy expenditure, consistent with enhanced hepatic lipid mobilization. This treatment furthermore decreased hepatic triglyceride content but elevated plasma triglyceride levels, likely due to increased hepatic VLDL production. These findings suggest that potential elevations in circulating triglycerides should be considered when developing glucagon receptor agonists, especially regarding their impact on hyperlipidemia and cardiovascular risk.

Bempedoic acid: real-world data and sex-specific analysis from an Italian cohort

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Elisa Acitelli

Abstract

Introduction: Bempedoic acid (BA) is a novel lipid-lowering agent, often used in statin-intolerant patients. Previous studies suggested greater LDL-c reductions in women within ASCVD/HeFH populations. This study evaluated real-world lipid-lowering efficacy of BA and described baseline characteristics of patients, with a focus on sex-specific differences in therapy initiation and response.

Methods: We conducted a retrospective study at the Internal Medicine and Metabolic Diseases Unit of Policlinico Umberto I, Rome. Demographic, clinical, anthropometric, and laboratory data were collected at BA initiation (T0) and first follow-up (T1). Parametric and nonparametric comparisons were performed using T-tests and Wilcoxon tests; binary variables were analyzed with McNemar tests; determinants of LDL reduction were assessed through ANCOVA and multivariate linear regression.

Results: Data from 120 patients were analyzed. The majority of patients were females (63.3%), statin-intolerant (67.7%) in primary prevention (80.7%). Median follow-up was 105 days (range 30–161), with no treatment discontinuations due to adverse events. Mean age was 64.6 ± 11.4 years, with females significantly older than males (66.5 ± 10.5 vs 61.3 ± 12.4 years; $p=0.019$); other baseline characteristics and therapies were similar between sexes. LDL reduction did not differ significantly by sex. In multivariate linear regression, baseline LDL ($\beta=0.628$, $p<0.001$), BMI ($\beta=1.85$, $p=0.007$), and statin discontinuation ($\beta=-25.84$, $p=0.017$) independently predicted LDL reduction, whereas sex, age, and statin intolerance did not.

Conclusion: BA is effective in lowering LDL-c in hypercholesterolemic patients, particularly statin-intolerant females. No sex differences in LDL response were observed after adjustment for baseline characteristics and therapy factors, partly contrasting prior literature. Differences in baseline LDL, BMI, and statin discontinuation may explain apparent sex-related disparities.

Cardiovascular disease and age-related macular degeneration in the general population

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Abstract

Introduction: Atherosclerotic cardiovascular disease (ASCVD) and age-related macular degeneration (AMD) are conditions that share biological mechanisms such as lipid dysregulation and chronic inflammation. However, evidence linking the two diseases remains limited. To investigate whether prior ASCVD is associated with an increased risk of developing AMD in the general population.

Methods: Data from two large cohorts, the Copenhagen General Population Study (CGPS, n = 97,090) and the UK Biobank (UKB, n = 360,723), were analyzed using Cox proportional hazards models adjusted for age, sex, smoking status, low-density lipoprotein cholesterol, diabetes mellitus, hypertension, and APOE genotype.

Results: Prior ASCVD was associated with increased risk of AMD in both cohorts, with the composite ASCVD variable showing elevated risks (Hazard Ratio (HR) (CGPS) [95% Confidence Interval (CI)], 2,00 [1,75-2,28]), (HR (UKB) [95% CI], 1,67 [1,56-1,80]). Among ASCVD subtypes, ischemic heart disease (IHD) was associated with the highest risk of AMD (HR (CGPS) [95% CI], 2,30 [1,95-2,70]), (HR (UKB) [95% CI], 1,95 [1,81-2,11]) for both cohorts, while other ASCVD subtypes, such as ischemic stroke (HR (CGPS) [95% CI], 1,41 [1,12-1,77]), (HR (UKB) [95% CI], 0,94 [0,78-1,14]) and ischemic cerebrovascular disease (HR (CGPS) [95% CI], 1,61 [1,35-1,91]), (HR (UKB) [95% CI], 1,13 [0,97-1,31]) showed weaker or inconsistent associations across the two cohorts.

Conclusion: Our findings support an association between ASCVD and AMD, especially IHD and AMD, likely driven by pathophysiological mechanisms such as lipid imbalance and chronic inflammation. Further studies, including genetic approaches such as Mendelian Randomization, are needed to clarify whether this relationship is causal.

Lipoprotein(a), age and sex-specific absolute and relative hazards of atherosclerotic cardiovascular disease: new insights from 16-year follow-up of the Norwegian HUNT study

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Abstract

Introduction: Atherosclerotic cardiovascular disease (ASCVD) develops through cumulative exposure to causal risk factors, such as lipoprotein(a) [Lp(a)]. Evidence on how high Lp(a) shapes long-term absolute and relative ASCVD hazards across age and sex remains limited. We quantified age and sex-specific absolute and relative ASCVD hazards associated with high Lp(a) and assessed whether these age-related patterns differed between men and women.

Methods: We included 19 495 adults without ASCVD at baseline with Lp(a) measured from the Trøndelag Health Study (HUNT3, 2006–08). Participants were followed for up to 16 years for first ASCVD event. Lp(a) was categorized as high (≥ 95 th percentile; ≥ 252 nmol/L) versus low (≤ 74 th percentile; ≤ 62 nmol/L). Standardized age and sex-specific hazard rates, hazard ratios (HRs), and hazard rate differences (HRDs) per 1000 person-years were estimated using multivariable cause-specific flexible parametric survival models.

Results: High Lp(a) was associated with higher ASCVD hazards at all ages. In both sexes combined, the HR for high versus low Lp(a) declined from 2.42 (95% CI: 1.14–5.14) at age 40 to 1.24 (95% CI: 0.91–1.70) at age 90, while corresponding HRDs increased from 1.22 (95% CI: -0.24–2.67) to 6.97 (95% CI: -4.08–18.02) extra ASCVD events per 1000 person-years. Men had higher ASCVD hazards than women at all ages. HRs were broadly similar between sex but tended to be slightly higher in women at midlife. However, the number of extra ASCVD events per 1000 person-years due to high Lp(a) increased with age in both sexes and was consistently higher in men compared to women.

Conclusion: High Lp(a) is a persistent risk factor for ASCVD across adulthood, with larger relative impact at younger ages but causes more excess events in older adults, and particularly in men. These risk profiles may help clinicians prioritize Lp(a) testing and identify patients who may benefit from future Lp(a)-lowering therapies.

Elevated plasma triglycerides in incidence of atherosclerotic cardiovascular disease versus acute pancreatitis in women and men: prospective and nationwide cohort studies

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Abstract

Introduction: Hypertriglyceridemia cause both atherosclerotic cardiovascular disease (ASCVD) and acute pancreatitis. We tested the hypothesis that plasma triglycerides at most levels are associated with higher incidence of ASCVD than acute pancreatitis.

Methods: We examined individuals from the Copenhagen City Heart Study (CCHS) 1976-78 (n=14,292; a median follow-up of 24 years) and 1991-94 (n=10,093; 20 years), the Copenhagen General Population Study (CGPS) 2003-15 (n=107,297; 13 years), the UK Biobank 2006-10 (n= 468,964; 14 years), and nationwide in Denmark 2008-21 (n=3,415,915; 6 years). Individuals were followed until events, death, emigration, or end of follow-up. The incidence of ASCVD and acute pancreatitis by triglyceride levels were analyzed by Poisson regression.

Results: The incidence was higher for ASCVD than for acute pancreatitis at any triglycerides almost up to 50 mmol/L (4,429 mg/dL) in all cohorts, and *vice versa* at higher levels. In women, age-adjusted incidence rates per 1,000 person-years per 1 mmol/L (89 mg/dL) higher triglycerides across all levels were 1·8 (95% confidence interval 1·2-2·3) for ASCVD versus 0·1 (0·02-0·2) for acute pancreatitis in the CCHS 1976-78, 1·9 (1·2-2·5) versus 0·1 (0·01-0·2) in the CCHS 1991-94, 0·9 (0·7-1·0) versus 0·1 (0·1-0·1) in the CGPS, 0·6 (0·6-0·7) versus 0·2 (0·2-0·2) in the UK Biobank, and 0·4 (0·4-0·5) versus 0·05 (0·04-0·05) nationwide in Denmark. Corresponding values in men were 1·5 (1·0-2·0) versus 0·1 (0·1-0·1), 0·9 (0·5-1·3) versus 0·04 (0·0-0·1), 1·1 (0·9-1·3) versus 0·04 (0·0-0·08), 1·1 (1·0-1·2) versus 0·1 (0·1-0·1), and 0·6 (0·5-0·6) versus 0·05 (0·05-0·06), respectively.

Conclusion: In women and men elevated triglycerides are associated with higher incidence of ASCVD than acute pancreatitis almost up to 50 mmol/L (4,429 mg/dL), and *vice versa* at higher levels.



Oral Presentations – Abstracts –

Other Topics

SESSION IV

Cardiometabolic risk factors, dietary habits and pharmacological treatment in Norwegian adults with severe mental illness

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Abstract

Introduction: Severe mental illness (SMI) is associated with increased cardiovascular disease (CVD) mortality driven by modifiable risk factors and antipsychotic medication. Somatic undertreatment is frequently reported. We aimed to characterize CVD risk factors, dietary habits and medication use in a Norwegian SMI cohort and compare findings with national population data.

Methods: Adults aged 20–88 years with schizophrenia or bipolar disorder were recruited from a psychiatric ward in South-Eastern Norway. Participants underwent anthropometric, biochemical, and dietary assessments. Medication use was extracted from medical records. Anthropometry was compared with HUNT4, and adherence to Norwegian Food-Based Dietary Guidelines with NORKOST3.

Results: Between 2021 and 2025, 86 patients were assessed (median age: 45 years). Compared with population data, overweight and obesity were more prevalent among younger, but not older, participants. 75% had overweight or obesity, 55% abdominal obesity, 47% elevated blood pressure, and 42% met criteria for metabolic syndrome. Former or current smoking was reported by 54%. Median non-HDL cholesterol was 3.5 mmol/L (1.8–7.1) and median LDL cholesterol 3.35 mmol/L (1.4–5.8). Ten participants had HbA1c >42 mmol/mol, of whom 7 had HbA1c ≥47 mmol/mol. Psychotropic medication was used by 76.7%, including olanzapine or clozapine in 40%. Cardiometabolic medications were identified in 14 participants (16.3%). Adherence to dietary guidelines was comparable to the general population.

Conclusion: Adults with SMI displayed multiple cardiometabolic risk factors, frequent smoking and widespread use of antipsychotics with metabolic liability. Lipid concentrations exceeded recommended targets for high-risk individuals, and elevated blood pressure and dysglycaemia were common. Cardiometabolic pharmacotherapy was infrequent, indicating a mismatch between cardiometabolic risk and preventive treatment in SMI and underscoring the need for improved somatic risk assessment and earlier intervention

Mast cell activation induced eosinophilia in pulmonary inflammation and atherosclerosis

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Iris J van Wissen

Abstract

Introduction: Patients with chronic obstructive pulmonary disease (COPD) have an increased risk of developing cardiovascular disease (CVD), primarily driven by atherosclerosis. Interestingly, patients who underwent a carotid endarterectomy with co-morbid COPD show increased levels of tryptase, a mediator released by activated MCs (non-COPD: 4.90 ± 0.30 vs COPD: 7.77 ± 2.2 $\mu\text{g/L}$, $P=0.05$), suggesting that MCs may contribute to the underlying inflammation.

Methods and Results: To assess the direct effects of MC activation, 57-61 week old *Ldlr*^{-/-} mice were treated with the MC activator C48/80 (4mg/kg, 3x weekly i.e. for 8 weeks). Although the %MC of CD45⁺ lung immune cells remained unchanged, their activation led to an increased myeloid infiltration, in particular that of alveolar macrophages (PBS: $1.48 \pm 0.21\%$ vs C48/80: $2.23 \pm 0.21\%$, $P=0.004$), inflammatory monocytes (PBS: $7.72 \pm 0.62\%$ vs C48/80: $10.4 \pm 0.65\%$, $P=0.006$) and most prominently, eosinophils (PBS: $2.25 \pm 0.21\%$ vs C48/80: $6.98 \pm 1.00\%$, $P<0.0001$). This notable increase in eosinophils was also observed in the atherosclerotic aorta (PBS: $0.71 \pm 0.22\%$ vs C48/80: $1.70 \pm 1.41\%$, $P=0.005$). Intriguingly, lungs of atherosclerotic MC deficient mice showed a decrease in alveolar macrophage (*ApoE*^{-/-}: $2.64 \pm 0.21\%$ vs *ApoE*^{-/-}/*KitW-sh/W-sh*: $1.79 \pm 0.14\%$, $P=0.005$) and a trend towards a diminished eosinophil content (*ApoE*^{-/-}: 1.98 ± 0.19 vs *ApoE*^{-/-}/*KitW-sh/W-sh*: 1.50 ± 0.16 , $P=0.09$), highlighting that these changes are MC-driven. In addition, hypercholesterolemia in *ApoE*^{-/-} mice resulted in a two-fold increase of activated eosinophils (CD11b^{hi}) in the lungs ($P=0.01$) and three-fold increase in the aorta ($P=0.01$) compared to WT mice with normal cholesterol levels.

Conclusion: Our findings demonstrate that MC activation promotes eosinophil accumulation in both lungs and aorta *in vivo*. Additionally, hypercholesterolemia is associated with a more activated eosinophil phenotype which together highlight the MC–eosinophil axis as a potential therapeutic target in COPD-associated CVD.

Many women with familial hypercholesterolemia do not receive lipid-lowering therapy and are diagnosed too late: results of a survey of women with FH across the world

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Abstract

Introduction: Previous studies suggest that CVD morbidity due to familial hypercholesterolemia (FH) is markedly elevated in women at all ages compared to men, however these are based predominantly on registry data. By asking the women themselves, we aimed to describe the treatment status and CVD burden in women with FH across 32 countries.

Methods: An anonymous online self-administered questionnaire was developed and translated to 17 languages and distributed via patient organizations and lipid networks.

Results: In total, 923 women with FH responded, representing 32 mostly European countries. The four countries with most responses were Norway (112 (12%)), the Netherlands (160 (17%)), Latvia (202 (22%)), and United Kingdom (235 (25%)). Mean (SD) current age of participants was 50 (14) years. In total 41% of the women were diagnosed after the age of 41 years, with variations between countries ranging from 15-67% diagnosed after the age of 41 years. A total of 208 (23%) women reported not using any lipid-lowering therapy at the time of completing the questionnaire, with large differences between countries ranging from 13-35% not using lipid-lowering therapy. A total of 141 (15%) women, ranging from 9-21 % across different countries, reported having one or more CVD events, which were mostly CHD (n=118 (84%)). Median (25th-75th percentile) age of first CHD event was 48 (36-59) years.

Conclusion: In this large survey, gaining knowledge from women with FH themselves, we found that women with FH were diagnosed late and a considerable number did not use lipid-lowering therapy. Age of FH diagnosis, treatment initiation and CVD events varied across countries. There is an urgent need for more focus on early treatment initiation, optimal treatment and close follow-up of compliance in women with FH.

Pregnancy complications and risk of chronic kidney disease

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Abstract

Introduction: The prevalence of chronic kidney disease (CKD) has increased rapidly in the last decades. Observational studies have found females at additional risk due to pregnancy complications, e.g. preeclampsia, gestational hypertension, and gestational diabetes. We aimed to examine the potential causal associations between these pregnancy complications and CKD.

Methods: We performed two-sample Mendelian Randomization (MR) using genetic instruments for preeclampsia (n=20,064 cases; n=703,117 controls), gestational hypertension (n=11,027; n=412,788), and gestational diabetes (n=12,332; n=131,109) and summary statistics for CKD from FinnGen (n= 12,787; n= 480,448) and UK Biobank (n=19,443; n= 358,001). We performed one-sample MR using individual level data from 202,879 women in the UK Biobank (n=9,324 cases). 80% power was reached at an odds ratio (OR) of 1.15 for gestational diabetes and 1.30 for preeclampsia and gestational hypertension.

Results: In two-sample MR associations between genetically proxied preeclampsia, gestational hypertension, and gestational diabetes and CKD, showed OR of 0.97 (95% CI: 0.90-1.04), 1.03 (0.96-1.11), and 1.07 (1.02-1.13), respectively. For gestational diabetes, excluding variants with type 2-predominant effects obtained similar results, OR 1.03 (0.99-1.07). Sensitivity analyses were consistent with the primary estimate and showed no signs of horizontal pleiotropy. In one-sample MR associations between genetically proxied preeclampsia, gestational hypertension, and gestational diabetes with and without type 2 diabetes-predominant variants and CKD showed OR of 0.97 (0.82-1.15), 1.04 (0.92-1.18), 1.22 (1.03-1.44), and 1.40 (1.03-1.90), respectively.

Conclusion: Genetic susceptibility to gestational diabetes was associated with increased risk of CKD later in life, suggesting a causal nature of the association. This emphasizes the importance of improved follow-up in women with pregnancy complications to target causal risk factors early.

The impact of menstrual cycle on lipid levels in healthy premenopausal women: a systematic review and meta-analysis

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Abstract

Introduction: Lipid concentrations may be affected by fluctuations in endogenous sex hormone levels during the menstrual cycle in healthy premenopausal women. Studies have assessed fluctuations in lipid levels throughout the menstrual cycle and yielded inconclusive findings. This study aimed to systematically review the existing evidence and conduct a meta-analysis to evaluate the association between cycle phase and lipid concentrations in healthy premenopausal women.

Methods: A systematic search was performed in MEDLINE, Embase, Cochrane Library, and Web of Science up to October 29th, 2020, and updated on November 26th, 2024. Prospective observational studies with ≥ 10 adult premenopausal women with regular menstrual cycle and no use of hormonal contraceptives, measuring total, LDL, and HDL cholesterol, or triglycerides on at least two occasions during the menstrual cycle were included. Risk of bias was assessed and a multilevel linear random-effects model accounting for within and between-study correlations is used for the meta-analysis. We investigate differences between the menstrual, mid-late follicular, ovulatory, early-mid luteal, and premenstrual phases of the menstrual cycle. PROSPERO ID: CRD42021220625

Results: The searches identified 2,924 records. One hundred thirteen papers underwent full-text review and 44 were included in the systematic review and meta-analysis ($n=610$). Most studies were small and there was between-study heterogeneity with respect to blood sample timing and cycle phase determination. The risk of bias ranged from moderate to serious. In preliminary meta-analysis of total cholesterol (33 studies), cycle phase significantly influenced the concentration ($p=0.02$). There is an estimated mean increase of 0.17 mmol/L (95%CI: 0.05, 0.29; $p=0.005$) from the menstrual to the mid-late follicular phase, followed by a decrease through the cycle.

Conclusion: Preliminary results indicate that total cholesterol fluctuates through the menstrual cycle.

Cetoleic acid in adipose tissue is inversely associated to the risk of atherosclerotic cardiovascular disease: a case-cohort study

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Iselin S. Holen

Abstract

Introduction: The long-chain monounsaturated fatty acid, cetoleic acid (C22:1; n-11) has been shown to exert anti-atherosclerotic properties. However, the role of cetoleic acid in development of atherosclerotic cardiovascular disease (ASCVD) is unknown. We investigated the association between the content of cetoleic acid in adipose tissue – a long-term objective biomarker - and the risk of total ASCVD. We hypothesised that a high content of cetoleic acid was inversely associated with the risk of ASCVD.

Methods: In this case-cohort study, we used data from the Danish Diet, Cancer and Health cohort established between 1993 and 1997. Gluteal adipose tissue biopsies were collected at baseline. Incident cases of ASCVD were identified by record linkage with nationwide registries and were defined as a composite of myocardial infarction, ischemic stroke and peripheral artery disease. The fatty acid composition was analysed by gas chromatography in a randomly drawn subcohort (n = 4,456) and all incident cases. Statistical analyses were conducted using weighted Cox proportional hazards regression models. The adipose tissue content of cetoleic acid was modelled as a restricted cubic spline with three knots and analyses were adjusted for age, sex, length of schooling, smoking, physical activity, waist circumference, body mass index, alcohol intake, hypertension and diabetes.

Results: During a median of 20.8 years of follow-up, we identified a total of 7210 incident ASCVD cases. In multivariable analyses, we observed a statistically significant inverse association (HR = 0.69 (95% CI: 0.59, 0.81)) between the content of cetoleic acid in adipose tissue and the rate of ASCVD.

Conclusion: We found an inverse association between adipose tissue levels of cetoleic acid and relative risk of ASCVD. Our findings highlight the need for further research into the underlying biological processes and additional studies evaluating ASCVD risk.

Midlife metabolic syndrome and rare functional GLP-1R variants and risk of late-life dementia

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Abstract

Introduction: Glucagon like peptide 1-receptor-agonists (GLP-1RA) are potent weight loss medicaments, and the *GLP-1R* gene is expressed in the brain and functions as a neurotransmitter. Post hoc analyses of clinical trials of GLP-1RA have shown a reduced risk of dementia in patients with type 2 diabetes. However, recent results from the EVOKE and EVOKE+ trials did not find a delay in progression of Alzheimer's disease (AD) with up to three years of semaglutide treatment. We examined the association of midlife metabolic syndrome and rare functional variants in the *GLP1R*-gene on risk of late-life AD and vascular-related dementia (VRD).

Methods: Including ~400,000 individuals (54% women) from the UKB risk of dementia was estimated as a function of metabolic syndrome and low frequency ($AF \leq 0.05$), predicted loss-of-function (pLoF) variants in the *GLP-1R* gene. The observational analyses were confirmed in the Copenhagen City Heart Study (CCHS) (n=9,103). Metabolic syndrome was having three of the following four: diabetes, BMI >30 kg/m², hypertension, or triglycerides >1.7 mmol/L. *GLP-1R*-variants were identified using Regenie, a computational framework designed for large-scale genome-wide association analyses.

Results: Using multifactorially adjusted Cox regression, midlife metabolic syndrome yielded hazard ratios (HRs) of 4.03(95% CI 3.10-5.23) for VRD and 1.89(95% CI 1.29-2.79) for AD. Results were similar in the CCHS. Using the Regenie survival model the gene-based burden *GLP-1R* pLoF variants yielded HRs of 1.76(95% CI 0.68-4.52) for VRD and 3.31(95% CI 1.09-10.10) for AD.

Conclusion: Midlife metabolic syndrome associated with increased risk of both late-life VRD and AD. Rare functional *GLP-1R* variants associated with late-life AD in a gene-based burden test. These findings suggest a potential preventive effect of GLP-1RA on AD risk; however, considering the results from the EVOKE and EVOKE+ trials, treatment initiation should be considered to start well before symptom debut.



Posters – Abstracts –
Inflammation and Vascular Biology

SESSION I

01

Temporal dynamics of systemic immune responses and exploratory molecular imaging in early experimental atherosclerosis

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Maria del Pilar Murillo Angarita

Abstract

Introduction: Atherosclerosis is a chronic inflammatory disease driven by metabolic dysregulation and immune activation. While local plaque inflammation has been extensively characterized, how systemic immune signatures evolve during early disease and whether they are reflected by molecular imaging remains incompletely understood. Here, we used a longitudinal, multimodal approach to define systemic immune remodeling in atherosclerosis progression and to evaluate the translational relevance of CxCR4-targeted molecular imaging.

Methods: Age- and sex-matched ApoE-deficient mice fed a high-fat diet and C57BL/6J control mice on a control diet were studied longitudinally for 20 weeks. Circulating immune cell dynamics were assessed by complete blood counts, and plasma levels of 31 chemokines/cytokines were quantified across multiple time points. Given the role of the CXCL12-CxCR4 axis in leukocyte trafficking, circulating CXCL12 was measured alongside exploratory CxCR4-targeted PET/MRI to assess concordance between systemic immune signatures and in vivo assessment of vascular inflammation.

Results: Atherosclerosis development was associated with a progressive systemic shift toward innate immune dominance. Despite this immune remodeling, multiplex plasma analysis showed a global reduction in circulating chemokine/cytokine levels, while CXCL12 concentrations remained stable over time. Exploratory CxCR4-targeted PET/MRI showed high variability in tracer uptake and did not consistently track disease progression. Ongoing histological analyses will further define vascular immune cell localization and plaque inflammation, providing spatial context for systemic and imaging findings.

Conclusion: This study identifies a distinct systemic immune phenotype in early atherosclerosis marked by myeloid expansion despite reduced circulating inflammatory mediators, suggesting altered immune signaling and potential tissue sequestration. No clear agreement between systemic immune signatures and CxCR4-targeted imaging highlights current challenges in translating molecular imaging approaches to detect early, low-grade vascular inflammation. Together, this work provides a robust framework for integrating systemic immune biomarkers with molecular imaging and informs the development of potential translational strategies for early cardiovascular assessment.

Effect of high intensity statin medication on circulating foamy monocytes in healthy individuals

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Abstract

Introduction: Circulating foamy monocytes (CFMs) are pro-inflammatory, display increased trans-endothelial migration, and are important drivers of atherosclerotic plaque progression. Elevated CFMs have mainly been demonstrated in familial hypercholesterolemia and hypertriglyceridemia. We aimed to determine if CFMs can be reliably quantified in healthy individuals and reduced by high-intensity statin treatment.

Methods: We performed an interventional clinical study with 11 healthy volunteers receiving 40 mg atorvastatin daily for 4 weeks. Plasma and white blood cell samples were collected weekly, including baseline and one-week washout. CFMs were quantified by measuring monocyte lipid droplet (LD) number, size, area, percent LD-positive cells, and low-density lipoprotein (LDL) uptake with a previously established semi-automated high-content based analysis platform.

Results: After one week of treatment, LDL-C, total cholesterol, and apolipoprotein B (ApoB) decreased by 52%, 30%, and 38%, respectively. LDL-C further decreased during treatment, reaching a 63% reduction from baseline by week four. One week after treatment, LDL-C, total cholesterol, and ApoB increased by 74%, 23%, and 37%, respectively, but remained below pre-treatment levels. At baseline, 15.6% of monocytes were LD-positive and 0.29 LDs were detected per monocyte. The number of LDs decreased in a stepwise manner with treatment and reached the lowest level (0.13, $p < 0.01$, Wilcoxon signed-rank test) at washout. Similar reductions were observed for the percent of LD-positive monocytes (8.7% at wash out, $p < 0.01$). Interestingly, reduced monocyte lipid storage coincided with increased cellular LDL uptake, suggesting enhanced monocyte LDL uptake when lipid storage is lowered.

Conclusion: Our results highlight a novel aspect on how atorvastatin can influence inflammation and atherosclerotic plaque progression through reducing circulating foamy monocyte abundance.

03

Modulation of histone-induced cellular dysfunction from NETs in atherosclerosis.

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Abstract

Introduction: There is increasing evidence that the release of extracellular cell traps by neutrophils (NETs) drives inflammation, lesion development and thrombosis in atherosclerosis, but the mechanisms involved are complex and not well understood. NETs consist of a DNA backbone and are very abundant in histones, which are cytotoxic and pro-inflammatory when present in the extracellular environment. In this study, we examined whether heparin and enoxaparin, a low-molecular mass derivative of heparin, could modulate histone driven cytotoxicity and inflammation, and influence the binding of histones to the extracellular matrix (ECM).

Methods and Results: Experiments were performed with a commercial histone preparation containing H1, H2A, H2B, H3, and H4 histones, which are present in NETs. Exposure of different cell types, including J774A.1 macrophage-like cells and human coronary artery smooth muscle cells (HCASMC) to histones resulted in a dose-dependent loss of viability. Histones also activated inflammatory signaling, resulting in the increased expression of different inflammatory markers, including monocyte chemoattractant protein 1 (both cell types), tumour necrosis factor α (macrophages) and interleukin 6 and vascular cellular adhesion molecule 1 (HCASMC). Pre-treatment of the histones with heparin derivatives could prevent the histone-induced toxicity and inflammatory signaling. Using an ELISA approach, we also showed that histones bind to the ECM, including cell-derived matrix produced by HCASMC. Heparin and enoxaparin decreased this binding, and could also facilitate the removal of pre-bound histones from the ECM. Importantly, heparin and enoxaparin could also prevent NET-induced cytotoxicity.

Conclusion: Together, these results suggest that heparin derivatives could have therapeutic value as a means to decrease histone-induced cellular damage resulting from aberrant NET release, which is seen in atherosclerosis and other chronic inflammatory pathologies.



YIA Poster Walk I – Abstracts
Inflammation and Vascular Biology

SESSION I

New insights into apolipoprotein B-100 degradation by proteases in vivo and ex vivo

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Abstract

Introduction: Apolipoprotein B-100 (ApoB) is the primary protein of low-density lipoproteins (LDL) with modified, fragmented and aggregated LDL are strongly associated with the progression of atherosclerosis. We have previously shown that ApoB fragments are present in advanced human carotid artery atherosclerotic plaques, and these differ between plaque phenotypes. Although most ApoB particles are degraded in lysosomes after cellular uptake, less is known about whether and how LDL might be processed and degraded by extracellular proteases. We hypothesized that identification of endogenous protease-mediated fragments could unveil new treatment targets and possible disease biomarkers in plasma.

Methods and Results: LDL isolated from human donors was treated with specific proteases and subsequently analyzed by N-terminal proteomics, yielding information on both in vivo generated (endogenous) fragments, and those generated by specific proteases added ex vivo. Sequence analysis allows specific sites of cleavage to be identified and thereby pinpoint potential culprit proteases in vivo. Data from multiple donors yielded a sequence coverage of ApoB of 71% and identification of > 1000 peptides. Neo-N-terminal fragments were identified in both untreated and protease-treated samples. The former is consistent with the presence of significant numbers of endogenous fragments in untreated LDL. Fragments unique to specific protease treatments were identified, including well-established cleavage signatures for MMP activity (e.g. Leu residues at position P1' for species generated by MMP11). Ongoing data analysis is investigating how fragments generated by exogenous proteases correlate with fragments detected in both 'healthy' control arteries, and a cohort of 76 human carotid artery plaques.

Conclusion: This work sheds new light on the presence and origin of ApoB fragments in human LDL and the role of specific proteases in particle processing in both normal physiology and the progression of atherosclerosis.

05

Age-associated B-cells serve as key precursors of antibody-secreting cells in atherosclerosis

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Abstract

Requested not to publish.

Integrative analysis of single-cell transcriptomics data reveals three distinct mast cell subpopulations in human atherosclerotic lesions

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Abstract

Introduction: Despite their modest presence within atherosclerotic lesions, evidence suggests an atherogenic role for mast cells. In this study, we leverage publicly available single-cell RNA sequencing datasets to increase the representation of mast cells and conduct a comprehensive analysis of the population's transcriptional heterogeneity within human atherosclerosis.

Methods and Results: Single-cell RNA and CITE sequencing data from human carotid plaques were obtained from the Gene Expression Omnibus (GSE155512, GSE159677, GSE253903) and integrated into one dataset. Following clustering of all cells, subclustering of the mast cells identified three distinct transcriptional profiles. All profiles contained high expression of canonical markers: KIT proto-oncogene, receptor tyrosine kinase (KIT), histidine carboxylase (HDC), and tryptase alpha/beta1 (TPSAB1). CCR3 surface proteins were detected on 43% of mast cells, evenly distributed across clusters. Two of the profiles reflect previously recognized tryptase-positive and tryptase-chymase-positive subsets (MCT and MCTC respectively). The MCTC profile was characterized by increased expression of chymase 1 (CMA1), cathepsin G (CTSG) and hydroxyprostaglandin dehydrogenase (HPGD). Increased IgE, Fc Epsilon Receptor 1a and CD59 surface protein abundance was found within this mast cell cluster. Pathway analyses showed upregulation of complement activation- and degranulation-associated genes. The third transcriptional profile conveyed a novel signature characterized by increased expression of amphiregulin (AREG), along with increased detection of transcripts encoding for inhibitor of NF- κ B (IkB) proteins, suggestive of pro-fibrotic, inflammation-resolving properties of mast cells expressing this signature.

Conclusion: This study provides a novel detailed overview of the mast cell transcriptomic landscape and cellular heterogeneity within human atherosclerosis, demonstrating the presence of three distinct subpopulations, including a previously unknown AREG⁺ cluster.

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Halofuginone enhances collagen remodeling during diet-induced atherosclerosis regression by beneficially impacting the systemic inflammatory status

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Andisyah Putri Sekar

Abstract

Introduction: Adopting a healthier diet is crucial for lowering lipid levels and mitigating cardiometabolic risk. Nonetheless, residual tissue inflammation can impede disease regression, particularly in metabolic-associated fatty liver disease and atherosclerotic cardiovascular disease. This study aimed to evaluate the anti-inflammatory effects of Halofuginone, a derivative of the natural alkaloid febrifugine, on fatty liver and atherosclerotic plaque remodeling during a low-fat diet-induced regression phase.

Methods: Hypercholesterolemic female low-density lipoprotein receptor knockout mice were initially fed a Western diet for six weeks to induce fatty liver disease and atherosclerosis. Following this phase, they were transitioned to a chow diet for six weeks to facilitate disease regression. During the regression period, Halofuginone (5 µg per mouse) or its solvent (DMSO in PBS) was administered intraperitoneally three times a week.

Results: The low-fat diet significantly lowered plasma and hepatic lipid levels ($p < 0.05$). There was a substantial reduction in CD68⁺ macrophage content, decreasing 2.2-fold in the liver and 1.4-fold in atherosclerotic plaques ($p < 0.001$). All liver samples showed no collagen presence. The switch in diet did not alter plaque size; however, collagen content within plaques increased by 8% ($p = 0.004$). Halofuginone treatment maintained plaque size but yielded an additional 5.3% increase in collagen content ($p = 0.031$). Notably, this effect correlated with a 14% rise in circulating Ly6Chigh pro-inflammatory monocytes ($p = 0.043$), suggesting a transformation into anti-inflammatory M2 macrophages during atherosclerosis regression. Further evidence was observed with a shift towards an M2 macrophage phenotype, as indicated by a ~3-fold increase in the hepatic Arg1/iNOS ratio ($p = 0.004$).

Conclusion: Halofuginone enhances collagen remodeling during diet-induced atherosclerosis regression by impacting systemic inflammatory status.

Organ-specific translomic insights of vascular endothelial cells and their association to human metabolic traits

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Abstract

Introduction: Endothelial cells (EC) are instructive gatekeepers for the uptake of dietary-derived nutrients such as glucose and fatty acids delivered by chylomicrons into metabolically active organs. Studying the endothelium remains challenging since all tissues have a cellular heterogeneity. The NuTRAP mouse model addresses this limitation by enabling the selective isolation of ribosomal RNA in a cell-type-specific manner, thereby allowing the determination of the translome specifically in ECs. We aim to identify EC-specific genes in BAT, heart and liver that are regulated by catabolic (warm vs cold housing) and anabolic (fasted vs postprandial) states. To assess the potential relevance of the identified EC genes in humans, we investigated the associations between variants of these genes with metabolic traits using data from the UK Biobank.

Methods: NuTRAP-CDH5^{E^{ERT2}}-Cre mice were exposed to either 6°C or 22°C for 24h followed by a 4h fasted or refed intervention. GFP-tagged ribosomes of ECs were immunoprecipitated (IP) and their RNA analyzed by bulk sequencing.

Results: We validated the enrichment of EC markers in the IP fractions and characterized the EC responses to cold exposure and changes in feeding status. Cold stimulation increased the expression of endothelial genes in BAT, heart and liver including *Mfsd2a*, *Fabp3*, and *Lpl*, which are involved in lipid metabolism and signaling. Refeeding led to an upregulation of the *Lpl*-regulating gene *Angptl8* in the ECs of BAT and liver but not in heart. Furthermore, we identified genes predominantly expressed and regulated in EC, that show strong associations with metabolic traits such as triglycerides, HDL, LDL and hyperlipidemia.

Conclusion: The NuTRAP model is a powerful tool to characterize the EC translome across metabolically active tissues. Our findings uncover unrecognized EC genes linked to human metabolic traits, highlighting their potential role in regulating lipid metabolism and energy homeostasis.

Characterisation of the protein composition and histone modification in neutrophil and eosinophil extracellular traps

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Abstract

Introduction: Extracellular traps (ETs) are released by neutrophils (NETs) and eosinophils (EETs) during inflammation and play a role in the pathology of inflammatory diseases. NETs are composed of chromatin decorated with histones and anti-microbial proteins, such as myeloperoxidase (MPO) and elastase, while the protein composition of EETs has not been well studied. Various studies highlight a role for extracellular histones in promoting tissue damage and disease, e.g. in atherosclerosis. In this study, we used a proteomic approach to compare the protein composition of NETs and EETs, and examined whether the histones contain post-translational modifications (PTMs), which could influence their reactivity.

Methods and Results: The NETs were isolated from purified neutrophils stimulated with calcium ionophore (A23187) using different DNA digestion times (15 or 5 min) to create different NET sizes. The abundance of histones and MPO was significantly higher in small sized NETs compared to large sized NETs. Interestingly, NET size was not associated with the presence of other NET associated proteins, like neutrophil elastase, α -enolase and transketolase. In contrast, the protein composition of EETs released by purified eosinophils stimulated with A23187 was significantly different from the proteins detected in NETs. Eosinophil cationic protein, eosinophil peroxidase (EPO) and different types of proteoglycans were the most abundant proteins in EETs and not identified in NETs, while MPO and Histone H4 were significantly elevated in NETs. PTMs of histones were determined, particularly on Tyr88 in histone H4, which was brominated in EETs and chlorinated in NETs, consistent with the formation of hypobromous acid by EPO and hypochlorous acid by MPO.

Conclusion: These results show for the first time that ETs from eosinophils contain different proteins and histone modifications than NETs, which could be important in determining the cellular nature of ETs in vivo and assessing their wider role in disease.



**Posters – Abstracts –
Cardiovascular Disease**

SESSION II

Platelet inhibiting effects by the novel nitric oxide-donor nitrosooxypropanol (PDNO)

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Abstract

Introduction: The multiple roles of nitric oxide (NO) in human physiology includes vasodilation and platelet inhibition, both important to prevent cardiovascular disease events like thrombosis and myocardial infarction. The novel organic nitrite Nitrosooxypropanol (PDNO) has shown potent cardiovascular effects *in vivo* and preclinical studies have confirmed the safety and efficacy in models of acute pulmonary hypertension. Compared to conventional NO-donors, PDNO exhibits a superior pharmacological profile, marked by rapid onset, lack of tolerance, and minimal impact on systemic blood pressure. These properties position PDNO as an ideal candidate for drug repurposing. This project aims to elucidate the potential inhibitory capacity of PDNO on platelets, which is not yet explored and could be beneficial in indications of thrombosis.

Methods: Effects of PDNO on human platelet aggregation and secretion were investigated using impedance aggregometry in whole blood and light transmission aggregometry in platelet-rich plasma and isolated platelets. Molecular evidence was investigated by measuring cytosolic calcium mobilization and shown by western blot.

Results: Platelet aggregation and secretion induced by the thrombin receptor agonist SFLLRN was concentration-dependently inhibited by PDNO. Pharmacological comparison of platelet inhibition revealed that PDNO was more potent than the clinically used NO-donor nitroglycerin. Moreover, PDNO triggered NO/cGMP signaling, demonstrated by Ser239-specific phosphorylation of vasodilator-stimulated phosphoprotein (VASP). Measurements of cytosolic calcium showed that PDNO had similar capacity to reduce Ca²⁺ mobilization as the spontaneous NO-donor SNAP. The platelet inhibitory capacity of PDNO showed a rapid on-set of action and a surprisingly long-acting effect, from 10 seconds to 60 minutes.

Conclusion: The novel NO-donor PDNO elicits significant platelet inhibitory capacity and antithrombotic therapeutic potential.

The AhR/P38 MAPK pathway mediates kynurenine-induced cardiomyocyte damage: The dual role of resveratrol in apoptosis and autophagy

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Abstract

Introduction: Chronic kidney disease increases the risk of cardiovascular disease, partly due to uremic toxins, such as Kynurenine (KYN). While KYN contributes to tissue damage, its role in cardiomyocyte apoptosis and autophagy remains unclear. Resveratrol (RSV) can protect against oxidative stress and inflammation, whereas its specific effects on KYN-induced cardiomyopathy are less understood. This study aimed to investigate the role of KYN in cardiomyocyte apoptosis and autophagy and examine the protective effects of RSV against KYN-induced damage.

Methods: H9C2 cardiomyocytes were cultured and treated with KYN in presence or absence of RSV or inhibitors of the AhR/Src/MAPKs pathway. Cell viability, apoptosis, mitochondrial membrane potential, and autophagy were assessed using MTT, TUNEL, JC-1, and autophagy detection assays.

Results: KYN induced apoptosis, and autophagy in H9C2 cells. RSV pretreatment reduced apoptosis but enhanced autophagy in KYN-treated cells. Inhibiting autophagy or blocking apoptosis, increased KYN-induced apoptosis and autophagy, respectively. Additionally, KYN treatment enhanced AhR activation and the phosphorylation of Src and MAPKs proteins, whereas RSV pretreatment decreased AhR activation and ERK phosphorylation. Inhibitors of p38 MAPK and JNK reduced expression of apoptotic proteins. AhR inhibition also reduced the phosphorylation of p38 MAPK and expression of apoptotic proteins while it enhanced autophagy-related protein expression in KYN treated H9C2 cells.

Conclusion: Our findings suggest that KYN induces cardiomyocyte apoptosis via the AhR/p38 MAPK pathway whereas RSV can protect against the KYN-induced apoptosis while promoting autophagy. Given the high cardiovascular risk in CKD patients, these findings provide in-sight into potential therapeutic strategies targeting KYN-induced cardiomyopathy.

Hypoxia drives a pro-atherogenic extracellular matrix that promotes myeloperoxidase retention and tissue damage that can be attenuated by heparin mimetics

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Abstract

Introduction: Atherosclerosis is the major underlying cause of cardiovascular disease, with this characterized by the accumulation of lipids and activated leukocytes. These cells release myeloperoxidase (MPO) which generates oxidants, resulting in arterial extracellular matrix (ECM) damage, endothelial cell dysfunction, inflammation and associates with hypoxia. The aim of this study was to determine whether hypoxia modulates ECM structure, enhances MPO retention and oxidant generation, and if heparin mimetics can displace MPO and attenuate damage.

Methods and Results: Exposure of human coronary artery endothelial cells to hypoxia (1% compared to 20% O₂) altered the expression of genes involved in endothelial dysfunction (*eNOS*), inflammation (*ICAM-1* and *IL-6*) and ECM composition, with hypoxia-induced ECM being characterized by an overabundance of the proteoglycan versican and associated matrix enzymes. This versican-rich ECM results in decreased HCAEC adhesion, enhanced proliferation, and increased the binding of MPO. These events increase the potential for MPO-mediated oxidative damage within the artery wall. Previous studies indicate that heparin infusion in humans with cardiovascular disease, results in higher plasma MPO levels and improved endothelial function, probably via displacement of MPO from the artery wall. The use of heparin is however limited by its anticoagulant properties. To circumvent this problem, we have screened multiple novel heparin mimetics which do not have this limitation. Multiple candidates displace ECM-bound MPO to a significant extent, and the lead compound also reduces MPO-derived oxidant generation.

Conclusion: Together, these findings suggest that the versican-rich ECM resulting from exposure to hypoxia promotes MPO retention and vascular oxidative injury, enhancing the risk of plaque rupture. Novel heparin mimetics can target MPO and release it from the ECM by disrupting MPO–ECM interactions. This may reduce oxidant damage, and therefore these compounds show potential as plaque stabilizing agents.

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Age-associated CD8+GZMK+ T-cells clonally expand and preferentially home to the atherosclerotic plaque in mice

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Abstract

Requested not to publish.

Cardiometabolic impact of Ramadan fasting in adolescents with MASLD

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Abstract

Introduction: Metabolic Dysfunction-Associated Steatotic Liver Disease (MASLD) is a spectrum of disorders ranging from isolated steatosis to more aggressive forms and is an independent risk factor for cardiovascular diseases. In adults with MASLD, Ramadan fasting (RF) has been shown to improve cardiometabolic health, but its effects in adolescents with MASLD are unknown. To fill this gap, we investigated the cardiometabolic impact of RF in this population.

Methods: We conducted a prospective study in 18 non-diabetic adolescents (14 males and 3 females, aged 9–17 y/o) with MASLD adhering to RF. Participants were assessed at three time points: before Ramadan (T1), during the second week (T2), and during the third/fourth week (T3). Dietary intake, physical activity, and sleep patterns were recorded at all visits. Anthropometrics, clinical biochemistry, and untargeted plasma lipidomics (LC-MS) were measured at T1 and T3.

Results: Total caloric intake (average 1901 kcal/day) and macronutrient composition, including fatty acid and sugar quality, did not differ significantly across time points. However, at T3, participants exhibited a 23.3% increase in hepatic insulin resistance (HOMA-IR, $p < 0.05$) and an 8.7% increase in LDL cholesterol ($p = 0.01$); other clinical variables remained unchanged. Exploratory lipidomic analyses revealed a significant increase in plasma triacylglycerols enriched in saturated and monounsaturated fatty acids, markers of heightened de novo lipogenesis in MASLD, which correlated positively with HOMA-IR. We speculate that the evening concentration of caloric intake may contribute to these changes, potentially via circadian misalignment. These mechanisms are currently under investigation.

Conclusion: These findings indicate that Ramadan fasting might negatively impact the cardiometabolic profile in adolescents with MASLD. Therefore, careful dietary counseling and monitoring are recommended for this population during fasting periods.

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LAGOM trial: longitudinal approach to generate positive cardiometabolic health outcomes in severe mental illness

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Abstract

Requested not to publish.

Real-world use of bempedoic acid in patients with heterozygous familial hypercholesterolemia, an Italian experience

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Abstract

Introduction: Bempedoic acid has emerged as a therapeutic option for patients not reaching their LDL-C targets despite maximal tolerated lipid lowering therapy. Real-world data about the use of bempedoic acid are still lacking especially in high-risk populations such as patients with heterozygous familial hypercholesterolemia (HeFH).

Methods: A total of 111 individuals were prescribed bempedoic acid between July 2023 and 2025 in the outpatient clinic of Policlinico Umberto I in Rome. Data regarding lipid modifying therapies, anthropometric and laboratories parameters were retrieved from electronic medical records at baseline and at 3.5 months follow-up. Statistical analyses were performed using SPSS 30.0 and p-value set at 0.05.

Results: Patients taking bempedoic acid were mainly females (62.2%) and a minority had a diagnosis of HeFH (18%). Non-HeFH patients were older (64.9, 55.7 years-old, p-value 0.016) and more often statin intolerant (76.9%, 35%, p-value <0.001) compared to HeFH individuals. Non-HeFH patients had higher total cholesterol values (221.0 mg/dL, 179.1 mg/dL, p-value 0.010) and triglycerides levels (107 mg/dL, 85 mg/dL, p-value 0.008) at baseline compared to HeFH. The LDL-C reduction was greater for non-HeFH patients (40.9 mg/dL, 19.1 mg/dL, p-value 0.036) whereas the percentage of LDL-C reduction was compatible among the two groups (26.3 %, 17.2 %, p-value 0.65).

Conclusion: Our pilot study suggests that bempedoic acid in HeFH is prescribed in younger and less frequently in statin intolerant individuals compared to the general population. The percentage of LDL-C reduction was compatible between the two groups even though non-HeFH patients had higher baseline LDL-C values and experienced a more significant reduction in terms of measured LDL-C in mg/dL. However, further studies are needed to better understand the applications and degrees of effectiveness of bempedoic acid across different patients' sub-groups such as those with HeFH.



YIA Poster Walk II – Abstracts –

Cardiovascular Disease

SESSION II

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The anti-ischemic activity of cardioprotective 6-piperaziny-purine analogues bearing nitrate esters is determined by the length of the carbon side chain

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Abstract

Requested not to publish.

Role of endothelial autophagy in atherosclerotic plaque development and composition

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Abstract

Introduction: Cardiovascular diseases (CVD) represent the leading cause of death, hereby affecting millions of people worldwide. Moreover, it is expected that the global CVD burden will rise even further over the next decades. Atherosclerosis is one of the most common vascular disorders and is characterised by lipid deposition and inflammation in the arterial wall. Endothelial cells (ECs) play a pivotal role in the initiation of atherosclerosis, as endothelial dysfunction and activation are key drivers of early lesion formation. Macroautophagy (hereafter referred to as autophagy) is a fundamental intracellular degradation and recycling process that maintains EC homeostasis. Accordingly, impaired EC autophagy may critically contribute to the initiation of atherosclerosis. This study aims to elucidate the role of EC autophagy in atherogenesis and plaque composition.

Methods and Results: Male and female ApoE^{-/-}Atg7^{fl/fl}VECadCre^{KI}ER^{T2} mice (treated with either tamoxifen to induce EC Atg7 knock-out or corn-oil as vehicle control) were fed a Western-type diet for both 8 and 16 weeks. Cre-negative ApoE^{-/-}Atg7^{fl/fl} mice, treated with tamoxifen, were included as additional controls. Mice were followed-up over 4 week intervals using echocardiography to evaluate *in vivo* pulse wave velocity (PWV), pulse propagation velocity (PPV) and velocity time integral (VTI). Atherosclerotic plaques of the proximal ascending aorta, brachiocephalic artery and carotid artery are currently being analyzed histologically to determine plaque size, composition and the expression of EC adhesion molecules. Furthermore, en face Oil Red O staining of thoracic and abdominal aortas is being conducted to quantify lipid burden and plaque distribution.

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Activated age-associated B cells accumulate in human atherosclerotic plaques

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Abstract

Requested not to publish.

N=1-studies in statin-intolerance; objectifying placebo effects (NISONE): a protocol for a randomized controlled trial assessing the implementability of N=1-studies to promote the use of statins

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Abstract

Introduction: Lipid-lowering therapies, particularly statins, are crucial in the prevention of cardiovascular disease. Yet their effectiveness is often compromised by statin-associated muscle symptoms, leading to non-adherence, discontinuation and/or switching to alternative, more expensive therapies such as PCSK9-inhibitors or bempedoic acid. Recent studies suggest that N=1-interventions may help distinguish true side effects from placebo-driven symptoms and support reinitiation of statin-therapy.

Methods and Results: The “N=1-studies In Statin-intolerance; Objectifying Placebo Effects” (NISONE) trial is a study that will include 249 patients with atherosclerotic cardiovascular disease or familial hypercholesterolemia who stopped using two or more statins due to perceived symptoms. Participants will be randomized (2:1) to an N=1-intervention or usual care. The intervention consists of four double-blind six-week periods of statin- (rosuvastatin 10mg 1-2 tablets/day or atorvastatin 20mg 1-2 tablets/day) or placebo-treatment. Patients are required to record their symptoms through questionnaires in an application developed for this study. During the subsequent fifth treatment period, feedback on symptoms during the intervention periods is provided in a report, which will be discussed with a healthcare professional. Statin continuation is encouraged, but remains voluntary. Statin-intolerant patients in the usual care group will be treated according to the cardiovascular risk management guidelines. The primary outcome, the percentage of patients continuing their statin after one year, will be analyzed using odds ratios and 95%-confidence intervals.

Conclusion: The NISONE trial assesses whether an N=1-intervention can promote statin-use in statin-intolerant patients and evaluates its feasibility for clinical implementation. This trial could provide an approach to enhance statin adherence and lower healthcare costs by decreasing prescriptions of more costly lipid-lowering therapies.

True statin-associated muscle symptoms that can be attributed to statin-therapy as determined by N=1-trials and cross-over randomized controlled trials: a systematic review and meta-analysis

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Abstract

Introduction: Statins are highly effective against cardiovascular disease. Although statin-associated muscle symptoms (SAMS) often lead to discontinuation, their prevalence is likely overestimated due to symptom misattribution and nocebo effects. This systematic review estimates the proportion of true SAMS in patients with a history of SAMS through N=1-trials and blinded crossover-RCTs.

Methods: Blinded crossover-RCTs and N=1-trials comparing statin- and placebo-treatment periods in adults with a history of SAMS were identified via a systematic search. Primary outcomes included the proportion of true SAMS, differences in SAMS-severity and willingness to restart therapy after the trials. Random-effects meta-analyses were performed.

Results: Eight studies were included. The pooled proportion of participants reporting true SAMS was 32% (95%-CI [18%, 50%], range across studies 15-44%). Some studies used a strict definition, requiring symptoms to occur only during statin periods, while others employed a threshold-based approach comparing symptom scores between statin- and placebo-treatment periods. Higher rates of true SAMS were observed when applying a strict definition versus a threshold-based definition (41 vs. 21%). No significant difference in SAMS-severity was found between statin- and placebo-treatment periods on a 0–100 visual analog scale (mean difference 1.43, 95%-CI [-1.39, 4.25]). The Brief Pain Inventory (scale 0-10) showed only a minimal, clinically irrelevant increase in pain comparing statin- with placebo-treatment periods (mean difference 0.25, 95%-CI [0.05, 0.44]). 59% of participants considered to restart statin-therapy after an N=1-trial (95%-CI [43%, 73%]).

Conclusion: N=1-trials showed that only a minority of 15-44% of reported SAMS-cases suffer from true SAMS and that the majority considered to restart statin-therapy after an N=1-trial. Thus, N=1-trials show promise for improving statin-use in patients who attribute symptoms to statins.



Posters – Abstracts –
Lipoproteins and Lipid Transport

SESSION III

Intra-individual variability in lipoprotein(a) in a large primary care dataset: predominantly analytical or biological variation?

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Abstract

Introduction: Lp(a) is a genetically determined, causal risk factor for ASCVD. Current guidelines assume lifelong stable plasma levels and recommend once-in-a-lifetime measurement. However, variability between repeated measurements may influence classification near clinically relevant thresholds. Whether this variation is biological or analytical remains unclear.

Methods: We analyzed a nationwide dataset from Fürst Medical Laboratory comprising 842,148 Lp(a) measurements from 457,334 individuals. Longitudinal analyses included individuals with ≥ 2 measurements during two assay periods: Roche (2000–2009, $n=40,502$) and Siemens (2018–2023, $n=32,933$). Variability was assessed using correlation analyses, change distributions, and category shifts across thresholds (<30, 30–50, 50–70, 70–90, 90–110, >110mg/dL).

Results: Lp(a) values were highly correlated between first and second measurements (Spearman $r=0.94$ for Roche; $r=0.96$ for Siemens). Most individuals with low (<30 mg/dL) or high (>110 mg/dL) baseline values remained in their respective category, whereas intermediate ranges showed meaningful reclassification. For Siemens, 22% of individuals in the 30–50 mg/dL range measured above 50 mg/dL at follow-up, while 15% measured below 30 mg/dL at follow-up. 29% in the 50–70 mg/dL range measured below 50 mg/dL and 15% measured above 70 mg/dL at follow-up. To achieve a 95% likelihood of remaining ≥ 50 mg/dL, the first measurement had to be ~ 67 mg/dL or higher. Assay comparison revealed substantially lower proportions with deviations >25%, >50%, >100% and >200% for Siemens versus Roche, with Roche showing greater variability at low and high Lp(a) levels, suggesting that much of the observed variation is analytical rather than biological. Around plasma levels of 50 mg/dL, variability was similar between assays.

Conclusion: Lp(a) is highly stable at the population level, but intra-individual variability - probably largely driven by analytical factors - can influence classification near clinically relevant thresholds. These findings support confirmatory re-testing before decisions with major clinical consequences and highlight the need for future assay harmonization.

Lack of perilipin 2 is not critical for lipid deposition in the aortic root and the aortic arch

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Abstract

Introduction: Early atherosclerosis is characterised by lipoprotein retention within the vascular intima, where macrophage uptake of lipoproteins promotes foam cell formation. The lipid excess is stored as cholesteryl esters (CEs) within lipid droplets (LDs) that are stabilised and regulated by LD-associated proteins such as perilipins (Plins). Accumulation of LDs in macrophages transforms them into foam cells and contributes to inflammation and lesion development, ultimately leading to thrombus formation and ischemic events. Plin2 is abundantly expressed in atherosclerotic lesions and surrounds the accumulating LDs, but its causal role in atherosclerosis development remains unclear. We aimed to investigate whether *Plin2* deletion influences macrophage functions and atherosclerotic development in mice.

Methods: Male *Plin2*^{+/+} and *Plin2*^{-/-} C57BL/6N mice received AAV-mediated overexpression of a mutated mouse Pcsk9 (AAV8-mPcsk9-D377Y) to deplete hepatic LDL receptors (Ldlr) and were fed an atherogenic diet for 15 weeks to induce hypercholesterolaemia. Body weight, body composition, and organ weights were monitored, and plasma and liver lipids were measured. Protein and mRNA expression were assessed by immunoblotting, ELISA, and RT-qPCR. Plaque burden was assessed in the aortic root and aortic arch by histological staining and en face analysis.

Results: The dietary AAV8-mPcsk9-D377Y model successfully induced hypercholesterolaemia independent of *Plin2* expression. *Plin2*^{-/-} mice had reduced hepatic and plasma triacylglycerol and total cholesterol levels, as well as reduced body weight and fat mass. *Plin2* deletion did not alter atherosclerotic lesion size in the aortic root or aortic arch under the tested conditions.

Conclusion: *Plin2* deletion in mice revealed hepatic and systemic effects under hyperlipidaemic conditions but did not seem to alter development of atherosclerotic lesions. We are currently investigating LD storage capacity and inflammation in cultured bone marrow-derived macrophages (BMDMs) treated with lipids to determine the role of *Plin2* in macrophage LD formation, CE-storage and inflammatory signalling.

A human-like bile acid composition attenuates atherogenesis in female *Ldlr*^{-/-} mice by reducing cholesterol absorption

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Abstract

Introduction: Emerging evidence links bile acid (BA) metabolism to cardiovascular disease, however, interspecies differences in BA profiles limit the translational value of murine models. In humans, chenodeoxycholic acid (CDCA) is a major BA, whereas mice express hepatic CYP2C70, which converts CDCA into hydrophilic muricholic acids (MCAs). Mice also express CYP2A12, which rehydroxylates secondary BAs into primary forms.

Methods and Results: To investigate the impact of varying degrees of BA humanization on atherogenesis and cardiac function, we generated male and female low-density lipoprotein receptor knockout (*Ldlr*^{-/-}) mice with liver-specific knockdown of *Cyp2a12*, *Cyp2c70* or both using CRISPR-Cas9. Mice were fed a low-fat, cholesterol-enriched diet for 12 weeks to induce atherogenesis. Knockdown of *Cyp2a12* (C12), *Cyp2c70* (C70), or both (double knockdown, DKD) resulted in distinct alterations in BA composition in plasma and bile. Female DKD mice developed significantly smaller atherosclerotic lesions and necrotic cores compared to wild-type mice, whereas no effect was observed in C12 and C70 mice. In males, BA humanization did not affect atherogenesis. Cardiac function remained unchanged across all groups and sexes. Mechanistically, female DKD mice showed reduced total and very-low-density-lipoprotein (VLDL) cholesterol in plasma, while hepatic cholesterol was significantly lower in both sexes. Serum plant sterols were reduced in all knockdown groups, most notably in DKD mice, indicating decreased intestinal cholesterol absorption. BA humanization had minimal effects on plaque macrophage content, circulating immune cells, or plasma cytokines.

Conclusion: These findings demonstrate that a humanized BA profile confers atheroprotection in female DKD mice, likely due to suppressed *Cyp8b1*-mediated 12 α -hydroxylation of taurocholic acid, and primarily through improved lipid metabolism rather than immune modulation.

Atherogenic lipid profiles and the association with historical malnutrition in Tanzanian and Zambian Cohorts: a cross-sectional study

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Abstract

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Abstract

Introduction: Familial Chylomicronaemia Syndrome (FCS) is a rare genetic disorder characterized by elevated plasma triglycerides (TG) levels leading to increased risk of acute pancreatitis. TG accumulates in the blood due to impaired or absent lipoprotein lipase (LPL) activity, that are caused by dysfunctional or non-functional LPL gene variants or genes that affect the folding and transport of LPL. The standard treatment of FCS patients is a strict diet of low-fat intake as no effective pharmacological treatment is available. Different strategies have been tested; inhibitor targeting and enzyme replacement by gene therapy. Inhibitor targeting is only available for FCS patients with impaired LPL activity, whereas enzyme replacement is in theory an efficacious treatment for all FCS patients. The first generation of enzyme replacement was based on the sequence of WT LPL, that are an inherent unstable protein, thus the treatment was later discontinued due to low outcome.

Methods and Results: Therefore, we designed, purified and tested several PROSS generated LPL variants to increase the thermostability of LPL. The increased thermostability of LPL reduced the enzymatic activity significant. We applied the FunLib software on the thermostable LPL PROSS variant to gain flexibility in the active site and hopefully increase activity. The LPL variant developed by combining the PROSS and FunLib software shows enhanced thermostability and decent enzymatic activity.

Conclusion: The LPL variant is a promising candidate to develop an enzyme replacement treatment for FCS patients.

The role of apolipoprotein M in intestinal lipid metabolism

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Abstract

Introduction: Apolipoprotein M (ApoM) is primarily produced in the liver and kidney and secreted to plasma. In plasma, ApoM is primarily bound to HDL particles, but it has been detected in all classes of lipoproteins. ApoM in plasma is a carrier of Sphingosine-1-phosphate (S1P), a bioactive lipid involved in endothelial barrier function, immune cell trafficking and angiogenesis. Mice with genetic alterations of ApoM have shown changes in plasma triglyceride clearance. These changes may in part be explained by changes in lipoprotein lipase activity, and in the uptake of lipids in brown adipose and hepatic tissue. However, these changes cannot account completely for the differences observed. Hence, the aim of this study was to explore the role of intestinally expressed ApoM in uptake, transport, and metabolism of dietary lipids and lipoproteins.

Methods and Results: Caco-2 cells express ApoM and will after 21 days in culture spontaneously differentiate to polarized enterocytes. Stimulation with a range of different fatty acids does not affect ApoM secretion to either the apical medium (resembling the intestinal compartment) or the basolateral medium (resembling the plasma compartment). However, we did observe that ApoM, surprisingly, is secreted to both compartments. The study is still ongoing, and the next experiments are planned to determine the size and composition of the particles ApoM is secreted with and to investigate the fate of ApoM secreted apically.



**YIA Poster Walk III – Abstracts –
Lipoproteins and Lipid Transport**

SESSION III

Variant effect predictions identify novel functional impact of APOE based on whole genome sequencing

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Abstract

Introduction: The strongest genetic risk factor for dementia and key player in lipid metabolism, the *APOE* gene, is a well-known modulator of atherosclerotic cardiovascular disease, age-related macular degeneration, gall-stone disease and other common lipid-related traits and diseases. Recent evidence from clinical trials and genome-wide association studies highlight the importance of taking *APOE* variation into consideration when designing randomized clinical dementia trials and performing drug discovery genomic analyses. Many studies have been conducted with the common $\epsilon 2/\epsilon 3/\epsilon 4$ *APOE* polymorphism, the evidence is however sparse concerning the totality of genetic variation obtained from whole-genome sequencing (WGS). We hypothesize that WGS data will reveal novel functional variation in *APOE* with impact on common lipid-related traits.

Methods: UK Biobank WGS data was analyzed to evaluate variation in *APOE*. After quality control, variants were annotated with the Ensembl Variant Effect Predictor (VEP). Splice site and truncating Loss-of-Function (LoF) variants were identified with LOFTEE and missense variants were further classified using state-of-the-art VEPs (AlphaMissense and REVEL). Given low frequency of most functional variants, gene-level burden testing was employed.

Results: AlphaMissense and REVEL identified functional variants were significantly associated with higher apoE ($p < 0.001$) and triglyceride concentrations ($p < 0.05$) and borderline with lower lipoprotein(a) ($p = 0.05$ and 0.10 , respectively). These analyses were adjusted for $\epsilon 2/\epsilon 4$, highlighting an independent $\epsilon 2$ -like LDL receptor ligand defect. LoF variants showed association with low apoE concentration ($p < 0.001$), also unaffected by $\epsilon 2/\epsilon 4$ adjustment.

Conclusion: WGS data revealed novel functional impact of the *APOE* gene on lipid-related traits, highlighting that both common and rare functional genetic information should be addressed in hypothesis generating association studies and genomics-driven drug discovery.

Cholesterol metabolism–linked regulators of brown adipose thermogenesis: Dhcr24 and 4931406C07Rik as novel modulators of UCP1-dependent respiration

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Abstract

Introduction: Thermogenic brown adipose tissue (BAT) is a key regulator of systemic lipid and cholesterol metabolism, accelerating clearance of triglyceride-rich lipoproteins and promoting reverse cholesterol transport, thereby mitigating atherosclerosis in preclinical models. Despite this strong link between BAT activity and vascular protection, the intrinsic gene networks shaping BAT thermogenic capacity and atheroprotection remain incompletely defined.

Methods: To identify novel regulators of BAT thermogenesis, RNA sequencing was performed on interscapular BAT from mice housed at room temperature or exposed to cold, a physiological stimulus of BAT activation. BAT samples were subjected to magnetic-activated cell sorting (MACS) or NuTRAP-based nuclear tagging to enrich adipocyte populations. Sequencing data were analyzed for differential gene expression and pathway enrichment. Dhcr24 and 4931406C07Rik were prioritized based on cold responsiveness and predicted roles in lipid and cholesterol metabolism. Their functional relevance was tested in primary brown adipocytes using siRNA-mediated knockdown, followed by qPCR of thermogenic markers, Seahorse extracellular flux analysis, and high-resolution Oroboros respirometry. Protein expression of UCP1 and mitochondrial OXPHOS complexes was assessed by immunoblotting. Dhcr24 and 4931406C07Rik were regulated by cold exposure in vivo.

Results: Acute knockdown of both genes in cultured brown adipocytes efficiently reduced target mRNA levels and altered Ucp1 transcript and protein abundance. Functionally, knockdown increased β -adrenergically stimulated oxygen consumption in Seahorse assays, with consistent trends toward higher respiratory capacity in Oroboros respirometry, supporting gene-dependent modulation of mitochondrial respiratory control.

Conclusion: This RNA-seq–guided screen identifies Dhcr24 and 4931406C07Rik as novel modulators of UCP1 expression in brown adipocytes and provides new entry points to enhance BAT-driven clearance of atherogenic lipoproteins.

ApoC3/non-LDL TG ratio as a potential novel predictor of reduced liver steatosis risk

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Abstract

Introduction: Apolipoprotein C3 (ApoC3) has been considered as a major driver of circulating triglycerides (TG) accumulation for decades. Previously, this role was primarily attributed to its inhibitory action on lipoprotein lipase (LPL), an enzyme deputed to TG hydrolysis in peripheral tissues. However, more recent evidence indicates that the predominant mechanism by which ApoC3 increases plasmatic TG involves the inhibition of the interaction between the low-density lipoprotein receptor (LDL-R) and circulating remnant lipoprotein particles (RLP), including VLDL and chylomicrons remnants. This impaired receptor binding reduces hepatic clearance of RLPs and increases their half-life in circulation. The aim of this investigation was to define whether subjects with different ApoC3 concentrations, but comparable TG levels, exhibit a relatively diverse risk of hepatic steatosis.

Methods: A cross-sectional analysis was conducted within the RISC Study, a multicenter European cohort comprising 990 healthy volunteers (aged 30-60) with an extensively characterized metabolic profile. Serum TG concentrations were quantified using an enzymatic colorimetric assay, while ApoC3 levels were measured via Multiplex Technology. The risk of hepatic steatosis was estimated using surrogate marker of liver steatosis.

Results: Participants were categorized into high or low ApoC3 groups based on whether their ApoC3 levels were above or below the mean value of serum non-LDL TG. Preliminary analyses indicated that individuals with elevated ApoC3/non-LDL TG ratios exhibited a lower estimated risk of hepatic steatosis, a finding that persisted after adjustment for HDL-associated ApoC3.

Conclusion: Individuals with higher ApoC3/non-LDL TG levels appear to have a reduced risk of hepatic steatosis. This phenotype is consistent with increased retention of triglyceride-rich lipoproteins in the circulation, a condition that may subsequently contribute to increased atherosclerotic cardiovascular disease risk. lipoproteins.

All-trans retinoic acid increases fatty acid oxidation in human myotubes in part through altered mitochondrial activity

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Abstract

Introduction: Previous *in vivo* studies have shown that *all-trans* retinoic acid (ATRA) can reduce body fat accumulation and enhance insulin sensitive. We investigated how ATRA, the bioactive metabolite of vitamin A, alters energy metabolism in human myotubes.

Methods: Primary human myoblasts were differentiated into myotubes and treated with ATRA. Substrate uptake, incorporation, and oxidation were assessed using radiolabeled glucose or oleic acid. Lipid uptake was measured by incubating cells with radiolabeled oleic acid or acetoacetate, followed by assessment of lipid distribution using thin layer chromatography. Mitochondrial function was evaluated by measuring oxidative capacity and reserve capacity following mitochondrial membrane uncoupling with FCCP. Global gene expression changes were analyzed using RNAseq, and global protein abundance was assessed by proteomics. Differential expression and pathway enrichment analyses were performed for both transcriptomic and proteomic datasets.

Results: ATRA treatment increased fatty acid uptake, oxidation, and incorporation into complex lipids. Enhanced mitochondrial reserve capacity was observed following uncoupling, indicating improved mitochondrial capacity. Glucose oxidation was also increased. Transcriptomic analyses revealed upregulation of pathways involved in lipid catabolism, mitochondrial remodeling, and nuclear receptor signaling. Proteomic profiling demonstrated increased abundance of mitochondrial proteins associated with fatty acid beta-oxidation, respiratory chain assembly, and energy metabolism. Integrated analyses identified both established retinoid-responsive genes, including pyruvate dehydrogenase kinase 4 and cytochrome P450 family 26 subfamily B member 1, and other candidate regulators of lipid metabolism.

Conclusion: ATRA enhances fatty acid uptake, oxidation, and incorporation into intracellular lipid pools in part through modulation of mitochondrial activity and metabolic gene networks.

Overeating polyunsaturated fat increases the HDL anti-inflammatory activity compared with saturated fat

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Abstract

Introduction: High-density lipoprotein cholesterol (HDL-C) is associated with reduced cardiovascular disease (CVD) risk, yet raising HDL-C levels has not improved outcomes. Current research focuses on function metrics of HDL, including its anti-inflammatory activity, which predicts CVD events in the general population. Diet quality represents a major modifiable CVD risk factor and current guidelines advocate replacing saturated (SFA) with polyunsaturated fatty acids (PUFA). However, the impact of different fat types on the anti-inflammatory function of HDL is unknown. To assess the effect of 8-week dietary overfeeding of SFA or PUFA in a double-blind randomized set-up (LIPOGAIN-2) on HDL anti-inflammatory activity and HDL lipidome.

Methods: Sixty overweight participants were randomized into two groups (n = 30 each) receiving muffins enriched with either PUFAs or SFAs to achieve an overall 3% body weight gain. The HDL anti-inflammatory activity was determined as its ability to suppress tumor necrosis factor α (TNF α)-induced vascular cell adhesion molecule-1 (VCAM-1) mRNA expression in endothelial cells in vitro, HDL profiling was performed using nuclear magnetic resonance (NMR) spectroscopy, and targeted lipidomics was carried out via liquid chromatography-tandem mass spectrometry (LC-MS/MS).

Results: Despite an increase in body weight, PUFA intake significantly increased HDL anti-inflammatory activity ($p < 0.01$), HDL particle numbers ($p < 0.05$) and HDL cholesterol levels ($p < 0.01$). No such effects were observed in the SFA group. HDL lipidomics revealed that lipid species containing linoleic and arachidonic acid were elevated after a PUFA-rich diet, while species containing eicosapentaenoic acid (EPA) were less abundant in the PUFA compared to the SFA group.

Conclusion: Short-term PUFA consumption enhances the HDL anti-inflammatory function and induces distinct lipidome remodelling. These findings suggest that dietary PUFAs improve HDL function, offering a potential mechanism for CVD risk reduction.

From silent plaque to clinical events: mass-spectrometry-based sphingolipid profiling to link subclinical carotid atherosclerosis with overt cardiovascular disease

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Abstract

Introduction: Atherosclerosis is the leading cause of heart attacks and strokes. Although it often progresses silently in its early stages, it can ultimately result in severe cardiovascular complications. Lipids play a crucial role in the pathogenesis of atherosclerosis. Sphingolipids are key regulators of lipid metabolism and strongly associated with early signs of cardiovascular dysfunction, including plaque development. The structural diversity of sphingolipids is important, as variations in their fatty acid chains and sphingoid bases reflect their biological activity. High-performance liquid chromatography coupled with mass spectrometry is a powerful method for their analysis. Our workflow includes two instruments: a Quadrupole-Time-of-Flight for high-accuracy initial screening, and a Triple Quadrupole for targeted sphingolipid characterization, enabling their sensitive quantification. This workflow will be applied to plasma from participants in the VIPVIZA randomized trial, nested in the Västerbotten Intervention Programme.

Methods: We will explore cross-sectional associations (N = 243) between sphingolipid profiles and carotid intima-media thickness, plaques area and plaque presence, and longitudinally relate baseline lipids to three-year plaque progression (N = 372). Candidate sphingolipid markers of subclinical atherosclerosis identified in VIPVIZA will be validated in the Umeå site of the Swedish CARDioPulmonary BiImage Study (SCAPIS), where carotid ultrasound and coronary CT angiography allow assessment of multi-bed plaque burden. Building on our preliminary data and evidence that specific circulating ceramides improve cardiovascular risk prediction beyond Framingham-type score, we will assess whether sphingolipid-based indices from VIPVIZA and SCAPIS enhance prediction of myocardial infarction and stroke in nested case-control studies within the Northern Sweden Health and Disease Study. Using pre-diagnostic samples several years before the clinical event, we will compare models including established risk factors and Framingham-type scores with and without sphingolipid markers. This project will determine whether targeted sphingolipid profiling can refine current cardiovascular risk assessment and support the development of clinically useful ceramide-based risk scores.



**Posters – Abstracts –
Other Topics**

SESSION IV

The SGLT2 inhibitor empagliflozin promotes increased fatty acid oxidation in skeletal muscle cells

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Abstract

Introduction: In this study, we investigated the potential of the sodium-glucose cotransporter 2 (SGLT2) inhibitor empagliflozin (EMPA) to modify energy metabolism in human primary skeletal muscle cells (myotubes) and mouse C2C12 skeletal muscle cells.

Methods and Results: Treatment of human myotubes with EMPA for 96 h decreased glucose oxidation as well as oxidation and uptake of acetoacetate, while complete oxidation of fatty acids and leucine was increased. There were no EMPA-induced changes in glucose, fatty acid, or leucine uptake, neither was lactate concentration in the culture medium affected. EMPA treatment increased phosphorylation of AMP-activated protein kinase (AMPK) and its downstream target acetyl-CoA carboxylase (ACC), without altering the expression of selected metabolic genes. Mitochondrial respiration and glycolytic function in C2C12 cells were assessed using a Seahorse XF assay. EMPA reduced basal respiration and glycolysis under standard conditions, but under conditions promoting fatty acid utilization, it enhanced maximal respiration and ATP production.

Conclusion: EMPA treatment of skeletal muscle cells *in vitro* induced metabolic shifts characterized by enhanced fatty acid and leucine catabolism, reduced glucose and acetoacetate metabolism, and suppressed glycolysis. The observed changes in energy metabolism may be related to AMPK activation.

Harnessing neural signals to resolve hepatic immuno-metabolic dysfunction

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Abstract

Introduction: The liver, as a central metabolic organ, orchestrates nutrient distribution to extra-hepatic tissues. Despite its dense innervation, the neural regulation of hepatic function, particularly under inflammatory conditions, remains poorly understood.

Methods: Male C57BL/6J mice were subjected to either sham surgery, surgical vagotomy (VX), or electrical vagus nerve stimulation (VNS), followed by i.p. injection of either the TLR2 agonist (zymosan) or PBS. Additional group of mice was placed on MCD diet and subjected to either sham surgery or VX, or to VNS. Animals were euthanized and tissues were collected 12 hours after zymosan injection and 24 hours after VNS in the MCD-fed group. Collected samples were analyzed using qPCR, RNA-seq, immunofluorescence and confocal microscopy, flow cytometry, and ELISA to assess molecular and cellular responses.

Results: Vagotomized (VX) mice exhibited elevating hepatic cytokine expression (TNF α , IL 1 β , MCP 1), compared to sham-operated controls. These elevations were further amplified following TLR2 activation, while VNS suppressed the expression of these inflammatory mediators. Plasma levels of MCP-1 mirrored hepatic mRNA expression, reinforcing the systemic impact of vagal modulation. Importantly, VNS increases circulating FGF21, whereas VX resulted in reduced plasma FGF21 levels. In MCD fed mice, VX led to increased plasma ALT, whereas VNS maintained ALT at baseline levels. Moreover, VNS reduced hepatic triglyceride level. RNA-seq of liver tissue revealed that vagal signaling modulates the expression of genes associated with HSC activation. Flow cytometry further confirmed a higher proportion of activated HSCs in VX mice compared to sham controls.

Conclusion: Our findings show that cervical vagus nerve signals act as systemic regulators of hepatic immune and metabolic responses, protecting against steatohepatitis. Further investigation into chronic VNS as a therapeutic strategy for MASLD is warranted.

Impact of the rare *TM6SF2* L156P variant and its interaction with E167K on liver disease and plasma lipids: a large-scale population study

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Abstract

Introduction: *TM6SF2* is essential for the hepatic and intestinal packaging of VLDL. While the common E167K variant is a well-established risk factor for metabolic dysfunction-associated steatotic liver disease (MASLD), cirrhosis, and hepatocellular carcinoma (HCC), the impact of the rarer L156P missense variant—alone and in combination with E167K—remains poorly defined.

Methods: We analyzed 393,742 individuals from the UK Biobank and 113,015 individuals from the Copenhagen Cohort. Participants were genotyped for *TM6SF2*E167K and L156P. We evaluated associations between these genotypes and MRI-measured liver fat content, plasma LDL-C and triglycerides, alanine transaminase (ALT) levels, cirrhosis, and HCC.

Results: In the UK Biobank, we identified 2,190 E167K homozygotes (KK), 63 L156P homozygotes (PP), and 855 compound heterozygotes. Both variants demonstrated a dose-dependent increase in liver disease risk. For L156P, the odds ratio (OR) for cirrhosis rose from 1.27 in heterozygotes to 9.96 in homozygotes compared to wild-type individuals. Similarly, for HCC, the OR increased from 1.46 (heterozygotes) to 10.1 (homozygotes). Compound heterozygotes appeared to exhibit higher risks for steatosis, cirrhosis and HCC compared to E167K homozygotes. Both variants were associated with reduced LDL-C and triglycerides, mirroring the "split" phenotype (high liver fat, low plasma lipids) characteristic of *TM6SF2* deficiency. These findings were generally validated in the Copenhagen Cohort.

Conclusion: The rare *TM6SF2*L156P variant has a deleterious effect on liver health that equals or slightly exceeds that of the common E167K variant. The marked increase in risk for compound heterozygotes highlights the clinical importance of considering both variants when assessing the genetic architecture of cirrhosis and HCC.

Role for the liver X receptor agonist 22-ketositosterol in preventing disease progression in an Alzheimer's disease mouse model

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Monique T. Mulder

Abstract

Introduction: Liver X receptors (LXRs) are promising therapeutic targets for alleviating Alzheimer's disease (AD) symptoms. We assessed the impact of the semi-synthetic LXR agonist 22-ketositosterol on disease progression in an AD mouse model.

Methods: From 5.5 months of age, APPswePS1ΔE9 (AD) mice and wild-type (WT) littermates received a regular or 22-ketositosterol-supplemented diet (0.017% w/w). Cognition was assessed with object location and recognition tasks and a spontaneous alternation Y-maze test. Amyloid β was quantified using immunohistochemistry (IHC) and enzyme-linked immunosorbent assay (ELISA), microglia (Iba1, CD68) and astrocyte (GFAP) markers using IHC. Sterols were determined in food, serum, liver and cerebellum.

Results: 22-Ketositosterol activated both liver X receptors- α and - β and promoted cholesterol efflux in cell cultures. Diet supplementation with 22-ketositosterol prevented a decline in the performance of APPswePS1ΔE9 mice in the object location task but not in the other two tasks. Without affecting amyloid β deposition, 22-ketositosterol decreased microglia (Iba1, CD68) and astrocyte (GFAP) markers in the cortex and hippocampus of APPswePS1ΔE9, suggesting potential anti-inflammatory effects. No lipid accumulation was detected in the liver or serum upon 22-ketositosterol supplementation.

Conclusion: Diet supplementation with 22-ketositosterol prevented the decline in spatial memory of APPswePS1ΔE9 mice. Our data suggest therapeutic benefits of 22-ketositosterol possibly by enhancing cholesterol efflux and mitigating inflammatory responses, without inducing hepatosteatosis or hypertriglyceridemia.



YIA Poster Walk IV – Abstracts –

Other Topics

SESSION IV

Using loss-of-function variation in *PNPLA3* to elucidate the mechanism of *PNPLA3* I148M

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Abstract

Introduction: The I148M variant in *PNPLA3* is the strongest common genetic determinant of steatotic liver disease. However, the mechanism remains incompletely understood. A key unanswered question is whether the pathogenicity of I148M reflects loss-of-function (LOF), gain-of-function, or a unique neomorphic effect. Predicted-loss-of-function variants in *PNPLA3* provide an experiment for dissecting this. To compare the consequences of pLOFs with the I148M variant, with the goal of clarifying whether I148M behaves as a LOF or displays distinct biology.

Methods: We identified all rare pLOFs in the UKB and generated a burden variable (0/1 carrier status). Analytical steps included burden tests, single-variant Firth logistic regression, and linear regression across I148M genotype backgrounds. We tested the association of pLOF and I148M with a range of traits in UK Biobank, including liver fat content, plasma ALT, ICD-defined liver diseases, and Olink proteome data. Beta–beta plots and protein–trait correlations were used to visualize the biological signatures of pLOF and I148M.

Results: pLOF carriers do not phenocopy the I148M variant. Instead, pLOF effects are small, directionally heterogeneous, and appear modified by I148M background. No consistent association between pLOF and ALT was observed in I148M homozygotes, but among IM heterozygotes pLOF were associated with higher ALT and liver fat with the association to ALT reaching statistical significance. *PNPLA3* pLOFs were associated with higher risk of HCC, but power was limited in this analysis. Proteomic analyses indicate largely distinct protein signatures for pLOF vs. I148M.

Conclusion: Overall, pLOF variants in *PNPLA3* do not appear to mimic the association patterns of I148M. The findings support the notion that I148M acts via a unique mechanism distinct from a simple loss or gain of function.

Eleven clinical risk factors for age-related macular degeneration identified using 600,000 individuals from two prospective cohorts

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Abstract

Introduction: To validate a panel of 20 clinical cardiovascular and other risk factor for neovascular and any age-related macular degeneration (AMD) and subsequently define composite high-risk profiles.

Methods: Participants: 107,977 individuals with 1,192 cases of incident neovascular AMD in the Copenhagen General Population Study (CGPS), and 501,443 individuals with 10,420 cases of incident any AMD in the UK Biobank. Methods and Main Outcome Measures: Multivariable adjusted Cox regression was used to obtain hazard ratios for 20 potential clinical risk factors for neovascular and any AMD to select concordantly significant clinical risk factors across cohorts. Competing risk regression was used to obtain 10-year cumulative incidences per 10,000 persons and post Cox population-attributable fractions for these risk factors. Risk profiles were created by combining the four risk factors with the highest population-attributable fractions across cohorts.

Results: The 11 concordantly significant clinical risk factors for neovascular and any AMD in the two cohorts were female sex, current/former smoking, high alcohol intake, low physical activity, C-reactive protein > 2mg/dL, low-density lipoprotein cholesterol \leq 3 mmol/L, high-density lipoprotein cholesterol > 4thquartile, cataract surgery, and ischemic heart disease. Risk factors measured in only one of the two cohorts were non-white ethnicity and plasma fibrinogen \geq 10.6 μ mol/L. The profile with the highest risk was female smoker with high alcohol intake and C-reactive protein > 2 mg/dL (hazard ratio 2.5 (95% confidence interval 1.6–3.9 for neovascular AMD in the CGPS and 1.9 (1.6–2.3) for any AMD in the UK Biobank) compared to male without risk factors.

Conclusion: We confirmed eleven commonly available clinical cardiovascular and other risk factors for neovascular and any AMD and defined high-risk profiles that may assist the early detection, prevention and management of AMD in clinical practice.

MumCare: a postpartum digital health companion for women following hypertensive disorders of pregnancy or gestational diabetes mellitus: preliminary retainment rate data

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Abstract

Introduction: Cardiovascular disease (CVD) is a leading cause of mortality and morbidity globally. A history of hypertensive disorders of pregnancy (HDP) and/or gestational diabetes mellitus (GDM) is associated with increased risk of long-term maternal CVD. Systematic cardio preventive follow-up strategies postpartum are lacking. The MumCare (Mum's cardiovascular health for life) application, a novel, personalized digital health companion, aims to improve control of modifiable risk factors of CVD.

Methods: The MumCare randomized clinical trial (RCT, CLinicalTrials.gov: NCT05835596) includes women with current or recent diagnosis of HDP or GDM at Oslo University Hospital, within 4 weeks postpartum. Women are randomized 1:1 to MumCare app access or not. The app provides feedback to home monitored blood pressures (validated device), tracks other modifiable risk factors and prompts booking of the nationally recommended follow-up at the general practitioner's 3 and 12 months postpartum. In this substudy we aimed to assess the retainment rate of the app, a common challenge of app interventions.

Results: The RCT is ongoing (330 of 400 women are recruited). Preliminary results from the first 90 MumCare app users show an overall app retainment rate of 60% (any health data registrations in the app) at 4 weeks postpartum, varying from 70% after HDP, to 42% after GDM. App retainment differed likewise at 6 months postpartum (52% after HDP, 29% after GDM), both $p < 0.05$.

Conclusion: Preliminary analyses showed that app retainment rates were moderate to low after 6 months for both women with prior HDP or GDM. In future analyses we will examine the associations between app use beyond 1 month postpartum and rates of modifiable risk factors for CVD. We expect that differences in app retainment will be reflected by more unfavourable rates of CVD risk factors and thus in line with the expected benefits of a personalized postpartum health app.

***Flavonifractor plautii* mediates the decrease of visceral fat during dietary interventions in metabolic syndrome through regulating bile acid metabolism**

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Abstract

Introduction: Individuals with metabolic syndrome (MetS), especially with increased visceral fat area (VFA), are at high risk of cardiometabolic diseases. Dietary interventions are widely applied to manage MetS, with a large inter-individual variation in decreasing VFA, possibly mediated by gut bacteria. Therefore, we aimed to identify a causal role of gut bacteria in reducing VFA.

Methods: Individuals with MetS (n=93) followed a 3-month dietary regimen, and VFA reduction assessed. Gut bacteria were quantified using metagenomics, and the metabolome was measured in plasma. A causal role of specific gut bacteria in reducing VFA was investigated by oral gavage to high-fat diet-fed APOE*3-Leiden.CETP.

Results: In patients responding to VFA reduction (>10%; n=40), enrichment with *Flavonifractor plautii* (*F. plautii*) was the dominant gut microbial signature, and the abundance of *F. plautii* was negatively correlated with VFA, BMI, HOMA-IR and serum triglycerides. Responders had elevated plasma levels of bile acids, mainly ursodeoxycholic acid (UDCA). Stable colonization of *F. plautii* in the gut of mice caused attenuated high-fat diet-induced weight gain (-84%) and visceral fat mass (-35%) without affecting food intake and fecal energy secretion. Mechanistically, *F. plautii* reduced the hepatic expression of Na⁺-taurocholate cotransporting polypeptide (NTCP) in vivo and in vitro, crucially involved in hepatic uptake of bile acids from the circulation, thereby increasing plasma levels of bile acids, especially UDCA, collectively activating adipose tissue thermogenesis to increase whole-body energy expenditure. In fact, oral treatment of mice with UDCA recapitulated the metabolic benefits of *F. plautii*.

Conclusion: *F. plautii* is associated with reduced VFA in individuals with MetS. Mechanistically, *F. plautii* decreases hepatic NTCP expression, thereby increasing circulating bile acids to enhance adipose tissue thermogenesis and increase energy expenditure.

Fructose-induced liver steatosis model to study the inter-organ crosstalk on the liver-heart axis

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Abstract

Introduction: My PhD project explores the concept of interorgan communication on the liver-heart axis, in a model of early-stage liver disease. We are currently exploring the themes of vascular changes and immune infiltration in our model, which I would hope to discuss with the experts in the field. Overall it is of my greatest interest to share some insights into the interplay between metabolic syndrome, liver steatosis, and cardiovascular health.

Methods: Male rats were given water ad lib (CON, n=12) or a 15% fructose drink (FRU, n=12) for 16 weeks, and body composition, blood pressure, serum cytokines and hepatokine levels were analyzed. Mitochondrial respiration and triglycerides (TG) were determined in tissue homogenates. Histology, immunostaining, RT-qPCR and western blot were used to assess changes in liver and heart. The study follows up with a cohort of female rats, which includes an ovariectomized group.

Results: Fructose intake increased body weight, % fat mass and induced liver steatosis with increased lipid droplets and TG levels. The heart weights were elevated in FRU group as well as mean arterial pressure. Serum levels of IL-6 and TNF- α and FGF21 were elevated in FRU rats. Complex I- mitochondrial oxidative phosphorylation (OXPHOS) and maximal respiratory capacity was lower in FRU livers. In the FRU hearts mitochondrial H₂O₂ production was altered. Notably, elevated mRNA expression of FGF21 in liver and heart as well as elevated cardiac mRNA expression of FGF21 co-receptor β -klotho suggest an endocrine effect of FGF21.

Conclusion: The model presents metabolic changes, mitochondrial stress and activation of the integrated stress response in liver and heart. Increased cytokines and FGF21 hepatokine levels may be the early signaling cues for changes in cardiac environment during liver steatosis.