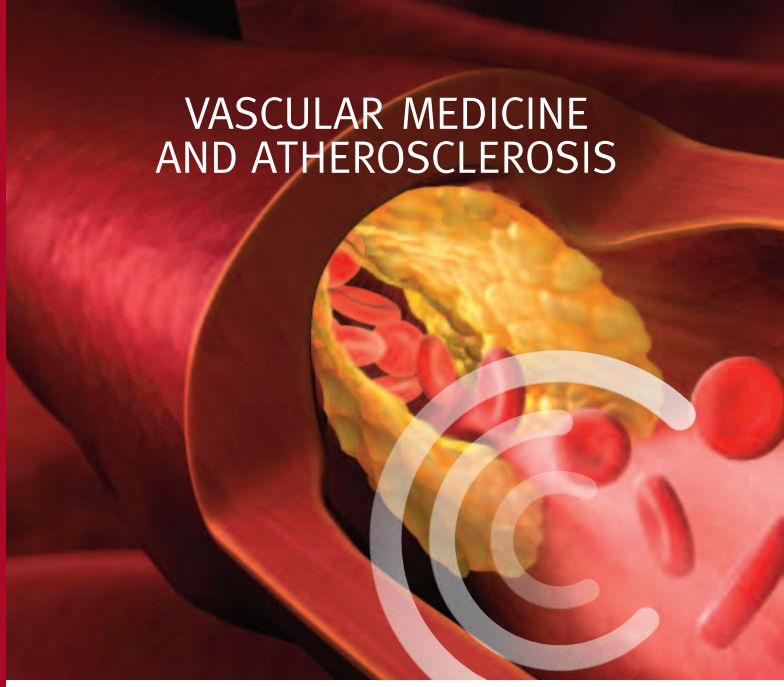
VASCULAR MEDICINE AND ATHEROSCLEROSIS



VMAC 2026

Vascular Medicine and Atherosclerosis

CONGRESS

PROGRAM

CME Points CME CERTIFIED ÄÄK NRW

5 – 7 February 2026

Leonardo Royal – Am Stadtwald
Köln

DACH Gesellschaft Prävention von Herz-Kreislauf-Erkrankungen e.V.

DGAF Deutsche Gesellschaft für Arteriosklerosetherapie e.V.

DGFL Deutsche Gesellschaft für Lipidologie e.V. – Lipid-Liga

AG 41. Atherosklerose in der Klinik

Einladung zum

Sobi Launch-Symposium

ApoC3 Hemmung – von der Evolution zur Revolution bei schwerer Hypertriglyceridämie

Donnerstag, 05.02.2026 | 16:45 – 17:30 Uhr | Raum: Hannover

Vorsitz: Prof. I. Gouni-Berthold, Köln

Einführung	**Prof. I. Gouni-Berthold,** Köln
Evolution: ApoC3-Hemmung der nächsten Generation beim Familiären Chylomikronämie-Syndrom – ein Vergleich	**PD Dr. U. Schatz,** Dresden
Revolution: Bedeutung der triglyceridreichen Lipoproteine für das kardiovaskuläre und Pankreatitis Risiko	**Prof. U. Laufs,** Leipzig
Dokumentation: CareHigh TG und die Genotyp-Phänotyp-Korrelation	**Prof. W. März,** Heidelberg
Evaluation: Erste Erfahrungen in Deutschland	**Prof. I. Gouni-Berthold,** Köln
Abschlussdiskussion	**Alle**

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VMAC 2026
Vascular Medicine and Atherosclerosis
CONGRESS

WELCOME

TO THE VASCULAR MEDICINE AND ATHEROSCLEROSIS CONGRESS 2026

Dear Colleagues and Friends,

We are thrilled to welcome you to the **VMAC meeting 2026**, a vital gathering of leading societies dedicated to cardiovascular prevention and the fight against atherosclerosis.

This year, we unite under the auspices of the German Atherosclerosis Society (DGAF), the German Society for Lipidology (DGFL), the German Society for Prevention of Cardiovascular Diseases (DACH), and the AG 41 of the German Cardiac Society (DGK) joint sessions with the International Atherosclerosis Society (IAS) and the European Society of Cardiology (ESC).

As we come together annually, we recognize the critical importance of collaboration in our shared mission: to combat one of the most preventable diseases—atherosclerosis. Through early and effective prevention strategies that address all cardiovascular risk factors, we can save lives and improve quality of life of our patients.

Let´s exchange knowledge, share groundbreaking research, and forge connections that will empower us to make a lasting impact in vascular medicine. Together, we can pave the way for a healthier future.

We wish you an inspiring VMAC 2026!

Ioanna Gouni-Berthold
President
D.A.CH

Daniel Sedding
President
DGAF

Oliver Weingärtner
President
DGFL

Wegovy®: In führende Adipositas-Leitlinien aufgenommen[1,2]

GESUNDHEIT IM FOKUS

Mit wegovy® mehr erreichen

Zusätzlich zu einer **lebensverändernden Gewichtsabnahme von durchschnittlich 15–17%*** demonstrierte Wegovy® die folgenden gesundheitlichen Verbesserungen:

≥ 20 %

Gewichtsabnahme
bei 1 von 3 Patient:innen
in der STEP-5-Studie[6]

Protektive Effekte

und die Verbesserung multipler **gewichtsbedingter Komorbiditäten** und der **Lebensqualität****

20 %

RRR für **Schlaganfall, Herzinfarkt und CV-Tod**
in der SELECT-Studie[11,***,†]

Fiktives Ärzt:innen- und Patient:innenbeispiel

Jetzt Beratung anfordern!

BMI: Body-Mass-Index; **CV:** kardiovaskulär; **CVD:** kardiovaskuläre Erkrankung; **DAG:** Deutsche Adipositas Gesellschaft e.V.; **HbA$_{1c}$:** glykiertes Hämoglobin; **HR:** Hazard Ratio; **MACE:** schweres kardiovaskuläres Ereignis; **MI:** Myokardinfarkt; **RRR:** relative Risikoreduktion; **SoC:** Standardtherapie.
***** In den Studien STEP-1 (ab Baseline) und STEP-4 (ab Woche 0, supportiver sekundärer Endpunkt) konnten Patient:innen einen durchschnittlichen Gewichtsverlust von 14,9% (STEP-1) bis 17,4% (STEP-4) erzielen und über die Dauer der Studie (bis Woche 68) halten sowie kardiovaskuläre Risikofaktoren verbessern.[3-5] Wegovy® wird als Ergänzung zu einer kalorienreduzierten Ernährung und verstärkter körperlicher Aktivität angewendet.[3] Die mögliche Gewichtsabnahme sowie der weitere Gewichtsverlauf nach Ende der Anwendung hängen vom Einzelfall ab und können von Patient:in zu Patient:in variieren. ****** In Studien konnten eine Verbesserung der Lebensqualität[7,8] sowie multipler gewichtsbedingter Komorbiditäten (für Typ 2 Diabetes[9] und Prädiabetes[10], schwere kardiovaskuläre Ereignisse [MACE][11], Kniearthrose[4] und Herzinsuffizienz-bedingte Symptome[7]) gezeigt werden. Zudem konnten protektive Effekte auf die Progression von Nierenerkrankungen[12], auf Typ 2 Diabetes[13] und auf die Lebergesundheit[14] beobachtet werden. **§** Der Begriff MACE, kurz für „major adverse cardiac event" oder auch „schweres kardiovaskuläres Ereignis", kann verschiedene kardiovaskuläre Ereignisse beschreiben. In der SELECT-Studie wurde die MACE-Inzidenz als kumulativer, zusammengesetzter Endpunkt gemessen: als die Zeit von der Randomisierung bis zum ersten Auftreten eines CV-bedingten Todes, nicht-letalen MIs oder nicht-letalen Schlaganfalls.[11,15,16] *******Gezeigt in der SELECT-Studie bei Patient:innen mit etablierter kardiovaskulärer Erkrankung (CVD) und Adipositas oder Übergewicht (BMI ≥ 27 kg/m^2), aber ohne Typ 2 Diabetes (HbA$_{1c}$ < 6,5%).[3,11] **†** Die kumulative MACE-Inzidenz wurde mittels Aalen-Johansen-Methode errechnet. Die HR wurde anhand eines Cox-Proportional-Hazard-Modells geschätzt. Der Anteil der Teilnehmer:innen mit MACE betrug 6,5% unter Semaglutid 2,4 mg + SoC und 8,0% unter Placebo + SoC.[11]

1. Deutsche Adipositas Gesellschaft e.V. (DAG). S3-Leitlinie „Prävention und Therapie der Adipositas". AWMF-Register Nr. 050/001. Version 5.0. Stand: 10/2024. **2.** Vrints C et al. Eur Heart J 2024;00:1–123. **3.** Fachinformation Wegovy®, aktueller Stand. **4.** Wilding JPH et al. N Engl J Med 2021;3841(11):989–1002. **5.** Rubino D et al. JAMA 2021;325(14):1414–1425. **6.** Garvey WT et al. Nat Med 2022;28(10):2083–2091. **7.** Kosiborod MN et al. N Engl J Med 2023;389(12):1069–1084. **8.** Bliddal H et al. N Engl J Med 2024;391(17):1573–1583. **9.** Davies M et al. Lancet 2021;397(10278):971–984. **10.** McGowan B et al. Lancet Diabetes Endocrinol 2024;12(9):631–642. **11** Lincoff AM et al. N Engl J Med 2023;389:2221–2232. **12.** Colhoun HM et al. Nat Med 2024;30:2058–2066. **13.** Kahn SE et al. Diabetes Care 2024;47(8):1350–1359. **14.** Meyhöfer SM et al. AASLD 2024 [Poster 52807]. **15.** Ryan DH et al. Am Heart J 2020;229:61–69. **16.** Lingvay I et al. Obesity 2023;31(1):111–122.

Zum Basistext: QR-Code scannen

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Deutsche Gesellschaft
für Arterioskleroseforschung e.V.

Deutsche Gesellschaft für Lipidologie e. V.
(DGFL) – Lipid-Liga

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with the participation of
Arbeitsgruppe Atherosklerose (AG41) der
Deutschen Gesellschaft für Kardiologie –
Herz- und Kreislaufforschung e.V.

European Society of Cardiology

endorsed by
International Atherosclerosis Society

ORGANISATION

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HÖR AUFS HERZ

JETZT GEMEINSAM DAS CV-RISIKO SENKEN

Bei hohem und sehr hohem CV-Risiko[1,2]

- ✓ **SCHNELL**[*,1,3]
- ✓ **STARK**[**,1,4-6]
- ✓ **PRÄVENTIV**[***,7]
- ✓ **EINFACH**[#,1]

* LDL-C-Senkung bereits ab Woche 1.[1,3]

** Ausgeprägte LDL-C-Senkung um etwa 55 bis 75 %.[1,4-6]

*** Mit Repatha® CV-Risikosenkung bei Patient:innen nach akutem MI um 25 %.[##,7]

\# Alle 2 Wochen Selbstapplikation durch die Patient:innen.[1]

\## Repatha® senkte das relative Risiko für weitere kardiovaskuläre Ereignisse (CV-Tod, MI oder Schlaganfall) bei Patient:innen, die innerhalb der letzten 12 Monate einen Myokardinfarkt erlitten, im primären Endpunkt um 19 % und im sekundären Hauptendpunkt um 25 %.[7]

1. Fachinformation Repatha®. **2.** Mach F et al. Eur Heart J. 2020;41(1):111–188. **3.** Kasichayanula S et al. Clin Pharmacokinet. 2018;57:769–779. **4.** Sabatine MS et al. N Engl J Med. 2017;376(18):1713–1722. **5.** Robinson JG et al. JAMA. 2014;311:1870–1882. **6.** Koren JM et al. J Am Coll Cardiol. 2019;74(17):2132–2146. **7.** Gencer B et al. JAMA Cardiol. 2020;5(8):1–6.

DEU-145-1214-00011

Program

THURSDAY, 5 FEBRUARY 2026

10:30 **CAREER WORKSHOP**
Room: Hannover

12:00 **PRESIDENTS' OPENINGS**
DGAF, D.A.CH, DGFF
Room: Hannover
Chairs: Ioanna Gouni-Berthold, Cologne/Germany
Daniel Sedding, Halle/Germany - Oliver Weingärtner, Jena/Germany

12:30 **KLINISCHE PRAXIS - VON RISIKO ZU THERAPIE - METABOLIK IM WANDEL**
Room: Hannover
Chairs: Ulrich Laufs, Leipzig/Germany - Stefan Lorkowski, Jena/Germany

Adipositas: Aktuelle therapeutische Optionen als Weg zur Reduktion des CV Risikos
Martin Merkel, Hamburg/Germany
CV Risiko bei Typ 1 Diabetes und CV Prävention
Dirk Müller-Wieland, Aachen/Germany
Inkretin-basierte Therapien
Florian Kahles, Aachen/Germany

14:00 *Break / Exhibition*
Location: Foyer

14:15 **KARDIOVASKULÄRE PRÄVENTION**
presented by Amgen
Room: Hannover
Chair: Stephan Baldus, Cologne/Germany

Kardiovaskuläre Prävention – welche Möglichkeiten haben wir?
Jörg Haas, Cologne/Germany
Elektive Bildgebung bei kardiovaskulären Hochrisikopatienten und was dann?
Felix Sebastian Nettersheim, Cologne/Germany
Ergebnisse der VESALIUS-CV Studie
Ioanna Gouni-Berthold, Cologne/Germany
Panel Diskussion

Program
THURSDAY, 5 FEBRUARY 2026

15:00 **YOUNG INVESTIGATOR SESSION ***
Room: Hannover
Chairs: Norbert Gerdes, Düsseldorf/Germany - Dennis Wolf, Freiburg/Germany

ChemR23 in Macrophages:
A Link Between PVAT Dysfunction and Vascular Inflammation in Atherosclerosis
Julia Schulz, et al., Bern/Switzerland

Hepatic CRISPR/dCas9-mediated overexpression of apolipoprotein A1 and paraoxonase 1 reduces the atherosclerotic burden in apoE deficient mice
Teodora Barbalata, et al., Bucharest/Romania

Short-term senolysis mitigates obesity-driven proarrhythmic cardiac remodeling
Camila Zöhner, et al., Düsseldorf/Germany

The role of Fumarate hydratase 1 (FH1) in atherosclerosis
Jan Wrobel1 et al., Cologne/Germany

Comparison of high-sensitivity C-reactive protein and leukocyte-derived scores in prediction of cardiovascular risk in hospitalized patients
Konstantin Rex, et al., Aachen/Germany

GLP-1 levels predict adverse cardiovascular events in hospitalized patients with residual inflammatory risk
Berkan Kurt, et al., Aachen/Germany

16:30 *Break / Exhibition 16:30 - 17:30*
Location: Foyer

16:45 **APOC3 HEMMUNG – VON DER EVOLUTION ZUR REVOLUTION BEI SCHWERER HYPERTRIGLYCERIDÄMIE**
presented by Sobi
Room: Hannover
Chair: Ioanna Gouni-Berthold, Cologne/Germany

Evolution: ApoC3-Hemmung der nächsten Generation beim Familiären Chylomikronämie-Syndrom - ein Vergleich
Ulrike Schatz, Dresden/Germany
Revolution: Bedeutung der TG-reichen Lipoproteine für das kardiovaskuläre und Pankreatitis Risiko
Ulrich Laufs, Leipzig/Germany

Dokumentation: CareHigh TG und die Genotyp-Phänotyp-Korrelation
Winfried März, Mannheim/Germany
Evaluation: Erste Erfahrungen in Deutschland
Ioanna Gouni-Berthold, Cologne/Germany

17:30 **AWARDS SESSION**
Room: Hannover

Verleihung der Schönheimer Medaille der DGAF an Prof. Dr. Ralf Kinscherf
Daniel Sedding, Halle/Germany

Verleihung des W. H. Hauss-Preis der DGAF
Daniel Sedding, Halle/Germany

18:30 **POSTER SESSION WITH "WINE & CHEESE" ****
Location: Foyer
Chairs: Yvonne Döring, Bern/Switzerland - Karsten Grote, Marburg/Germany
Florian Kahles, Aachen/Germany - Sabine Steffens Munich/Germany

* YI Presentations and their abstracts are listed from page 19

** Poster Presentation and their abstracts are listed from page 26

Program
FRIDAY, 6 FEBRUARY 2026

09:00 **KLINISCHE PRAXIS - PERSONALISIERTE MEDIZIN**
Room: Hannover
Chair: Ulrike Schatz, Dresden/Germany

Umwelt als unterschätzter Risikofaktor
Thomas Münzel, Mainz/Germany
Proteomics klinisch wichtig?
Manuel Mayr, London/United Kingdom
Lebensstilmaßnahmen - sinnvoll oder Quatsch
Stefan Lorkowski, Jena/Germany

10:30 *Break / Exhibition*
Location: Foyer

11:30 **BASIC SCIENCE (JOINT SESSION ESC) - EVS AND THEIR CARGO**
Room: Hannover
Chairs: Claudia Goettsch, Aachen/Germany - Karsten Grote, Marburg/Germany

HDL/LDL/EVs
Soumaya Ben-Aicha Gonzalez, London/United Kingdom
Extracellular Vesicle Subtypes for Cardiac Therapeutic Application
Joost P.G. Sluijter, Utrecht/Netherlands
Decoding Extracellular Vesicle Long Non-Coding RNAs as Master Regulators and Novel Therapeutics in Aortic Stenosis
Mohammed Rabiul Hosen, Bonn/Germany
Senescent Adventitial Fibroblasts Drive IL-6–Dependent Endothelial Dysfunction in Diabetic Vasculature and Are Targetable by Senolysis
Alexander Lang, Düsseldorf/Germany

13:00 *Break / Exhibition*
Location: Foyer

13:45 **ATHEROSKLEROSE: PRÄVENTION UND BEHANDLUNG IN THEORIE UND PRAXIS**
presented by Daiichi Sankyo
Room: Hannover
Chair: Ioanna Gouni-Berthold, Cologne/Germany

Was läuft schief in der Prävention und wie können wir es besser machen?
Veronika Sanin, Munich/Germany
Das Update 2025 der ESC-Leitlinie Dyslipidämie: Umsetzung in der Versorgung von Hochrisikopatienten
Phillip Breitbart, Frankfurt/Germany

10:30 *Break / Exhibition*
Location: Foyer

11:30 **KLINISCHE PRAXIS - VON NIERE BIS NACHWUCHS UND KASKADE - LIPIDTHERAPIE NEU GEDACHT**
Room: Köln
Chairs: Winfried März, Heidelberg/Germany - Volker Schettler, Göttingen/Germany

Wenn es um Lipide geht, und die Niere nicht mitspielt
Reinhard Klingel, Cologne/Mainz/Germany
Lipidtherapie bei Kindern, Jugendlichen und in der Schwangerschaft
Veronika Sanin, Munich/Germany
Care High - neue Daten
Felix Fath, Mannheim/Germany

13:00 *Break / Exhibition*
Location: Foyer

Program
FRIDAY, 6 FEBRUARY 2026

14:30 **BASIC SCIENCE (JOINT SESSION AG41 DGK) - UNDERLYING MECHANISMS OF MODIFIABLE RISK FACTORS**
Room: Hannover
Chairs: Ingo Hilgendorf, Berlin/Germany - Hendrik Sager, Munich/Germany

Innate immune training
Niels Riksen, Nijmegen/Netherlands
Microbial Metabolites driving Atherosclerosis
David Sancho, Madrid/Spain
Amino acids: a healthy supplement or cardiovascular risk factors?
Henning Wackerhage, Munich/Germany

16:00 *Break / Exhibition*
Location: Foyer

16:15 **INFLAMMATION – FROM BENCH TO BEDSIDE**
presented by Novo Nordisk
Room: Hannover
Chair: Ingo Hilgendorf, Freibug/Germany

Targeting inflammation in atherosclerosis
Florian Leuschner, Heidelberg/Germany
Colchicine – effects beyond the NLRP3 inflammasome
Ingo Hilgendorf, Berlin/Germany
Role of cardiovascular inflammation in clinical practice
Ulrich Laufs, Leipzig/Germany

17:00 **KEYNOTE - Jan Boren**
Room: Hannover
Chair: Ioanna Gouni-Berthold, Cologne/Germany

Metabolism of triglyceride-rich lipoproteins and their role in atherogenesis
Jan Boren, Gothenburg/Sweden

18:00 **DGAF MEMBERS ASSEMBLY**
Room: Köln

19:30 **CONFERENCE DINNER**
Location: Peters am Hahnentor
››› more information on page 15

14:30 **CLINICAL PRACTICE - NEW GOALS, NEW DATA, NEW OPPORTUNITIES (JOINT SESSION IAS)**
Room: Köln
Chairs: Ksenija Stach, Mannheim/Germany - Oliver Weingärtner, Jena/Germany

Lp(a) in focus: New therapeutic approaches and clinical perspectives
Julia Brandts, Aachen/Germany
Register DLAR
Volker Schettler, Göttingen/Germany
ANGPTL3 inhibition for the treatment of dyslipidemias
Ioanna Gouni-Berthold, Cologne/Germany

16:00 *Break / Exhibition*
Location: Foyer

Daiichi Sankyo in der Kardiologie

Daiichi-Sankyo

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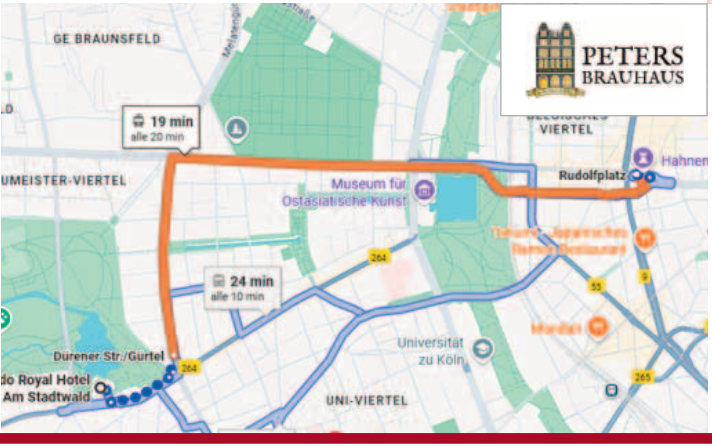
Friday February 6th, 2026
at 19:30 - 22:00

FEE*: **59,00** EUR

* The fee includes the conference dinner, wine, beer and soft drinks. Other beverages must be paid by your own.



Peters am Hahnentor
Hahnenstr. 22
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from Leonardo Royal 7 min walk, 500 m to Stop: Dürener Str./Gürtel **S 7 Zündorf** 11 min (6 Stops) **to Rudolfplatz**
1 min walk, 130 m to **Peters am Hahnentor**

Program
SATURDAY, 7 FEBRUARY 2026

09:00 **BASIC SCIENCE CVD COMORBIDITIES**
Room: Hannover
Chairs: Yvonne Döring, Bern/Switzerland - Michael Torzewski, Stuttgart/Germany

Diabetes and cardiovascular disease
Nikolaus Marx, Aachen/Germany
Targeting Early Innate Immune Cell Activation to Protect the Brain After Stroke
Vikramjeet Singh, Essen/Germany
The aryl hydrocarbon receptor (AhR) is a novel regulator of lipid metabolism and atherosclerosis development
Emiel van der Vorst, Aachen/Germany

10:30 *Break / Exhibition*
Location: Foyer

11:00 **BASIC SCIENCE - VASCULAR DISEASE AND DISSECTION**
Room: Hannover
Chairs: Sabine Steffens Munich/Germany - Holger Winkels, Cologne/Germany

Translational therapeutic value of heterogenuous inflammatory acitvity in AAA
Albert Busch, Dresden/Germany
Exploration and modulation of innate immune responses in syndromic and non-syndromic aortopathy
Hafid Ait-Oufella, Paris/France
Nitrated fatty acids as a promising pharmacological treatment for abdominal aortic aneurysm
Hannah Seelhorst, Cologne/Germany
PI3 kinase-α-deficiency in vascular smooth muscle cells increases atherosclerosis and plaque instability
Mario Zierden, Cologne/Germany

12:30 **YOUNG INVESTIGATOR AWARDS AND CLOSING REMARKS**
Room: Hannover
Chairs: Ioanna Gouni-Berthold, Cologne/Germany
Daniel Sedding, Halle/Germany
Oliver Weingärtner, Jena/Germany

CME Points CME CERTIFIED ÄK NRW

www.**vmac-2026.de**

Wir sind viele.
Sind Sie eine*r von uns?

300 Mio. Menschen sind weltweit von atherosklerotischen Herz-Kreislauf-Erkrankungen betroffen.[1]

LDL-Cholesterin – ein Risikofaktor für Herz-Kreislauf-Erkrankungen[2]

Kennen Sie Ihr Risiko?

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WIR SIND UNSICHTBAR
MENSCHEN MIT ATHEROSKLEROSE IM FOKUS

NOVARTIS

1. Roth GA, et al. J Am Coll Cardiol. 2020 Dec 22;76(25):2982–3021. doi: 10.1016/j.jacc.2020.11.010. [Erratum in: J Am Coll Cardiol. 2021 Apr 20;77(15):1958–1959.]

2. Ference BA, et al. J Am Coll Cardiol. 2018;72(10):1141–1156. https://doi.org/10.1016/j.jacc.2018.06.046.

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[1] EVKEEZA® ist ein ANGPTL3 (Angiopoietin-like 3)-Inhibitor, der als adjuvante Therapie zusätzlich zu Diät und anderen Low-Density-Lipoprotein-Cholesterol (LDL-C)-senkenden Therapien zur Behandlung von homozygoter familiärer Hypercholesterinämie (HoFH) bei Erwachsenen und pädiatrischen Patienten ab 12 Jahren verwendet wird.

[2] EVKEEZA® Fachinformation. Ultragenyx Germany GmbH; 2022.

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▼ **Dieses Arzneimittel unterliegt einer zusätzlichen Überwachung. Dies ermöglicht eine schnelle Identifizierung neuer Erkenntnisse über die Sicherheit. Angehörige von Gesundheitsberufen sind aufgefordert, jeden Verdachtsfall einer Nebenwirkung zu melden.**

Evkeeza® 150 mg/ml Konzentrat zur Herstellung einer Infusionslösung. **Wirkstoff:** Evinacumab, hergestellt mittels rekombinanter DNA-Technologie in Ovarialzellen des chinesischen Hamsters. **Qualitative und quantitative Zusammensetzung:** 1 ml Konzentrat enthält 150 mg Evinacumab; 1 Durchstechflasche mit 2,3 ml bzw. 8 ml Konzentrat enthält 345 mg bzw. 1.200 mg Evinacumab. *Sonstige Bestandteile:* Prolin, Arginin-Hydrochlorid, Histidin-Hydrochlorid-Monohydrat, Polysorbat 80, Histidin, Wasser für Injektionszwecke. **Anwendungsgebiete:** Adjuvante Therapie zu Diät und anderen Therapien zur Senkung des Spiegels des Lipoprotein-Cholesterins niedriger Dichte (LDL-C) zur Behandlung von Erwachsenen, Jugendlichen und Kindern ab einem Alter von 6 Monaten mit homozygoter familiärer Hypercholesterinämie (HoFH). **Gegenanzeigen:** Überempfindlichkeit gegen den Wirkstoff oder einen der sonstigen Bestandteile. **Nebenwirkungen:** *Sehr häufig:* Nasopharyngitis; Fatigue/Ermüdung (bei pädiatrischen Patienten). *Häufig:* Infektion der oberen Atemwege; Schwindelgefühl; Rhinorrhö; Übelkeit; Abdominalschmerz; Obstipation; Rückenschmerzen; Schmerz in einer Extremität; grippeähnliche Erkrankung; Asthenie; Reaktion im Zusammenhang mit einer Infusion; Reaktionen an der Infusionsstelle. *Gelegentlich:* Anaphylaxie. **Verschreibungspflichtig. Inhaber der Zulassung:** Ultragenyx Germany GmbH, Rahel-Hirsch-Str. 10, 10557 Berlin, Deutschland. **Stand der Information:** 07/2025

Ausführliche Informationen zu diesem Arzneimittel sind auf den Internetseiten der Europäischen Arzneimittel-Agentur verfügbar: https://www.ema.europa.eu/en/documents/product-information/evkeeza-epar-product-information_de.pdf

Presentations

YOUNG INVESTIGATOR SESSION

THURSDAY, 05 FEBRUARY 2026 // 15:00 - 16:30 // Room Hannover

Chairs: Norbert Gerdes, Düsseldorf/Germany - Dennis Wolf, Freiburg/Germany

PRESENTATION 1

ChemR23 in Macrophages: A Link Between PVAT Dysfunction and Vascular Inflammation in Atherosclerosis

Julia Schulz[1,2], Bryce Evans[2,3], Manovriti Thakur[2,3], Nico Angliker[2,3], Mark Siegrist[2,3], Emiel van der Vorst[4], Yvonne Jansen[5], Marc Schindewolf[3], Alexander Bartelt[5,6], Drosos Kotelis[1], Yvonne Döring[2,3,5,6]

1: Department of Vascular Surgery, Inselspital, Bern University Hospital, Bern, Switzerland; et al.

Most atherosclerosis-prone blood vessels are surrounded by perivascular adipose tissue (PVAT), which is contiguous with the adventitial layer of arteries. PVAT is a physiologically and metabolically active endocrine tissue that regulates vascular biology through paracrine signalling. Adipose tissue macrophages (ATMs) within PVAT are key players in obesity-associated inflammation, metabolic stress and atherosclerosis due to their capacity to switch from an alternatively activated anti-inflammatory M2 to a classically activated pro-inflammatory M1 phenotype. The receptor ChemR23 appears to play a crucial role in regulating this phenotypic switching and thereby influences the crosstalk between PVAT and arteries during atherosclerosis.

We use an atherosclerotic mouse model with a systemic knockout of ChemR23 expressing eGFP (Apoe-/-ChemR23-knockout/knockin mice). These mice are fed either a Normal Chow Diet (NCD) or a Western Diet (WD) for 4 weeks. White and brown adipose tissue depots, particularly PVAT, are analysed by flow cytometry and immunohistochemistry. In addition, macrophages are metabolically characterized using SCENITH, and their phenotype is determined by immunofluorescence and flow cytometry.

After 4 weeks of WD, the weight of adipose tissue depots was increased, accompanied by adipocyte hypertrophy and whitening of brown adipose tissue (BAT). The number of macrophages was elevated across all adipose tissues, indicating an inflammatory state. This was associated with reduced PDGFRα^+ adipose progenitor cells and lower plasma levels of IL-33 and FGF21, both key effectors of adipose tissue beiging. Interestingly, bone marrow-derived macrophages (BMDMs) from ChemR23 knockout mice exhibited a metabolic M2-like phenotype. FACS-sorted PVAT macrophages ($CD45^+CD11b^+$) are currently analysed at the transcriptomic level using single-cell RNA sequencing.

Future studies will investigate PVAT immune cell types and their immunometabolic influence on the aorta under homeostatic and inflammatory conditions using spatial biology (MACSima™ Imaging Cyclic Staining, MICS) and adipocyte–macrophage cell culture assays to elucidate ChemR23-dependent mechanisms of cellular crosstalk.

PRESENTATION 2

Hepatic CRISPR/dCas9-mediated overexpression of apolipoprotein A1 and paraoxonase 1 reduces the atherosclerotic burden in apoE deficient mice

Teodora Barbalata[1], Gabriela M. Sanda[1], Laura Toma[1], Jessica I.C. Haratau[1], Elena V. Fuior[1], Madalina I. Fenyo[1], Loredan S. Niculescu[1], Shlomo Sasson[2], Anca V. Sima[1], Camelia S. Stancu[1]

1: Institute of Cellular Biology and Pathology "Nicolae Simionescu" of the Romanian Academy, Bucharest, Romania; 2: Department of Pharmacology, Institute for Drug Research, Faculty of Medicine, The Hebrew University of Jerusalem, 9112002, Jerusalem, Israel

INTRODUCTION: The present study aimed to enhance the endogenous expression of apolipoprotein A1 (apoA1) or paraoxonase 1 (PON1) in the liver of apolipoprotein E deficient (apoE-/-) mice and to investigate their atheroprotective effects. ApoA1, the major structural component of HDL, facilitates reverse cholesterol transport, while PON1, an HDL-associated enzyme, exerts potent antioxidant effects. Together, these molecules contribute to the atheroprotective activity of HDL, but efficient therapies to increase their levels in pathological conditions are not yet available. The clustered regularly interspaced short palindromic repeats (CRISPR)/deactivated CRISPR-associated protein 9 (dCas9) enables the control of gene expression without DNA editing, and has generated interest for therapeutic applications due to its high efficiency and specificity.
METHODS: CRISPR/dCas9 plasmids were used to transcriptionally activate the endogenous ApoA1/PON1 genes in apoE–/– mice, which is a common animal model of spontaneous atherosclerosis. The ApoA1/PON1 and control plasmids (40 µg DNA plus in vivo-jetPEI®) were administered by tail vein injection and the animals were sacrificed 30 days after that.
RESULTS: The results showed that the endogenous ApoA1/PON1 genes in the liver of apoE–/– mice were successfully overexpressed by using CRISPR/dCas9 system, as it was proven by the significantly increased gene and protein expression of these molecules in liver tissue homogenates. Most importantly, ApoA1 and PON1 stimulation was maintained for four weeks after a single dose of CRISPR/dCas9 plasmids. Results also showed an increase in the levels of ApoaA1 and PON1 in the sera of mice. Notably, the increased serum apoA1 was distributed between HDL (83%), low density lipoproteins (LDL) (200%) and its lipid-free form (140%) compared to the corresponding lipoprotein fractions isolated from the Control group. We have demonstrated that the overexpression of ApoA1 in the liver led to the increase of cholesterol levels in serum HDL, liver and gallbladder. The implicated mechanisms involved the upregulation of hepatic scavenger receptor class B1 (SCARB1), 7α-hydroxylase (CYP7A1), and ATP-binding cassette sub-family G member 8 (ABCG8) transporter. The stimulation of PON1 led to an increase in the antioxidant potential of the serum (measured as Thiobarbituric Acid Reactive Substances - TBARS and PON1 enzymatic activity). A very important finding of our study was that the area of the lipid deposits (stained by Oil Red O) in the thoracic aorta was markedly reduced in the treated mice.
CONCLUSIONS: We successfully activated the endogenous hepatic apoA-I and PON1 genes by using the CRISPR/dCas9 system in apoE–/– mice and we demonstrated that the liver-secreted apoA-I or PON1 impede atheroma progression. This approach initiates the way for the future use of CRISPR/dCas9 transcriptional activation of endogenous genes for atherosclerosis treatment.
FUNDING: This research was funded by the Romanian Academy and by the PNRR program, CF 197-2022/PNRR-III-C9-2022-I8 (760059/23.05.2023).

PRESENTATION 3

Short-term senolysis mitigates obesity-driven proarrhythmic cardiac remodeling

Camila Zöhner1[1], Stephan Angendohr[1], Julian Wagner[2], Ashley Duplessis[1], Kevin Brors[1], Sara Kreci[1], Christin Elster[1], Joleen Kirchmann[1], Susanne Pfeiler[1], Malte Kelm[1,4], Obaida Rana[1,3], Nikolaj Klöcke[1,3,4], Norbert Gerdes[1,3], Alexander Lang[1]

1: Division of Cardiology, Pulmonology and Vascular Medicine, Düsseldorf, Germany; 2: Institute of Cardiovascular Regeneration, Goethe University, Frankfurt am Main, Germany; 3: Cardiovascular Research Institute Düsseldorf, (CARID), Medical Faculty, Heinrich Heine University, Düsseldorf, Germany; 4: Institute of Neuro- and Sensory Physiology, Medical Faculty, Heinrich-Heine University Düsseldorf, Germany

BACKGROUND: Obesity and diabetes are important cardiovascular risk factors that are accelerate biological aging. On microscopical level, aging is defined as cellular senescence, characterized by permanent cell cycle inhibition, disturbed cell-cell communication and resistance to apoptosis. Accumulation of cellular senescence contributes to increased susceptibility to ventricular arrhythmias (VA). The application of senolytic compounds, that selectively eliminate senescent cells, may offer a novel therapeutic approach to reduce VAs in aging and metabolically-challenged hearts.
METHODS AND RESULTS: In a clinical cohort, patients were stratified by body mass index above or below 30 to assess VA inducibility. Patients with obesity (BMI › 30) displayed increased VA vulnerability. To study the mechanisms underlying the relation between obesity and arrythmia, male C57BL/6J mice were fed a high-fat diet for 12 weeks to induce diet-induced obesity (DIO). Animals were treated with vehicle or a senolytic combination of dasatinib (5 mg/kg) and quercetin (50 mg/kg), administered orally three times within one week. Cardiac senescence was assessed by quantifying Cdkn1a and Cdkn2a mRNA expression using qPCR and was further confirmed by senescence-associated β-galactosidase staining. Senolytics-treated DIO mice showed a significant reduction in cardiac senescence compared to controls. Senolytic treatment reduced susceptibility to VAs, as demonstrated by programmed ventricular stimulation and epicardial fluorescence imaging in isolated perfused hearts. Cardiac fibroblasts were identified as the predominant senescent population and the principal source of arrhythmia-stimulating IL-6 by single cell RNA sequencing and flow cytometry.
Histological analysis and qPCR of fibrosis-associated genes showed attenuated myocardial fibrosis following senolysis, consistent with the susceptibility of cardiac fibroblasts to senolytic treatment. Furthermore, senolytic treatment improved mitochondrial respiration and network organization. In vitro, conditioned medium from senescent human cardiac fibroblasts impaired mitochondrial network complexity in tdTomato-COX8–labeled human cardiomyocytes, an effect abrogated by IL-6 neutralization.
CONCLUSION: Senescent fibroblasts contribute to obesity- and metabolically-associated cardiovascular dysfunction by promoting IL-6 production and cardiac fibrosis. Administration of senolytics reduces cardiac senescence, fibrosis, and decreases the susceptibility of VAs in preclinical models. These findings underscore the therapeutic potential of targeting senescent fibroblasts to prevent arrhythmias in obesity- and metabolism-related cardiovascular disorders.

PRESENTATION 4

The role of Fumarate hydratase 1 (FH1) in atherosclerosis

Jan Wrobel[1,2,3], Dennis Kagan[1,2,3], Sina Steinhofer[1,2,3], Désirée Schatton[4], Mehrnaz Babaki[3], Marie Depuydt[5], Eva Bartok[6], Harshal Nemade[1,2,3], Samuel Jung[1,2,3], Katharina Tinaz[1,2,3], Patrik Schelemei[1,2,3], Siting Wei[7,8], Michal Mokry[7,8], Menno de Winter[9], Manolis Pasparakis[3,10], Martin Mollenhauer[1,2,3], Stephan Baldus[1,2,3], Christian Frezza[4,10], Holger Winkels[1,2,3]

1: Uniklinik Köln, Köln, Deutschland; 2: Center of Cardiovascular Medicine (CCM ABCD) – Aachen, Bonn, Cologne, Düsseldorf; 3: Center for Molecular Medicine Cologne (CMMC), University of Cologne, Cologne, Germany; et al.

BACKGROUND: Atherosclerosis is a lipid-driven vascular inflammation in which macrophages play a central role in plaque initiation and progression. Excessive cholesterol uptake drives metabolic dysregulation in macrophages, promoting foam cell formation and disease progression. The mitochondrial TCA cycle enzyme fumarate hydratase (FH1) has been implicated in macrophage metabolic regulation and pro-atherosclerotic cytokine release, but its role in foam cell formation and atherosclerosis remains entirely unknown.
AIM: To investigate the role of FH1 in foam cell formation and atherosclerotic plaque progression, and to explore its potential clinical relevance in humans.
Methods/Results: In silico analysis of single-cell RNA sequencing of leukocytes from murine atherosclerotic aortas revealed decreased Fh1 expression in Trem2$^+$ macrophages. Immunofluorescent imaging of atherosclerotic plaques in low-density lipoprotein receptor knock-out (LDLr-/-) mice fed western-type diet for 12 weeks confirmed reduced Fh1 abundance in CD68pos BODIPYpos foamy macrophages compared to CD68pos BODIPYneg macrophages (n=3; P<0.001). FACS confirmed decreased FH1 abundance in aortic foamy macrophages in LDLr-/- mice (n=4/group; P=0.029). In silico CRISPR screen-analysis of BV2 myeloid cells undergoing foam cell formation ranked Fh1 as the TCA enzyme most associated with oxLDL uptake (n=5/group; P<0.001). Interestingly, in vitro, Fh1 expression was unchanged in oxLDL-treated bone marrow-derived macrophages (BMDMs), but co-stimulation with LPS, mimicking plaque inflammation, significantly reduced FH1 (n=3/group; P=0.001). Compared to vehicle, pre-stimulation with the FH1 inhibitor (FHIN1) reduced DIL-labeled oxLDL uptake in BMDMs (n=3/group; P=0.015). Genetic Fh1-deficiency in BMDMs reduced expression of foam cell associated genes including Trem2 (n=3/group; P=0.001), Cd36 (P=0.034) and Plin2 (P=0.044). In vivo, macrophage-specific Fh1 deletion (Cx3cr1-CreERT2 x Fh1-flox-flox (Cx3cr1Fh1) mice) showed reduced Fh1 expression in peritoneal Cx3cr1$^+$ leukocytes after 1 week of tamoxifen-containing HFD ((TAM-HFD) n =3/group; P=0.034). In comparison to controls, transplantation of Cx3cr1Fh1 bone marrow into lethally-irradiated LDLr-/- mice increased atherosclerotic burden after 12 weeks of HFD followed by 4 weeks TAM-HFD (n=7/group; P=0.021). Ongoing work is investigating phenotypic and inflammatory changes in the plaque microenvironment. In 1071 patients undergoing carotid endarterectomy, higher FH1 expression in plaques was associated with lower occurrence of stroke/TIA at the time of surgery (OR 0.84; 95% CI 0.73–0.96; P=0.009), independent of risk factors and lipid biomarkers.
CONCLUSION: Fh1 is downregulated in foam cells both in vitro and in vivo, and higher Fh1 expression in human plaques is associated with reduced cerebrovascular events, suggesting potential predictive relevance. FH1 deficiency decreased oxLDL uptake, altered foam cell gene expression, and increased atherosclerotic burden in mice. These findings highlight FH1 as a potential target for atherosclerosis prevention and therapy.

PRESENTATION 5

Comparison of high-sensitivity C-reactive protein and leukocyte-derived scores in prediction of cardiovascular risk in hospitalized patients

Konstantin Rex[1], Berkan Kurt[1], Anna Giacin[1], Marieke Mertens[1], Alessandra Antwerpen[1], Justus Bornemann[1], Kaan Aygar[1], Martin Reugels[1], Rutuja Salagundi[1], Susanne Just[1], Jens Spießhöfer[2], Andrea Milzi[3], Kinan Kneizeh[1], Jörg Schröder[1], Dirk Müller-Wieland[1], Edgar Dahl[4], Michael Lehrke[1], Nikolaus Marx[1], Florian Kahles[1]

1: Department of Internal Medicine I - Cardiology, University Hospital Aachen, RWTH Aachen University, Aachen, Germany; et al.

BACKGROUND: Systemic low-grade inflammation is a key driver of atherosclerotic cardiovascular disease (ASCVD). While high-sensitivity C-reactive protein (hsCRP) is the guideline-recommended biomarker reflecting residual inflammatory risk, the clinical utility of leukocyte-derived scores, such as the neutrophil-to-lymphocyte ratio (NLR) and further indices, remains unclear in hospitalized patients with ASCVD. More information from large, well-characterized cardiovascular (CV) cohorts comparing hsCRP with leukocyte-derived inflammatory indices using contemporary approaches for head-to-head comparison will help clarify their combined clinical utility for risk assessment in high-risk patients.
METHODS: In this prospective, single-center cohort study, inflammatory biomarkers including hsCRP, differential leukocyte counts, and leukocyte-derived scores were analyzed in 1649 hospitalized patients. The primary endpoint of this analysis was a composite of non-fatal myocardial infarction, non-fatal stroke and CV death (MACE: major adverse cardiovascular events). Kaplan-Meier and uni- and multivariable Cox regression analyses were performed. Model performance of biomarkers was compared with likelihood ratio Chi2 statistics to assess incremental value for prediction of MACE.
Results: During a median follow-up period of two years, MACE was observed in 114 out of 1649 subjects. Kaplan-Meier curve analyses demonstrated higher incidence of MACE in individuals with hsCRP levels above the guideline-based cut-off of 2 mg/L or those with an NLR above the cohort median of 2.28 (log-rank p (hsCRP) = 0.031; log-rank p (NLR) <0.001). Combined assessment of hsCRP and NLR identified those patients with both markers elevated at highest risk, while risk was intermediate when only one marker was elevated and lowest when both were below the cut-off (log-rank p=0.002). These findings were confirmed in Cox regression analyses showing a 2.8-fold higher risk of MACE in those with high NLR and hsCRP compared with those with low levels of both (Hazard ratio (HR): 2.76; 95% confidence interval (CI): 1.57, 4.84; p<0.001). In further univariable analyses, hsCRP, neutrophil percentage, lymphocyte count and percentage, NLR, neutrophil-to-monocyte ratio (NMR), lymphocyte-to-monocyte ratio (LMR) and monocyte-to-lymphocyte ratio (MLR) were associated with MACE. In multivariable analyses adjusted for age, sex, body mass index, systolic blood pressure, type 2 diabetes, smoking, creatinine, and low-density lipoprotein cholesterol, only hsCRP, neutrophil percentage, lymphocyte percentage, NLR and NMR, but not LMR and MLR, remained independently associated with MACE. In the extended models, hsCRP provided the highest incremental model performance based on likelihood ratio Chi2 statistics, followed by lymphocyte and neutrophil percentages, NMR and NLR, with LMR and MLR contributing least.
CONCLUSIONS: In hospitalized patients with high cardiovascular risk, hsCRP and leukocyte-derived indices, particularly NLR and NMR, were independently associated with adverse cardiovascular outcomes. Among all parameters, hsCRP demonstrated the strongest predictive performance, underscoring its role as the most robust established inflammatory biomarker for cardiovascular risk assessment in clinical practice.

PRESENTATION 6

GLP-1 levels predict adverse cardiovascular events in hospitalized patients with residual inflammatory risk

Berkan Kurt[1], Marieke Mertens[1], Alessandra Antwerpen[1], Konstantin Rex[1], Justus Bornemann[1], Kaan Aygar[1], Anna Giacin[1], Martin Reugels[1], Rutuja Salagundi[1], Susanne Just[1], Jens Spießhöfer[2], Andrea Milzi[3], Kinan Kneizeh[1], Jörg Schröder[1], Dirk Müller-Wieland[1], Edgar Dahl[4], Michael Lehrke[1], Nikolaus Marx[1], Florian Kahles[1]

1: Department of Internal Medicine I - Cardiology, University Hospital Aachen, RWTH Aachen University, Aachen, Germany; et al.

BACKGROUND: Glucagon-like peptide-1 (GLP-1) is a gut-derived incretin hormone secreted in response to food-intake and pro-inflammatory stimuli. Secretion of GLP-1 leads to post-prandial insulin secretion and subsequent glucose lowering. Beyond metabolic effects, GLP-1 has pleiotropic and cardioprotective effects and GLP-1 receptor agonists reduce cardiovascular (CV) events in patients with diabetes or obesity. Direct anti-inflammatory effects are likely to contribute to beneficial effects of GLP-1RA. Clarifying the prognostic relevance of endogenous GLP-1 levels in CV disease could improve our understanding of how inflammation interacts with incretin pathways.
METHODS: Circulating GLP-1 levels were measured in 888 fasted hospitalized patients in a cardiology department within a prospective single-center biobank study. The primary endpoint was a composite of non-fatal myocardial infarction, non-fatal stroke and CV death (MACE: major adverse cardiovascular events). Analyses were performed in the full cohort and stratified after individuals with and without residual inflammatory risk, defined by high-sensitivity C-reactive protein (hsCRP) levels above 2 mg/L. The association of GLP-1 with MACE was assessed using Kaplan-Meier curve, multivariable Cox proportional hazards and variable importance analyses.
Results: Median age of the cohort was 70 years, 65% were male and median GLP-1 levels were 31.5 pM. During a median follow-up period of two years, MACE was observed in 72 out of 888 patients. In Kaplan Meier curve analyses, GLP-1 levels above the median were associated with a higher rate of MACE (log-rank p=0.018). In univariable analyses, higher GLP-1 concentrations were associated with increased risk of MACE (GLP-1 above median: Hazard ratio (HR): 1.77; 95% confidence interval: 1.10, 2.85; p=0.019). These results remained significant after multivariable adjustment for age, sex, BMI, smoking, hypertension, type 2 diabetes, statin use, coronary artery disease, creatinine, LDL cholesterol and NT-proBNP (p=0.026). In variable importance analyses assessing the individual contribution of each variable from the multivariable model to prediction of MACE, GLP-1 ranked among the top predictors of outcome, outperforming traditional CV risk markers such as LDL cholesterol and creatinine. Importantly, in patients without systemic low-grade inflammation (hsCRP <2 mg/L), GLP-1 was not associated with MACE (log-rank p=0.391; HR: 1.39; 95% CI: 0.68, 2.67, p=0.393) and ranked last in variable importance analyses. Whereas in patients with hsCRP levels ≥2 mg/L, higher GLP-1 levels were strongly associated with MACE (log-rank p=0.019; HR: 2.25; 95% CI: 1.12, 4.52; p=0.023) and showed high variable importance, ranking second after NT-proBNP.
CONCLUSIONS: In hospitalized stable patients with CVD elevated circulating GLP-1 levels independently predicted MACE, with the strongest associations in those with residual inflammatory risk. These findings support the hypothesis of GLP-1 as an endogenous counter-regulatory peptide that rises in response to inflammatory activation. GLP-1 may serve as a marker of residual inflammatory risk, representing a compensatory, anti-inflammatory mechanism.

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Weitere Angaben zu den besonderen Warnhinweisen und Vorsichtsmaßnahmen für die Anwendung, Wechselwirkungen mit anderen Arzneimitteln und sonstige Wechselwirkungen, Fertilität, Schwangerschaft und Stillzeit, Nebenwirkungen sowie ggf. Gewöhnungseffekten sind der veröffentlichten Fachinformation zu entnehmen.

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Posters

MODERATED POSTERS WITH "WINE & CHEESE"

THURSDAY, 05 FEBRUARY 2026 // 18:30 - 21:00 // Room:Foyer

Chairs: Yvonne Döring, Bern/Switzerland - Karsten Grote, Marburg/Germany
Florian Kahles, Aachen/Germany - Sabine Steffens, Munich/Germany

POSTER PRESENTATION 1

CRISPR/dCas9 long-term transcriptional activation of apolipoprotein A1 and paraoxonase 1 in hepatocytes to ameliorate endothelial cell dysfunction

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The CRISPR/dCas9 system, which facilitates control of gene expression without DNA editing, has generated important attention for therapeutic applications due to its high efficiency and specificity. Enhancing the quantity and quality of anti-atherogenic high-density lipoproteins (HDL), primarily produced in the liver, represents a promising therapeutic target in atherosclerosis. The present study aimed to use CRISPR/dCas9 activation technology to stimulate the transcription of key HDL-associated apolipoprotein A1 (ApoA1) and paraoxonase 1 (PON1) in hepatocytes (Hep). Hep belonging to the Huh7 human-derived hepatocyte cell line were transfected with CRISPR/dCas9 activation plasmids targeting ApoA1 or PON1. Following antibiotics selection homogenous cell cultures stably overexpressing the targeted proteins were obtained. ApoA1 and PON1 were secreted in the culture media, which were collected and serve as conditioned media (CM). The CM were used to investigate the functional activities of the secreted ApoA1 and PON1 by determining the effect on oxidative stress (total reactive oxygen species, ROS), inflammatory stress (vascular cell adhesion protein 1, VCAM-1 and monocyte chemoattractant protein 1, MCP-1) and endoplasmic reticulum stress markers (glucose-regulated protein 78, GRP78, spliced X-box binding protein 1, sXBP1, activating transcription factor 4, ATF4) in TNFα-treated endothelial cells (EA.hy926, EC) compared to Control EC. Bulk long-RNA sequencing (RNAseq) analysis was done on total RNA isolated from selected transfected Hep. Bioinformatic analysis of transcriptomic data was performed using the principal component analysis (PCA) and the functional enrichment analysis of differential expressed genes (DEG) using Gene Ontology (GO), Kyoto Encyclopedia of Genes and Genomes (KEGG) and Reactome databases.
RESULTS indicate that: (i) the CRISPR/dCas9 activation system generated an elevated transcription of ApoAI and PON1, as demonstrated by the increased mRNA expression 10- and 18-fold respectively, whereas protein levels in the Hep were augmented 5-fold for both ApoAI and PON1. Concomitantly, protein content in the CM increased 22-fold for ApoA1 and 6-fold for PON1; (ii) CM from transfected Hep added to the EA.hy926 cells reduced significantly the TNFα-induced oxidative stress by decreasing ROS production by 20% for ApoA1 and 10% for PON1. ›››

Gene expression for VCAM-1 was reduced by 40% for ApoA1 and 70% for PON1, whereas for MCP-1 was lowered by 20% for both ApoA1 and PON1). The treatment of TNFα-stimulated EC with the CM also decreased significantly the gene expression of endoplasmic reticulum stress sensors : GRP78 (30% for ApoA1 and 80% for PON1), ATF4 (30% for ApoA1 and 60% for PON1 and sXBP1 (20% for ApoA1 and 70% for PON1); (iii) bioinformatic analysis of RNAseq data showed that CRISPR/dCas9-mediated activation of ApoA1 and PON1 induced significant changes in the metabolic profiles of the transfected hepatocytes by modulating the lipid metabolic pathways (lipid transport, fatty acid metabolism, plasma lipoprotein assembly, regulation by nuclear receptors, bile secretion) and insulin signaling and resistance in hepatocytes.

CONCLUSION: Long-term upregulation of ApoA1 or PON1 has been achieved in human Huh7 hepatocytes using CRISPR/dCas9 activation system. The robust overexpression of these major HDL proteins obtained by CRISPR/dCas9 technology offers a promising strategy to enhance their hepatic biosynthesis and secretion, which can be used to alleviate the inflammatory stress induced EC dysfunction and to impede vascular atherosclerosis.

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POSTER PRESENTATION 2

Circulating GLP-2 levels predict cardiovascular death in hospitalized patients with atherosclerotic cardiovascular disease

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BACKGROUND: GLP-1 and GLP-2 (glucagon-like peptide-1/2) are incretin hormones which are secreted in the gastrointestinal tract following food intake. GLP-1 and GLP-1 receptor agonists (GLP-1RA) have been extensively studied for their glucose-lowering, weight-reducing and cardioprotective pleiotropic effects, highlighting a mechanistic link in the gut–heart axis. In contrast, GLP-2 does not stimulate insulin secretion, but enhances gut barrier function. In clinical practice, GLP-2RA are indicated in patients with short-bowel syndrome. However, the role of GLP-2 for cardiovascular disease (CVD) is largely unknown.
Methods: Circulating GLP-2 levels were assessed in 539 hospitalized patients which were over the age of 50, fasted and had established atherosclerotic cardiovascular disease (ASCVD). The primary endpoint of this analysis was CV death. Associations of GLP-2 levels with the primary outcome were assessed with Kaplan-Meier curve and uni- and multivariable Cox proportional hazard regression analyses.
RESULTS: Median GLP-2 levels of the cohort were 3.24 ng/mL. Over a median observation time of two years, CV death occurred in 31 out of 539 subjects. Kaplan Meier curve analyses demonstrated that individuals with GLP-2 levels above the median had a higher rate of CV death than those below the median (log-rank p=0.016). In univariable Cox regression analyses, continuous GLP-2 levels were significantly associated with CV death (Hazard ratio (HR): 1.31; 95% confidence interval (CI): 1.12, 1.52; p<0.001). Moreover, the association between GLP-2 and CV death remained significant in different multivariable models. In model 1 adjusted for age and sex (HR: 1.30; 95% CI: 1.12, 1.52; p<0.001), in model 2 adjusted for low-density lipoprotein cholesterol, high-sensitivity C-reactive protein and lipoprotein (a) (HR: 1.31; 95% CI: 1.12, 1.54; p<0.001) and in model 3 adjusted for N-terminal pro-B-type natriuretic peptide, estimated glomerular filtration rate and total bilirubin (HR: 1.32; 95% CI: 1.13, 1.54; p<0.001) GLP-2 was independently associated with CV death. In model 4, which included standard modifiable risk factors (SMuRF: hypertension, dyslipidemia, type 2 diabetes and smoking) as covariables, this association persisted (HR: 1.20; 95% CI: 1.01, 1.42; p=0.042).
CONCLUSIONS: In hospitalized patients with established ASCVD elevated circulating GLP-2 levels were independently associated with CV death. Future studies are needed to investigate whether GLP-2 could be a novel CV risk marker and potential therapeutical target for CVD.

POSTER PRESENTATION 3

SHASTA-5 Rationale and Design: Randomized, Double-Blind, Placebo-Controlled Study to Evaluate Plozasiran Efficacy For Reduction of Pancreatitis Risk

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INTRODUCTION: Persistent chylomicronemia confers an increased risk of acute pancreatitis (AP). Chylomicronemia-associated AP is a substantial source of morbidity, mortality, reduced quality of life and financial burden to health care systems. Currently available therapies are often insufficient to reduce triglycerides (TG) and prevent AP. Plozasiran, an investigational siRNA, inhibits hepatic production of apolipoprotein C3 (APOC3), a key regulator of lipoprotein lipase-mediated TG metabolism and clearance. In a phase 2 study of severe hypertriglyceridemia (sHTG) patients, TG 500-4000 mg/dL, plozasiran demonstrated durable reductions in TG levels of approximately -80%, 12 weeks after the last dose, and in the majority of patients decreased circulating TG below 500 mg/dL, the threshold for increased risk for AP, with a numerical decrease in incidence of AP of 82% with a similar magnitude of reduction in AP achieving significance in the phase 3 PALISADE study of FCS. The SHASTA-5 trial will evaluate efficacy of plozasiran for reduction in AP rates, in patients with sHTG at high risk of AP.

METHODS: HASTA-5 is a randomized, double-blind, placebo-controlled, multi-center trial. Key inclusion criteria are 2 consecutive mean fasting TG level ≥ 1000 mg/dL and at least 2 prior documented AP events not attributed to other causes, one within 12-months from screening. Key exclusion criteria include use of any hepatocyte targeted siRNA treatments that target lipids and/or TGs within 1-year, and a screening HbA1c › 9.0%. Patients will agree to dietary counseling, maintaining a stable low-fat diet and receiving lipid-lowering medications throughout the study.

RESULTS: In this global time-to-first event study, approximately 140 patients will be randomized 1:1 to receive plozasiran 25 mg subcutaneous dose quarterly or matching placebo over the double-blinded period with maximum expected follow up of 3 years followed by an optional open label extension. Randomization will be stratified based on number of documented AP events within 1-year of screening and baseline TG levels (≥ 2000 mg/dL vs ‹ 2000 mg/dL). The primary efficacy endpoint is time-to-first occurrence of positively adjudicated AP events. Secondary endpoints include percent change in fasting TG from baseline to month-12 with plozasiran; proportion of patients who achieve fasting TG of ‹880 mg/dL; achievement of fasting TG of ‹ 500 mg/dL; time to first major abdominal pain event occurring; and change from baseline in patient-reported productivity and activity impairment (WPAI-SHP score) and health status (EQ-5D-5L score).

CONCLUSIONS: SHASTA-5 is designed to determine whether the quarterly-dosed APOC3 siRNA plozasiran safely reduces the rate of AP in patients with sHTG.

POSTER PRESENTATION 4

"Wild-Athero": Generation of an Apoe-/- mouse model with a natural microbiome to improve modeling of human immune responses in experimental atherosclerosis

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AIM

Atherosclerosis is shaped by innate and adaptive immune responses against Apolipoprotein B-100 (ApoB) and low-density lipoprotein (LDL) cholesterol. A growing body of evidence has identified the microbiome as a fundamental modulator of immune cell maturation and -function. Here, we describe the generation of an ApoE-knockout-wildling mouse model with a C57BL/6 genetic background engrafted with a natural microbiome derived from wild mice ("wildling-mice").

METHODS

ApoE-/- mice with a wildling-microbiome (Wild-ApoE-/-) mice were generated by a fostering model, involving the transfer of newborn ApoE-/- mice from a specific-pathogen-free (SPF) facility to wildling mice. Wild-ApoE-/- and conventional SPF-ApoE-/- mice were subsequently fed a western diet for 16 weeks and assessed for their metabolic and inflammatory phenotypes by single-cell RNA Sequencing, histology, flow cytometry, and plasma metabolomics.

RESULTS

The presence of a natural gut microbiome in Wild-ApoE-/- mice resulted in a more human-like immune phenotype with evidence of chronic immune activation compared to SPF-ApoE-/- controls. Wild-ApoE-/- mice gained significantly less weight compared to SPF-ApoE-/- mice, displayed reduced blood fasting glucose, and revealed a wide range of differences in circulating plasma metabolites. Moreover, a more natural gut microbiome resulted in a smaller atherosclerotic lesion size in the aortic root and features associated with a more stable plaque phenotype, including reduced plaque lipid deposition, an increased lesional collagen content, and smaller necrotic cores. Notably, immune and metabolic phenotypes remained stable across several generations of animals.

CONCLUSION

The natural microbiome potently modulates immune cell phenotypes and predisposition to cardiometabolic diseases, including atherosclerosis. The use of Wild-ApoE-/- mice may improve modeling of adult human immune responses and accuracy of therapeutic outcomes in preclinical atherosclerosis studies.

Vascular Medicine and Atherosclerosis Congress | 5. – 7. Februar 2026 | in Köln

SYMPOSIUM im Rahmen des VMAC-Kongresses

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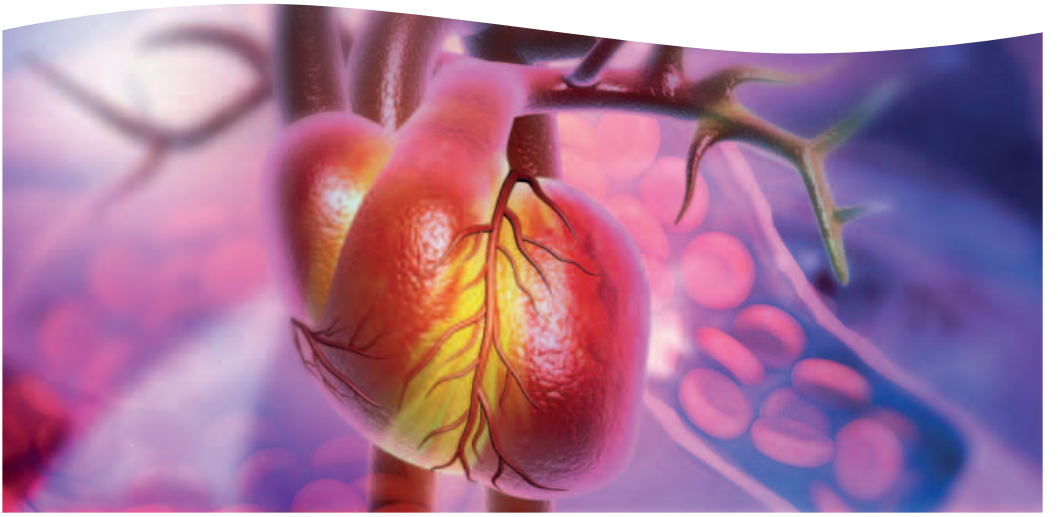

Freitag | 6. Februar 2026 | 13:45 – 14:30 Uhr | Raum Hannover

Atherosklerose: Prävention und Behandlung in Theorie und Praxis

Leitung und Moderation: Prof. Dr. med Ioanna Gouni-Berthold (Köln)

13:45 – 13:50 Uhr	**Begrüßung**
13:50 – 14:05 Uhr	**Was läuft schief in der Prävention und wie können wir es besser machen?** Dr. med Veronika Sanin (München)
14:05 – 14:20 Uhr	**Das Update 2025 der ESC-Leitlinie Dyslipidämie: Umsetzung in der Versorgung von Hochrisikopatienten** PD Dr. med Philipp Breitbart (Frankfurt)
14:20 – 14:30	**Diskussion**

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POSTER PRESENTATION 5

A CHIP model: Differential hypomethylation and gene expression in hiPSC-derived DNMT3A-deficient HSC and monocytes

Debora Scheuermann[1], Tsai-Sang Dederichs[1], Virginia Haacke[1], Tamara Antonela Vico[1], Alexander von Ehr[1,2], Ruba Hammad[3], Jamal Alzubi[3], Richard Schäfer[3], Claudio Mussolino[3], Toni Cathomen[3], Sebastian Preissl[4], Dirk Westermann[1], Ingo Hilgendorf[1,2]

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INTRODUCTION: CHIP (clonal hematopoiesis of indeterminate potential) is an acquired, genetic risk factor of cardiovascular diseases. The most common CHIP-driver gene is DNMT3A, an epigenetic regulator. Studies in human and mice suggest that inflammatory myeloid cells mediate CHIP-associated cardiovascular risks. We aim to establish an in vitro system that models myelopoiesis in a milieu with DNMT3A-mutated cells, using human induced pluripotent stem cells (hiPSC).
METHODS: We generated DNMT3A-mutated hiPSC lines using CRISPR/Cas9-mediated gene editing techniques to eliminate the enzymatic domain of the DNMT3A gene (exon 21-23). Next, we differentiated hiPSC into hematopoietic stem cells (HSC) and further into monocytes with a newly established extrinsic factor-guided differentiation protocol. We collected the mutated and non-mutated hiPSC-derived HSC and monocytes using fluorescence-activated cell sorting. Genomic DNA isolated from the sorted cells was subjected to bisulfite sequencing for the examination of genome-wide DNA methylation. RNA sequencing was performed to profile transcriptome. We plan to co-culture mutated and non-mutated hiPSC-derived HSC during monocyte differentiation for modelling the clonal chimerism in vivo.
RESULTS: Our CRISPR/Cas9 system effectively edited 30% of hiPSC, from which we produced 24 single cell-derived hiPSC clones. Applying multiple quality control measures, we identified two pure hiPSC clones, one had truncated DNMT3A (the mutated) while the other had intact DNMT3A (the non-mutated). Bisulfite sequencing of these two hiPSC lines and the derived HSC and monocytes revealed a distinctive genome-wide DNA methylation between the mutated and non-mutated cells. DNMT3A-mutated cells are significantly hypomethylated compared to non-mutated cells. Hypomethylated promoters or enhancers of genes, such as IL6 and TNF receptors, however, may indicate a higher expression of proinflammatory cytokines in the mutated cells. Transcriptomes showed a more inflammatory and proliferative phenotype in mutated cells, and thus correlated with the results of the methylation analyses.
CONCLUSION: Our in vitro model demonstrated a genome-wide hypomethylation during DNMT3A-deficient myelopoiesis, leading to a more inflammatory and proliferative phenotype. This model serves as a foundation for studying hematopoiesis and will support deciphering how CHIP mutations lead to cell function changes, on the basis of which therapeutic strategies can be developed against CHIP-aggravated cardiovascular diseases.

POSTER PRESENTATION 6

A History of Periodontal Inflammation Exacerbates Experimental Aortic Aneurysm Formation

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BACKGROUND: Periodontitis is a highly prevalent chronic inflammatory disease of the gum tissue and has been epidemiologically linked to heightened cardiovascular risk, even after clinically successful treatment. Recent experimental evidence indicates that periodontal inflammation can epigenetically reprogram hematopoietic stem cells, generating myeloid progeny with exaggerated inflammatory potential. However, whether such inflammatory memory influences the development of future cardiovascular disease remains unknown.
AIMS: To investigate the impact of antecedent periodontitis on abdominal aortic aneurysm (AAA) formation in mice.
METHODS: Juvenile male C57BL/6J mice (mean age: 10 +/-1.5 weeks) underwent bilateral ligature-induced periodontitis (LIP) or sham surgery (n=8-10/group). Ligature placement elicited consistent periodontal disease by day 21, after which ligatures were removed and a 2-week healing period was allowed. Mice were then subjected to porcine pancreatic elastase–induced AAA formation via transient intraaortic infusion. Longitudinal blood sampling and high-resolution ultrasonography were used to assess leukocyte dynamics and aneurysm progression.
RESULTS: At day 3 following elastase infusion, mice with prior LIP exhibited significantly elevated circulating leukocyte counts (10x10^x/uL +/- 2.34 SD) compared to sham controls (7.83x10^3/uL +/- 1,45 SD; p=0.03), driven predominantly by neutrophilia and monocytosis. By day 28, mice previously exposed to LIP developed greater aortic dilation (204% ± 21.19 fold change compared to baseline) than sham-treated animals (180.5% ± 23.62; p = 0.044), despite normalization of peripheral leukocyte numbers.
CONCLUSION: These findings indicate that previous periodontal inflammation can influence subsequent aortic aneurysm development in this murine model. Ongoing work aims to clarify the underlying mechanisms and to determine whether similar processes contribute to cardiovascular risk in humans.

POSTER PRESENTATION 7

Cathelicidin antimicrobial peptide limits bacterial inflammation in monocytes and endothelial cells

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BACKGROUND

Antimicrobial peptides can kill or inhibit pathogenic bacteria and thus play an important role in the innate immune defence. Cathelicidin antimicrobial peptide (CAMP, mouse homologue = CRAMP) is one of these peptides; it binds lipopolysaccharide (LPS) and thereby neutralises the pathogenic effects of the Toll-like receptor 4 (TLR) ligand LPS, e.g. in sepsis-induced myocardial dysfunction (cardiomyopathy). Here, we investigate LPS-dependent and -independent effects of CRAMP on NF-κB activation, cytokine expression, endothelial adhesion and transmigration of monocytes.

METHODS AND RESULTS

As expected, CRAMP almost completely blocked NF-κB activation in THP-1 reporter cells by LPS ($p<0.001$), but not by the TLR2/6 agonist Pam2 or the TLR 2/1 agonist Pam3. In endothelial cells (MyEND) and monocytes (J774A.1), real-time PCR analysis showed that Cramp expression was strongly upregulated by LPS (>250-fold, $p<0.001$) and remained significantly upregulated by Pam2 and Pam3 (2-50-fold, $p<0.01$-$p<0.001$). The LPS-dependent upregulation of the proinflammatory cytokines Il-1β, Il-6, Tnf-α, Ccl-2 in both MyEND and J774A.1 cells was markedly attenuated by the addition of CRAMP (real-time PCR, $p<0.001$). In MyEND cells, the LPS-induced expression of the adhesion molecules Vcam-1, Icam-1, E-selectin, P-selectin was likewise inhibited by CRAMP (real-time PCR, $p<0.001$), and subsequently, the adhesion of J774A.1 cells to a MyEND cell monolayer (425 vs. 505 cells/hpf, $p<0.01$).

In addition, we also observed LPS-independent effects of CRAMP. Thus, CRAMP led to a moderate induction of inflammatory genes in MyEND and J774A.1 cells and E-selectin and P-selectin in MyEND cells (real-time PCR, $p<0.01$-$p<0.001$). Accordingly, we observed a slightly increased adherence of J774A.1 cells to a MyEND cell monolayer with CRAMP and in transmigration assays with J774A.1 cells through a MyEND cell monolayer, CRAMP was even more potent than LPS as a chemoattractant.

CONCLUSION

CRAMP is a potent inhibitor of LPS-dependent cytokine induction in monocytes and endothelial cells and of adhesion of monocytes to the endothelium, with potential benefits in curbing the cytokine storm and blood monocyte activity in sepsis, including sepsis-induced cardiomyopathy.

POSTER PRESENTATION 8

CKD increases cardiac dysfunction, inflammation and metabolic alterations after myocardial infarction

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Patients with chronic kidney disease (CKD) show a highly increased cardiovascular risk. Beyond a higher risk of myocardial infarction (MI), CKD patients also suffer from a reduced survival following MI, but the underlying mechanisms remain largely unclear. Here, we examined the impact of CKD on cardiac remodeling and function post-MI using a mouse model of adenine-induced CKD, with validation of main identified mediators in patients.

After MI, CKD mice showed a stronger cardiac dysfunction compared to non-CKD controls. While immunohistochemical and immunofluorescence analyses did not reveal changes in cardiomyocyte apoptosis, infarction size or myofibroblast content, we uncovered a disturbed cardiac tissue metabolism with impaired glycolysis, a reduced glycerol-3-phosphate shuttle and a shortage of the cellular energy metabolite Coenzyme A in CKD vs. non-CKD mice post-MI by integrating metabolomics and RNAseq data. Furthermore, CKD mice exhibited an increased amount of circulating myeloid cells post-infarction and an increased neutrophil infiltration in the heart, as shown by flow cytometry. Combining RNAseq, untargeted kinome profiling, western blotting and mass spectrometry revealed that post-MI, CKD enhanced the accumulation of the acute stress protein complex S100A8/A9 in circulation and the heart, and enforced MAP-kinase p38 activation and NR4A1 phosphorylation in the myocardium as pathways underlying cardiomyocyte dysfunction. S100A8/A9 also exerted a direct detrimental impact on calcium flux and sarcomere shortening in primary cardiomyocytes ex vivo. Increased myeloid cell-derived S100A8/A9 expression was confirmed in the infarcted human heart based on single nuclear RNAseq data, and patients with CKD were shown to present with higher post-infarction S100A8/A9 levels compared to patients without kidney dysfunction.

In summary, our study reveals innate immune activation, inflammatory and metabolic alterations to underlie worsened cardiac dysfunction post-MI in CKD vs. non-CKD conditions. This could contribute to the worsened outcome of CKD patients post-MI.

POSTER PRESENTATION 9

Comparative efficacy and safety of olezarsen versus volanesorsen in familial chylomicronemia syndrome: results from a matching-adjusted indirect comparison (MAIC)

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BACKGROUND: Familial chylomicronemia syndrome (FCS) is a rare genetic disorder characterized by extreme hypertriglyceridemia and recurrent acute pancreatitis (AP). While volanesorsen is approved by the European Medicine Agency (EMA) for treatment of FCS, olezarsen, a new apolipoprotein C-III (apoC-III) inhibitor with a longer dosing interval and potentially improved safety profile, has been approved by both the Food and Drug Administration and the EMA. This analysis compared the efficacy and safety of olezarsen versus volanesorsen.

OBJECTIVE: To indirectly compare the efficacy and safety of olezarsen 80 mg Q4W and volanesorsen 300 mg QW in pivotal phase 3 trials among adults with FCS using an MAIC.

METHODS: An anchored MAIC was performed using individual patient data from Balance (NCT04568434; olezarsen, placebo) weighted to match baseline characteristics from APPROACH (NCT02211209; volanesorsen, placebo). Matching variables included fasting triglycerides (TG) and other treatment effect modifiers with significant ($p < 0.05$) or exploratory ($p < 0.20$) treatment-by-covariate interactions (variables considered were age, sex, body-mass index, race, and 5-year AP history). Post-weighting, outcomes were compared at 26 and 52 weeks for mean percent change in fasting TG, apoC-III, and for risk of AP and adverse events (AEs). Sensitivity analyses were conducted without matching to assess the impact of the matching procedure, and sensitivity MAICs were conducted with different sets of matching variables to assess the robustness of the results to different choices of covariates.

RESULTS: The MAIC included 22 patients receiving olezarsen and 23 receiving placebo in Balance, and 33 patients receiving volanesorsen and 33 receiving placebo in APPROACH. After weighting, patient characteristics were well balanced between Balance and APPROACH, and the effective sample size for the entire Balance trial ranged from 33.6 to 41.0 depending on the outcome.

At 26 weeks, reduction in fasting TG was greater for volanesorsen (mean difference [MD] for olezarsen vs. volanesorsen: 17.9 %-points; 95% CI: –20.0, 55.8; not significant), whereas reduction in apoC-III was similar for both therapies (MD: –2.6 %-points; 95% CI: –28.3, 23.2). Both studies imputed missing long-term data (1 placebo patient discontinued in each study, while 3 and 14 patients discontinued in the studies' olezarsen and volanesorsen arms, respectively). At 52 weeks, olezarsen showed greater reduction in fasting TG versus volanesorsen (MD: –27.5 %-points; 95% CI: –69.4, 14.5) and greater reduction in apoC-III (MD: –21.3 %-points; 95% CI: –61.9, 19.2), though differences were not statistically significant. Olezarsen was associated with a 77% lower risk of ≥1 AP event (risk ratio [RR]: 0.23; 95% CI: 0.01, 5.02) and 94% fewer AP events per patient-year ›››

(incidence rate ratio : 0.06; 95% CI: 0.003, 1.41) compared with volanesorsen, as well as lower risk of serious AEs (RR: 0.50; 95% CI: 0.08, 3.26) and treatment-related AEs (RR: 0.52; 95% CI: 0.16, 1.70), however these differences were not statistically significant. Sensitivity analyses yielded consistent results, supporting the primary results.
CONCLUSIONS: In this indirect comparison, olezarsen was associated with numerically greater reductions in fasting TG and apoC-III and lower risks of AP and AEs compared with volanesorsen over 52 weeks, though differences were not statistically significant. These results support olezarsen as a therapeutic option for patients with FCS and may represent a viable alternative for individuals currently receiving volanesorsen.
Sponsorship: Analysis funded by Ionis. Publication funded by Sobi.

POSTER PRESENTATION 10

VEGFA/VEGFR2 axis regulates the crosstalk between senescent vascular smooth muscle cells and intraplaque neovessels in atherosclerosis

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Atherosclerosis, the leading cause of cardiovascular disease, progresses from fatty streaks to unstable rupture-prone plaques that trigger thrombotic events. A hallmark of plaque instability is intraplaque angiogenesis (IPA), the growth of leaky neovessels from the adventitial vasa vasora, that promote intraplaque hemorrhage (IPH) and inflammation. While hypoxia is a known trigger, additional pro-angiogenic mechanisms remain unclear. As an age-related disease, atherosclerosis is characterized by the accumulation of senescent vascular smooth muscle cells (VSMCs), which are metabolically active and adopt a senescence-associated secretory phenotype (SASP) that promotes chronic inflammation and tissue remodeling.
Despite growing recognition of the detrimental role of senescent VSMCs in atherosclerosis and their spatial proximity to the vasa vasora, whether their SASP directly drives IPA and IPH has remained unexplored. Here, we investigated the link between VSMC senescence, SASP production, and angiogenesis, and assessed whether targeting SASP-related pathways could provide novel therapeutic opportunities.
Re-analysis of a scRNASeq dataset of human carotid atherosclerosis revealed a distinct population of senescent VSMCs within atherosclerotic lesions, identified by high expression of a 24-genes senescence signature. Moreover, gene ontology and gene set enrichment analyses further showed that these senescent VSMCs overexpress genes that are associated with angiogenesis. ›››

Importantly, immunohistochemical analysis confirmed that senescent VSMCs are significantly more abundant in unstable human carotid plaques than in stable ones.
To investigate their functional impact, we established two in vitro models of senescent VSMCs, replicative and doxorubicin-induced, and found that both models secreted significant higher levels of pro-angiogenic molecules, including VEGFA, compared to young control cells.
Conditioned media from senescent VSMCs enhanced endothelial proliferation, migration, and tube formation in HUVECs.
Mechanistically, pharmacological inhibition of VEGFR2 in HUVECs abrogated these pro-angiogenic effects, identifying the VEGFA/VEGFR2 axis as a central mediator of VSMCs senescence-driven angiogenesis.
Our findings demonstrate that VSMC senescence actively contributes to plaque progression and instability through a strong pro-angiogenic SASP secretome. Targeting vascular senescence and the VEGFA/VEGFR2 pathway emerges as a promising strategy to inhibit intraplaque angiogenesis and stabilize high-risk atherosclerotic lesions.

POSTER PRESENTATION 11

Deciphering pathophysiological roles of long non-coding RNAs MIAT and MEG3 in aortic disease

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RATIONALE: Aortic valve stenosis (AVS) and coronary artery disease (CAD) are highly prevalent comorbidity in elderly populations. Accumulation of atherosclerotic plaques triggers chronic inflammation and leads to progressive calcification in AVS. With transcatheter aortic valve replacement (TAVR) as the sole effective treatment, the urgent need for novel therapeutic targets is apparent. Long non-coding RNAs (lncRNAs) are crucial epigenetic regulators, yet their roles in AVS and CAD remain largely unexplored. Our preliminary transcriptomic data from calcified human aortic valves identified a significant upregulation of MIAT and MEG3, lncRNAs implicated in fibrosis and endothelial dysfunction. This study investigates their specific contribution to AVS and CAD pathogenesis to identify new RNA-based diagnostic and therapeutic strategies.
METHODS AND RESULTS: Using primary human valvular interstitial (VICs) and endothelial cells (VECs) from calcified and non-calcified valves, as well as human coronary artery endothelial cells (HCAEC) and smooth muscle cells (HCASMC), we performed siRNA-mediated knockdown of MIAT and MEG3. Silencing either lncRNA reduced cellular senescence and cytotoxicity without affecting viability. Functional assays revealed that knockdown attenuated endothelial cell proliferation and migration, while simultaneously affecting its angiogenic capacity. Upon oxLDL and TNFα stimulation on HCAEC, siMIAT and siMEG3 decreased the expression of pro-inflammatory genes. To model AVS pathogenesis, we induced endothelial-to-mesenchymal transition (EndMT) in VECs and calcification in VICs. siMIAT and siMEG3 potently suppressed key EndMT markers (ACTA2, TAGLN, COL1A1) in VECs and downregulated osteogenic drivers (BMP2, RUNX2, BGLAP) in VICs, indicating a profound amelioration of core disease phenotypes. ›››

Furthermore, intercellular communication studies via extracellular vesicles (EVs) and co-culture models demonstrated that silencing MIAT or MEG3 in donor VECs significantly reduced inflammatory markers (IL-6, TGF-β, ICAM-1, VCAM-1) in recipient VICs. An integrated in silico and proteomic approach identified caspase-3, p53, and HIF1α as potential downstream effectors mediating these lncRNA-driven inflammatory and calcification pathways.
CONCLUSION AND OUTLOOK: Our findings establish MIAT and MEG3 as critical promoters of calcification and EndMT in AVS, as well as drivers of cellular inflammation in CAD. Their silencing restores endothelial integrity and mitigates osteogenic differentiation, positioning them as promising therapeutic targets. Future work will employ RNA immunoprecipitation sequencing (RIP-seq) and pull-down assays to delineate the precise molecular mechanisms, supported by validation in valvular organoids and murine models to translate these findings towards clinical application.

POSTER PRESENTATION 12

Increased CCL15 chemokine associated with disease progression and cardiovascular risk in chronic kidney disease

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BACKGROUND: Patients with chronic kidney disease (CKD) present with an increased cardiovascular risk. Chemokines play an important regulatory role in inflammation and cardiovascular disease but have been understudied in CKD.
METHODS AND RESULTS: In a chemokine profiling, we identified CCL15 as the strongest upregulated chemokine in CKD patients compared to healthy controls. Blood CCL15 levels inversely correlated with kidney filtration function and were associated with kidney interstitial fibrosis and tubular atrophy in kidney biopsies. Furthermore, CCL15 predicted future cardiovascular events in the NEFRONA study and was an independent predictor of decompensated heart failure and death in the CARE for HOMe study. In the UK population biobank, CCL15 also independently predicted heart failure risk in the general population. Single-cell RNAseq of human kidney biopsies indicated that CCL15 is expressed in tubules and injured endothelium and is upregulated in CKD. Mechanistically, CCL15 was able to induce fibrosis in human cardiac organoids and kidney pericytes beyond its effect on inflammatory cell recruitment, may contributing to disease progression and increased cardiovascular risk.
CONCLUSION: Overall, we identify CCL15 as the first chemokine biomarker predicting heart failure risk and mortality in CKD. CCL15 was able to drive fibrosis, and could thereby contribute to CKD progression and increased cardiovascular risk.

POSTER PRESENTATION 13

Inhibition of MLKL impairs abdominal aortic aneurysm development by attenuating smooth muscle cell necroptosis

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Medial smooth muscle cell depletion is a characteristic feature of aortic aneurysms, with necroptosis-mediated by RIPK3 and MLKL-potentially driving SMC death, the release of DAMPs, and inflammation.Even though the role of MLKL induced-necroptosis is well understood in several diseases, its role in development of aortic aneurysm remains largely uncertain. ›››

In this study, we monitored PPE-perfusion induced progression of AAA in C57BL/6N (WT) and MLKL knockout (Mlkl-/-) mice by ultrasound measurements, histological analyses and bulk mRNA sequencing to assess structural and molecular aortic changes. Additionally, we investigated the therapeutic potential of a new MLKL inhibitor for AAA. Ultrasound analysis showed that ~70% of the WT animals developed PPE induced-AAA with significant aortic structural alterations and enhanced myeloid cell infiltration. In contrast, Mlkl-/- mice were protected from AAA. This protection was associated with reduced adverse extracellular matrix (ECM) remodeling and leukocyte infiltration. MLKL deficiency was associated with a significant downregulation of genes involved in fibrinolysis, anti-inflammatory response, immune response and complement activation in aortic tissue in AAA. We also show that the WT animals treated with MLKL inhibitor were protected from the PPE induced aneurysm formation. Overall, these findings indicate that MLKL-induced necroptotic SMC death and subsequent proinflammatory cytokine and DAMP release might play a causative role in AAA development. We also show that pharmacological inhibition of MLKL represent a promising treatment strategy for AAA disease.

POSTER PRESENTATION 14

MAdCAM-1-dependend intestinal leukocyte trafficking regulates metabolism and inflammation in mice with obesity

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BACKGROUND:
Obesity is a global health burden and a chronic life-threatening disease associated with low-grade inflammation and metabolic dysfunction. The intestinal immune system has emerged as a central regulator of systemic inflammation and glucose homeostasis. Inhibition of gut immune cell trafficking may therefore represent a novel mechanism linking intestinal immunity to metabolic dysfunction. The mucosal adhesion molecule MAdCAM-1 mediates the recruitment of $\alpha 4\beta 7$ expressing lymphocytes to the intestinal mucosa, but its contribution to obesity-associated inflammation and metabolic dysfunction remains unknown. The aim of this study was to investigate the effect of MAdCAM-1-deficiency on metabolism and obesity.
METHODS:
Male MAdCAM-1–/– mice (n=13) and wild type mice (n=10) were fed a high-fat diet (HFD) and compared to control groups (MAdCAM-1–/–, n=5, MAdCAM-1 WT, n=6) fed chow diet for 20 weeks. Body weight, fasted blood glucose levels, and insulin tolerance (ITT) were assessed. Systemic immune cell profiling was performed by multicolor Aurora flow cytometry (FACS) of blood, white adipose tissue (WAT), liver, kidney, spleen, and bone marrow. In addition, intestinal immune cell subsets were analyzed in the lamina propria (LP) and intraepithelial lymphocytes (IEL) of the small intestine.
RESULTS:
Despite similar body weight gain under HFD, MAdCAM-1–/– mice showed a non- significant trend to reduced fasting blood glucose levels (10.48 ± 1.35 vs. 7.98 ± 0.41 mmol/l in WT vs. MAdCAM-1–/– mice, p=0.08). Furthermore, mice lacking MAdCAM-1 had improved insulin tolerance compared to WT mice (ITT AUC of blood glucose levels over time: 742.3 ± 0.48 vs. 985.4 ± 0.37, p=0.02). FACS analysis revealed a reduction of Ly6Chigh monocytes in the blood (33%), WAT (49%) and in the kidney (28%) in MAdCAM-1–/– mice vs. WT mice. In WT mice, obesity induced by HFD led to a distinct redistribution of intestinal immune cells, characterized by a 11-fold increase in lamina propria (LP) leukocytes and a reduction in intraepithelial lymphocytes (IEL) compared to control mice without obesity (chow diet), indicating obesity-associated intestinal immune cell activation.
CONCLUSION:
These data suggest that HFD-induced obesity shifts intestinal immune cells from the epithelial layer to the lamina propria, which might indicate gut immune cell activation. Despite similar body weight under HFD, MAdCAM-1 deficiency protected against obesity- induced metabolic dysfunction by improving insulin sensitivity and limiting inflammatory monocyte expansion. MAdCAM-1 associated intestinal inflammation might be a novel potential therapeutic target in obesity and metabolic dysfunction.

POSTER PRESENTATION 15

Myocardial infarction accelerates melanoma growth in mice

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Clinical data suggests that cardiovascular diseases, including myocardial infarction (MI), increase the risk to develop different malignancies. Patients with MI have a 46% increased Hazard Ratio to develop cancer compared to those without (Rinde, 2017). First interfaces of cross communication in other tumor entities, like breast cancer, point to immune cell reprogramming (Koelwyn, 2020), the mechanistic crosstalk underlying MI-accelerated melanoma progression remains uncharacterized.
We here aim to investigate the impact of MI on melanoma growth in mice. C57BL/6J mice (10 to 14-week-old, male and female) underwent LAD-Ligation to induce MI or sham surgery (thoracotomy only). B16F10 melanoma cells were injected subcutaneously at day -3 or day 7 of surgery. Tumor size was determined by micrometer calliper daily, heart function was analysed by echocardiography once weekly. At the end of the experiment (day 15 post B16F10 injection), immune cell changes of tumor tissue, lymph nodes, blood and spleen were determined by spectral flow cytometry and heart tissue was used for histological analysis.
Our results demonstrate that MI accelerates melanoma growth in mice. Flow cytometry analysis of circulating immune cells in blood revealed a systemic reprogramming, characterized by an increase in pro inflammatory Ly6Chigh CCR2+ monocytes and a decrease in CD4+ T cells and Tregs (FoxP3+CD25+) in MI affected mice vs. controls. Future experiments will reveal the role of these altered immune cell subsets for acceleration of tumor growth.

POSTER PRESENTATION 16

Myocardial infarction accelerates tumor growth of chronic lymphocytic leukemia

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Cardiovascular disease (CVD) and cancer, the leading causes of death worldwide, share risk factors and appear to also interact pathomechanistically. Patients with chronic lymphocytic leukemia (CLL) have a 9% higher risk of developing CVD – however concise pathomechanisms remain poorly understood (Larsson et al., Br J Haematol 2020).
We here aim to investigate whether myocardial infarction (MI) might influence growth of TCL1-tg B cells, a B cell lymphoma model.
TCL1-tg cells were adoptively transferred five days prior MI induction by permanent ligation of the left descending anterior artery (LAD). ›››

Cardiac function was assessed biweekly by echocardiography. In parallel, CLL burden (CD5+CD19+ cells) and immune cell changes in the blood were determined by flow cytometry (FACS), using a pan leukocyte panel and markers of exhaustion, memory and proliferation. Once mice reached termination criteria, bone marrow, spleen, lymph nodes, heart, and blood were collected for FACS and histological analysis.
Echocardiographic and histological analyses confirmed the successful induction of MI. By FACS, accelerated tumor growth was observed in mice with MI (week 6: 38.73 ± 17.78%) vs. sham (23.19 ± 17.73%). In addition we observed increased frequencies of Tregs and Ly6Chi monocytes in blood and spleen upon harvest (week 8). Both cell types are well-established contributors to tumor progression. We further observed more exhausted T and NKT cells, as well as a trend toward more Tregs in the tumor microenvironment (TME) of MI mice. Future directions will unravel how MI impacts on the observed immune cell changes in the TME.

POSTER PRESENTATION 17

Myocardial infarction promotes neutrophil-like monocyte expansion in the bone marrow via interleukin-6 signaling

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Myocardial infarction (MI) triggers a systemic inflammatory response, mainly sustained by emergency hematopoiesis in the bone marrow (BM). While it is well established that hematopoietic progenitors and precursors react to MI by increasing leukocyte production, it remains elusive whether immune cell phenotypes also change during the inflammatory response.
We performed single-cell RNA sequencing (scRNA-seq) on BM leukocytes from C57BL/6 mice at steady state and at 12-, 24-, 48-, and 72-hours post-MI (permanent ligation of the left ascending coronary artery). This analysis identified an expansion/the occurrence of a distinct subpopulation of Ly6Chigh monocytes in response to infarction. In particular, this population expressed genes typically associated with neutrophils, including S100a9, S100a8, Lcn2, and Camp. Thus, this subpopulation was classified as “neutrophil-like monocytes” (Neu-Mo). We validated Neu-Mo dynamics over time in the BM, blood, and heart of infarcted mice using flow cytometry and identified this population as S100A9highMHCIInegLy6Chigh monocytes. Our analysis indicates that Neu-Mo represent a small monocyte subpopulation (6.98±2.92% of circulating monocytes). Following MI, Neu-Mo numbers start to rise first in the BM, then in the blood and ultimately in the heart at 48 hours post-infarction (15.36±9.03 cells/mg). These Neu-Mo kinetics were further confirmed using S100a9EGFP/+ transgenic mice, which allow tracking of Neu-Mo post-MI.
We next investigated potential blood-borne factors driving Neu-Mo production. In-vitro experiments identified interleukin 6 (IL-6) as a primary inducer of Neu-Mo production. Wild-type mice injected with IL-6 confirmed Neu-Mo expansion in the BM (15,093±14,359 cells/femur vs. 98,025±57,775 cells/femur). Conversely, experiments in Il6-/- mice demonstrated a significant reduction in Neu-Mo accumulation in the ischemic area 48 hours after MI (21.66±10.29 cells/mg vs. 4.139±2.382 cells/mg). To explore whether MI induces phenotypic shifts in monocyte precursors, we performed RNA-seq on sorted BM monocyte precursors at steady state and 12 hours post-MI. ›››

Monocyte precursors upregulate neutrophil-related genes such as Lcn2 and S100a9 in response to MI, indicating that Neu-Mo expansion is a direct consequence of phenotypic changes in upstream monocyte precursors.
Our findings identify a previously uncharacterized monocyte subpopulation that significantly contributes to the inflammatory response post-MI, highlighting the active role of the BM in modulating leukocyte phenotypes. Rather than representing a simple acceleration of baseline hematopoiesis, emergency hematopoiesis following MI involves a more specialized and branched hematopoietic process. This process facilitates the expansion of distinct subpopulations, such as Neu-Mo cells, which do not arise during typical hematopoiesis. Additionally, we demonstrate the critical role of IL-6 in regulating the heart-BM axis to promote Neu-Mo production. Ongoing research aims to elucidate the specific functions of Neu-Mo in the context of MI.

POSTER PRESENTATION 18

Olfr2 induces lipid metabolic stress in macrophages

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Macrophages play a pivotal role in inflammation and metabolic dysfunction. In obesity, adipose tissue macrophages (ATMs) expand in number and contribute to chronic low-grade inflammation. Recent studies have revealed that ATMs are heterogeneous, comprising distinct subsets with unique signaling pathways and functions. However, the specific ATM subsets responsible for obesity-induced inflammation remain unclear. Notably, olfactory receptor 2 (Olfr2), an odorant receptor, has recently been implicated as an inflammatory signaling mediator in macrophages. Here, we identified Olfr2-expressing ATMs in the epididymal adipose tissue (EAT) of diet-induced obese mice. Genetic deletion of Olfr2 protected against obesity and metabolic dysfunction by attenuating inflammation in EAT. Among ATM subtypes, lipid-associated macrophages displayed the highest expression of Olfr2 and enriched fatty acid metabolism signatures, which were dimin.ished in Olfr2-deficient mice. Loss of Olfr2 did not affect the respiratory exchange ratio or energy expenditure. Together, our findings identify an inflammatory ATM subset, Olfr2 macrophages, that contributes to obesity-induced inflammation, implicating Olfr2 as a potential therapeutic target

POSTER PRESENTATION 19

PACAP influences the morphology of mitochondria, as well as the migratory ability of HCASMC

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AIM:
Vascular smooth muscle cells (VSMCs) are involved in all stages of atherosclerosis, from early lesions to advanced plaques. Thinning of the fibrous cap of the plaque, caused by the death of VSMCs and the degradation of collagen and extracellular matrix (ECM), increases the risk of plaque rupture. Previous studies have shown that PACAP (pituitary adenylate cyclase-activating polypeptide) deficiency in ApoE-/- mice fed a standard diet has proatherogenic effects. The cellular mechanisms of these effects are still unclear. Therefore, the aim of this study is to investigate the effects of PACAP on viability, migratory ability, and mitochondrial dynamics/dysfunction in human coronary artery smooth muscle cells (HCASMC).
METHODS AND RESULTS:
To investigate the effects of PACAP deficiency in atherosclerosis development under standard chow (SC), PACAP–/– mice were crossbred with ApoE–/– mice to generate PACAP–/– /ApoE–/– mice. Plaque areas in the aorta were analyzed using ORO staining and ImageJ (Fiji). In vitro, HCASMC were treated with 25 µg/ml oxLDL with/without PACAP38. Viability was analyzed with PrestoblueTM, and oxLDL uptake and accumulation were analyzed with BodipyTM, measured by ELISA. Cell migration was assessed using the scratch assay and the MRI wound healing tool in ImageJ (Fiji). Mitochondrial morphology was examined by immunofluorescence staining with MitoTrackerTM and antibodies against cytochrome c. Mitochondrial morphology was analyzed using the MiNA tool in ImageJ (Fiji). In vivo data show that PACAP deficiency increased the plaque area in the aorta in ApoE–/– mice after 30 weeks SC. In vitro data reveal that PACAP38 had no effect on lipid accumulation, but increased viability in oxLDL-treated HCASMC. Both, oxLDL and PACAP38 slowed cell migration after 5 hours compared to negative control. Analyses of mitochondrial morphology indicate that oxLDL and PACAP38 increase individual (puncta, rods) and network structure of mitochondria with a reduction in the mean number of branches per network.
CONCLUSION:
Our data suggest that PACAP plays an important regulatory role in HCASMC migration and improves mitochondrial health by promoting fission and fusion processes independent of the lipid content. Thus, PACAP appears to have a protective function in HCASMC.

POSTER PRESENTATION 20

Physical Activity and its impact on immunity in CVD

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BACKGROUND:
Regular physical activity (PA) and structured exercise are associated with a reduced incidence and mortality of cardiovascular disease (CVD). Accordingly, current guidelines recommend at least 150 minutes of moderate-intensity or 75 minutes of vigorous-intensity PA per week (or equivalent combinations). Nevertheless, approximately one-third of the global population fails to meet these recommendations, with physical inactivity continuing to rise. From a pathophysiological perspective, sedentary behavior promotes chronic low-grade systemic inflammation, thereby accelerating the development and progression of inflammatory diseases of the vessel wall, ultimately leading to atherosclerosis.
METHODS:
To investigate immune adaptations induced by PA, C57BL/6 mice were subjected to six weeks of voluntary wheel running or maintained under sedentary conditions. Circulating leukocyte subsets and bone marrow hematopoiesis were assessed by flow cytometry. To determine whether PA induces leukocyte-intrinsic changes affecting vascular recruitment, adoptive transfer experiments were performed using FACS-sorted monocytes and neutrophils from physically active or sedentary donor mice transferred into ApoE$^{-/-}$ recipient mice. Aortic recruitment and peripheral blood distribution were quantified 36 hours post-transfer.
RESULTS:
Voluntary PA significantly reduced circulating leukocyte counts, including neutrophils, B cells, T cells, and Ly6C^hi monocytes, and induced distinct alterations in bone marrow leukocyte composition. In adoptive transfer experiments, monocytes and neutrophils derived from physically active donors exhibited markedly reduced recruitment to atherosclerotic vascular sites compared with cells from sedentary donors. Importantly, this effect was independent of the recipients' activity status, indicating a leukocyte-intrinsic reprogramming induced by physical activity.
TRANSLATIONAL PERSPECTIVE:
To translate these findings to humans, the ISAR Inflex Trial evaluates the effects of different exercise intensities and durations on total leukocyte counts, subsets and systemic inflammation in a randomized cross-over design. Thirty-three sedentary, overweight but otherwise healthy adults undergo moderate-intensity continuous exercise (MICEx), vigorous-intensity continuous exercise (VICEx), and short maximal exercise bouts (SMEx). Comprehensive immunophenotyping, plasma proteomics, and transcriptomic profiling are performed before, during and after each intervention to delineate intensity- and duration-dependent immune responses.
CONCLUSIONS:
Physical activity induces systemic and leukocyte-intrinsic immune adaptations that attenuate inflammatory leukocyte recruitment in cardiovascular disease. Ongoing translational studies will clarify how exercise intensity and duration shape immune cell function in humans, supporting physical activity as a targeted, non-pharmacological immunomodulatory strategy in CVD.

POSTER PRESENTATION **21**

Preventing pancreatitis in severe hypertriglyceridemia: clinical response to olezarsen, an LPL-independent triglyceride-lowering therapy

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AIM:
Patients affected by severe hypertriglyceridemia currently have limited therapeutic options. Olezarsen is an antisense oligonucleotide, which lowers triglycerides reducing the hepatic synthesis of apolipoprotein C-III. The aim of this case report is to describe the clinical response to olezarsen in a patient with severe hypertriglyceridemia and poor control under standard-of-care therapy, causing recurrent pancreatitis.
METHODS:
We describe the case of a 63-year-old patient affected by severe hypertriglyceridemia and pancytopenia, carrying a pathogenic variant of LPL combined with a variant of unknown significance. The patient was initially enrolled in the clinical study Core, during which she received placebo and was observed throughout the study period. Subsequently, during the open-label extension phase, she was dosed with Olezarsen 80 mg. Clinical and biochemical parameters were monitored during both phases to assess changes in disease activity, safety, and treatment response.
RESULTS:
During placebo exposure, the patient experienced recurrent pancreatitis (3 episodes in 6 months), additionally to the 14 episodes reported in her medical history. After initiation of olezarsen, a clinically significant reduction in triglycerides levels could be observed, together with a prevention of pancreatitis episodes, and an unexpected improvement of the pancytopenia. No treatment-limiting adverse events were observed.
CONCLUSIONS:
This case report suggests that olezarsen may represent a life-changing therapeutic option for patients with severe hypertriglyceridemia inadequately controlled with standard-of-care treatment. The marked biochemical and clinical improvements observed support further treatment and evaluation of medications targeting APO-C III in patients with similar clinical and biochemical profiles.

POSTER PRESENTATION 22

T cell dynamics in elastase-induced abdominal aortic aneurysm formation and progression using single cell RNA-sequencing

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Abdominal aortic aneurysm (AAA) is a life-threatening cardiovascular disease characterized by chronic inflammation and immune cell infiltration. T cells are among the predominant immune cell types in AAA and play an important role in the inflammatory response. Moreover, T cells responding to AAA-related antigens in the aortic wall may contribute to an initial and disease-causing immune response. This study aimed to provide a detailed analysis of T cell subsets and their functions in AAA formation and progression.

We performed single-cell RNA-sequencing and single-cell T cell receptor-sequencing of murine AAA at day 3, 7, 14 and 28 after elastase-perfusion and compared these to saline-perfused and non-perfused control aortae. Differentially-expressed genes were identified for each cluster to identify the different subpopulations and their distribution over AAA progression. Gene ontology, signaling pathway activities and cell-cell communication were analyzed to gain insights into the functional roles of the different lymphocyte subsets. In addition, clonality of T cell receptors was examined.

Natural killer (NK) cells, NKT cells, innate lymphoid cells (ILC) type 2 and 3, Cd4+ T cells, Cd8+ T cells, pro-inflammatory T cells and regulatory T cells (Treg) were identified in elastase-induced AAA. NK and NKT cells together constituted the majority of lymphocytes at all stages of AAA formation. While they peaked at day 3 and decreased with AAA progression, ILCs and Cd4+ T cells increased with AAA progression and peaked at day 28. Cd4+ T helper cells represented the largest T cell subset in AAA and were associated with T cell activation and differentiation as well as leukocyte cell-cell adhesion. They were predicted to strongly communicate with dendritic cells and macrophages via CD40-CD40L signaling, thus driving inflammation. Cd8+ T cells expressed genes associated with a memory phenotype and were mainly involved in lymphocyte differentiation. Tregs represented only a small subset in AAA and were relatively more abundant in controls. Furthermore, clonal-expanded T cells were detected in 11 of 16 AAA samples, but only in one control sample. The number of expanded clones ranged from 2 to 25 copies.

This study provides a detailed characterization of lymphocytes and particularly T cells in experimental AAA formation and progression and highlights a central role of T cells in the inflammatory response. Evidence of clonal expansion of T cells was found, supporting the notion that specific antigen-driven T cells facilitate AAA formation.

POSTER PRESENTATION 23

Establishment and characterization of a murine model of mitral valve insufficiency

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BACKGROUND:
Mitral valve insufficiency (MI) is among the most prevalent valvular heart diseases worldwide and represents a major cause of morbidity and mortality. Despite its clinical relevance, the molecular and cellular mechanisms underlying MI pathogenesis remain poorly understood. Current therapeutic strategies are largely limited to symptomatic treatment or surgical intervention, underscoring the urgent need for a deeper mechanistic understanding and the development of targeted therapies. One major limitation to advancing research in this field is the lack of an appropriate mouse model that faithfully recapitulates MI. In this study, with the genetic knock-out mouse model dzip1S14R/+ we established and characterized a new model of MI to investigate the underlying mechanisms contributing to disease onset and progression.
METHODS:
For our study, male and female dzip1S14R/+-mice (n=16) were used as well a wildtype(wt)-mice (n=4) as control group. From 12 weeks of age onward, echocardiography was performed in parasternal long axis, parasternal short axis, as well as apical four chamber view and suprasternal view on a weekly basis to monitor methodological effects and the temporal onset of a MI. Right before harvest, we additionally performed MRIs and PET-CTs. After harvesting the mice, autoradiography and gamma counting was performed to visualize MI effects. Hearts were embedded in paraffin, sliced in 4 um slices and the heart as well as the mitral valves leaflets were stained for calcification via von kossa staining and for structural analysis via HE-staining.
RESULTS:
Female dzip1S14R/+-mice showed a MI between 19-20-week-old, ultrasound revealed mild regurgitation. Interestingly, male dzip1S14R/+-mice showed a MI between 23-24-week-old with a mild regurgitation. Ejection fraction was higher in dzip1S14R/+-mice compared to wt-mice, calcification of the valves could not be detected using PET-CT, autoradiography, gamma counting or von Kossa staining. The model appears to have a primarily degenerative component, as the E-to-A wave ratio was not significantly altered. Stainings revealed an alteration of the mitral valve leaflets, which appear to undergo a measurable thickening. Suprisingly, the aortic valve showed no significant difference in the dzip1S14R/+-mice which already showed an MI.
CONCLUSIONS:
Our study enabled the establishment of a novel MI models (dzip1S14R/+-model) that reflects distinct aspects of the pathology. Nevertheless, the models requires thorough characterization following its initial development before it can be considered for use as standard model.

POSTER PRESENTATION 24

Lipoprotein apheresis meets the UK Biobank

Reinhard Klingel for the Pro(a)LiFe Study Group

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Evidence from epidemiologic as well as Mendelian randomization studies is in favor of an independent and causal association of high lipoprotein(a) (Lp(a)) concentrations with atherosclerotic cardiovascular disease (ASCVD) and cardiovascular mortality. Lipoprotein apheresis (LA) is an effective option for lowering plasma concentrations of atherogenic lipoproteins. High Lp(a) associated with clinically progressive ASCVD was approved as an indication for regular LA with reimbursement in 2008. To become eligible, the Lp(a) concentration should exceed 60 mg/dl or as equivalent 120 nmol/l, LDL-C concentration should be in normal range, i.e. close to current treatment targets with maximally tolerated lipid lowering medication, and ASCVD should be progressive despite optimal treatment of all other cardiovascular risk factors.
The protocol for a randomized controlled trial to investigate efficacy of LA in such patients had been proposed, but had not received ethical approval in Germany. Therefore, the observational Pro(a)LiFe multicenter study enrolled 170 consecutive patients with high Lp(a) and progressive ASCVD as required for approval of reimbursement to analyse the long-term effect of LA on mean annual ASCVD event rates. Pro(a)LiFe patients were finally investigated after completion of 12 years of regular LA. ASCVD events per 100 patient years were compared to a UK-Biobank cohort (UKBBC) with essentially identical ethnicity, incident ASCVD, and verified impact of elevated Lp(a) on ASCVD risk as published by the study group of Welsh et al.. The Pro(a)LiFe cohort was compared to corresponding clinical trajectories of the UKBBC subgroups stratified by low (6 [3-12] mg/dl ; 12 [5.7-25.4] nmol/l) and high Lp(a) concentrations (98 [81-120] mg/dl ; 209.9 [174.6-258.6] nmol/l). The high-concentration subgroup was essentially identical to the Pro(a)LiFe cohort (104 [81-130] mg/dl; 224 [174-278] nmol/l).
Patients were investigated retrospectively over a 5-year period before initiation of regular LA, prospectively 5 years after commencing LA, and again retrospectively until completion of 12 years of LA comprising a total trajectory of 17 years. 154 patients (90.6%) completed 5 years follow-up, 129 patients (75.9%) were available in year 12. A rapid, significant, clinically relevant and sustained reduction in the mean annual rate of cardiovascular events per patient was observed from y-5 to y-1 (0.27±0.25) versus y+1 until y+12 (0.06±0.08) ($p<0.001$).
The Pro(a)LiFe cohort exhibited very high mean event rates per 100 patient years regarding cardiovascular events one year before commencing LA, which for the primary composite of MACE plus ischemic stroke (IS) and for coronary revascularization was significantly higher compared to both UKBBC subgroups one year after the first ASCVD event. This demonstrated the exceptional selectivity of the Pro(a)LiFe cohort. After one year of LA treatment Pro(a)LiFe patients exhibited in all disaggregated parameters significantly lower event rates compared to one year before, which for the primary composite of MACE including IS and for nonfatal MI was significantly lower compared to both UKBBC subgroups one year after the first ASCVD event. An essentially identical pattern, but less pronounced than one year before, was seen when comparing the 5-year period after commencing LA with the corresponding median follow-up of 4.7 years after the first ASCVD event in the UKBBC.
Results support the clinical efficacy of LA to bring progressive ASCVD associated with high Lp(a) to a halt. While not replacing a true control group, the comparison with the UKBBC can help fill part of the scientific knowledge gap caused by the lack of a control group and strengthen existing evidence of LA's clinical efficacy in preventing cardiovascular events associated with high Lp(a). The association of elevated Lp(a) with increased rate of subsequent cardiovascular events has highlighted a high-risk population that may benefit from earlier and more targeted intervention for Lp(a) and other cardiovascular risk factors.

POSTER PRESENTATION 25

The pharmacological inhibition of matrix metalloproteinase 13 for the targeted treatment of abdominal aortic aneurysm

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BACKGROUND: The abdominal aortic aneurysm (AAA) is a multifactorial disease with a high prevalence in individuals over 65 years of age, associated with significant mortality and morbidity. There is no specific pharmacological approach that directly targets AAA, and surgery remains the only treatment option. Matrix metalloproteinases (MMPs) constitute a family of enzymes capable of degrading nearly all components of the extracellular matrix (ECM). Among them, the secreted collagenase MMP13 is one of the few enzymes able to cleave the intact triple helix of collagen types I, II, and III. These collagens represent the most abundant structural proteins in the human body and collagenases play a pivotal role in maintaining matrix homeostasis. Owing to its markedly higher enzymatic activity compared to other MMPs, MMP13 is considered substantially more efficient and is thought to be a major contributor to the pathogenesis of AAA, thereby representing a potential therapeutic target. In this study, we explored MMP13 as a potential target for pharmacological inhibition for AAA in mice.
METHODS: Four groups were established: An untreated wildtype (wt)-group with AAA; a wt-group receiving MMP13 inhibitor injections every second day starting three days before aneurysm induction (prophylactic); a wt-group receiving daily MMP13 inhibitor injections every second day starting three days after aneurysm induction (therapeutic); and a MMP13-/-- group. AAA was induced in wt-mice as wells as in MMP13-/--mice via surgery. The abdominal aorta was ligated, blood flow interrupted and filled with porcine-pancreas-elastase (PPE) for five minutes. Mice were harvested on day 6 after PPE to assess acute inflammation or on day 28 after PPE for tissue remodeling and fibrosis. Ultrasounds were performed to monitor surgery effects, aneurysm induction and growth. Snap-frozen aortas were embedded for histological analysis and stained for collagen, elastin, decorin, alpha-SMA, MMP activity and CD45/CD68.
RESULTS: In both the prophylactic and therapeutic settings, the AAA diameter in mice with 28 days of MMP13-inhibiton was not different from MMP13-/--mice (p=0.289; p=0.877). MMP13-inhibited groups and MMP13-/--mice showed significantly smaller (p=0.039; p=0.009; p=0.007) AAA diameter compared to the control group. In the both settings as well as in MMP13-/--mice, picro sirius staining revealed a higher amount of collagen as well as elastic fibers in aortic tissue when compared to the control group. Likewise, quantification of decorin and alpha-SMA showed increased levels of these structural proteins in both experimental settings and in MMP13-/--mice relative to the control groups. Also, in both settings as well as in MMP13-/--mice, we could observe less immune cell recruiting and less MMP-activity compared to the control group.
CONCLUSIONS: MMP13 as a potential target for pharmacological inhibition for AAA in mice shows a significant effect on diameter growth. Also, MMP13 inibition shows similar effectiveness as a knockout of MMP13 gene in mice. Stainings revealed that MMP13-Knockout as well as an inhibition stabilizes the aortic wall in AAA disease and lowers immune cell migration. Nevertheless, the pharmacological inhibition of MMP13 requires thorough characterization.

POSTER PRESENTATION 26

Analysis of CD40-CD40L plasma levels and potentially associated signaling molecules in diabetic and non-diabetic patients following acute myocardial infarction

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BACKGROUND: Acute myocardial infarction (AMI) is a leading cause of worldwide mortality. Acute occlusion of a coronary artery results in myocardial ischemia followed by cardiomyocyte death, triggering local inflammation. While inflammatory processes contribute to the expansion of tissue injury and adverse cardiac remodeling, they are also essential for cardiac wound healing. These processes are driven by various immune cells, membrane-bound receptor-ligand dyads and cytokines, which regulate pro-inflammatory and regulatory intracellular signaling pathways. The pathophysiology of AMI is significantly influenced by cardiovascular risk factors like type 2 diabetes (T2D). Diabetic patients generally have a worse outcome after AMI, which is partly attributed to chronic inflammation. Among the key immunomodulatory signaling system, the co-stimulatory receptor-ligand dyad CD40–CD40L plays a pivotal role in both innate and adaptive immune response by regulating T-cell function, macrophage activation and immune cell differentiation, proliferation and survival. Previous studies have demonstrated an important role of CD40–CD40L interaction in processes involved in AMI and myocardial wound healing. Increased CD40–CD40L activity – also observed in diabetic patients – was associated with adverse cardiac outcome. However, the dynamics of CD40–CD40L and other, potentially associated, intercellular signaling molecules following AMI remain partially understood and require further investigations.
METHODS: Plasma levels of soluble (s) CD40, sCD40L, CD27 and various cytokines were determined in patients with ST-segment elevation myocardial infarction (STEMI) using NULISA-Seq (n = 44) and Luminex (n = 19) multiplex assays. Development of plasma levels during the first 24 hours after STEMI and differences between patients with and without T2D were analyzed using 2way ANOVA with repeated measurements and Sidak's multiple comparisons test. Correlation between plasma level changes were determined using Pearson correlation analysis.
RESULTS: During the first 24 hours after STEMI, a general downregulation of intercellular signaling molecules (such as sCD40L, interleukin (IL)-4, IL-7, IL-10 and IL-18) was observed in NULISA analysis, while sCD40 plasma levels showed no significant alteration. Downregulation was attenuated in diabetic patients, with sCD40 plasma levels showing a tendency to increase and sCD40L plasma levels decreasing less in patients with than in patients without T2D. Luminex analysis showed more ambiguous results while still supporting some findings of the NULISA analysis, such as downregulation of sCD40L and IL-7. Correlation analysis of plasma level changes in the first 24 hours after STEMI showed correlation between CD40 and sCD40L in NULISA analysis. Furthermore, both NULISA and Luminex analysis showed strong correlations between the CD40–CD40L dyad and both IL-7 and IL-18 in diabetic and non-diabetic patients.
CONCLUSION: Diabetic patients show signs of prolonged inflammation after STEMI with attenuated downregulation of intercellular signaling molecules, while indicating a larger role of CD40–CD40L interaction in post-ischemic mechanisms compared to non-diabetic patients. Correlation analysis points to possible co-regulation of CD40–CD40L and both IL-7 and IL-18 after AMI.

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