ANGIO UPDATE **2024**

15. und 16. März

pAVK: Konservativ

Christine Espinola-Klein, Mainz

Interessenkonflikte

Forschungsunterstützung: Abbott

Vortrags- oder Beratertätigkeit:

Abbott, Amarin, Amgen, Bayer, Boehringer, Bristol-Myers Squibb, Daiichi Sankyo, Novartis, Pfizer, Sanofi-Aventis

Epidemiologie, Risikofaktoren und Prognose

Risikofaktoren und Prognose

The Global Cardiovascular Risk Consortium
N Engl J Med 2023; 389: 1273-1285

112 Kohortenstudien
> 1,5 Millionen Teilnehmer

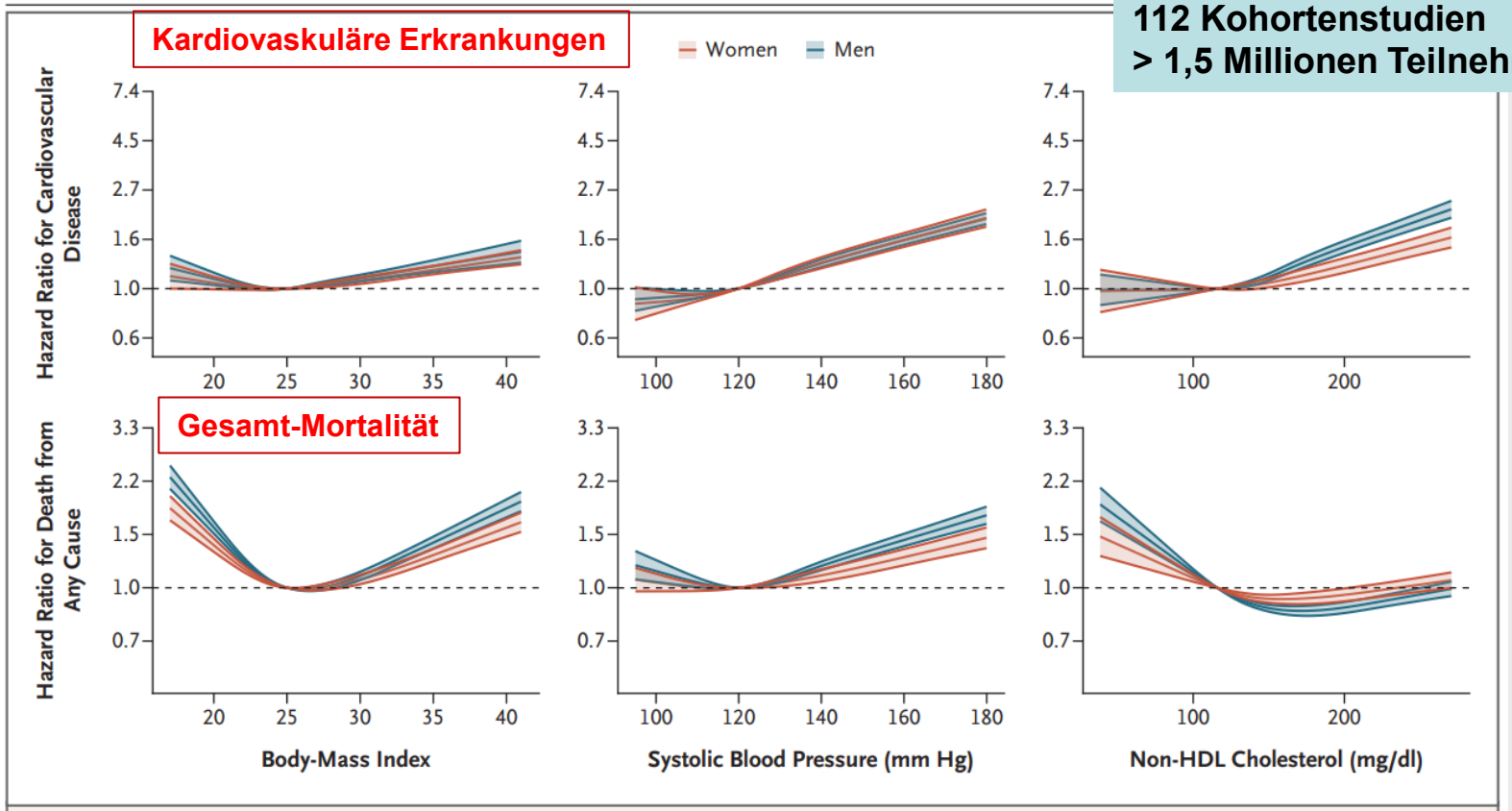


Figure 1. Associations of Continuous Risk Factors with Cardiovascular Disease and Death from Any Cause.

OMT nach infrapoplitealer PTA

Wittig T et al. J Clin Med 2023; 12, 5146.
https://doi.org/10.3390/ jcm1215514

Major Amputations-freies Überleben

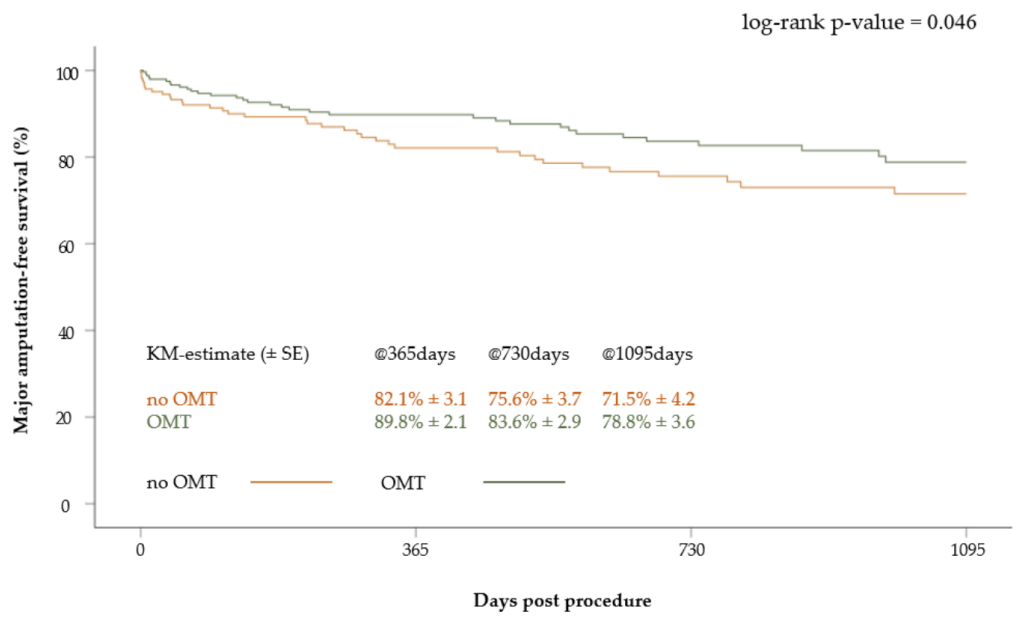


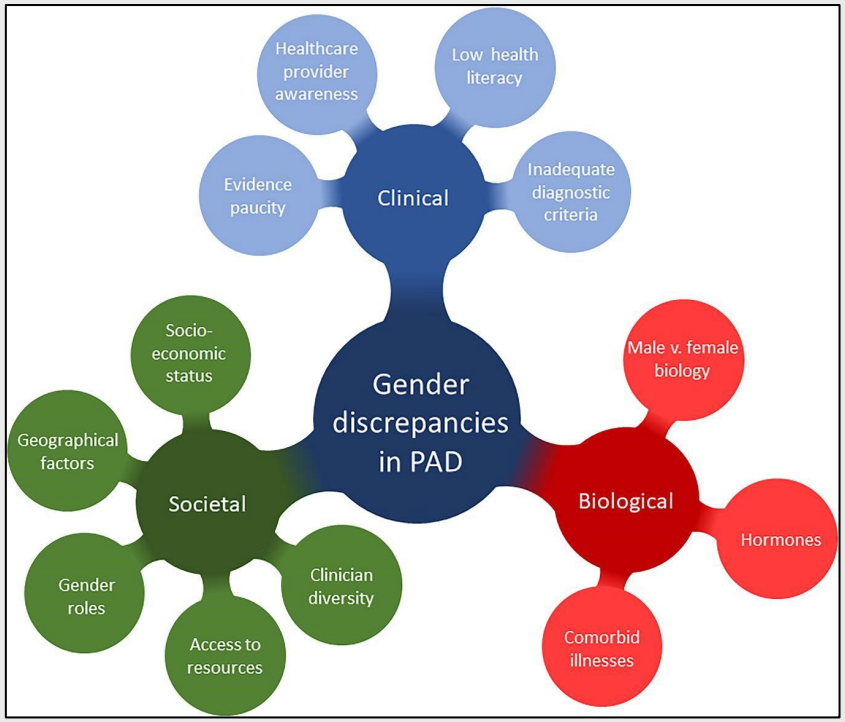
Figure 5. Kaplan–Meier curve of major amputation-free survival after 3 years according to medication at discharge (OMT versus no OMT).

Gesamt N = 552 (100%)
CI N = 145 (26%)
CLTI N = 407 (74%)

OMT = optimale medikamentöse Therapie mit TZAH, Statin und RAS Inhibitor

PAVK bei Frauen

Kavurma M.M. et al. Eur Heart J 2023; 9: 342-350

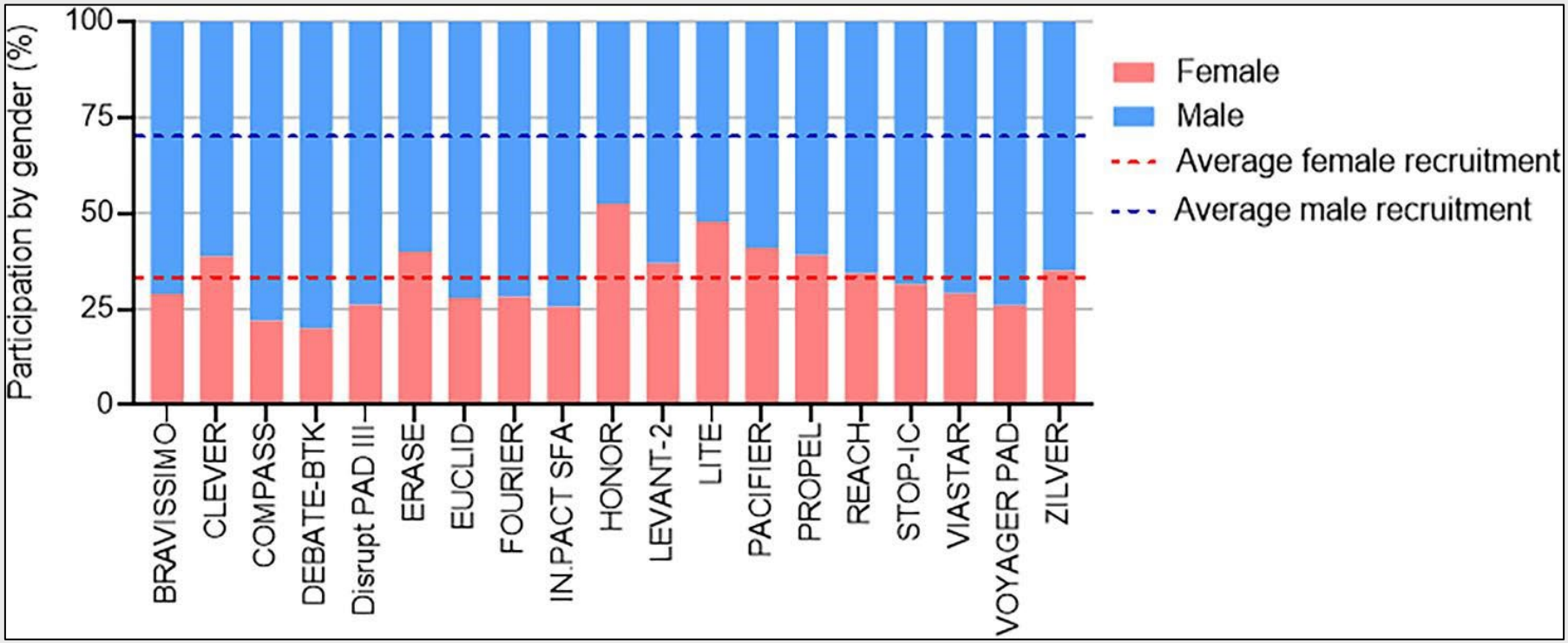


Prävalenz und Symptome	Höhere Prävalenz nach der Menopause und höheres Lebensalter Fehlende oder atypische Symptome Häufiger CLTI und Mehretagen-PAVK als Erstmanifestation
Therapie	Niedrigere Rate von leitliniengerechter Therapie Seltener interventionelle oder operative Revaskularisation Schlechtere Prognose nach Revaskularisation (V.a. Bypass)
Biologische Unterschiede	Höheres Thromboserisiko Kleinerer Gefäßdiameter Höhere Koinzidenz von Diabetes mellitus und arterieller Hypertonie

PAVK bei Frauen

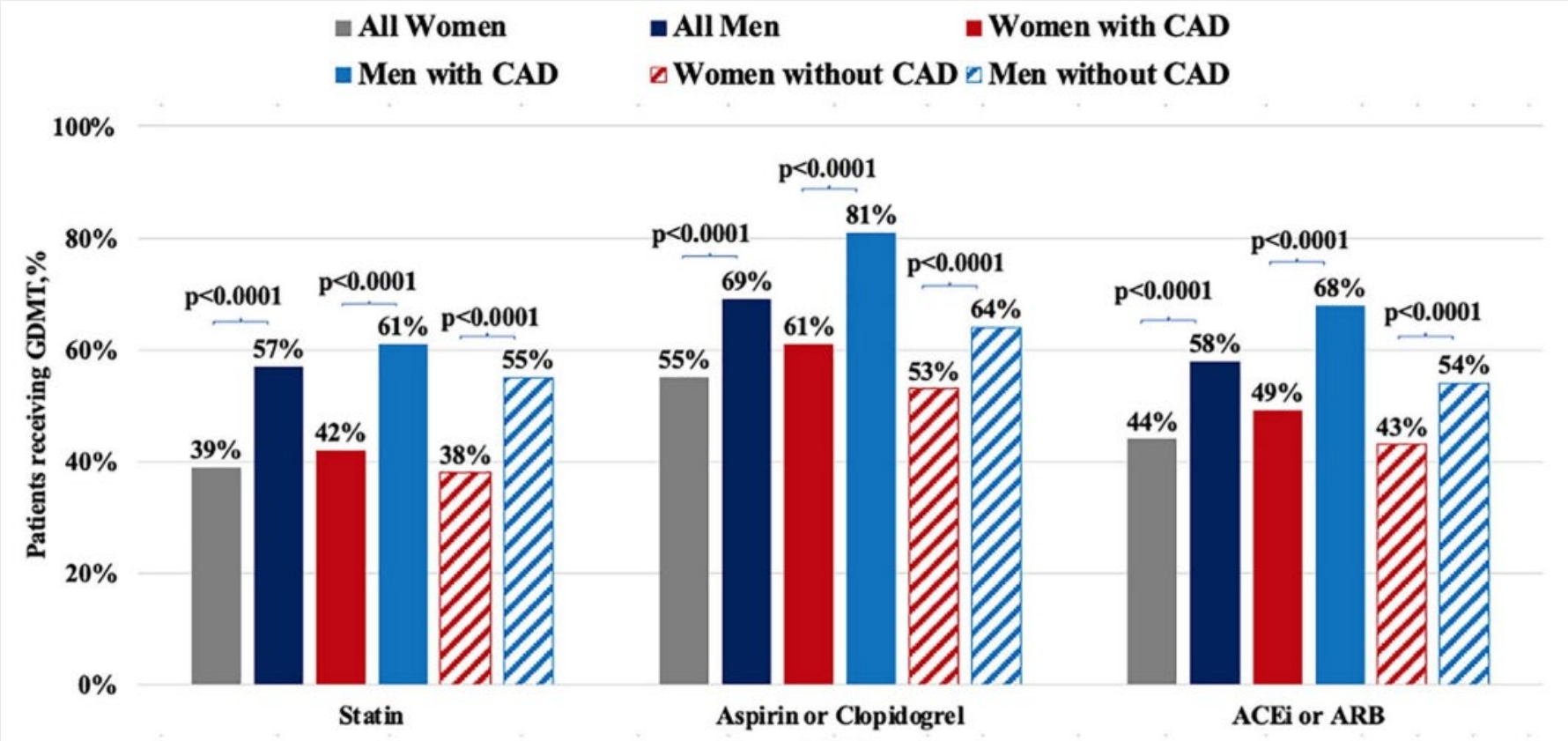
Kavurma M.M. et al. Eur Heart J 2023; 9: 342-350

Anteil Frauen in klinischen Studien zur PAVK



Sekundärprävention bei Frauen

Canonico ME et al. Vascular medicine 2023; 1-3



Fazit für Klinik und Praxis

- **Frauen mit PAVK haben eine schlechtere Prognose und weniger konsequente Einstellung der Risikofaktoren als Männer.**
- **Hypertonie, Diabetes, Übergewicht, erhöhte Lipidwerte und Rauchen sind noch immer die wichtigsten Risikofaktoren der Atherosklerose.**
- **Die medikamentöse Sekundärprävention ist daher ein zentraler Faktor der Therapie.**

Diabetes

ESC Leitlinien Diabetes

Marx N. et al., Eur Heart J 2023; 44: 4043-4140

ESC European Society of Cardiology

European Heart Journal (2023) **00**, 1–98
https://doi.org/10.1093/eurheartj/ehad192

ESC GUIDELINES

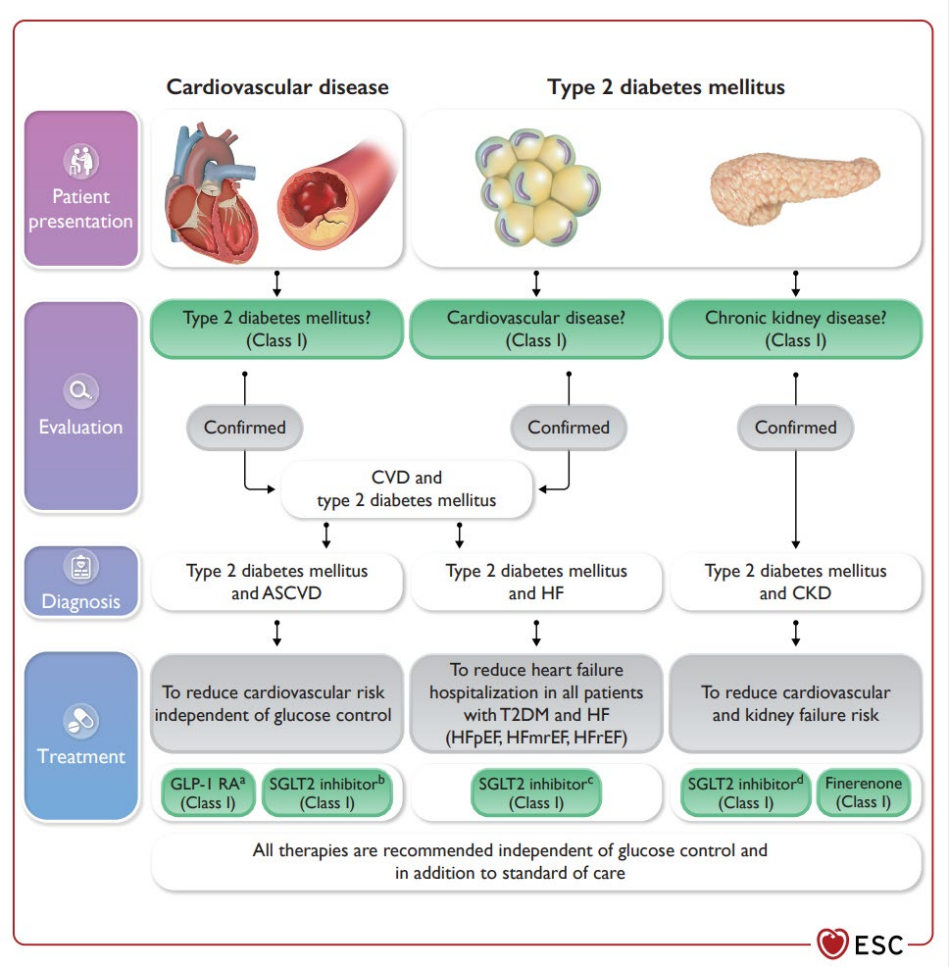
2023 ESC Guidelines for the management of cardiovascular disease in patients with diabetes

Developed by the task force on the management of cardiovascular disease in patients with diabetes of the European Society of Cardiology (ESC)

Authors/Task Force Members: Nikolaus Marx *†, (Chairperson) (Germany), Massimo Federici *†, (Chairperson) (Italy), Katharina Schütt ‡, (Task Force Co-ordinator) (Germany), Dirk Müller-Wieland ‡, (Task Force Co-ordinator) (Germany), Ramzi A. Ajjan (United Kingdom), Manuel J. Antunes (Portugal), Ruxandra M. Christodorescu (Romania), Carolyn Crawford (United Kingdom), Emanuele Di Angelantonio (United Kingdom/Italy), Björn Eliasson (Sweden), Christine Espinola-Klein (Germany), Laurent Fauchier (France), Martin Halle (Germany), William G. Herrington (United Kingdom), Alexandra Kautzky-Willer (Austria), Ekaterini Lambrinou (Cyprus), Maciej Lesiak (Poland), Maddalena Lettino (Italy), Darren K. McGuire (United States of America), Wilfried Mullens (Belgium), Bianca Rocca (Italy), Naveed Sattar (United Kingdom), and ESC Scientific Document Group

ESC Leitlinien Diabetes

Marx N. et al., Eur Heart J 2023; 44: 4043-4140



SCORE 2 Diabetes

SCORE2-Diabetes Working Group et al., Eur Heart J 2023; 44: 2544–2556

Development process

Original SCORE2 algorithms:
Predictors: age, sex, smoking, diabetes, SBP, total and HDL cholesterol

Calibrated to predict CVD risk in:
low, moderate, high and very high risk regions of Europe

Adaptation of SCORE2 for individuals with type-2 diabetes:
Added predictors: age at diabetes diagnosis, HbA1c and eGFR

→ SCORE2-Diabetes

Data used: 229,460 individuals with type-2 diabetes from electronic health records, diabetes registry, cohort studies

Validation of SCORE2-Diabetes:
External validation in 217,036 individuals with type-2 diabetes from Sweden, Spain, Malta and Croatia

SCORE2-Diabetes 10-year CVD risk models

Key features

- **Estimates** 10-year risk of CVD events in individuals with type-2 diabetes
- **Discriminates risk** in individuals with type-2 diabetes using conventional CVD risk factors and those specifically related to diabetes
- **Calibrated** to predict CVD risk in: low, moderate, high and very high risk regions of Europe
- **Aligned** with SCORE2 risk predictions for individuals without diabetes
- **Separate** risk scores for men and women with type-2 diabetes

SCORE 2 Diabetes

SCORE2-Diabetes Working Group et al., Eur Heart J 2023; 44: 2544–2556

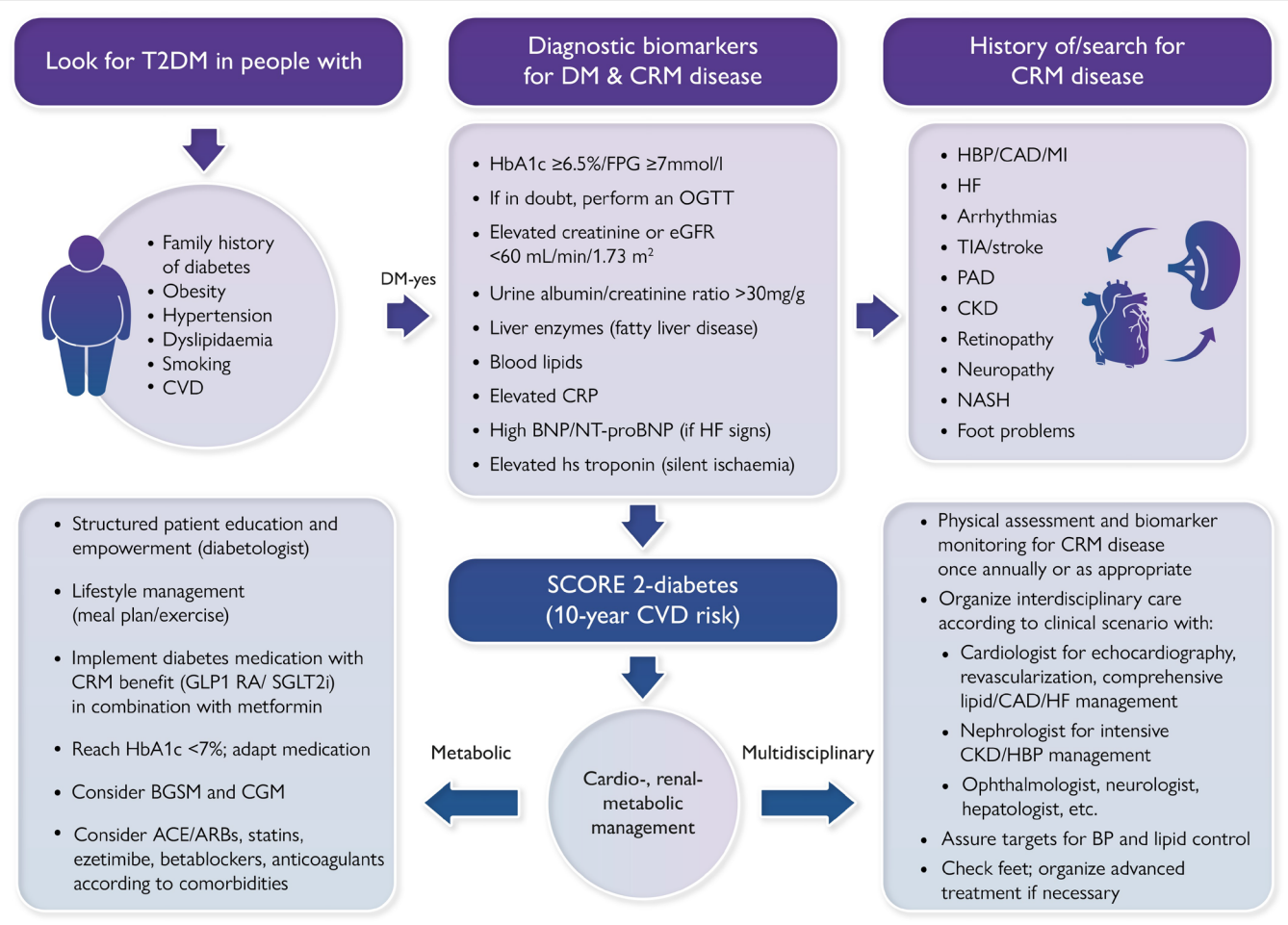
Example: 60 year old non-smoking individual with diabetes, SBP = 140 mm Hg, total cholesterol = 5.5 mmol/L and HDL = 1.3 mmol/L

	Low risk region		Moderate risk region		High risk region		Very-high risk region	
	Man	Woman	Man	Woman	Man	Woman	Man	Woman
Newly diagnosed diabetes (i.e. at age 60), HbA1c of 50 mmol/mol, eGFR of 90 ml/min/1.73m²	8.4%	6.1%	11.0%	7.6%	12.5%	11.1%	20.3%	20.6%
Diabetes diagnosed age 50, HbA1c of 70 mmol/mol, eGFR of 60 ml/min/1.73m²	12.9%	9.8%	17.2%	12.7%	21.0%	20.4%	31.2%	34.0%

Deutschland

SCORE 2 Diabetes

Ryden L et al., Eur Heart J 2023; 44: 2557–2559

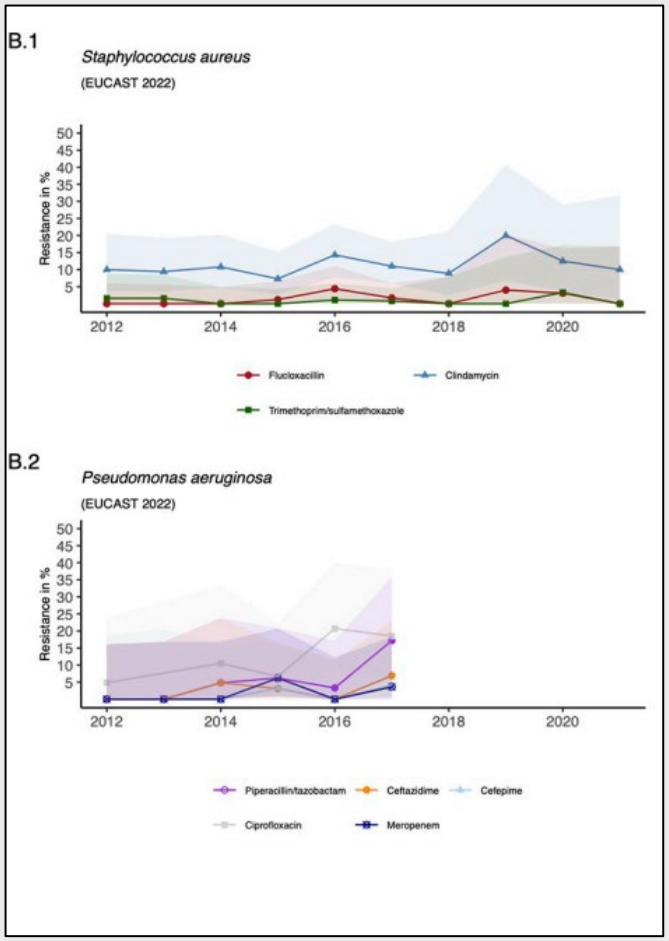


Arterielle Wunden

Salm J, et al. Plos one 2023; 18(8): e0290103.

Keime

- **Stapylococcus aureus** **18%**
- **Enterococcus faecalis** **9,1%**
- **Staphylococcus epidermidis** **7,8%**
- **Pseudomonas aeroginosa** **5,6%**
- **Proteus mirabilis** **3,7%**
- **Echerichia coli** **3,4%**



Arterielle Wunden

Salm J, et al. Plos one 2023; 18(8): e0290103.

***11% Resistenz gegen Clindamycin**

Keime

- **Staphylococcus aureus***
- **Enterococcus faecalis**
- **Staphylococcus epidermidis**
- **Pseudomonas aeroginosa**
- **Proteus mirabilis**
- **Echerichia coli**

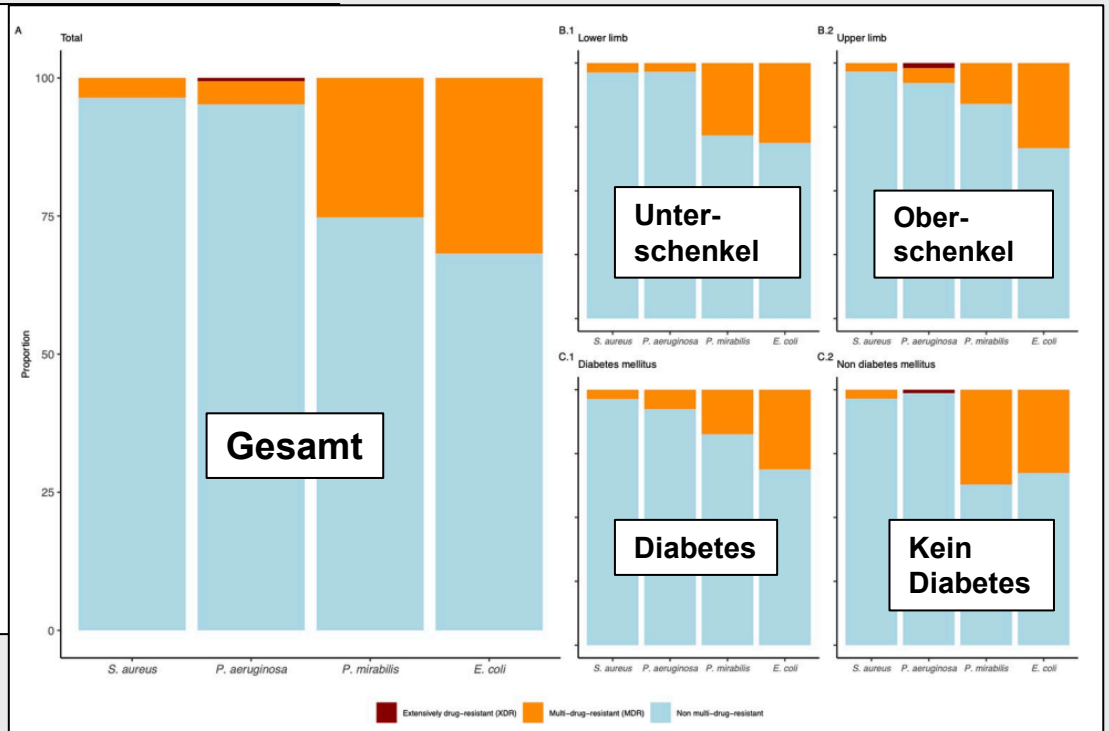


Fig 3. Multi-drug resistance according to Magiorakos et al. in bacteria isolated from patients with peripheral artery disease Rutherford category 5 and 6, stratified by site of intervention and diabetes status, 2012 to 2021. (A Bacterial isolates detected in ischaemic ulcers that are multi- or extensively drug resistant according to Magiorakos et al. in total (A) and stratified by PAD site (B.1 and B.2) as well as diabetes status (C.1 and C.2).

Keine Resistenz

Multiple Resistenzen

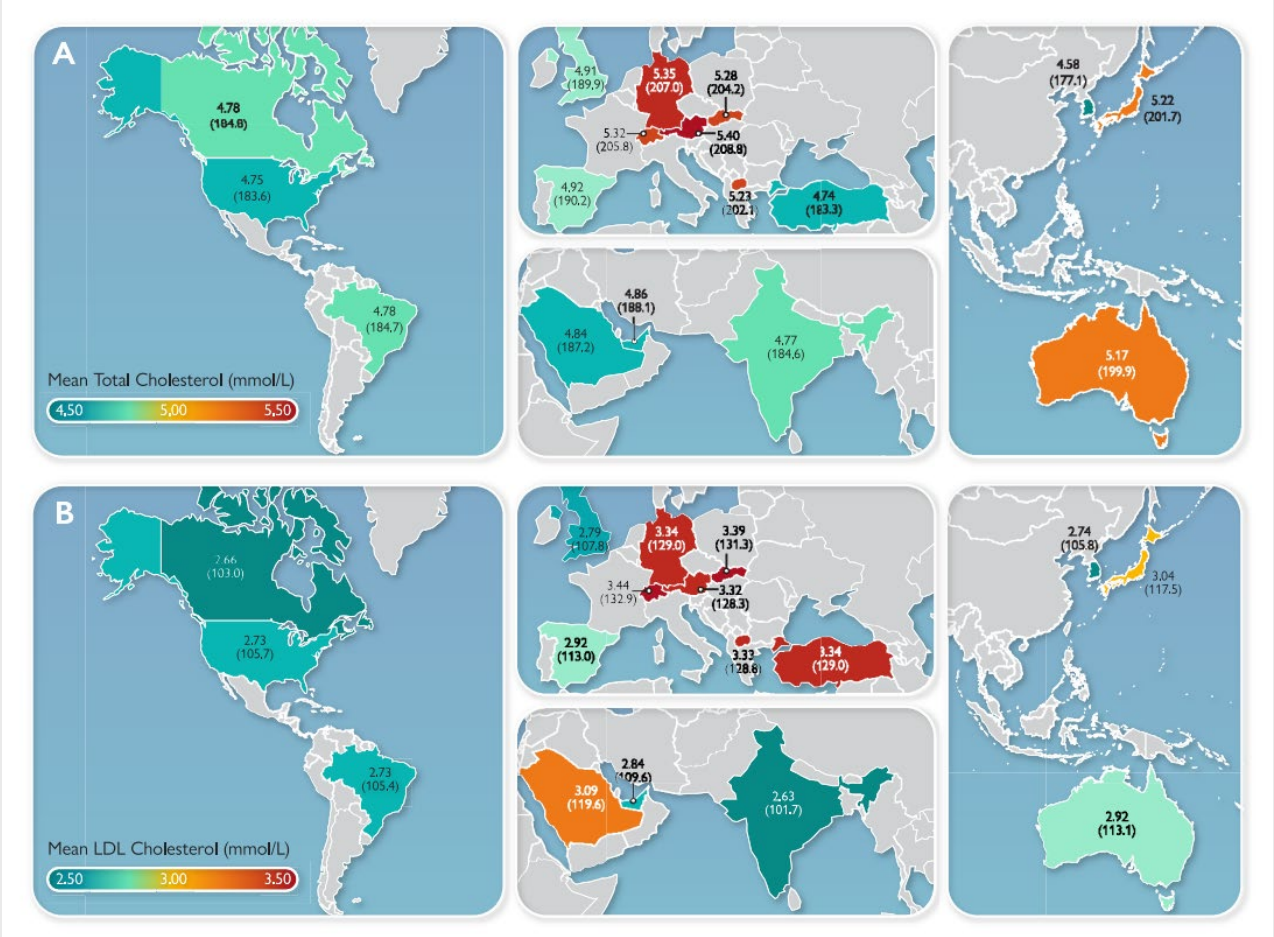
Fazit für Klinik und Praxis

- **In der neuen ESC Leitlinie wird der Diabetes mellitus als zentrale Komponente eines kardio-reno-metabolischen Kontinuums gesehen.**
- **Das Management muss daher auch die inter-disziplinäre Therapie der Begleiterkrankungen erfassen.**
- **Bei superinfizierten arteriellen Wunden ist mit einem komplexen Keimspektrum und Antibiotikaresistenzen zu rechnen.**

Lipide

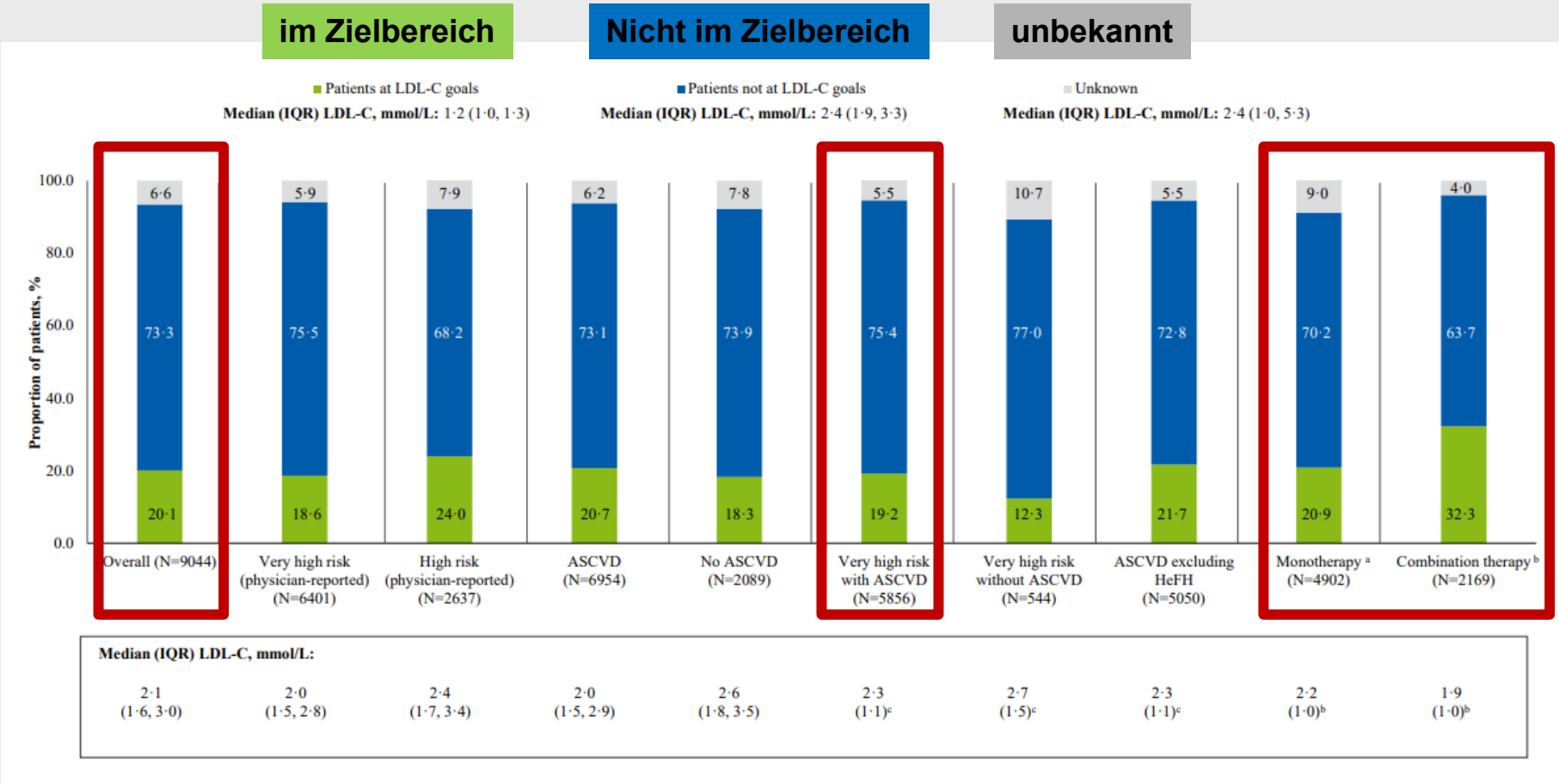
LDL-Cholesterin weltweit

Martin SS, et al. Eur Heart J 2023; 44, 2305-18



SANTORINI Studie

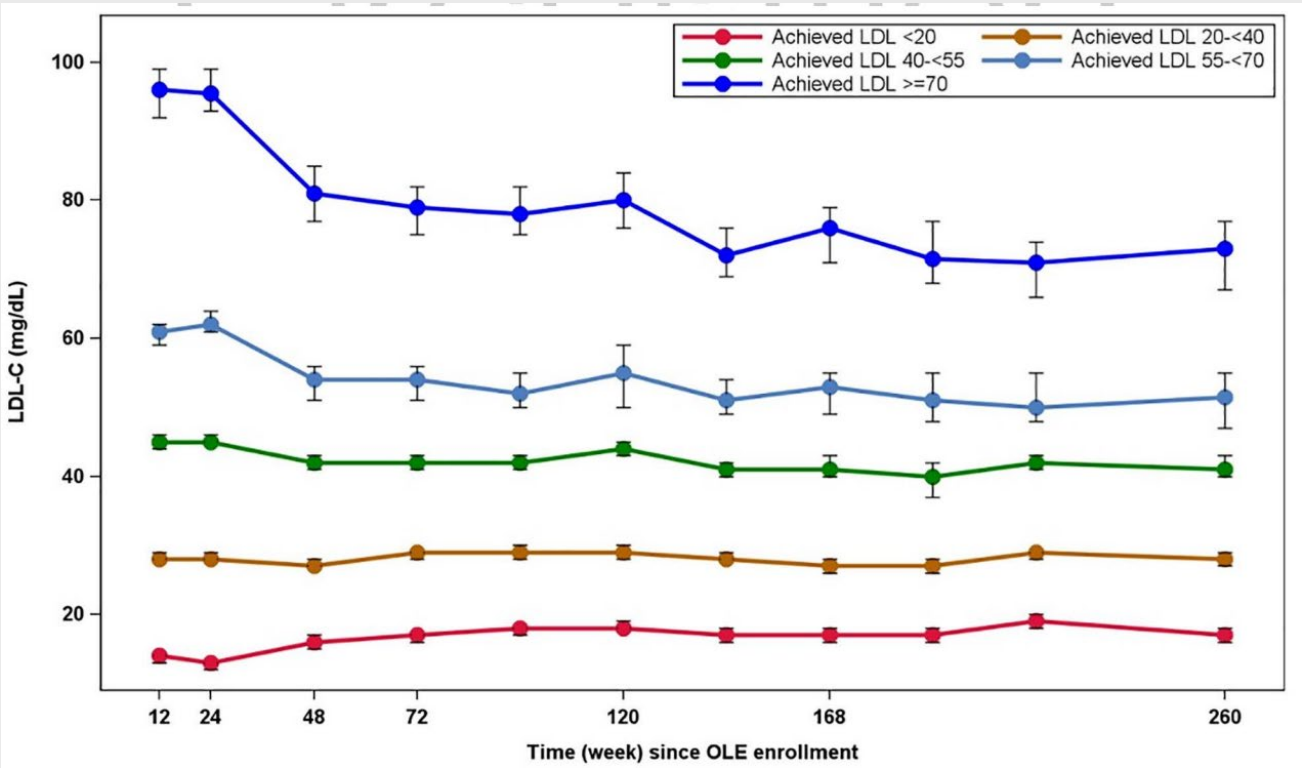
Ray KK, et al. The Lancet Global Health 2023; 29: 100624



Sehr niedriges LDL-Cholesterin

Gaba P et al. Circulation 2023; 147: 1192-1203

FOURIER-OLE (Further Cardiovascular Outcomes Research With PCSK9 Inhibition in Subjects With Elevated Risk Open-Label Extension) Studie



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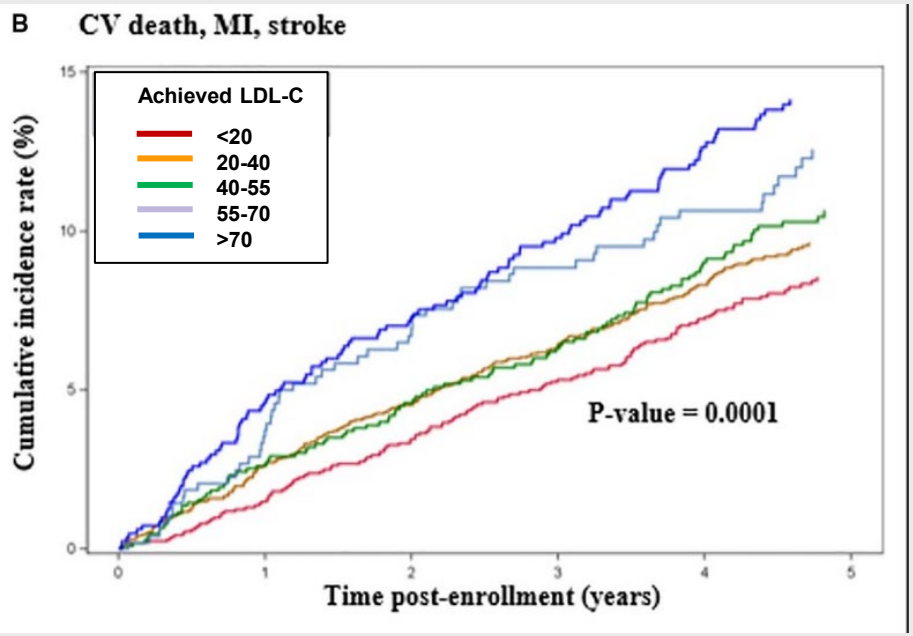
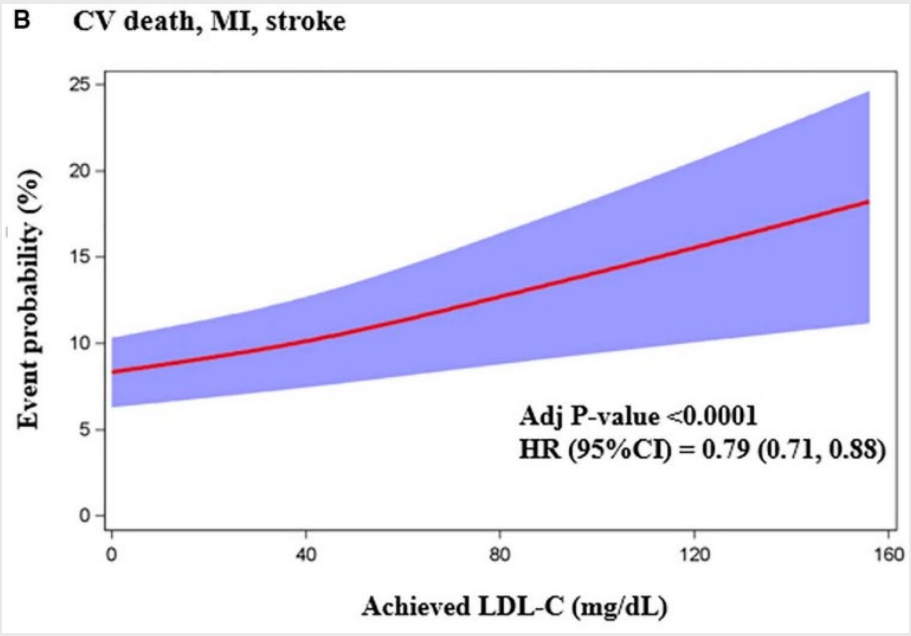
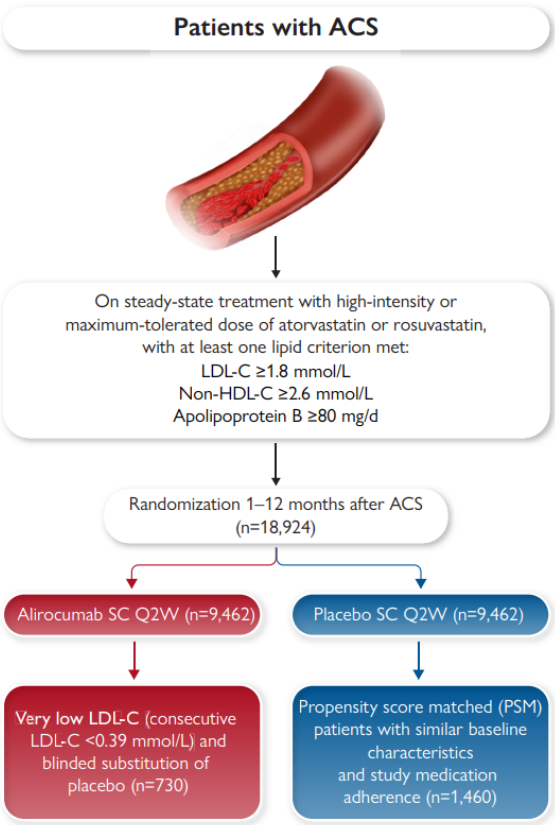


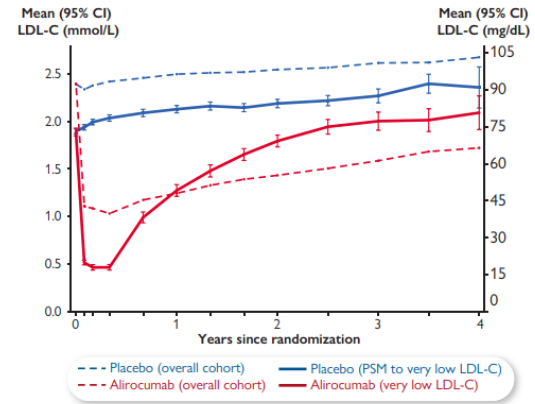


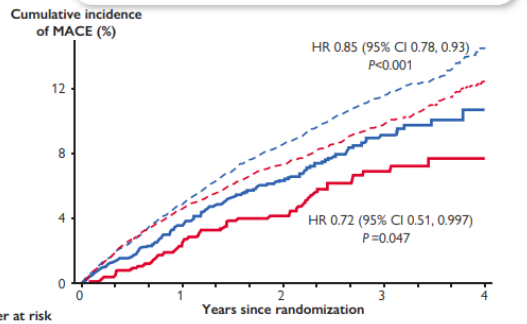
Sehr niedriges LDL-Cholesterin

Schwartz GG, et al. Eur Heart J 2023; 44: 1408–17

ODYSSEY OUCOMES Studie





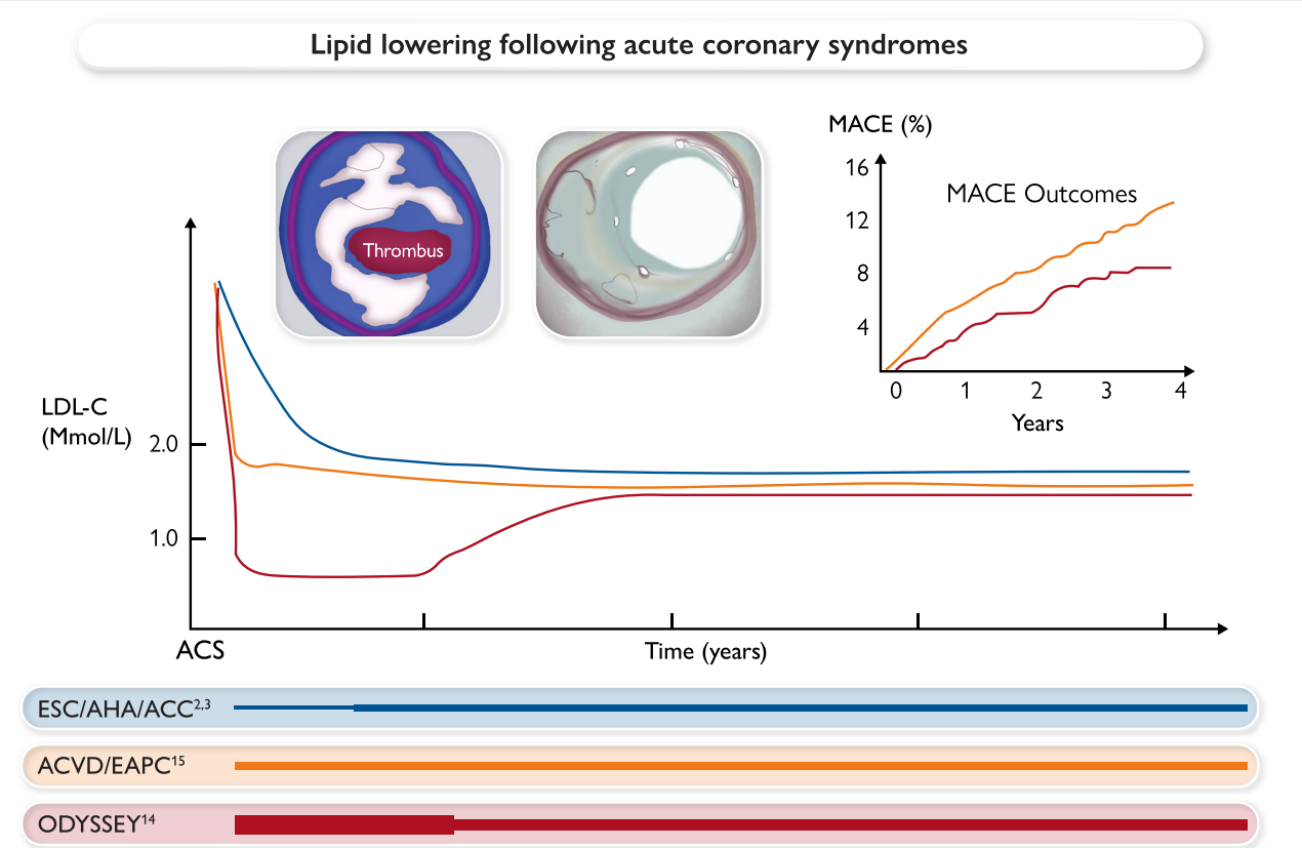


Number at risk					
Placebo (overall)	9,462	8,805	8,201	3,471	629
Alirocumab (overall)	9,462	8,846	8,345	3,574	653
Placebo (PSM)	1,460	1,359	1,244	494	89
Alirocumab (very low LDL-C)	730	702	669	309	78

Sehr niedriges LDL-Cholesterin

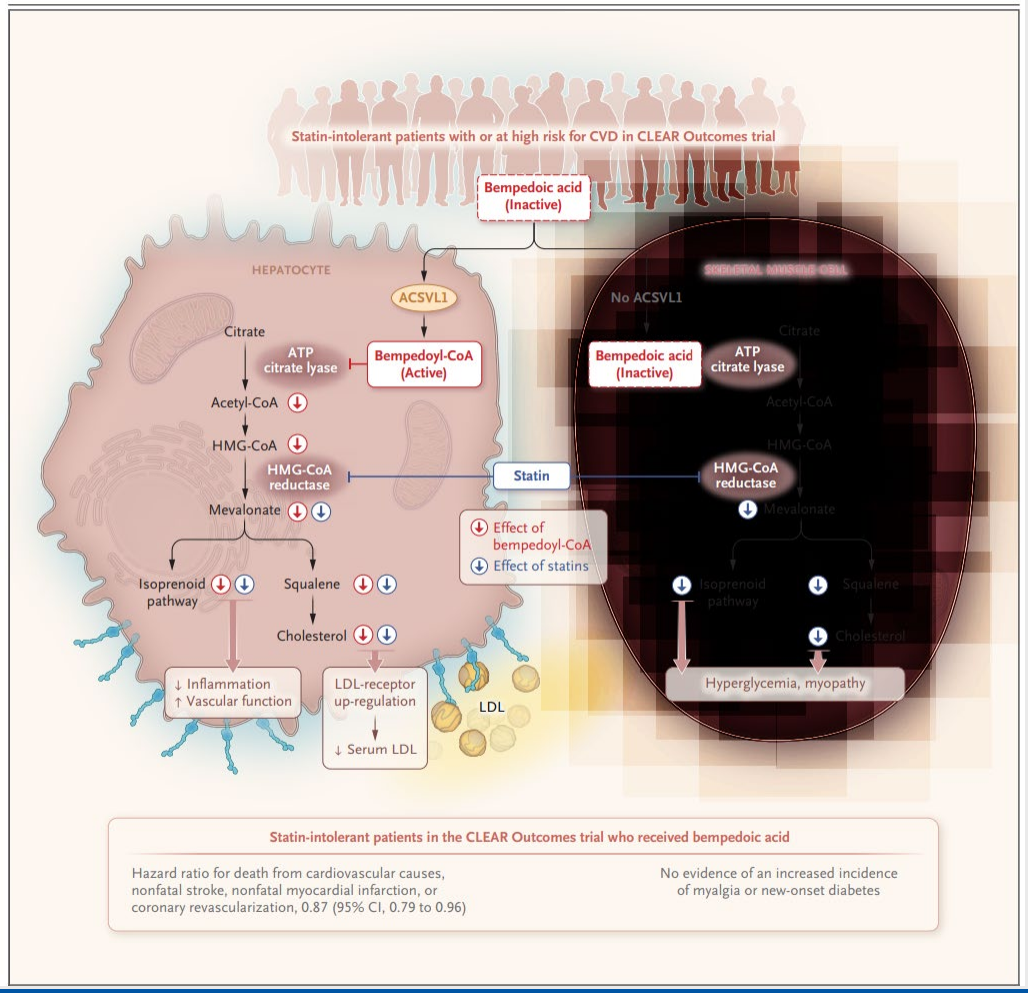
Schwartz GG, et al. Eur Heart J 2023; 44: 1408–17

ODYSSEY OUCOMES Studie



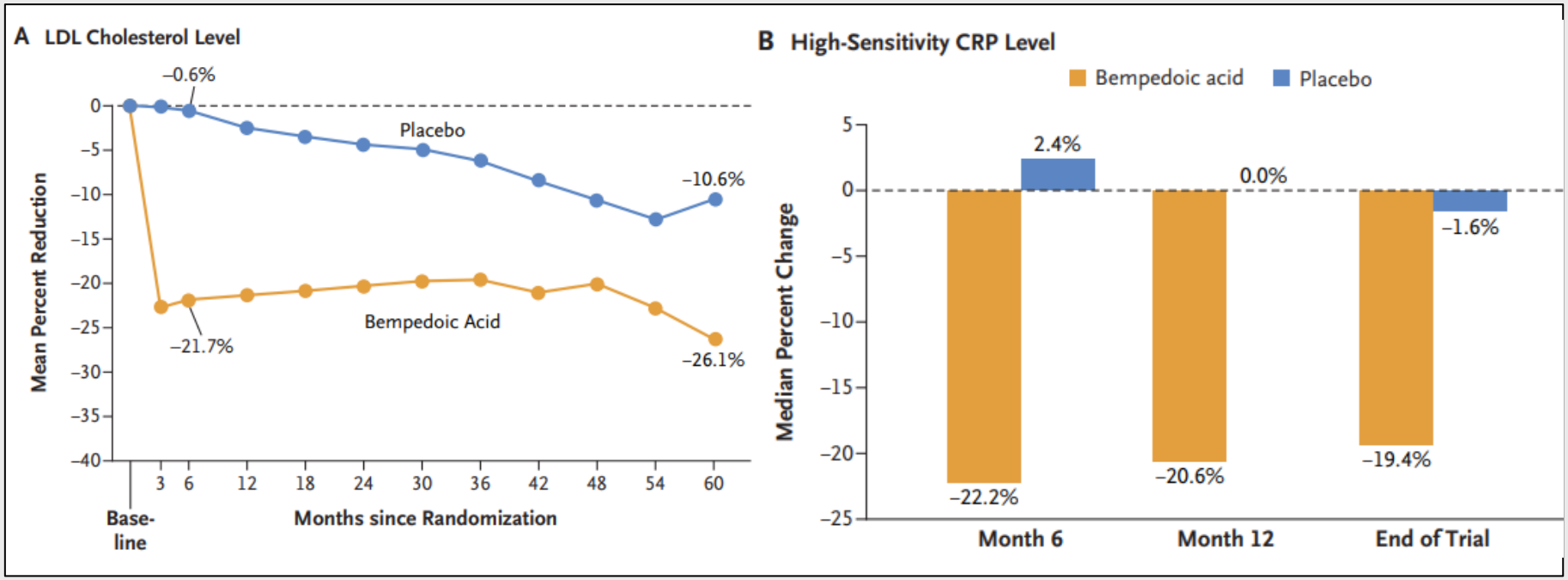
Bempedoinsäure

Keany J, et al. N Engl J Med 2023; 388: 1427-1430



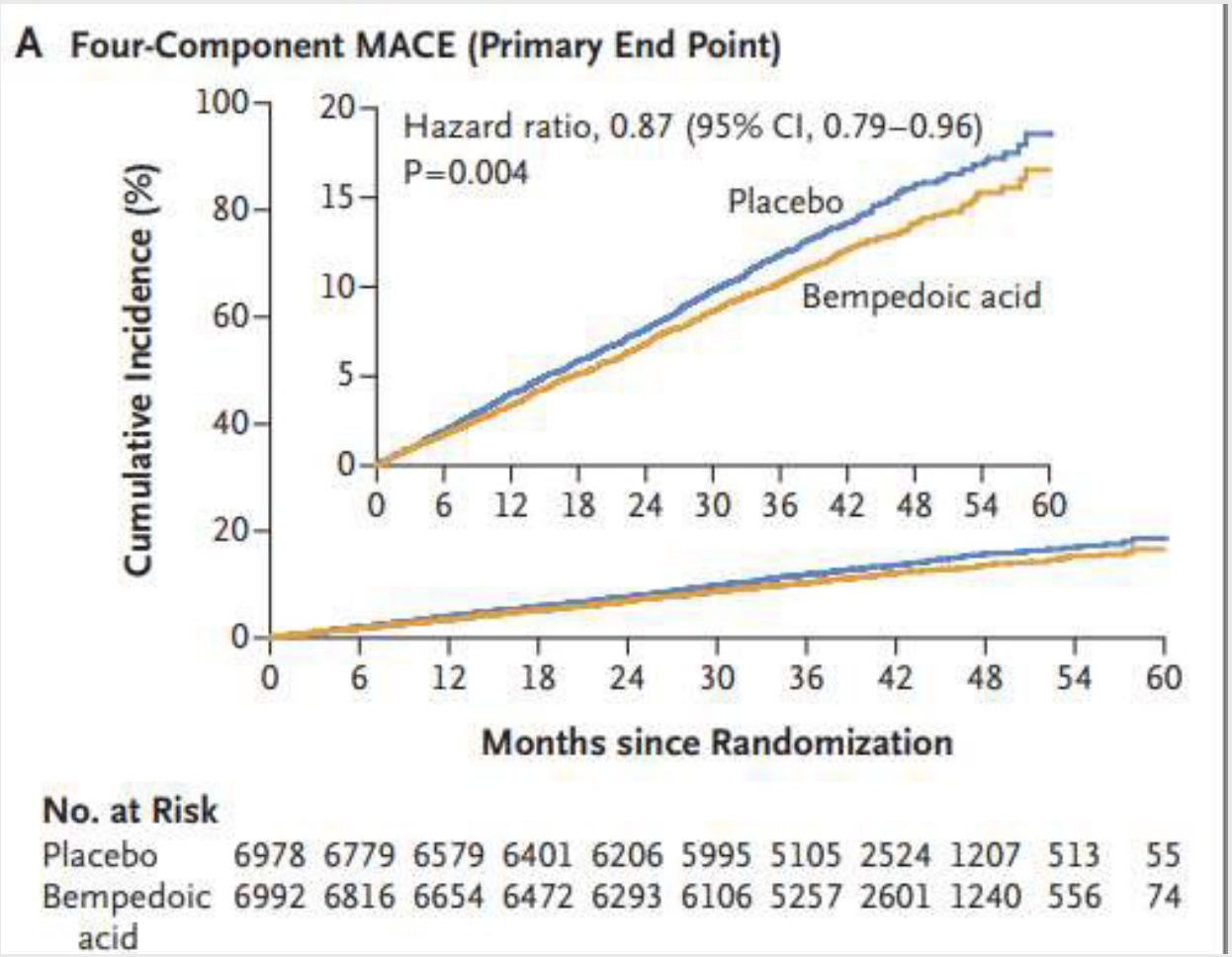
Bempedoinsäure

Nissen SE, et al. N Engl J Med 2023; 388:1353-1364



Bempedoinsäure

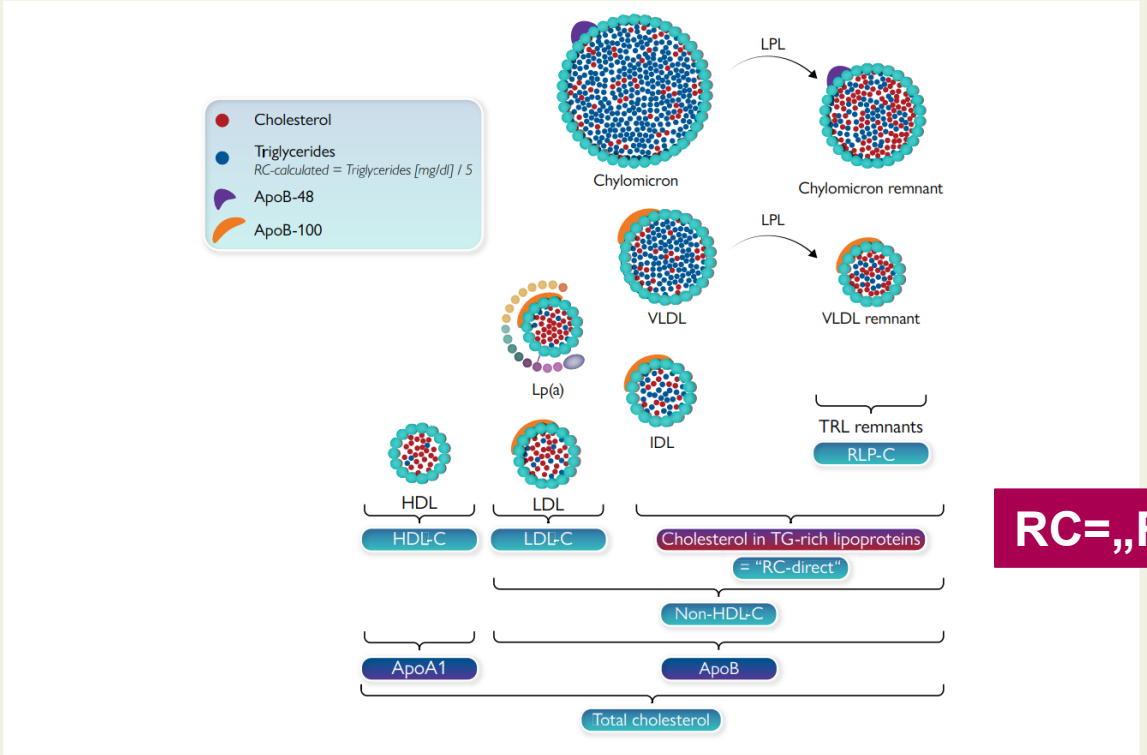
Nissen SE, et al. N Engl J Med 2023; 388:1353-1364



Definitionen Lipide

Stützebecher PE et al. Eur Heart J 2023; 44: 1446-48.

Graphical Abstract



Lipoproteins and definitions of 'remnants. The serum cholesterol and triglycerides are transported in lipoproteins of different size and composition. Triglycerides of exogenous origin are carried in apoB-48-containing chylomicrons, while the triglycerides synthesized in the liver are mainly released in VLDL particles. Chylomicrons and VLDL undergo hydrolysis by lipoprotein lipase, and thus reducing the triglyceride content, and forming chylomicron and VLDL remnants, respectively. Both are also referred to as 'triglyceride-rich lipoprotein (TRL) remnants', and their cholesterol content is denoted 'remnant lipoprotein particle cholesterol' (RLP-C). Another definition of remnants used by the group of Nordestgaard, the 'remnant cholesterol' (RC), additionally encompasses the cholesterol content of VLDL, chylomicrons, and IDL, and therefore the cholesterol carried by all TRL. This 'remnant cholesterol' can either be measured ('RC-direct') or approximated by dividing total serum triglycerides in mg/dL by 5 or in mmol/L by 2.2 ('RC-calculated').

RC=„Remnant Cholesterin“

Remnant Cholesterin

Wadstrom BN, et al. Eur Heart J 2023; 44: 1432–45

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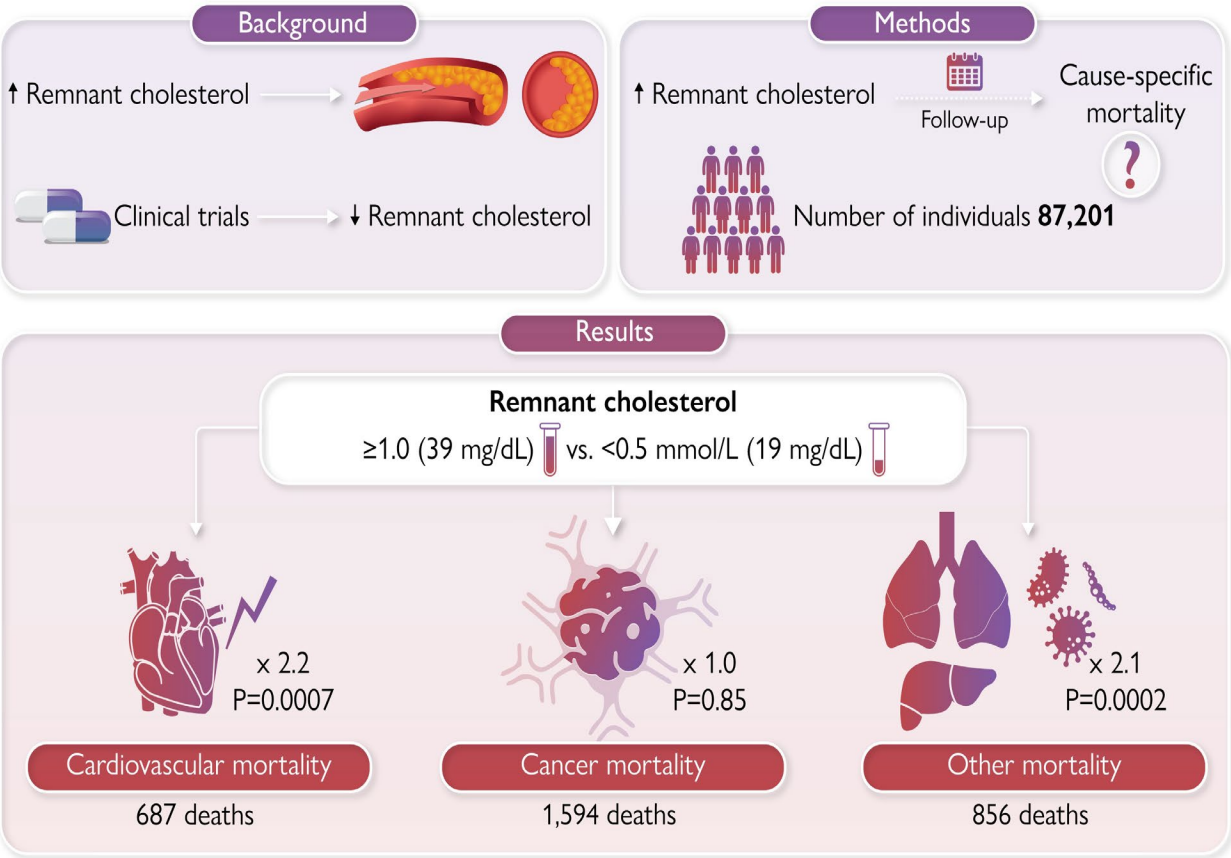
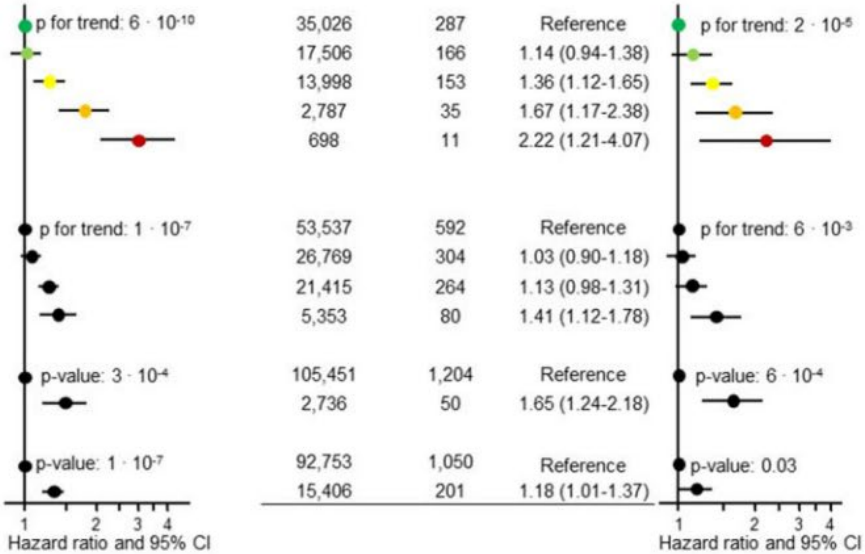


Lipoprotein (a)

Thomas PE, et al. J Am Coll Cardiol 2023; 82: 2265-2276

Figure 1. Risk of peripheral arterial disease and abdominal aortic aneurysms by categories of plasma lipoprotein(a), *LPA* kringle IV type 2 repeats, *LPA* rs3798220, and *LPA* rs10455872.

Lipoprotein(a)			Peripheral arterial disease			Abdominal aortic aneurysms		
Percentile	mg/dL	nmol/L	Individuals	Events	Hazard ratio (95% CI)	Individuals	Events	Hazard ratio (95% CI)
Observational analyses								
1-50	≤9	≤17	34,847	524	Reference	35,026	287	Reference
51-75	10-29	18-60	17,424	272	1.02 (0.88-1.18)	17,506	166	1.14 (0.94-1.38)
76-95	30-94	61-201	13,882	259	1.27 (1.09-1.47)	13,998	153	1.36 (1.12-1.65)
96-99	95-142	202-306	2,755	75	1.79 (1.40-2.29)	2,787	35	1.67 (1.17-2.38)
>99	≥143	≥307	681	32	2.99 (2.09-4.30)	698	11	2.22 (1.21-4.07)
Genetic analyses								
***LPA* kringle IV type 2 no. repeats percentiles**								
51-100	7 (4-13)	11 (4-24)	53,537	1,119	Reference	53,537	592	Reference
26-50	12 (6-35)	22 (9-73)	26,769	600	1.07 (0.97-1.18)	26,769	304	1.03 (0.90-1.18)
6-25	41 (10-69)	85 (17-146)	21,415	559	1.26 (1.14-1.40)	21,415	264	1.13 (0.98-1.31)
1-5	72 (50-111)	154 (104-239)	5,353	149	1.39 (1.17-1.64)	5,353	80	1.41 (1.12-1.78)
***LPA* rs3798220**								
Non-carrier	10 (5-27)	17 (6-56)	105,451	2,362	Reference	105,451	1,204	Reference
Carrier	93 (8-123)	199 (14-264)	2,736	88	1.48 (1.19-1.83)	2,736	50	1.65 (1.24-2.18)
***LPA* rs10455872**								
Non-carrier	8 (4-16)	14 (5-32)	92,753	2,016	Reference	92,753	1,050	Reference
Carrier	62 (48-81)	131 (101-173)	15,406	433	1.32 (1.19-1.47)	15,406	201	1.18 (1.01-1.37)

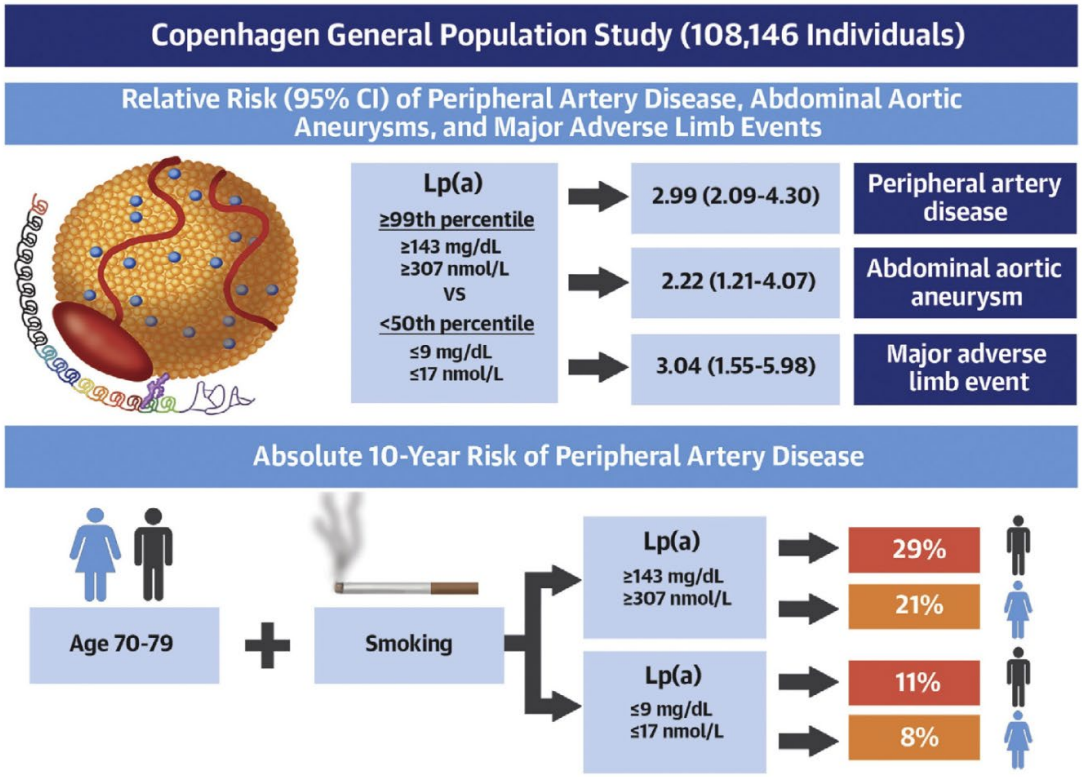


Observational Cox regression analyses were multivariable adjusted for age (as underlying timescale), sex, non-HDL-cholesterol corrected for lipoprotein(a) cholesterol, systolic blood pressure, smoking status, years of education, diabetes mellitus, body mass index, and in women for menopause status and hormone replacement therapy. Genetic analyses were adjusted for age and sex. Lipoprotein(a) values according to genotype are reported as median and interquartile range. CI: confidence interval.

Lipoprotein (a)

Thomas PE, et al. J Am Coll Cardiol 2023; 82: 2265-2276

CENTRAL ILLUSTRATION: Lipoprotein(a) and Risks of Peripheral Artery Disease, Abdominal Aortic Aneurysm, and Major Adverse Limb Events



Thomas PE, et al. J Am Coll Cardiol. 2023;82(24):2265-2276.

Fazit für Klinik und Praxis

- **Fettstoffwechselstörungen sind ein weltweites Problem und trotz neuer Therapieoptionen werden die Zielwerte in der Mehrzahl der Fälle unter lipidsenkender Therapie nicht erreicht.**

- **Neben dem LDL-Cholesterin spielen weitere Lipide wie das Remnant Cholesterin, Triglyzeride oder Lipoprotein (a) in der Pathogenese der Atherosklerose eine Rolle.**

Bewegungs-therapie

Effekte Bewegungstraining

Wang B, et al. J. Clin. Med. 2022, 11, 7511

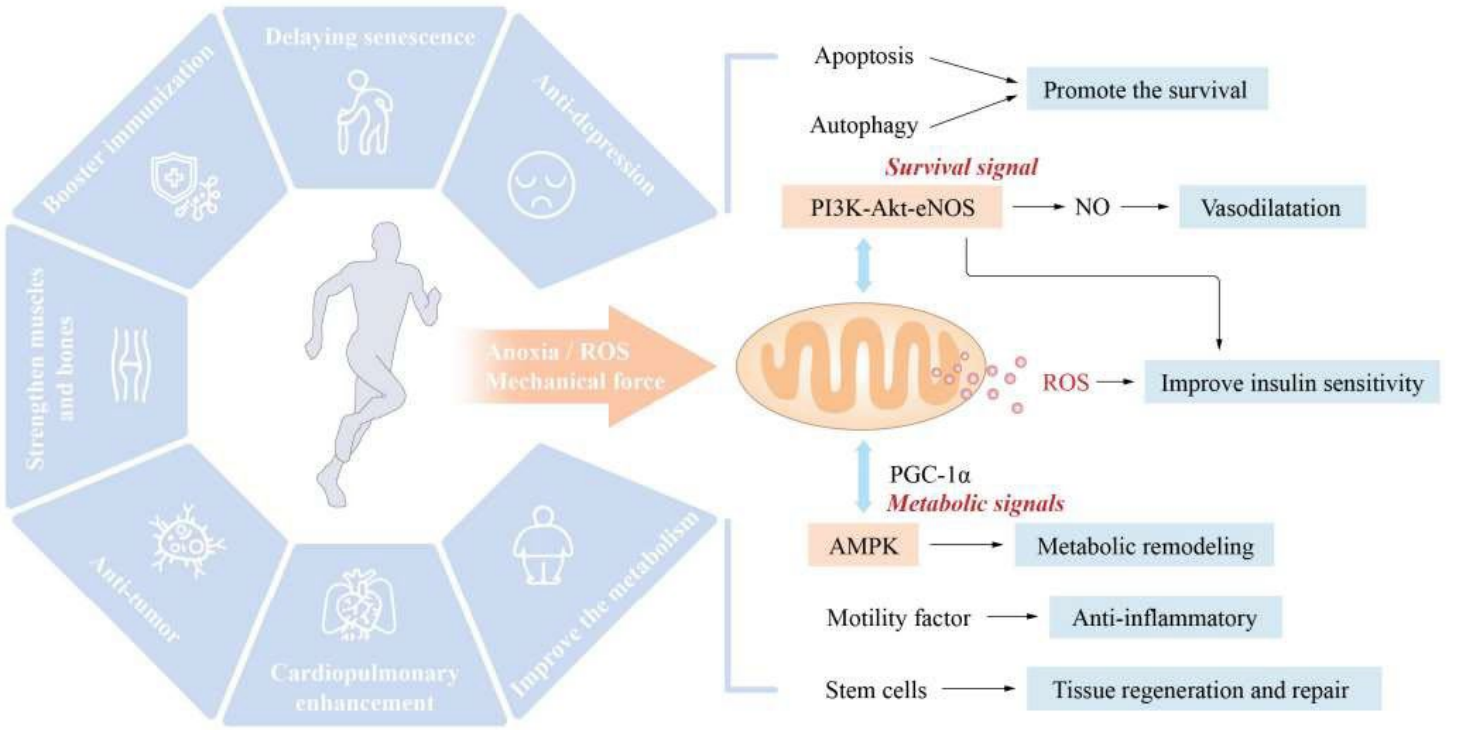
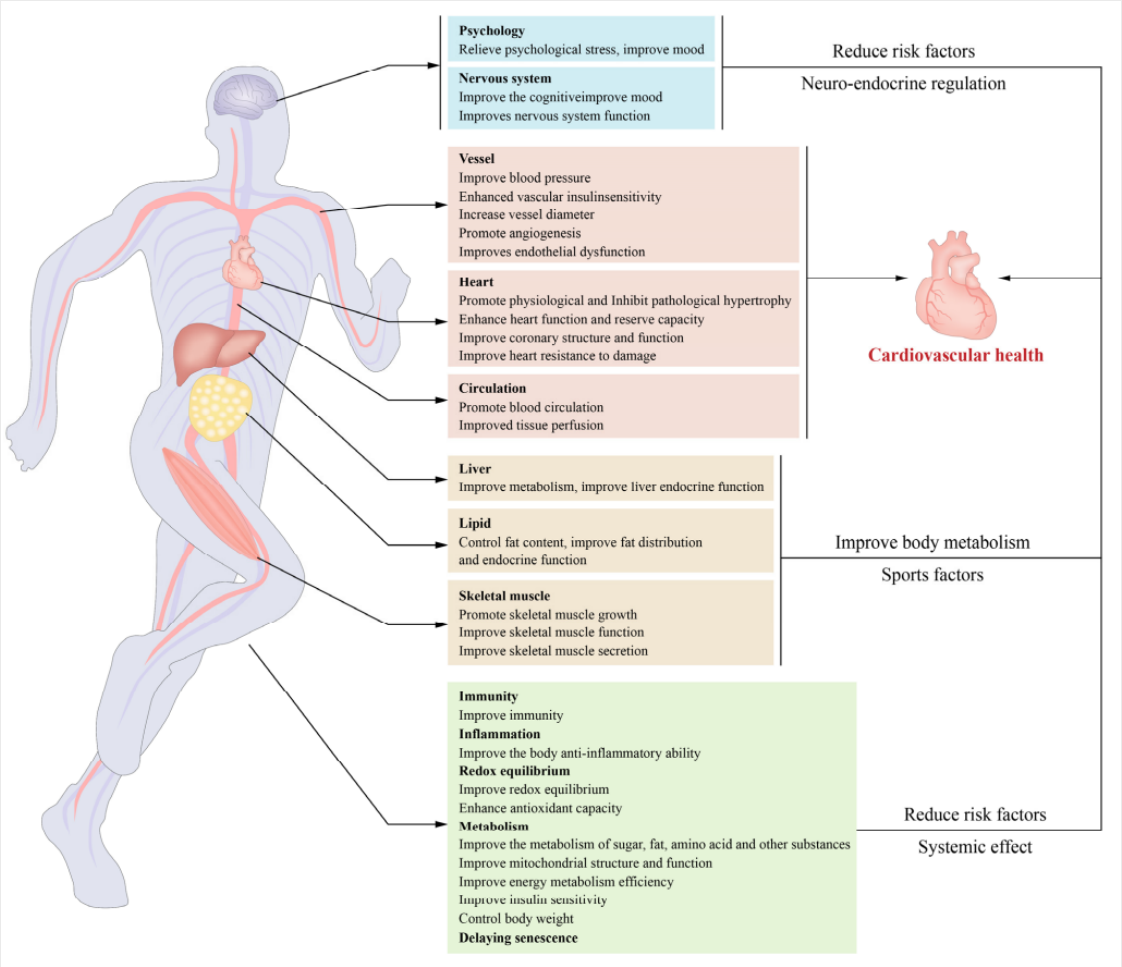


Figure 1. Exercise-induced health effects and central role of mitochondria: Hypoxia, oxidative stress, mechanical force, and other variables play a role in activating endogenous defensive systems when exercise is performed. These endogenous defensive mechanisms include the survival signalling pathways of PI3K-Akt-eNOS-NO and the metabolic signalling pathways of PGC-1-AMPK-mTOR. Mitochondria are an extremely important factor in the positive health impacts of exercise.

Effekte Bewegungstraining

Wang B, et al. J. Clin. Med. 2022, 11, 7511



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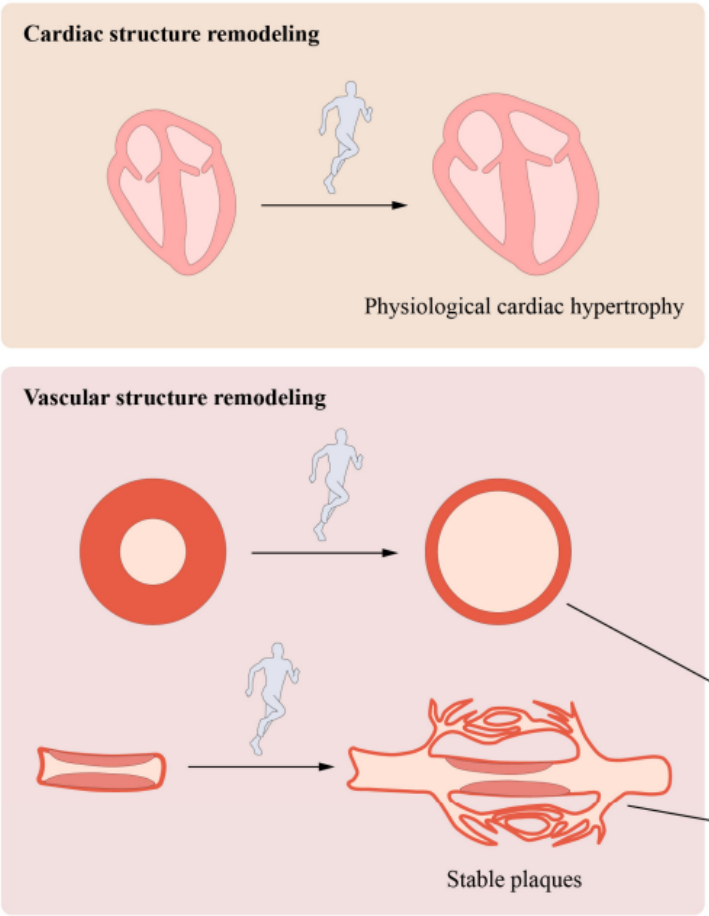

Cardiac function remodeling

- Mitochondrial synthesis and function were enhanced
- Increased energy metabolism capacity, efficiency and plasticity
- The antioxidant, anti-inflammatory and anti-apoptotic abilities were increased
- Increase the strength of the heart's contractions
- Coronary circulation and diastolic ability improved
- Akt-eNOS activation
- Increased heart rate variability and cardiopulmonary fitness

Vascular function remodeling

- Enhanced vascular insulin sensitivity
- Vascular systolic and diastolic function was improved
- Vascular elasticity improvement
- Endothelial function was improved and NO synthesis was increased
- Lower blood pressure

The lumen becomes larger and the wall becomes thinner

Collateral is formed and angiogenesis occurs

Effekte Bewegungstraining

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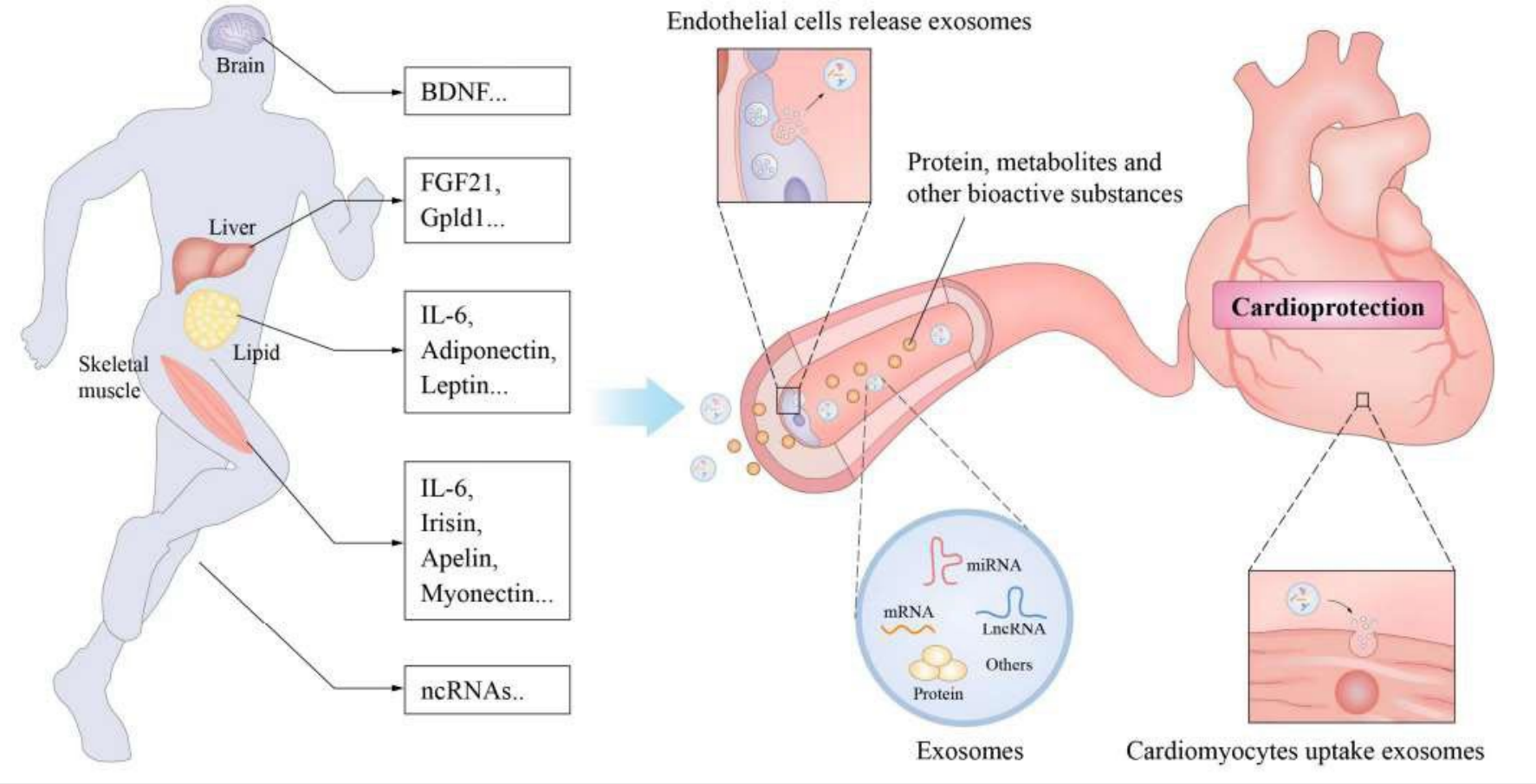


Limitationen: Patienten

Yi L, et al. Vasa 2023, 52; 218-223

Gründe warum keine Teilnahme an Gefäßsport
Umfrage unter Patienten (N=235 Patienten mit Claudicatio)

Table II. Free text responses on the reasons for not participating in a walking exercise programme of 127 patients with symptomatic lower extremity peripheral arterial disease

Reasons for not participating in a walking exercise programme	Number, n
Walking exercise was not offered or recommended to the patient; no information about the pros and cons of walking exercise were available	81
The patient is immobile or has other physical or mental reasons for not participating in a walking exercise programme	20
Time restrictions/limitations	15
No access to or information about local/regional walking exercise programmes available	12
The patient prefers home-based training	9
The patient has no interest in walking exercise programmes	6
Financial reasons	1

Limitationen: Gefäßmediziner

Rother U, et al. Vasa 2023, 52; 224-229

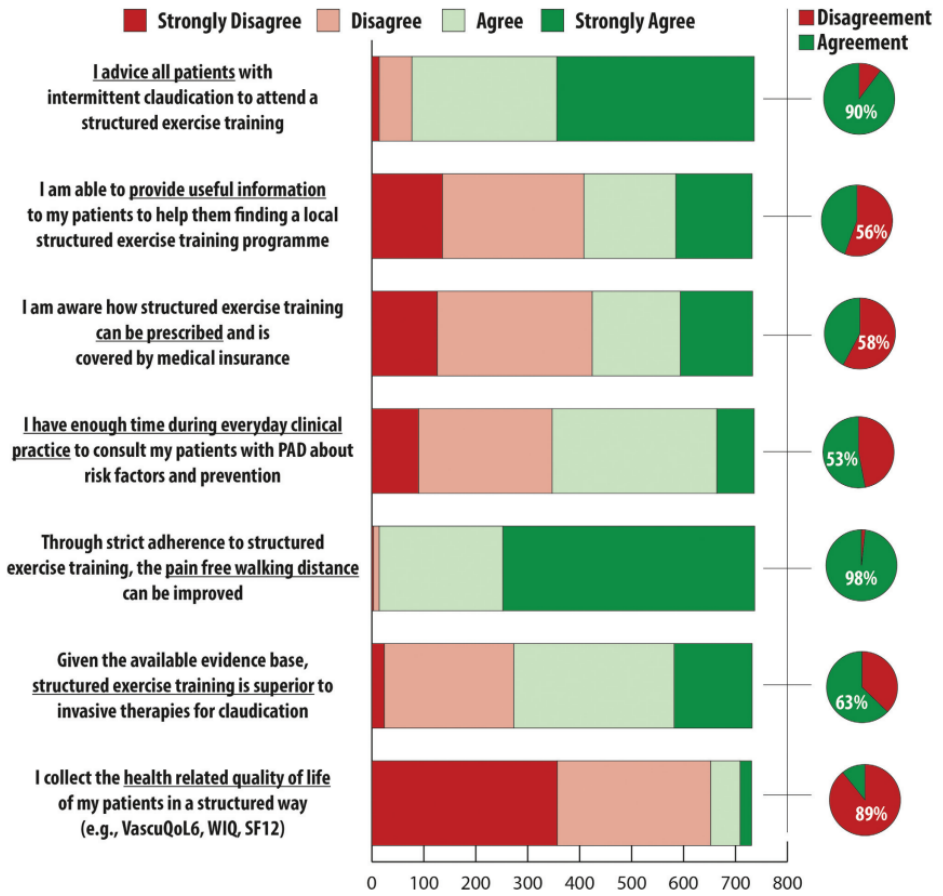
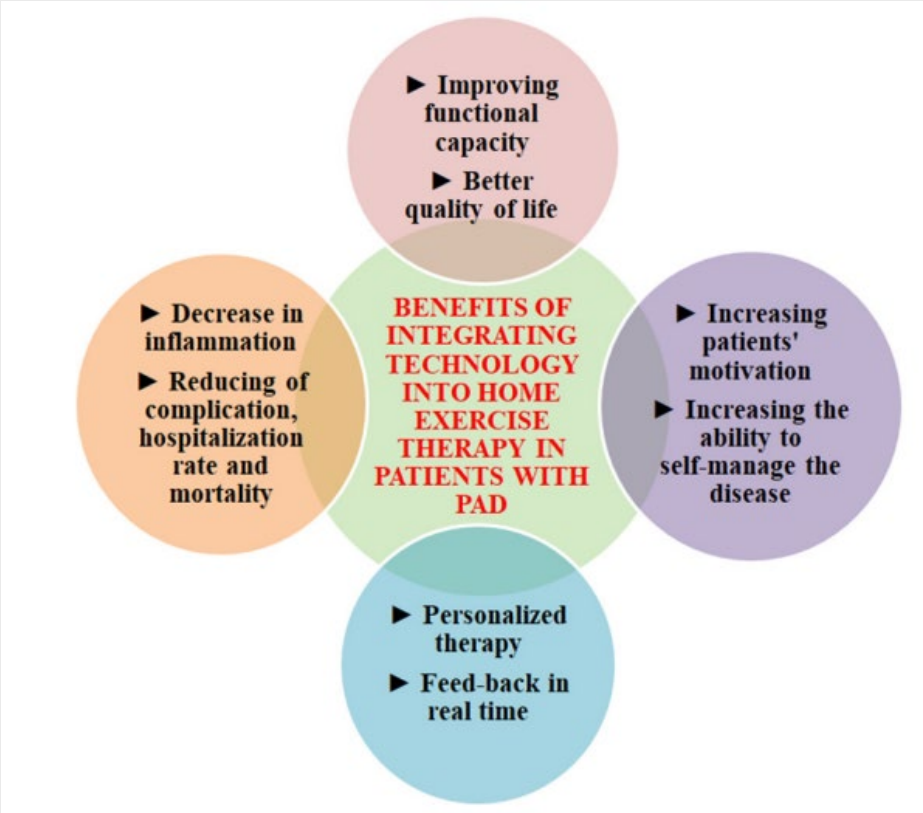


Figure 1. Left: Results from the seven-question matrix using a 4-point Likert scale from strongly disagree to strongly agree. Right: Summarised results and level of disagreement vs. agreement. VascuQoL6: Vascular Quality of Life Questionnaire 6. WIQ: Walking Impairment Questionnaire. SF12: Short Form 12. PAD: Peripheral Arterial Disease.

Apps zum Training

Rotundu A et al. J Clin Med 2023; 12; 7635

Vorteile eines Trainings mit technologischer Unterstützung



Fazit für Klinik und Praxis

- **Nur wenige Patienten mit PAVK führen im klinischen Alltag ein konsequentes Gefäßsporttraining durch. Die Limitationen sind vielfältig und liegen sowohl auf der Seite der Patienten als auch auf der Seite der Gefäßmediziner.**

- **Zusätzliche Maßnahmen wie Anpassung des Trainings an die individuellen Vorlieben und die Hilfe von technischer Unterstützung wie Apps können die Adhärenz und Effektivität verbessern.**