

DGK CARDIO UPDATE 2024

16. und 17. Februar

23. und 24. Februar

Prävention und stabile KHK

Ulrich Laufs, Leipzig

Interessenkonflikte

Honoraria / reimbursements for lectures, participation in studies, scientific cooperations with Leipzig University, consulting, travel, support of colleagues or support of scientific meetings within the last 5 years:

ABDA, Amarin, Amgen, Ariba, AstraZeneca, Bayer, Berlin-Chemie, BMBF, Boehringer, DACH, Daiichi-Sankyo, DFG, DGK, EU, i-cor, Lilly, Medtronik, MSD, Novartis, NovoNordisk, Pfizer, Roche, Sanofi, Servier, SLÄK, Stifterverband, Synlab, UdS, UKL, UKS

Gliederung

**Chronisches
Koronarsyndrom**

**Lebensstil:
körperliche Aktivität
Ernährung**

DISKUSSION

Diabetes

Adipositas

Lipide

Bemepedoidsäure

PCSK9-Hemmer

Lipoprotein(a)

Screening

Winterschlaf

Alkohol & Zigaretten

Gliederung

CKM Syndrom
MASLD
NuSHs

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State of the Art

Angioplastie verbessert Prognose und Symptome bei **akutem** Koronarsyndrom

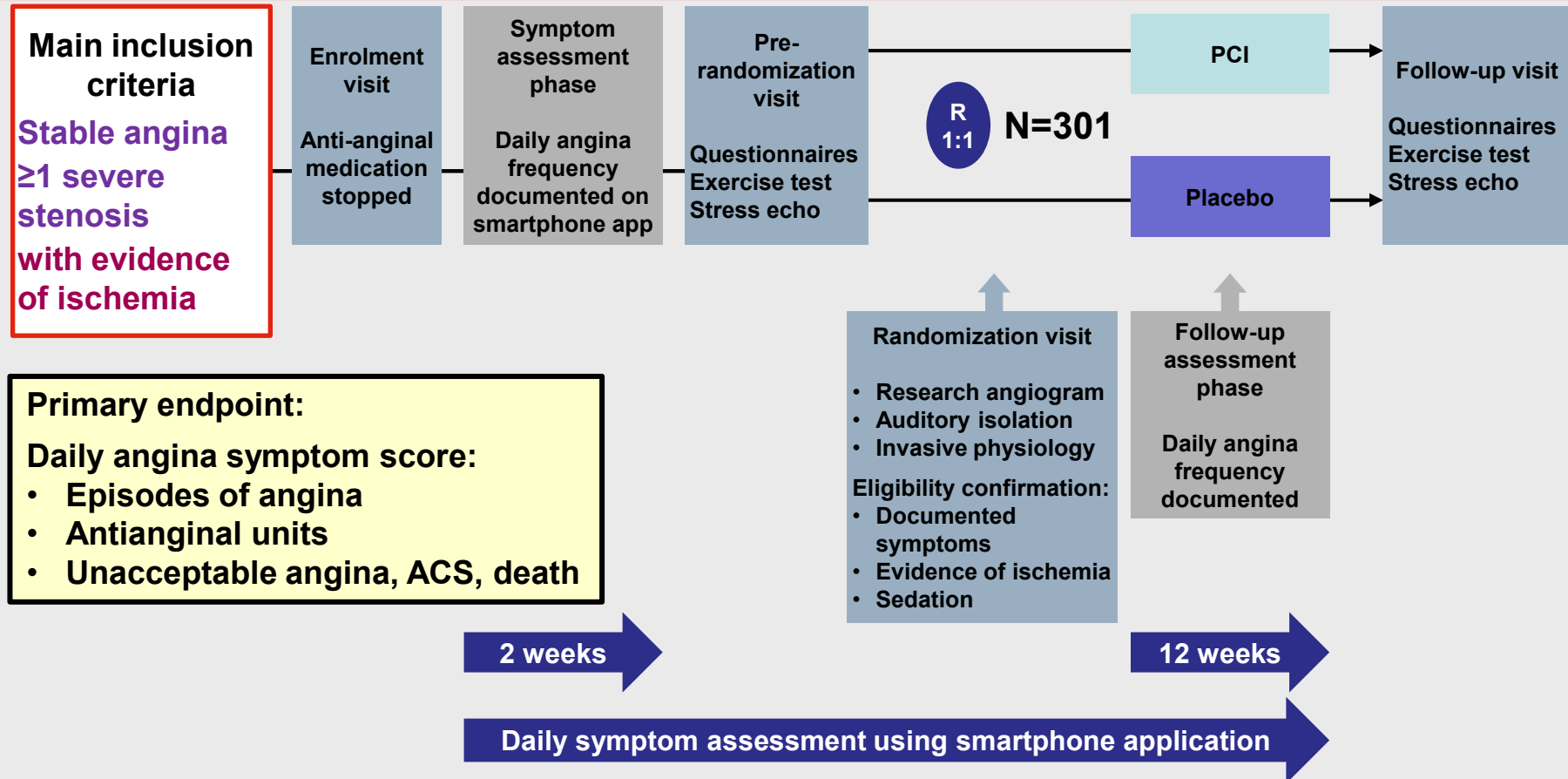
Effekte bei chronischem Koronarsyndrom ?

ORBITA I Studie vor 5 Jahren mit neutralem Ergebnis

ORBITA I, Lancet 2018;391(10115):31-40

ORBITA-2: Design

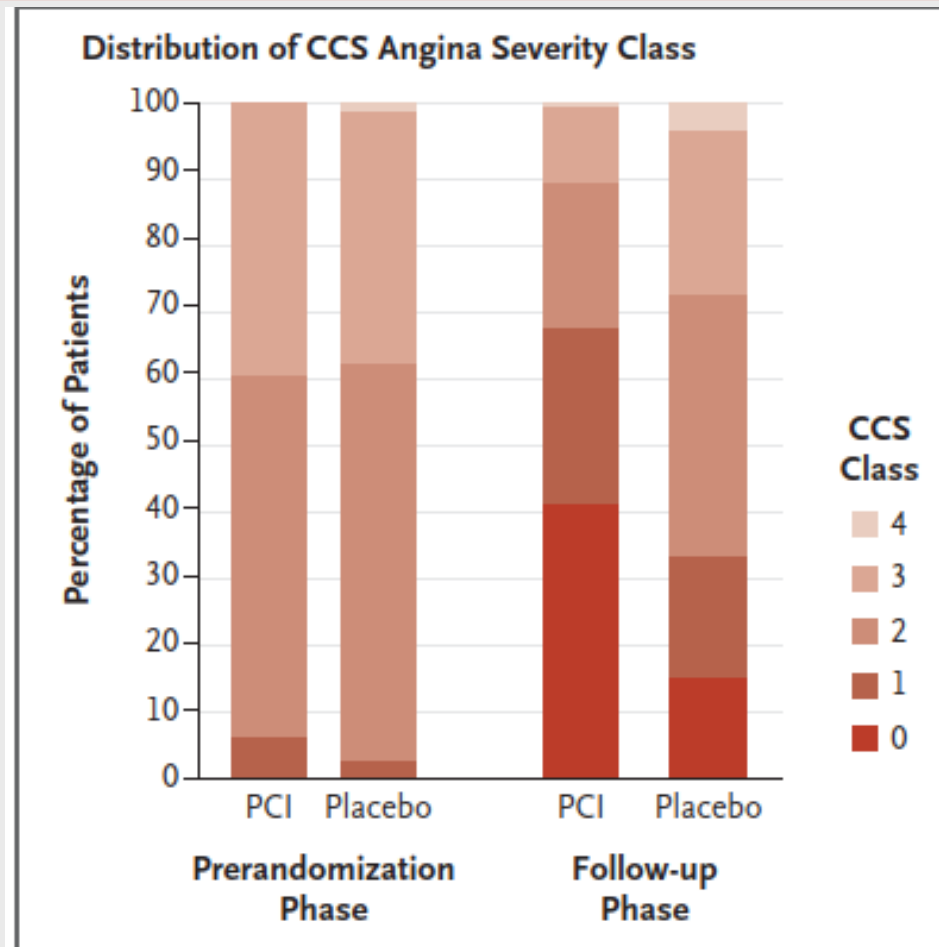
Randomized, double-blind, placebo-controlled; coronary angioplasty vs placebo procedure on symptoms of stable angina in patients with single- or multivessel disease



Rajkumar CA, et al. N Engl J Med 2023; doi 10.1056/NEJMoa2310610

ORBITA-2

**Primary end point: mean angina symptom score at 12-week
2.9 in PCI vs 5.6 in placebo group**



N=301

**59% with
residual
symptoms**

Rajkumar CA, et al. N Engl J Med 2023; doi 10.1056/NEJMoa2310610

State of the Art: hämodynamische Beurteilung von Koronarstenosen

**Angioplastie verbessert Prognose bei Patienten mit CCS
bei hämodynamischer Relevanz einer Koronarstenose
(FFR < 0,8)**

FAME 2; De Bruyne B et al., NEJM 2012;367:991-1001

**IFR gleichwertig zu FFR in der SWEDEHEART- und
DEFINE-FLAIR-Studie**

Davies JE et al., NEJM 2017; 376:1824-34
Göteborg M et al., NEJM 2017; 376:1813-23

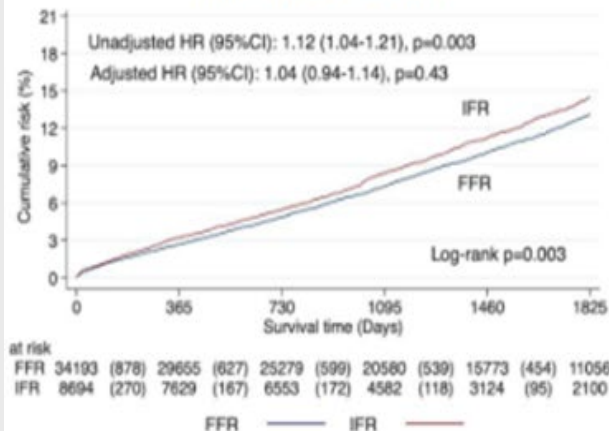
Aktuelle Diskussion: Signale für höhere Sterblichkeit in
IFR-Gruppe im Vgl. zu FFR nach 5 Jahren

Eftekhari A et al., EHJ 2023; 44:4376-84
Berry C et al., EHJ 2023; 44:4388-90

Ähnliche IFR vs. FFR 5-Jahres Ergebnisse im SWEDEHEART Register

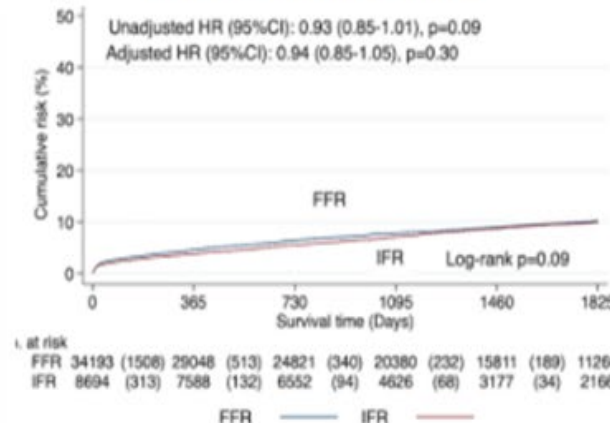
42.000 Patienten, ~34.000 FFR, ~8.600 IFR

All-cause death



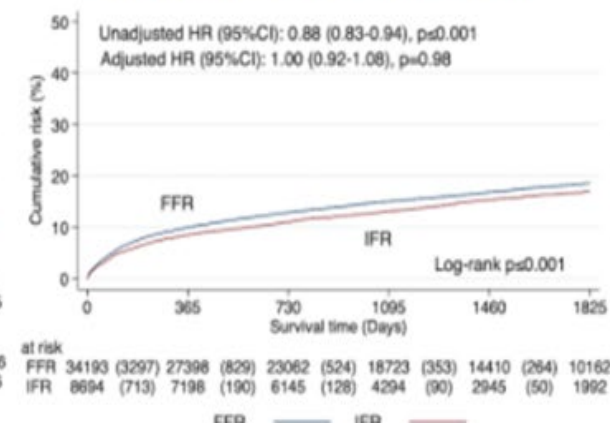
Adjusted HR 1.04 (0.94-1.14)
 $p=0.43$

Myocardial infarction



Adjusted HR 0.94 (0.85-1.05)
 $p=0.30$

Unplanned revascularization

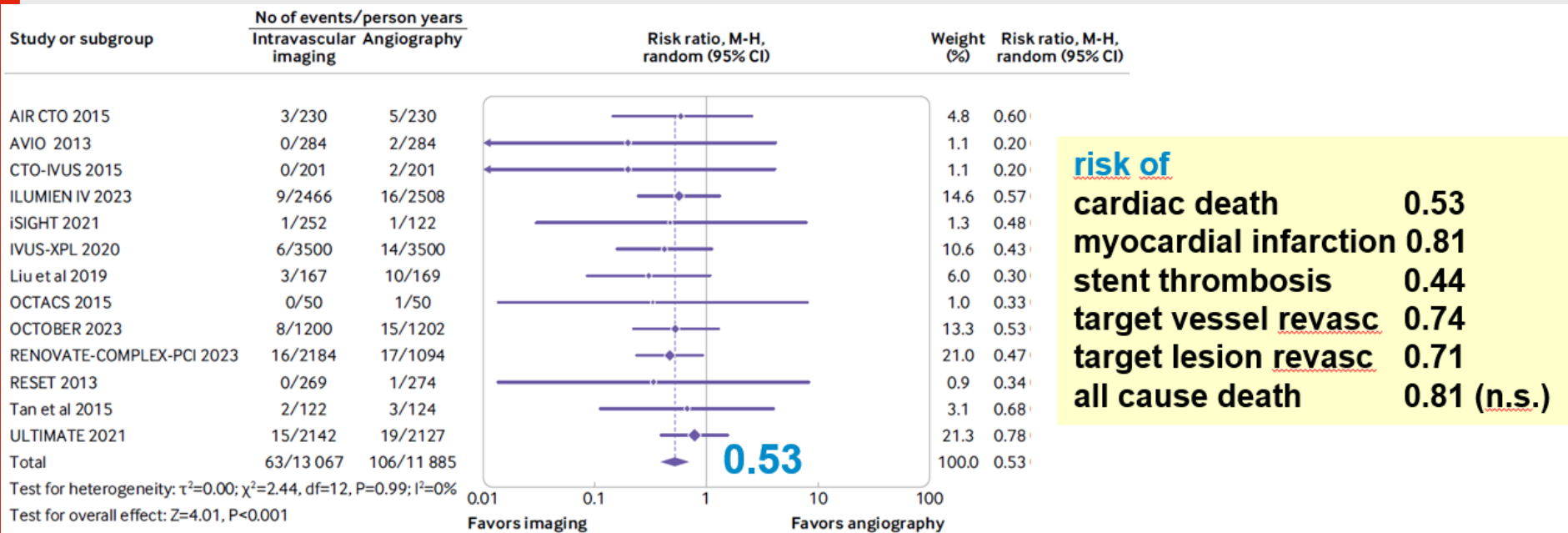


Adjusted HR 1.00 (0.92-1.08)
 $p=0.98$

M. Götberg: TCT Kongress 2023, 23. – 26. Oktober 2023, San Francisco, Kalifornien

Überlegenheit PCI mit intrakoronarer Bildgebung versus rein Angiographie-gesteuerter PCI

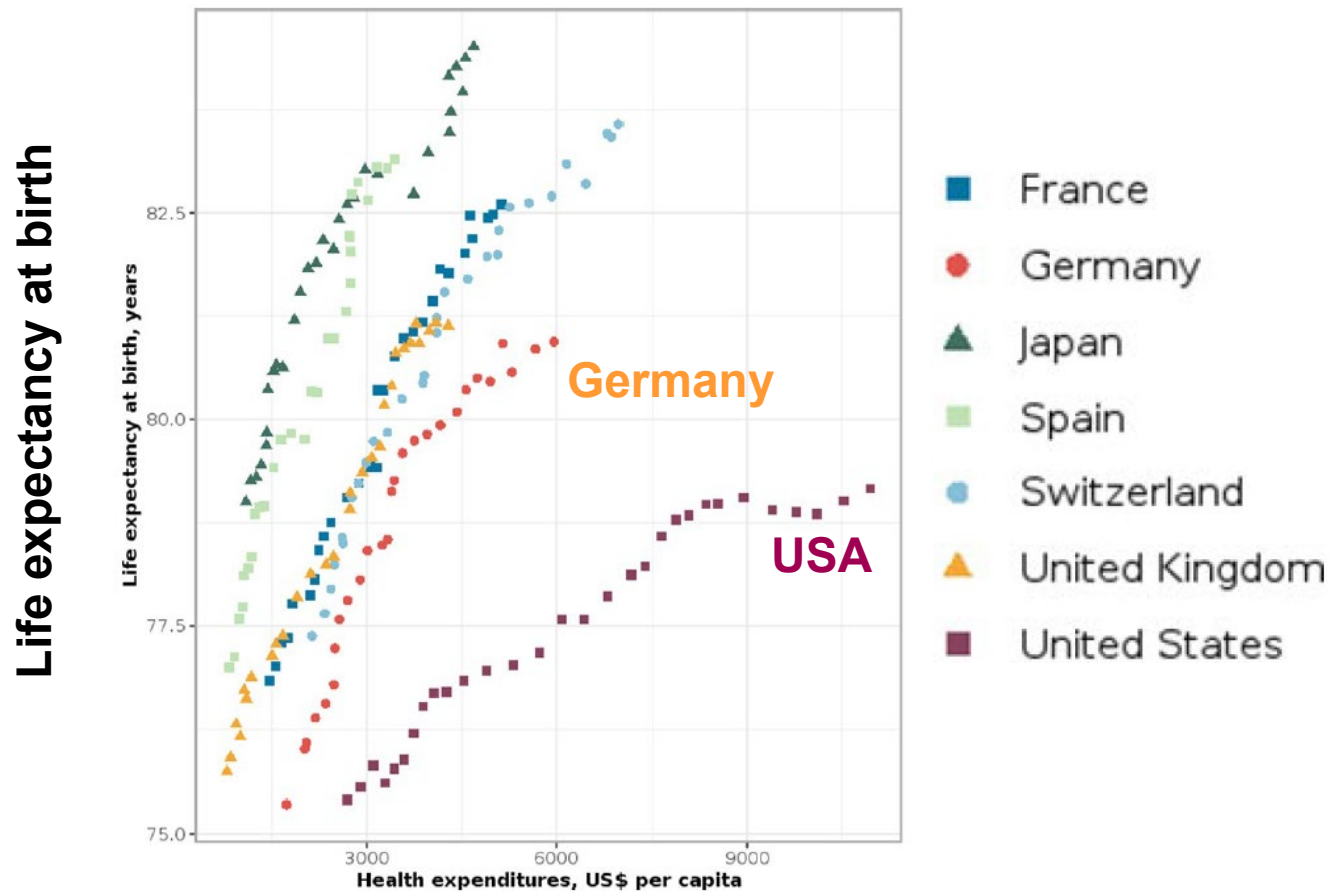
Meta analysis, 20 trials, n=11 698



Khan et al., BMJ 2023;383:e077848

The *underwhelming* German life expectancy

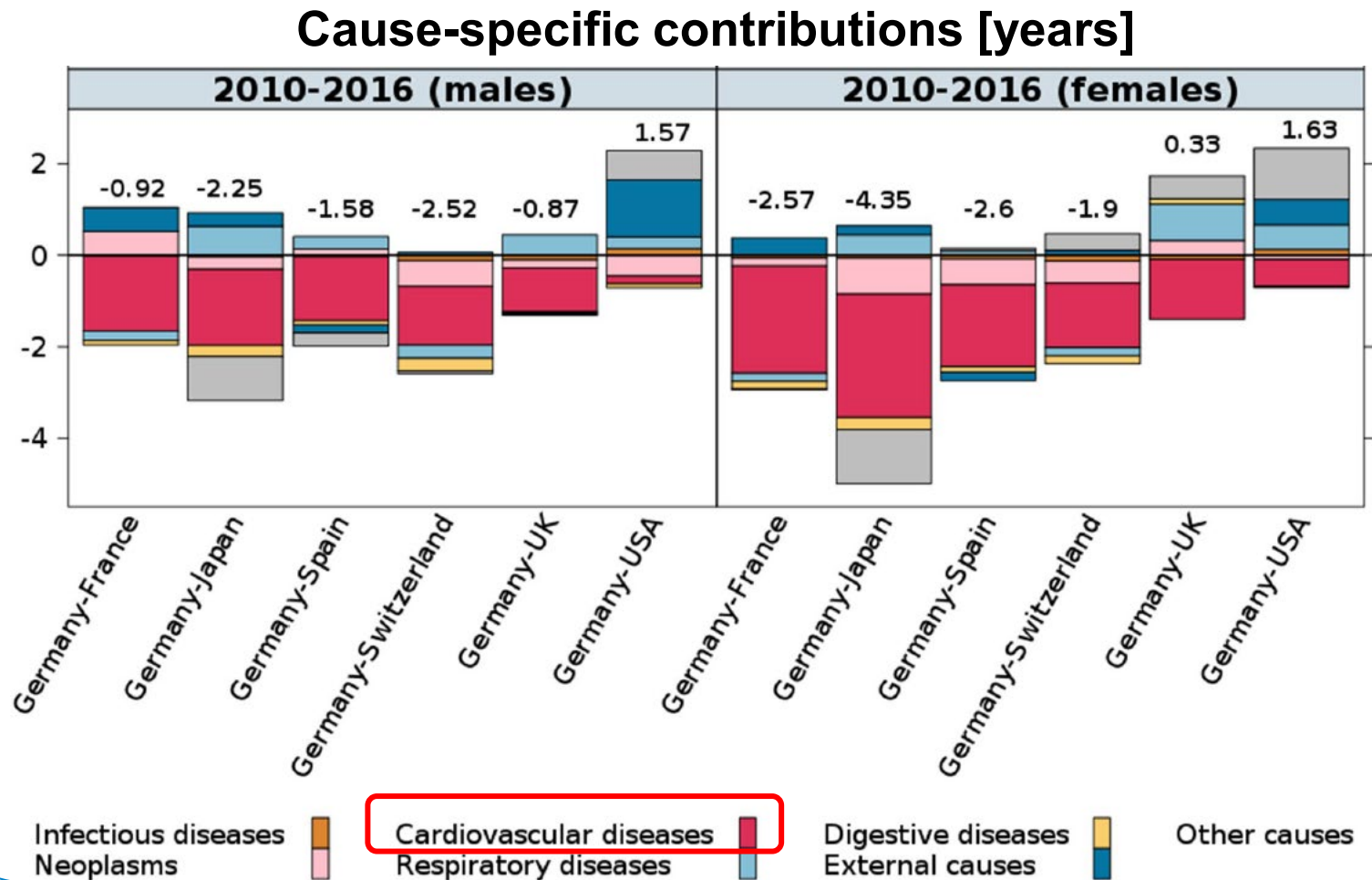
Jasilionis et al., Eur J Epidemiol 2023; doi.org/10.1007/s10654-023-00995-5



Health expenditures per capita (in US\$), 1990–2019

The *underwhelming* German life expectancy

Jasilionis et al., Eur J Epidemiol 2023; doi.org/10.1007/s10654-023-00995-5



State of the Art

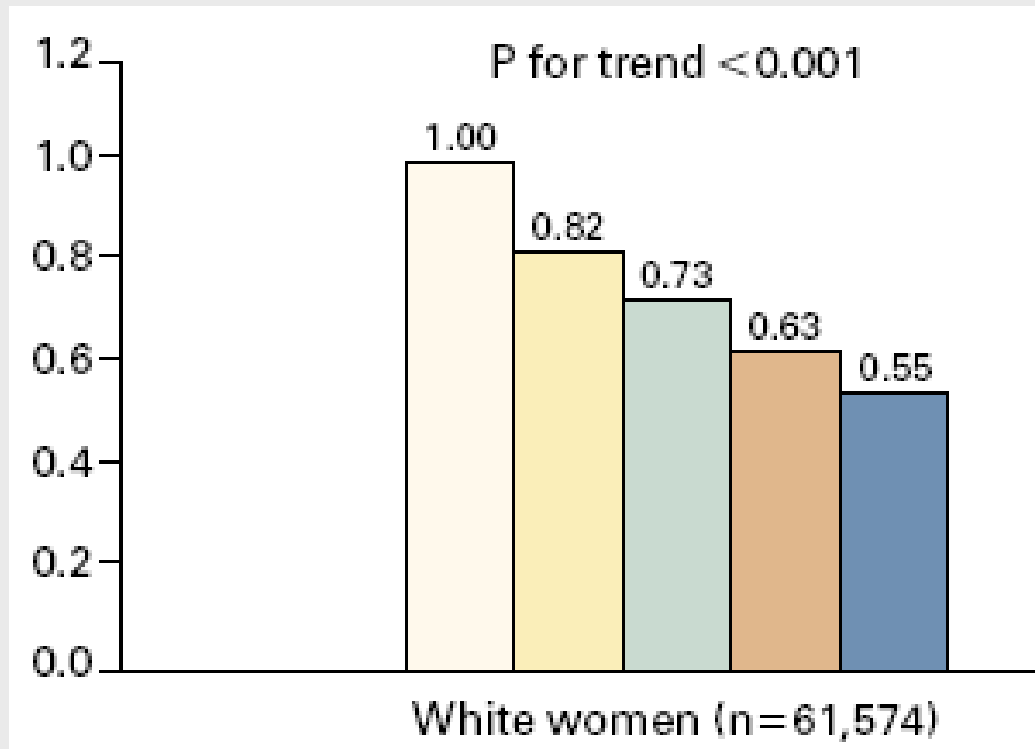
2020 ESC Guidelines on Sports Cardiology; EHJ 2021;42(1):17-96

Bewegung und Sport sind zentrale Bausteine kardiovaskulärer Prävention und Therapie

Epidemiologische Assoziation = Kausalität ?

Ist die Beziehung von Sport zu Gesundheit linear ?

Cardiovascular Risk



Women's Health Initiative
73,743 postmenopausal women
50 to 79 years of age

Metabolic Equivalents

1	2	3	4	5
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Lowest ← → Highest

Manson et al., NEJM 2002; 347(10):716-25

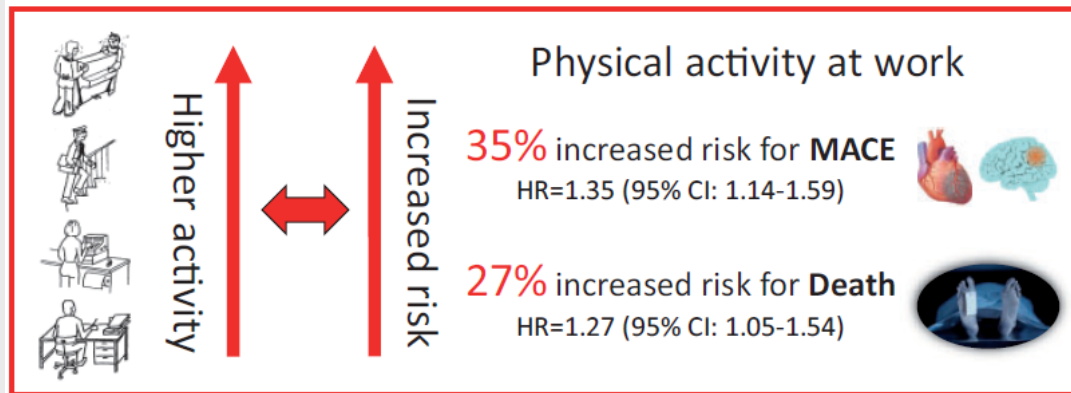
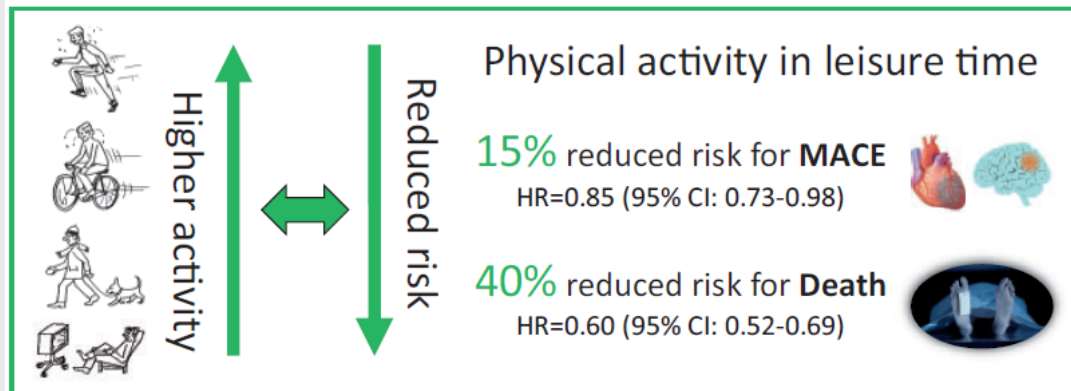
Recommendations	Class ^a	Level ^b
It is recommended for adults of all ages to strive for at least 150 - 300 min a week of moderate-intensity or 75 - 150 min a week of vigorous-intensity aerobic PA, or an equivalent combination thereof, to reduce all-cause mortality, CV mortality, and morbidity.^{371,372}	I	A

371. Kraus et al., Physical Activity Guidelines Advisory Committee. Physical Activity, All-Cause and Cardiovascular Mortality, and Cardiovascular Disease. *Med Sci Sports Exerc* 2019;51:1270-81.
372. Powell et al. The Scientific Foundation for the Physical Activity Guidelines for Americans, 2nd Edition. *J Phys Act Health* 2018;1-11.

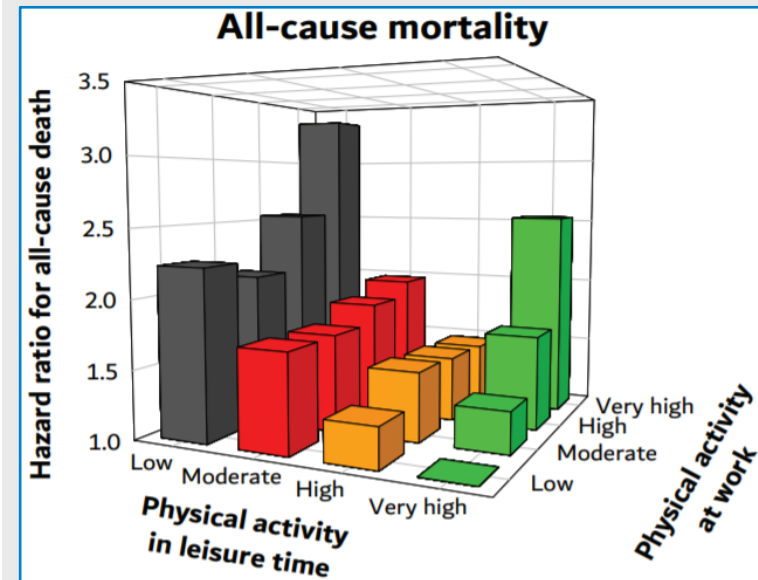
ESC Guidelines on cardiovascular disease prevention. *EHJ* 2021;42:3227-337

Physical Activity Paradoxon

Körperliche Aktivität in der Freizeit reduziert CV Ereignisse und Tod, dagegen ist körperliche Aktivität im Beruf mit erhöhtem Risiko assoziiert

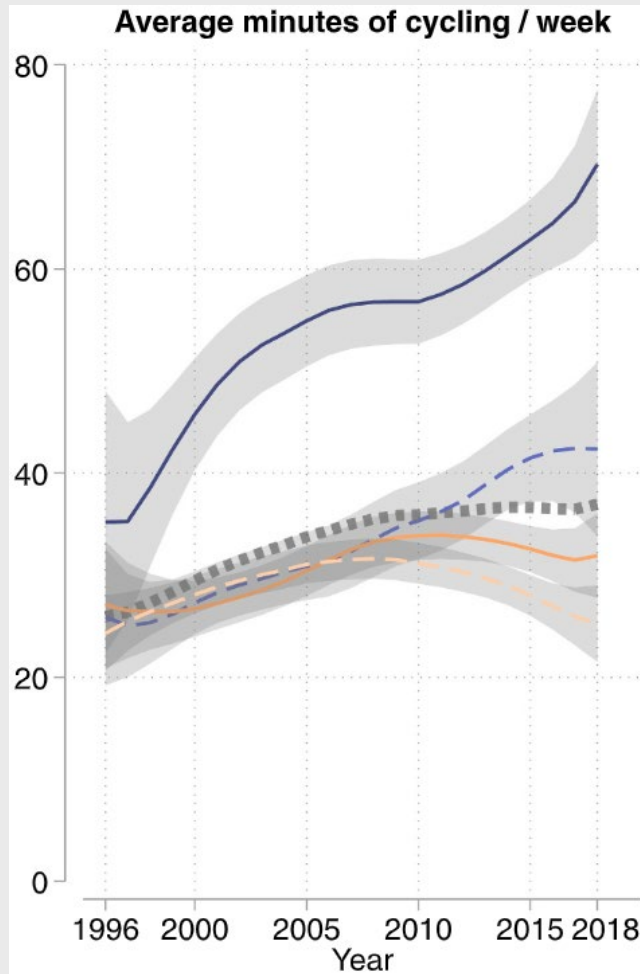


Copenhagen General Population Study,
n= 104 046; 10 years follow-up

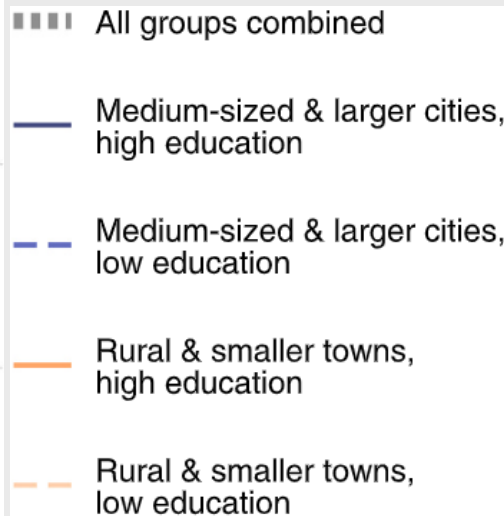


Holtermann et al.,
EHJ 2021; 42:1499–511

Bildungsunterschiede und Verkehrsmittel: Menschen mit Abitur fahren häufiger Rad



representative German Mobility Panel; 1996 to 2018
28,000 persons; 730,000 reported trips



25.9 - 36.9

35.2 - 70.2

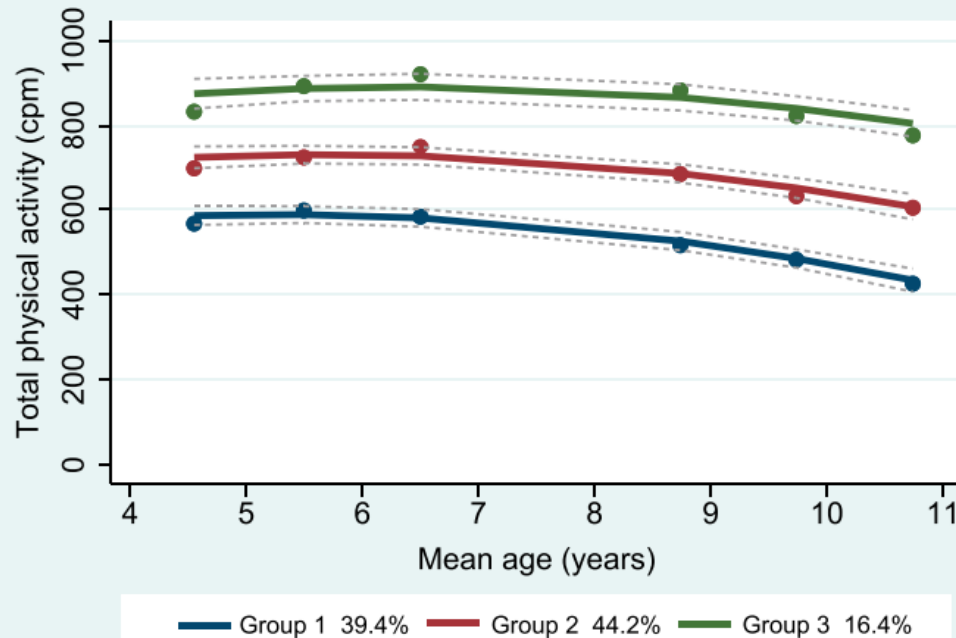
24.3 - 25.3

Hudde a. J Transport Geography, 2022,98:103244

Welche Kinder machen Sport?

Physical Activity Trajectories in Childhood Correlate with Income

N=279; accelerometry
at 6 timepoints



	Group 1		Group 2		Group 3	
	Coefficient Estimate	P	Coefficient Estimate	P	Coefficient Estimate	P
TPA						
Income	0.414	0.429	0.262	0.764	23.811	0.059
P. influence	0.166	0.898	15.346	0.008	0.124	0.900
Tot. min·d ⁻¹	0.082	0.206	0.038	0.549	0.090	0.490

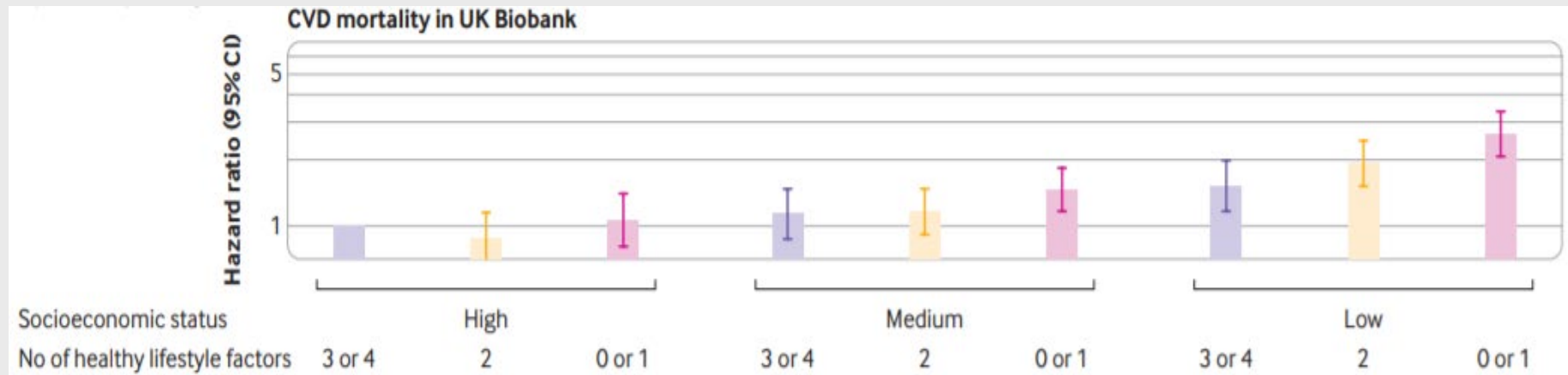
McPhee et al., Med Sci Sports Exerc 2023;55(7):1232-40

LEBENSSTIL

Sozio-ökonomischer Status bestimmt kardiovask. Risiko

44462 US adults (US NHANES) and 99537 UK adults (UK Biobank)

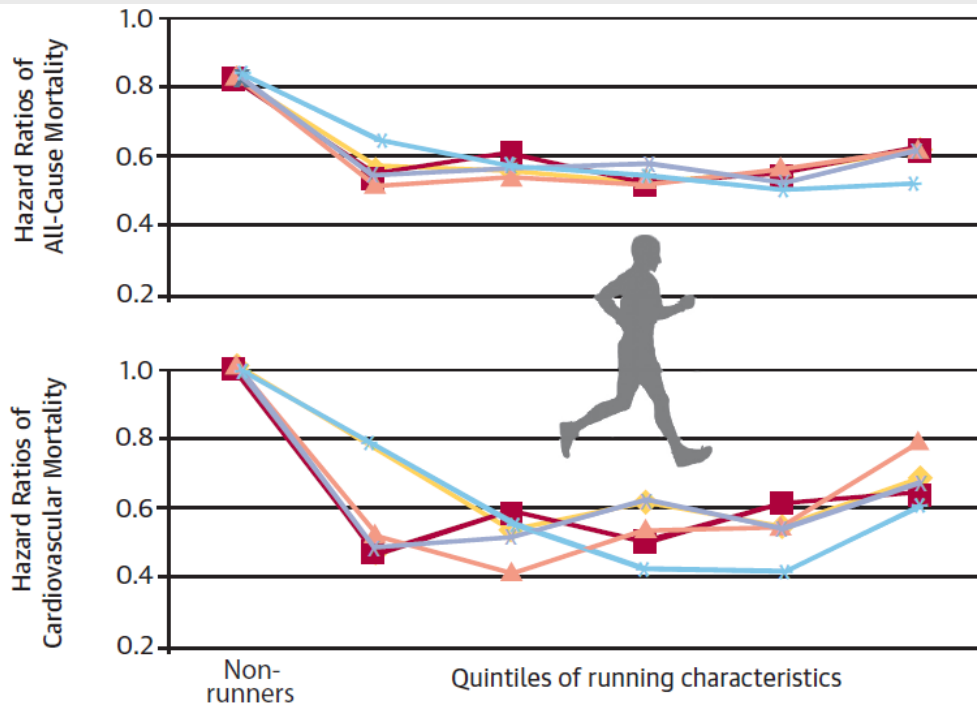
Health lifestyle: never smoking, no heavy alcohol, top third physical activity, higher dietary quality



Gesunder Lebensstil reduziert das Risiko in allen Gruppen, ist aber nur für 3-13% des soz-ökonomischen Effektes verantwortlich

Zhang et al., BMJ 2021;372:n604

Positive Effekte geringer Bewegung versus negative Effekte von Inaktivität



N=55.137
mean fu 15 y

	Time (min/wk)	0	<51	51-80	81-119	120-175	≥176
	Distance (miles/wk)	0	<6	6-8	9-12	13-19	≥20
	Frequency (times/wk)	0	1-2	3	4	5	≥6
	Total amount (MET-min/wk)	0	<506	506-812	813-1199	1200-1839	≥1840
	Speed (mph)	0	<6.0	6.0-6.6	6.7-7.0	7.1-7.5	≥7.6

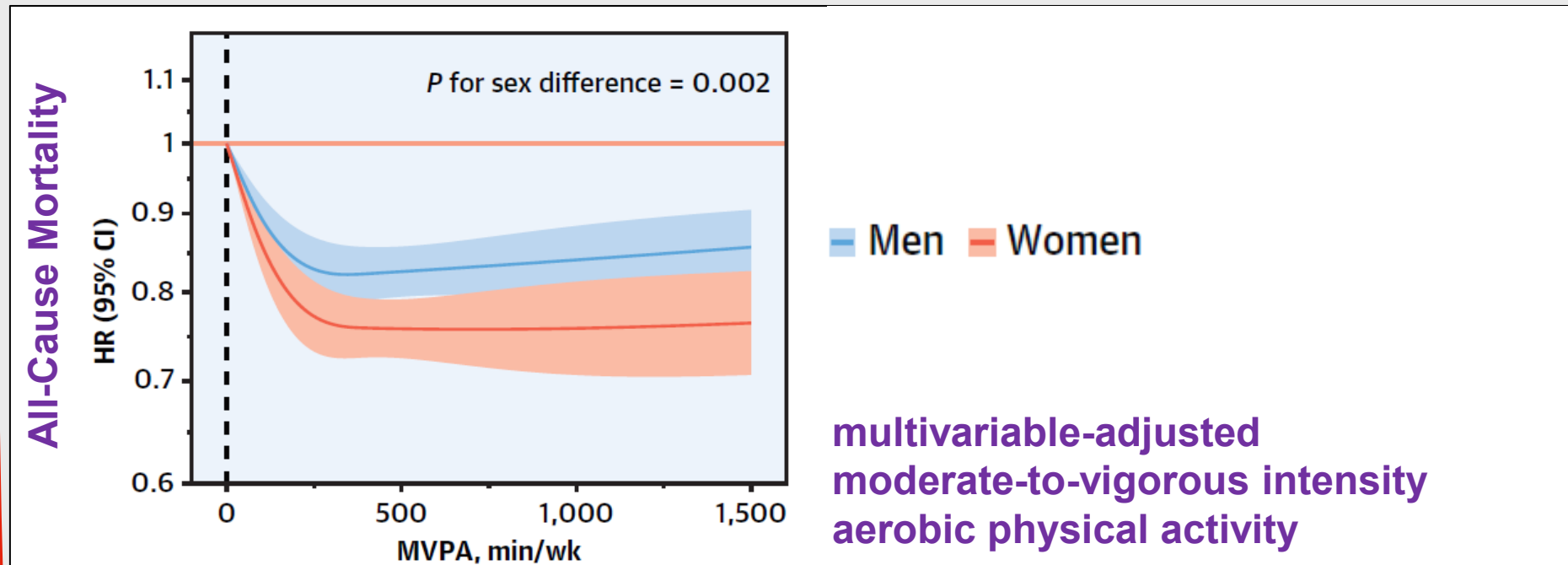
Lee et al., JACC 2014; 64:472-481

Sex, Physical Activity, and Mortality Risk

Profitieren Frauen pro Training mehr als Männer?

Ji et al., JACC 2024; 83(8):783-93

National Health Interview Survey; 412,413 U.S. adults (55% female)

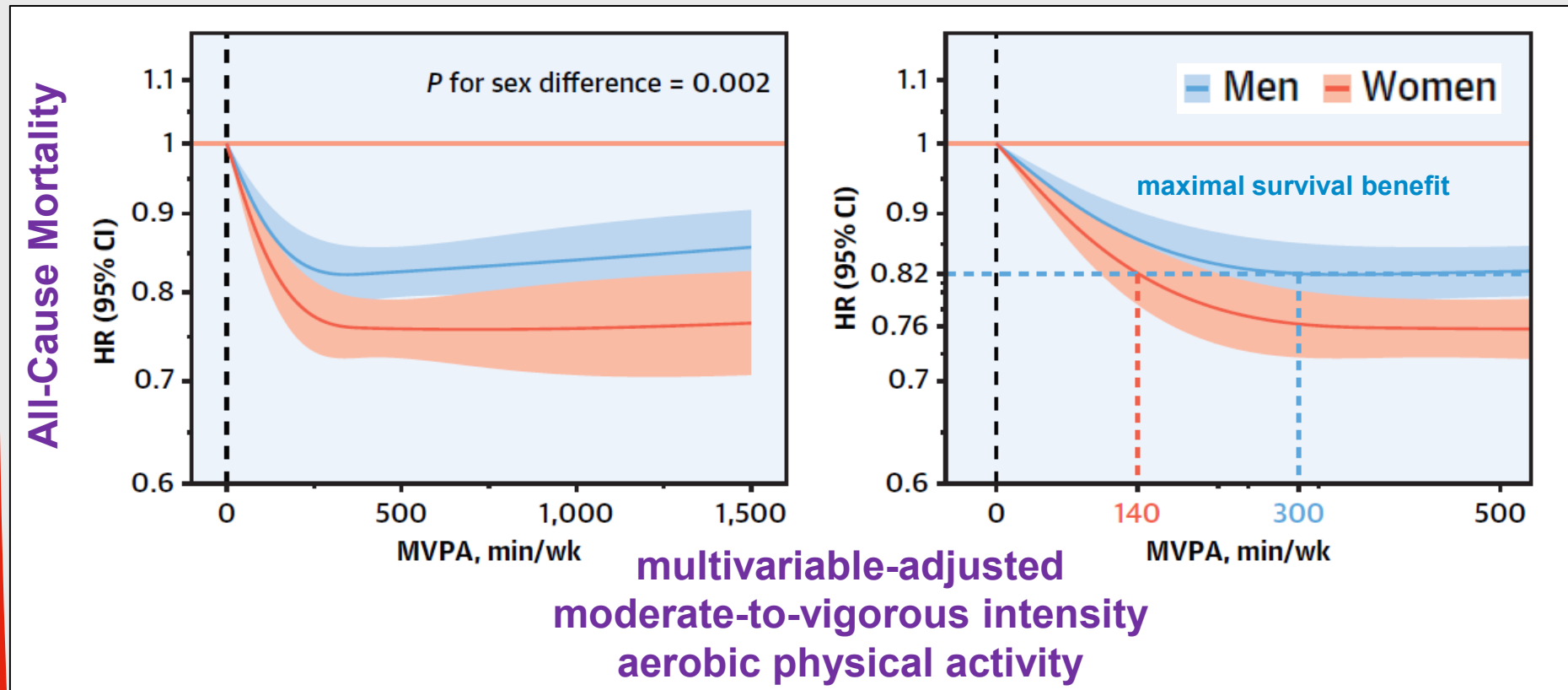


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Ji et al., JACC 2024; 83(8):783-93

National Health Interview Survey; 412,413 U.S. adults (55% female)



Hot Debate

Lifelong endurance exercise and coronary atherosclerosis ?



176

Controls



191

Late-onset
endurance
athletes



191

Lifelong
endurance
athletes

Absence of cardiovascular disease and of established risk factors for coronary artery disease

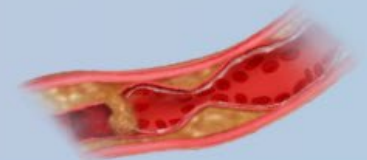
No current or past history of smoking, no body mass index $>27.2 \text{ kg/m}^2$

Sampled at random for inclusion to minimize the risk of selection bias



Primary endpoint

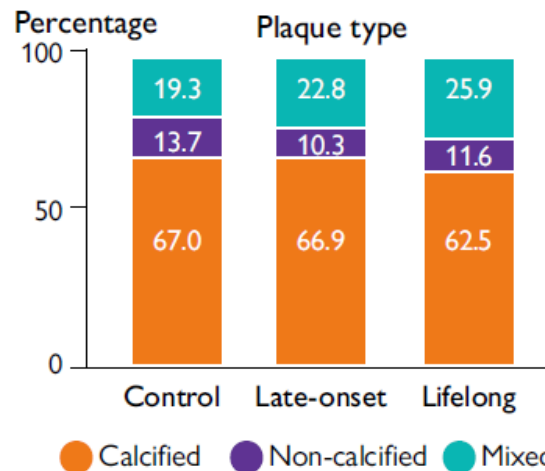
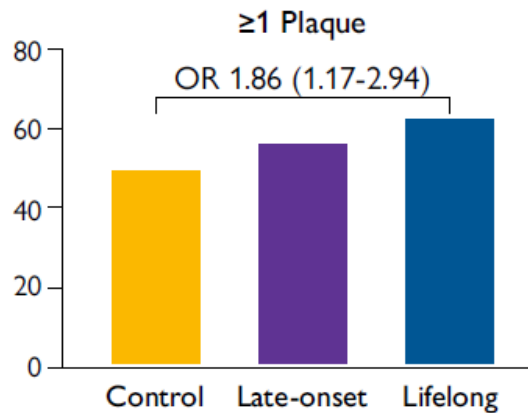
Prevalence of any coronary plaques (calcified, mixed, non-calcified) by computed tomography



De Bosscher et al., EHJ 2023; doi.org/10.1093/eurheartj/ehad152

Lifelong endurance exercise associated with **INCREASED** coronary atherosclerosis

Plaque burden and plaque composition by endurance exercise group



Odds of having coronary plaque in *lifelong endurance athletes* compared to *controls*

≥ 1 mixed plaque	1.78
≥ 1 coronary plaque	1.86
≥ 1 non-calcified plaque	1.95
≥ 1 proximal plaque	1.96
≥ 1 proximal non-calcified plaque	2.80

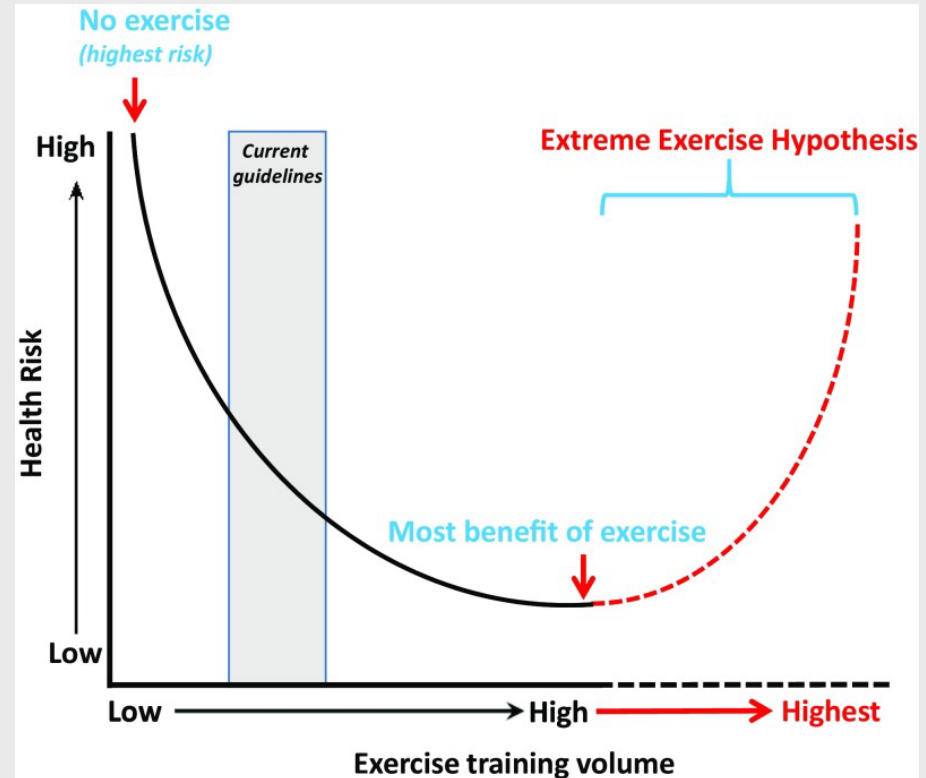
Odds ratios were adjusted for other risk factors

The extreme exercise hypothesis

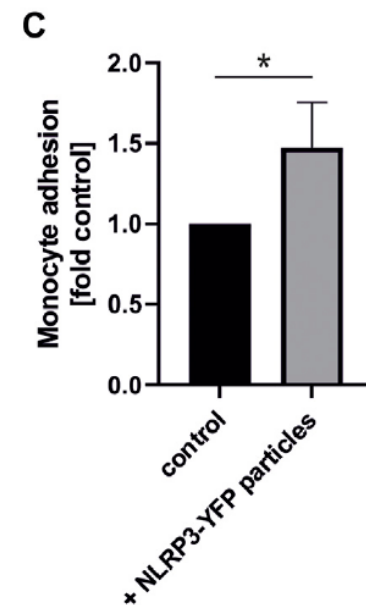
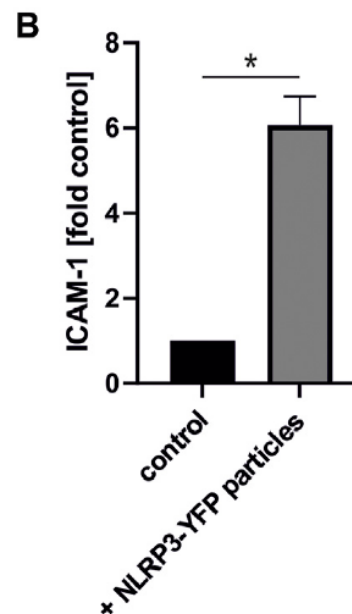
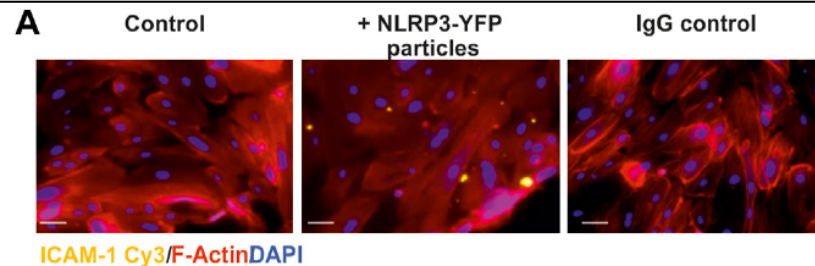
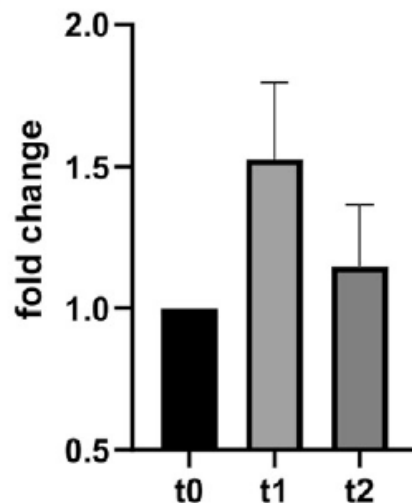
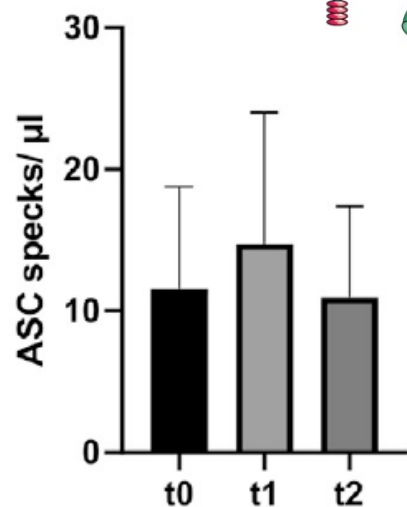
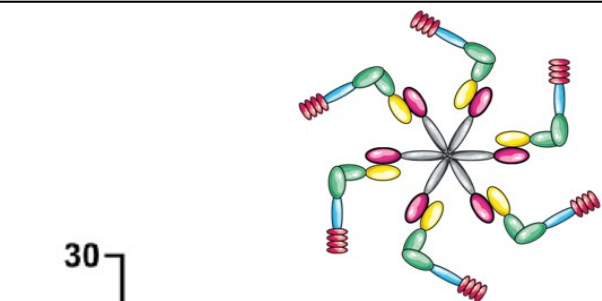
Low physical activity and a sedentary lifestyle are risk factors for cardiovascular morbidity and mortality

BUT adverse cardiovascular events may occur more often following high-volume high-intensity exercise

Excessive bouts of physical activities are associated with inflammation and oxidative stress



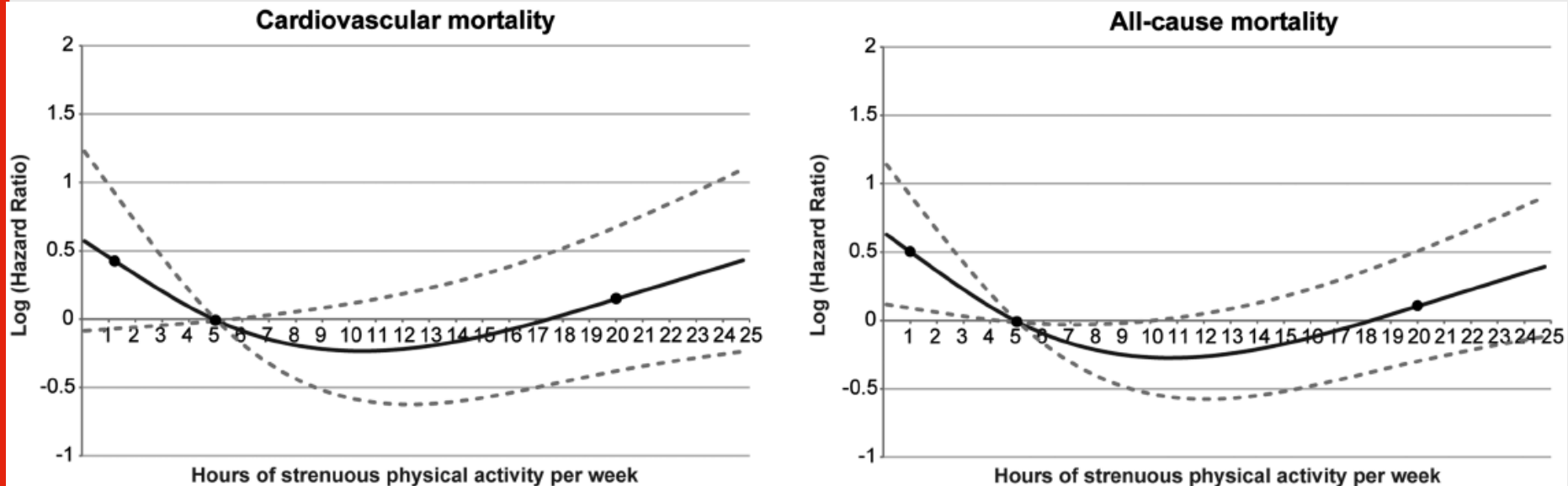
Extracellular Inflammasome Particles Are Released After Marathon Running and Induce Proinflammatory Effects in Endothelial Cells



52 marathon runners
24–72 h before, immediately after,
and 24–58 h after the run

Kogel et al., Front. Physiol. 2022; 13:866938

Kann zu viel körperliche Belastung für Patienten mit KHK ungünstig sein?



KAROLA; N=1.038 with stable CHD; physical activity assessed over 10 years

models adjusted for season, sex, age, education, employment status, study site, cotinine-validated smoking status, BMI, self-reported poor health, history of MI, diabetes mellitus, hypertension and number of affected vessels

Mons et al., Heart. 2014; 100:1043-49

„UKL Rezept für Bewegung“

Name, Vorname Patient/Patientin

geb. am
Datum

REZEPT FÜR BEWEGUNG

Ich empfehle Ihnen ein Bewegungstraining mit folgendem Inhalt:

Moderat:
(1) zügiges Spaziergehen
(2) Walken
(3) Radfahren in der Ebene
(4) Tennis (Doppel)
(5) Aqua-Fitness
(6) Volleyball
(7) Ski-Wandern
(8) Schwimmen (Brust/Rücken)
(9) _____

Intensiv:
(10) Joggen
(11) Aerobic
(12) Tennis (Einzel)
(13) Radfahren (Schnell/Berge)
(14) Fußball
(15) Schwimmen (Kraul/Schnell)
(16) Ski-Langlauf (Skating)
(17) Kampfsport (Karate/Judo)
(18) _____

Krafttraining:
(19) Übungen mit Körpergewicht (Liegestütze, Sit-ups)
(20) Pilates
(21) Yoga
(22) Krafttraining mit Gewichten
(23) Rückentraining/-schule
(24) Statische Kraftübungen
(25) Cross-Fit
(26) _____

Woche 1-4	MO	DI	MI	DO	FR	SA	SO
Trainingsform							
Trainingszeit							

Woche 5-8	MO	DI	MI	DO	FR	SA	SO
Trainingsform							
Trainingszeit							

Woche 9-12	MO	DI	MI	DO	FR	SA	SO
Trainingsform							
Trainingszeit							

Unterschrift
Patient/Patientin

Unterschrift
Arzt/Ärztin

Ich empfehle Ihnen ein Bewegungstraining mit folgendem Inhalt:

Moderat:

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Woche 1-4	MO	DI	MI	DO	FR	SA	SO
Trainingsform							
Trainingszeit							

Patient/-in unterschreibt das Rezept ebenfalls

Higher intakes of non-sugar sweeteners associated with

- higher BMI and risk of obesity
- increased risk of diabetes T2, CVDs, CVD mortality, and all-cause mortality
- increased risk of bladder cancer (saccharin)

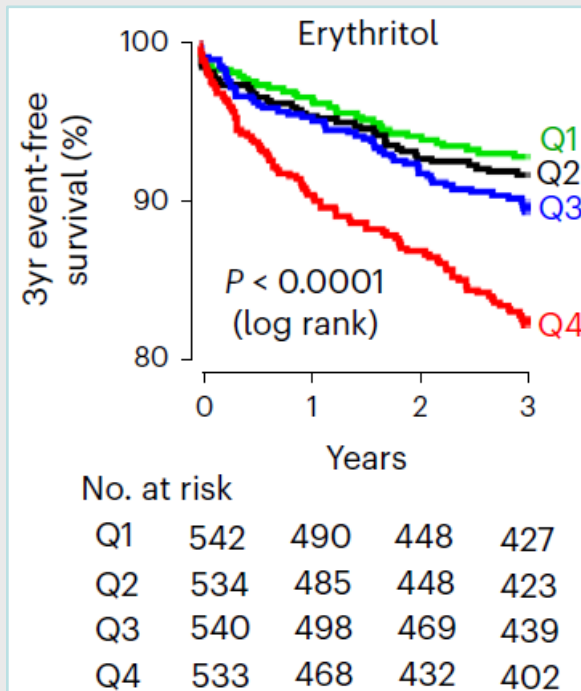
WHO recommendation

WHO suggests that non-sugar sweeteners not be used as a means of achieving weight control or reducing the risk of noncommunicable diseases (*conditional recommendation*).

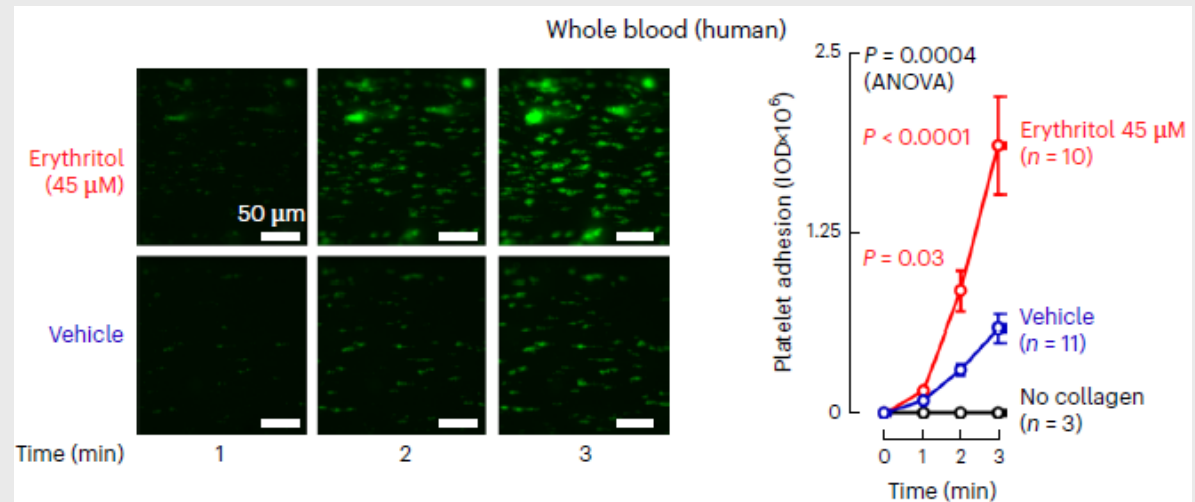
Erythritol

Süßstoffe mit Atherosklerose assoziiert

Metabolomics studies ($n = 1,157$): circulating levels of polyol sweeteners associated with incident MACE; confirmed in independent US ($n = 2,149$) and European ($n = 833$) validation cohorts

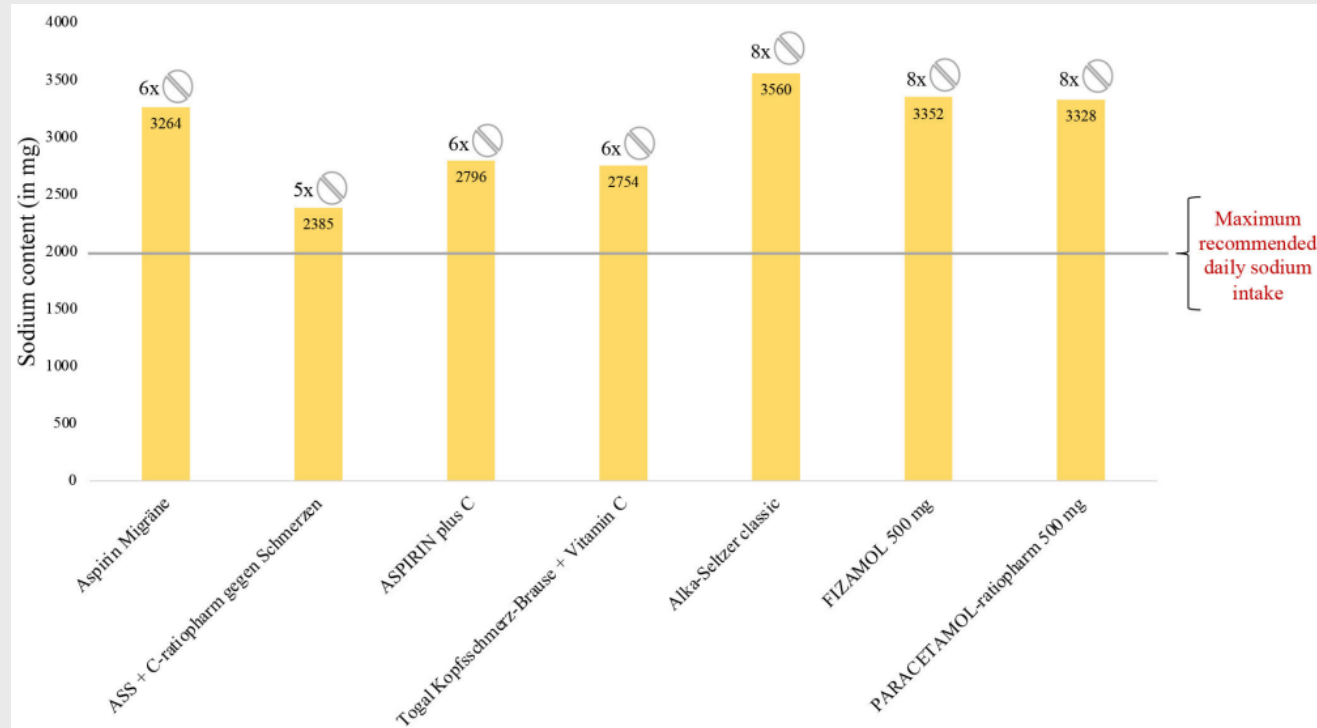
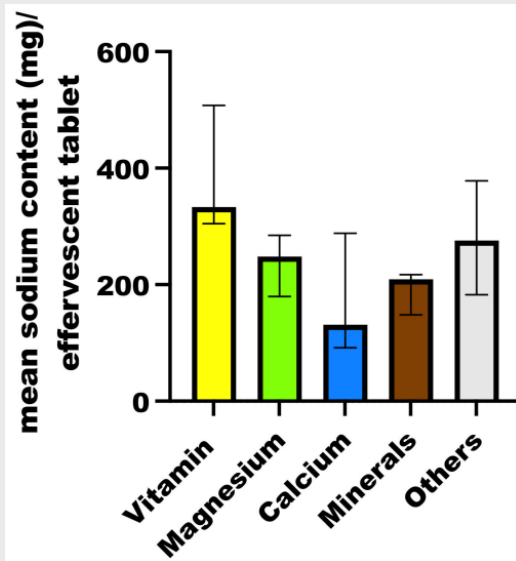


Erythritol enhanced platelet reactivity in vitro and thrombosis formation in vivo



Witkowski et al., Nat Med 2023;29:710-8

Hoher Salzgehalt (NaCl) in frei verkäuflichen Brause-Tabletten



Kunz M et al. BMJ Open 2023;13:e076302. doi:10.1136/bmjopen-2023-076302

Gliederung

CKM Syndrom
MASLD
NuSHs

**Chronisches
Koronarsyndrom**

**Lebensstil:
körperliche Aktivität
Ernährung**

DISKUSSION

Diabetes

Adipositas

Lipide

Bemepedoidsäure

PCSK9-Hemmer

Lipoprotein(a)

Screening

Winterschlaf

Alkohol & Zigaretten

State of the Art

SGLT2-Inhibitoren

Empagliflozin

Canagliflozin

Dapagliflozin

Ertugliflozin

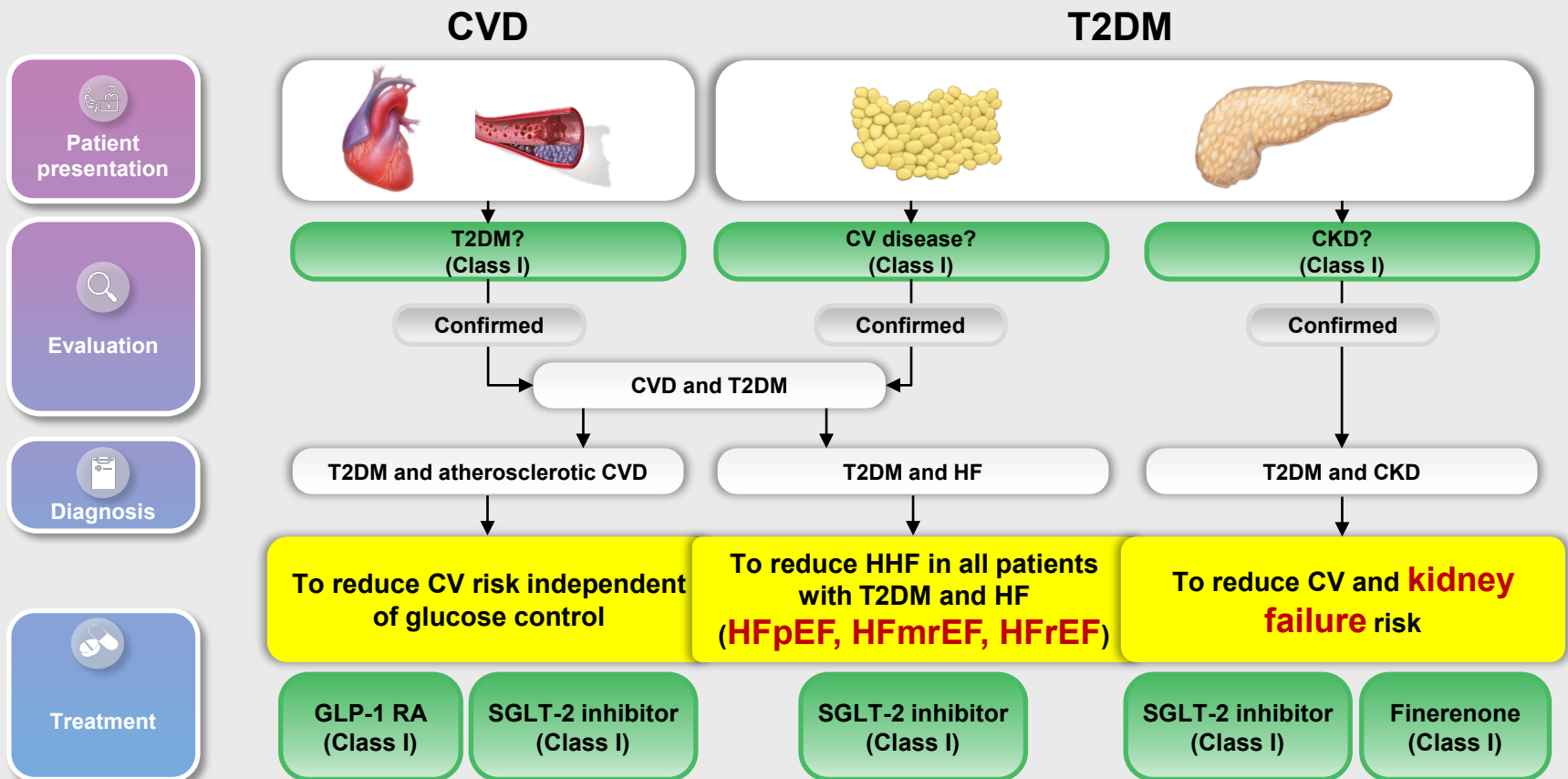
Sotagliflozin

- 1) Glukose-Senkung bei DMT2
- 2) Reduktion Herzinsuffizienz-Ereignisse
- 3) Verzögerung Niereninsuffizienz
- 4) Verminderung Sterblichkeit
- 5) Effekte unabh. von Diabetes
- 6) Effekte unabh. von LV-EF

New ESC Guidelines

Management of CVD in patients with T2DM

Marx N, et al. EHJ 2023; 44(39):4043-140



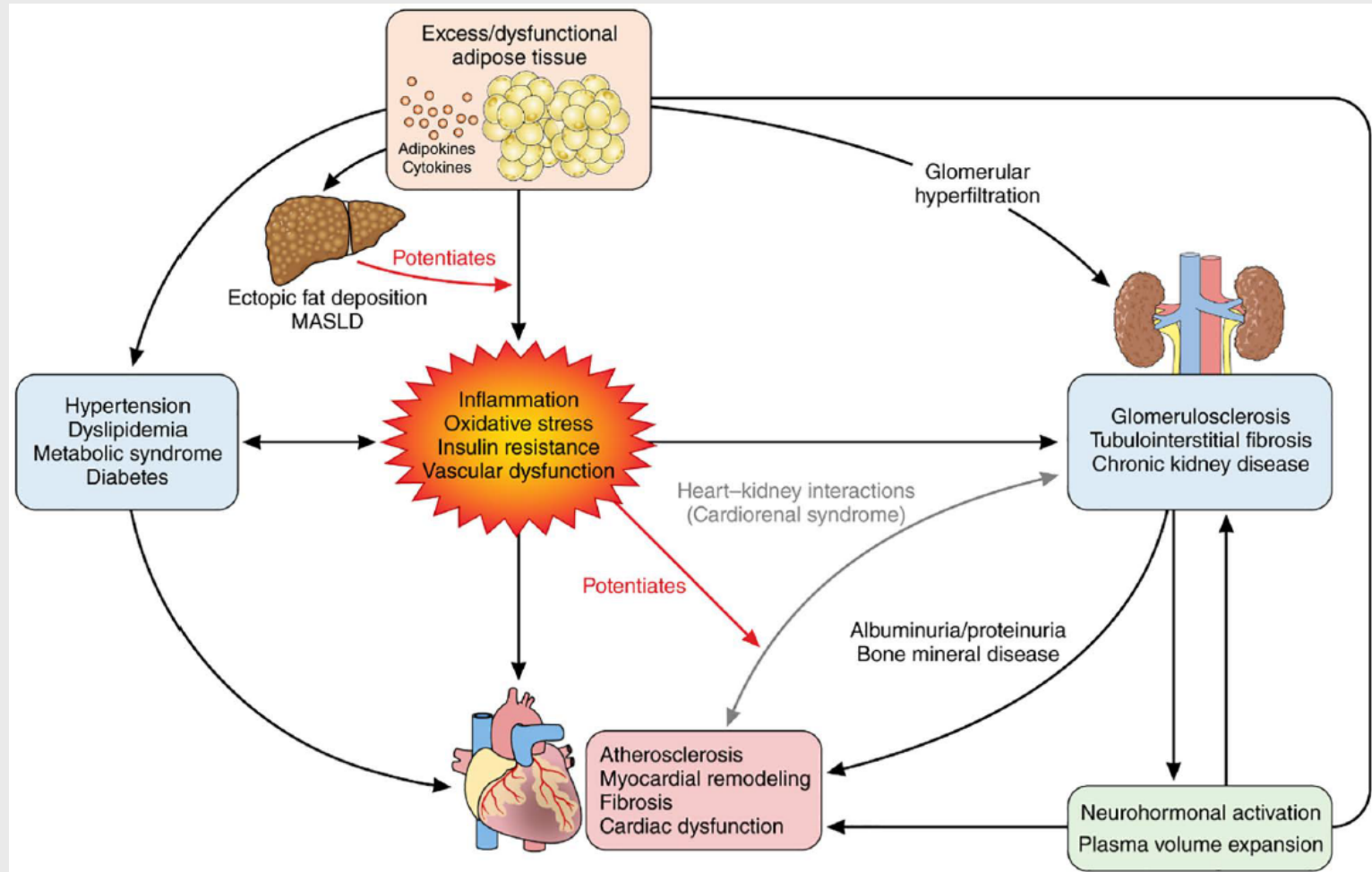
GFR und Albumin **im Urin** bestimmen Nierenfunktion

Einteilung der chronischen Niereninsuffizienz nach KDIGO				Albuminausscheidung im Urin		
				A1	A2	A3
				Normal bis leicht erhöht	Mäßig erhöht	Stark erhöht
				<30mg/g	30–300mg/g	>300mg/g
Glomeruläre Filtrationsrate (GFR) ml/min/1,73m ²	G1	Normal oder hoch	≥90			
	G2	Leicht erniedrigt	60–89			
	G3a	Leicht bis mäßig erniedrigt	45–59			
	G3b	Mäßig bis stark erniedrigt	30–44			
	G4	Stark erniedrigt	15–29			
	G5	Nierenversagen	<15			

Eckardt K-U et al. DMW 2022;147:1398–1406

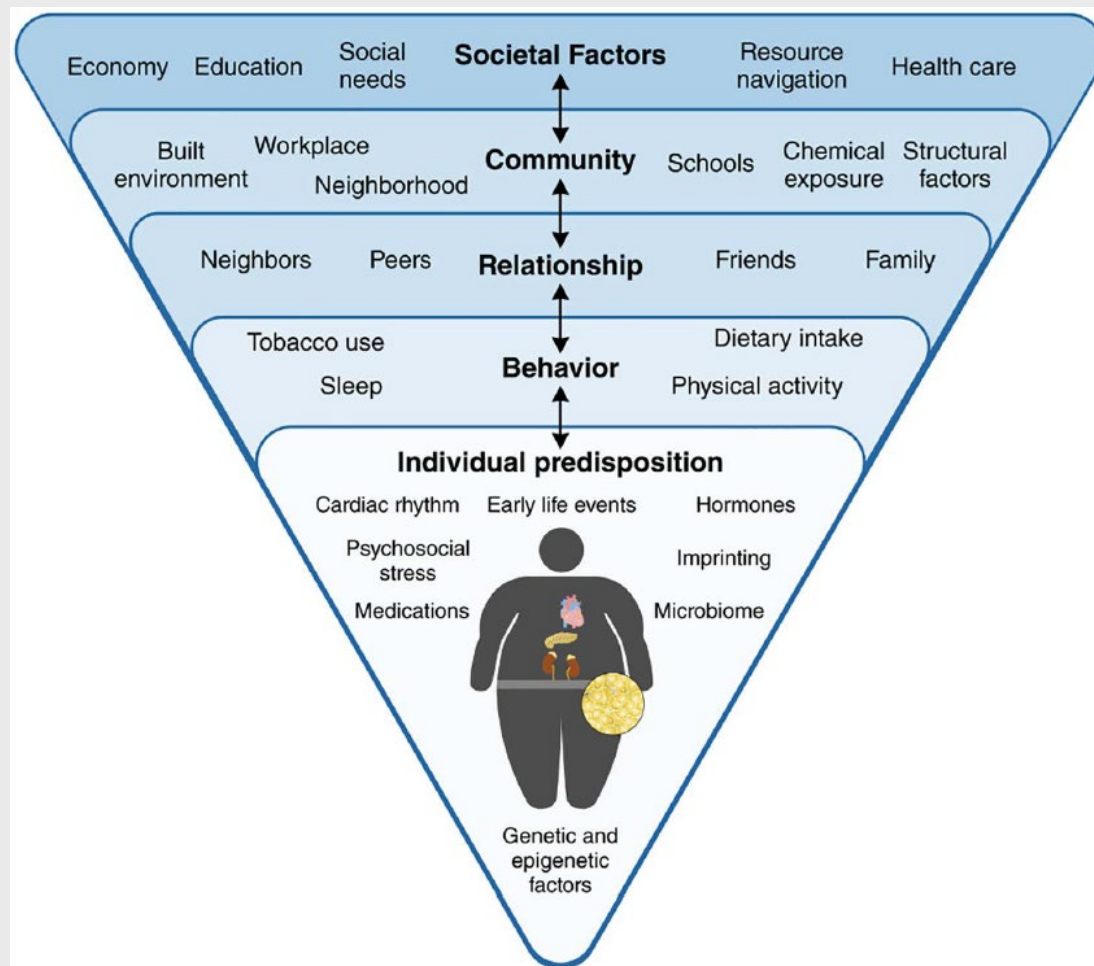
Cardiovascular-Kidney-Metabolic (CKM) Syndrom

Ndumele et al., Circ 2023;148:1636–64



Socioecological framework for CKM syndrome

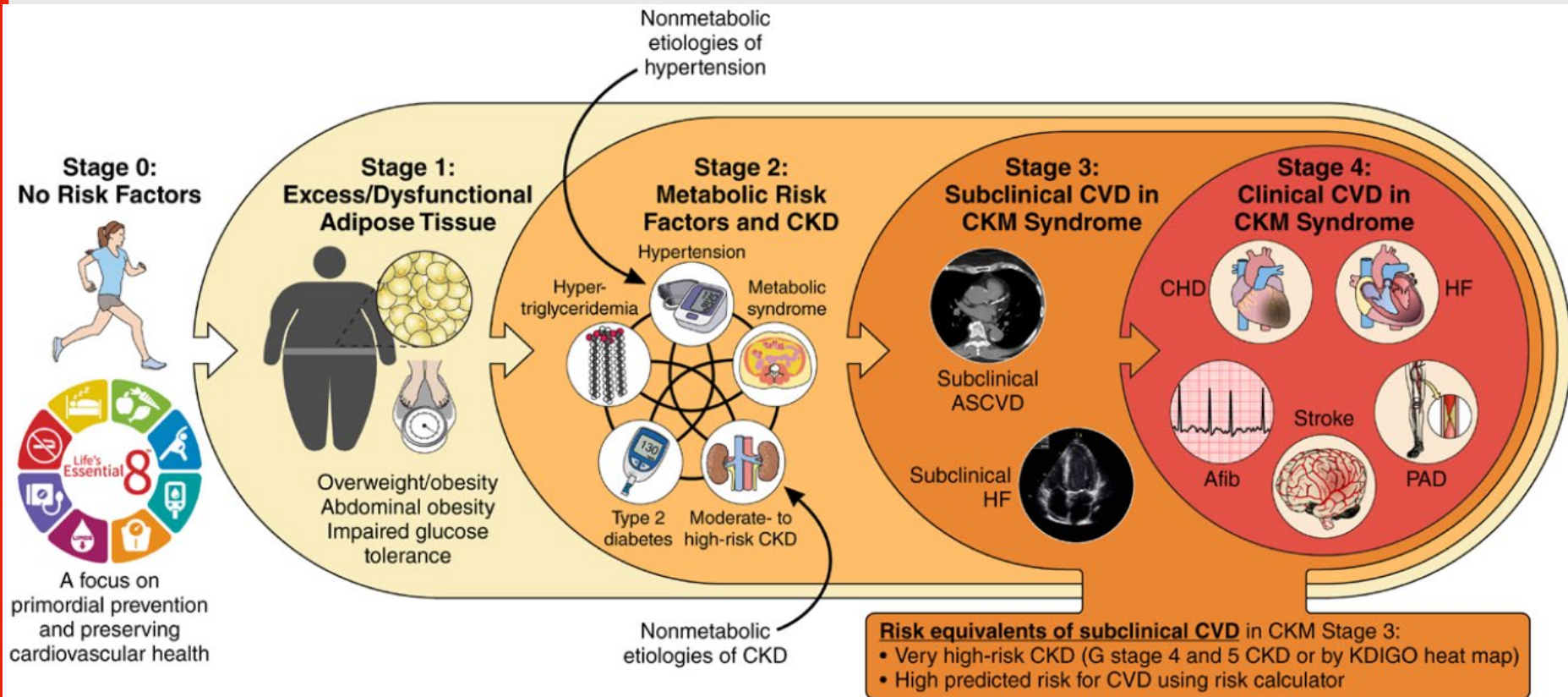
Ndumele et al., Circ 2023;148:1636–64



Cardiovascular-Kidney-Metabolic (CKM) Syndrom

4 Stadien

Ndumele et al., Circ 2023;148:1636–64 & 1606–35



Änderungen zur Nomenklatur für Fettlebererkrankungen

helle + vergrößerte Leber im US; GOT, GPT, gGT können erhöht sein

Steatotische Lebererkrankung (SLD)

Metabolische
Dysfunktion +
assoziierte Steatotische
Lebererkrankung
MASLD

**MASLD +
Erhöhter
Alkoholkonsum
MetASL**

Spezifische Ätiologien

Kryptogene SLD

**Alkohol assoziierte
Lebererkrankung
ALD**

European Association for the Study of the Liver (EASL)
Rinella et al. J Hepatol 2023 doi: 10.1016/j.jhep.2023.06.003
Berg & Messer. Gastro-News 2023;10(5):21-22

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Steatotische Lebererkrankung (SLD)

mindestens 1 Kriterium von 5

- ▶ BMI $\geq 25 \text{ kg/m}^2$ (Asien: 23)
ODER WC $> 94 \text{ cm}$ (Männer), 80 cm (Frauen)
ODER ethnische Anpassung
- ▶ Nüchtern-Serumglukose $\geq 5,6 \text{ mmol/L}$ (100 mg/dl)
ODER postprandiale Glucosespiegel $2 \text{ h} \geq 7,8 \text{ mmol/L}$ (140 mg/dL)
ODER HbA_{1c} $\geq 5,7 \%$ (39 mmol/L)
ODER Diabetes mellitus Typ 2
ODER antidiabetische Therapie
- ▶ Blutdruck $\geq 130/85 \text{ mmHg}$
ODER antihypertensive Therapie
- ▶ Plasma-Triglyzeride $\geq 1,70 \text{ mmol/L}$ (150 mg/dL)
ODER lipidsenkende Therapie
- ▶ Plasma-HDL-Cholesterol $\leq 1,0 \text{ mmol/L}$ (40 mg/dL) (Männer),
 $\leq 1,3 \text{ mmol/L}$ (50 mg/dL) (Frauen)
ODER lipidsenkende Therapie

**Metabolische
Dysfunktion +
assoziierte Steatotische
Lebererkrankung
MASLD**

European Association for the Study of the Liver (EASL)
Rinella et al. J Hepatol 2023 doi: 10.1016/j.jhep.2023.06.003
Berg & Messer. Gastro-News 2023;10(5):21-22

Nutrient-Stimulated Hormone-based therapiesu

NuSHs

State of the Art

Glucagon-like peptide-1 (GLP-1)

released in response to food intake -> reduces energy intake

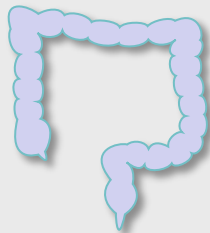
GLP-1

is synthesised and secreted by two sites

Neurons in
hindbrain



L-cells of
the gut



GLP-1 receptor
is expressed in
several organs



Brain



Lungs



Heart (AV node)



Pancreas



Kidney



GI tract

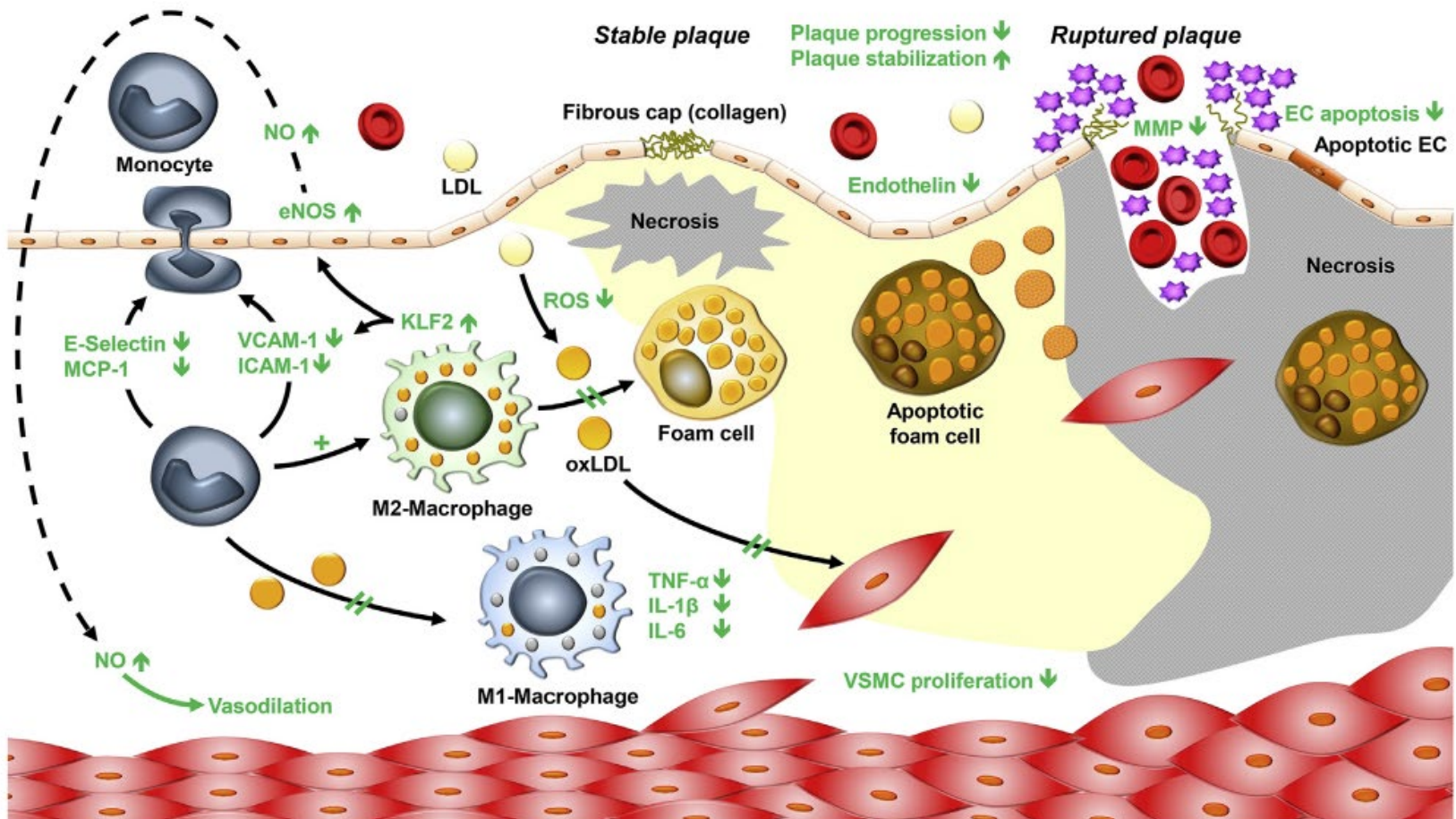


Muscle

GLP-1R is not
expressed in the liver

Potential anti-atherosclerotic effects of GLP-1 in vascular cells

Nauck et al. Mol Metab, 2021; 46:101102



GLP1-RA for Diabetes mell. Typ 2

Meta-Analysis

CVOT:
ELIXA
LEADER
SUSTAIN-6
EXSCEL
Harmony
REWIND
PIONEER 6
AMPLITUDE-O

60 080 Patients

MACE -14%

Death -12%

Hospital admission for heart failure -11%

Kidney outcomes -21%

No increase of severe hypoglycaemia

No heterogeneities, including structural homology

More GI symptoms

GLP-1 RA: Nebenwirkungen

Aroda et al., Diabetes Obes Metab 2023;25:1385–97
Bezin et al., Diabetes Care 2023;46(2):384–90

Gastro-intestinal symptoms in ~40% of patients

Transient, mostly mild

To do: Inform patient, start with low dose and uptitrate, recommend reduced food volume and fat content

Cholelithiasis - probably associated with extend of weight loss

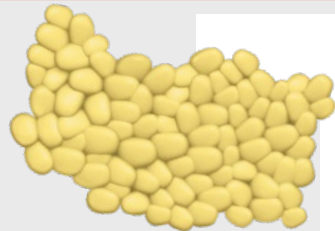
Increase of lipase and amylase levels & risk of pancreatitis, partially associated with cholelithiasis

Increased pulse rate ~ 3 bpm

Adipositas bei Erwachsenen in Deutschland

19% mit BMI >30

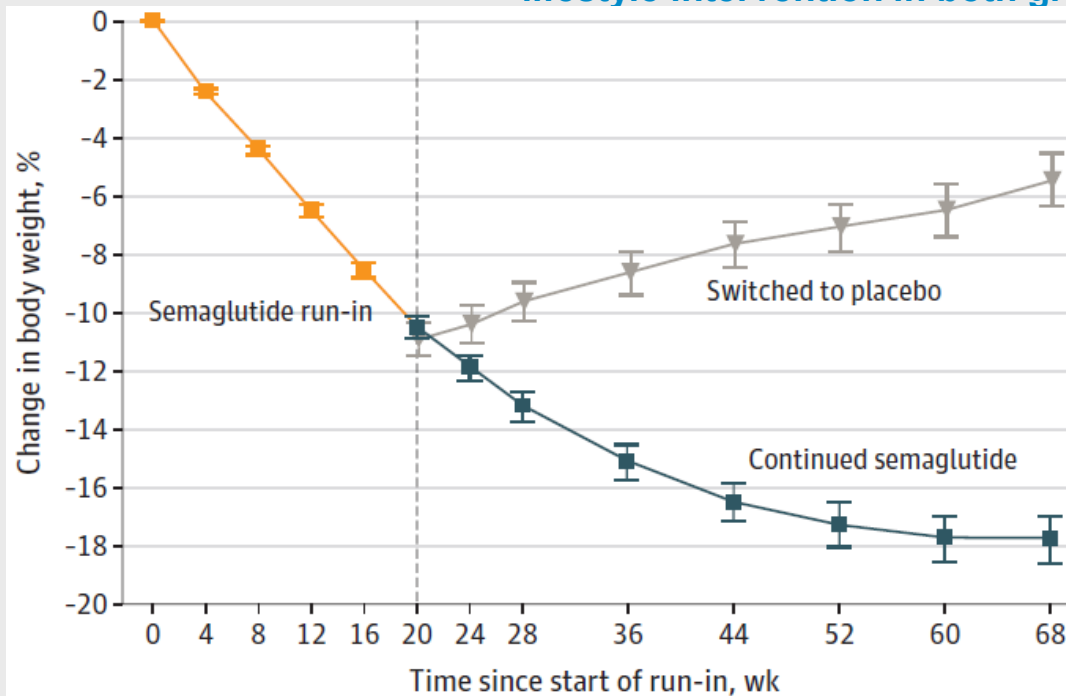
RKI; GEDA 2019/2020-EHIS; Schienkiewitz et al., J Health Monitor 2022 7(3)



	Frauen		Männer	
18–29 Jahre	10,0	(7,5–13,2)	9,3	(7,2–12,1)
Untere Bildungsgruppe	7,7	(3,6–15,7)	16,0	(9,8–25,1)
Mittlere Bildungsgruppe	12,7	(9,2–17,4)	7,9	(5,6–11,1)
Obere Bildungsgruppe	3,1	(1,7–5,6)	5,9	(3,6–9,6)
30–44 Jahre	14,6	(12,4–16,9)	18,7	(16,3–21,5)
Untere Bildungsgruppe	19,4	(11,3–31,3)	25,9	(16,4–38,3)
Mittlere Bildungsgruppe	16,4	(13,6–19,7)	21,3	(17,7–25,4)
Obere Bildungsgruppe	9,1	(7,2–11,5)	12,1	(10,1–14,5)
45–64 Jahre	22,9	(21,1–24,8)	23,8	(21,7–26,0)
Untere Bildungsgruppe	39,0	(31,7–46,9)	36,6	(27,4–47,0)
Mittlere Bildungsgruppe	21,4	(19,4–23,6)	25,2	(22,4–28,2)
Obere Bildungsgruppe	15,5	(13,7–17,5)	17,0	(15,3–18,9)
≥ 65 Jahre	22,4	(20,4–24,5)	19,7	(17,6–21,9)
Untere Bildungsgruppe	24,9	(20,4–30,1)	24,4	(15,5–36,4)
Mittlere Bildungsgruppe	22,9	(20,7–25,3)	20,2	(17,4–23,3)
Obere Bildungsgruppe	12,9	(11,1–14,9)	16,8	(15,0–18,8)

Effect of Continued Weekly Subcutaneous Semaglutide on Weight Loss Maintenance in Adults with Obesity

N=803, mean body weight, 107.2 kg; 20 wk run-in, 48 weeks, semaglutide 2.4 mg sc once per week lifestyle intervention in both groups



-5.0%

GI events
49.1% vs 26.1
% of
participants

discontinuation
because of AE
2.4% vs 2.2%

-17.4%

No. of participants

Semaglutide run-in

803 803 803 802 801

Continued semaglutide

535 527 531 525 523 521 516 520

Switched to placebo

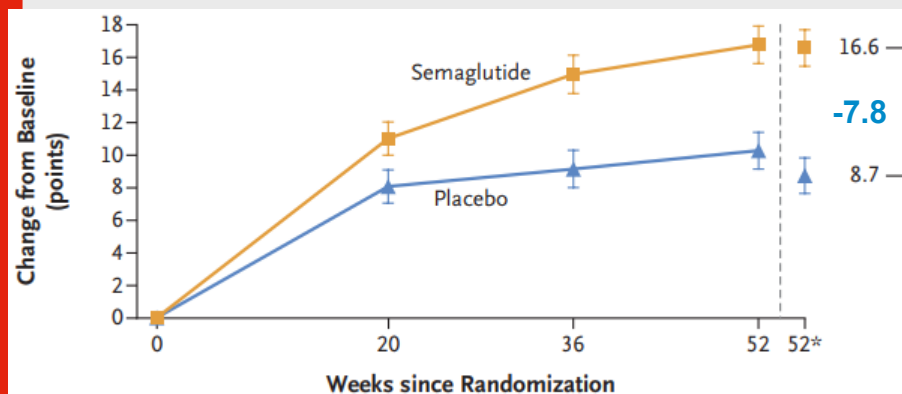
268 267 265 258 260 254 246 250

STEP 4;
Rubino et al.,
JAMA 2021;
325(14):1414-25

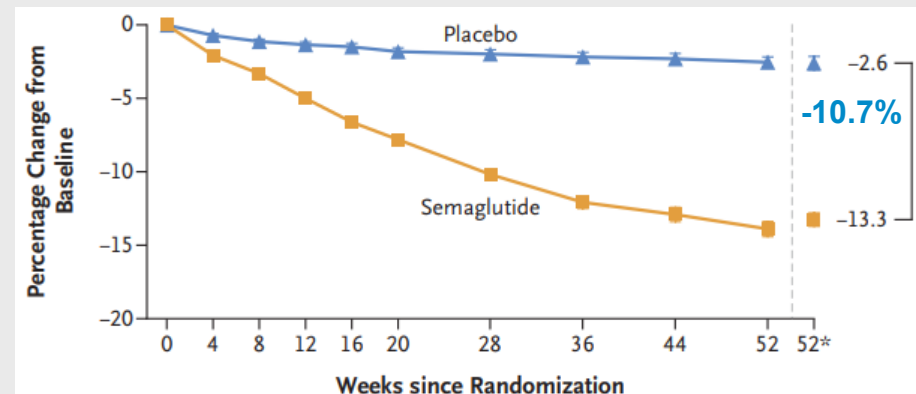
STEP-HFpEF: Semaglutide in Patients with Heart Failure with Preserved Ejection Fraction and Obesity

HFpEF and BMI >30, N=529, 56% females, LVEF 57%; 1:1 semaglutide 2.4 mg s.c. 1x/week; 52 weeks
dual primary endpoint: change in KCCQ-CSS and body weight

Change in KCCQ-CSS



Change in Body Weight

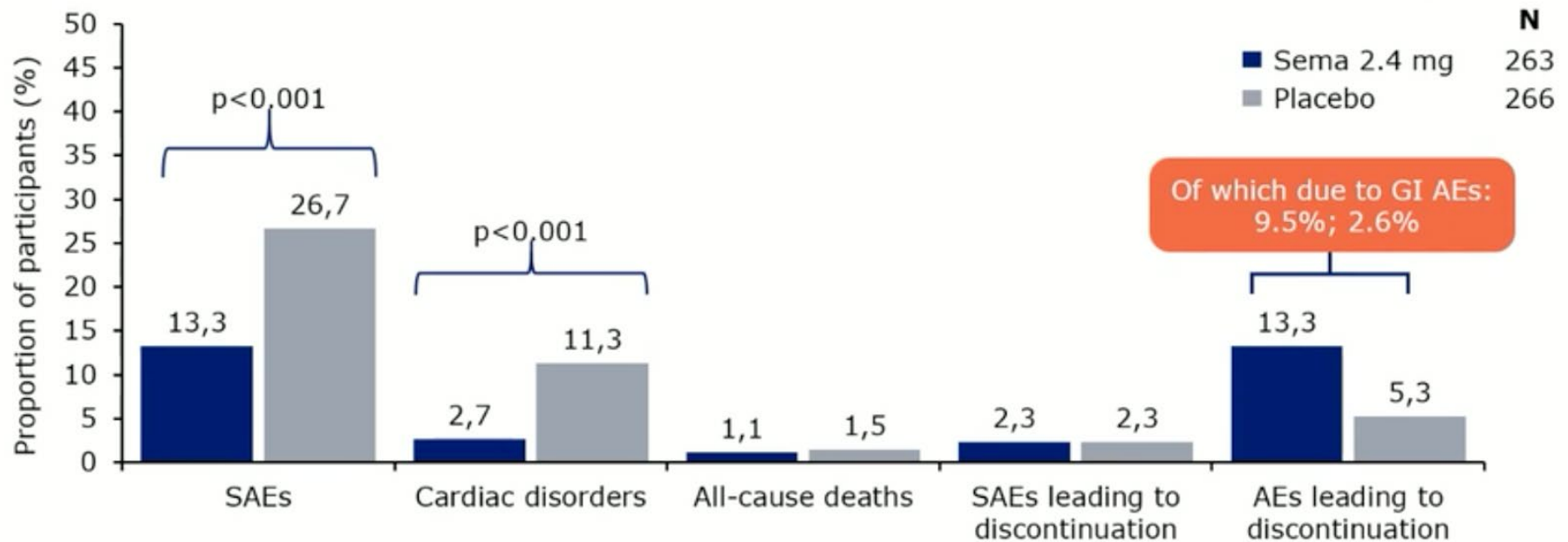


Kosiborod et al, NEJM 2023, 389(12):1069-84

STEP-HFpEF

Verträglichkeit und Sicherheit

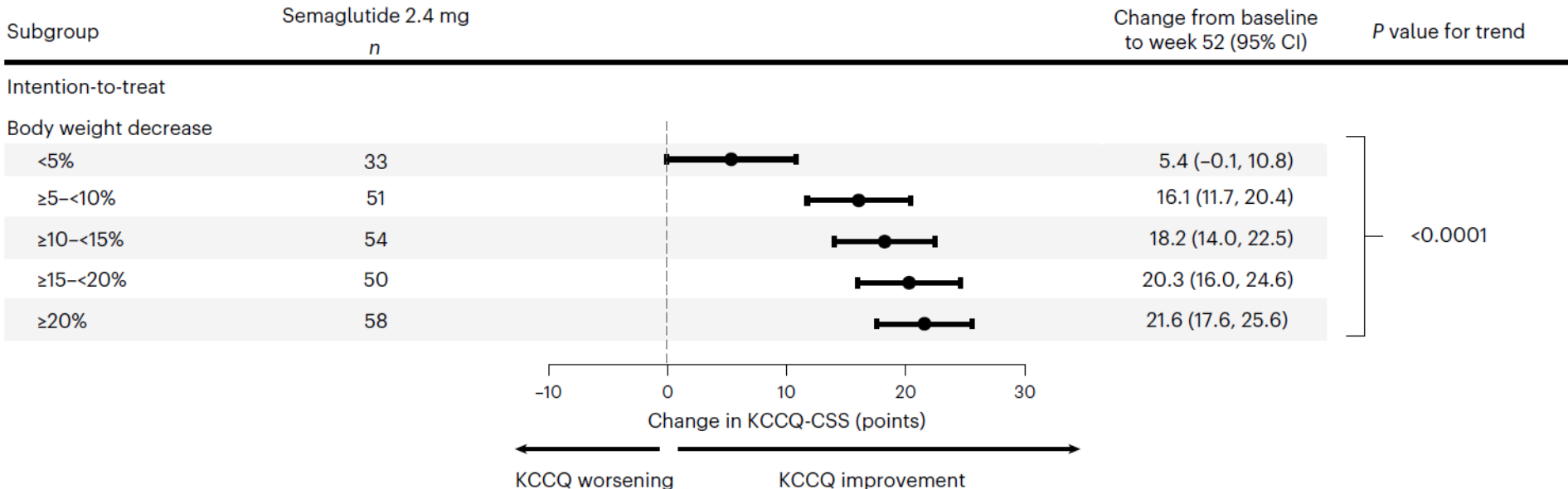
HFpEF and BMI >30, N=529, 56% females, LVEF 57%; 1:1 semaglutide 2.4 mg s.c. 1x/week; 52 weeks
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Kosiborod et al, NEJM 2023, 389(12):1069-84

Verbesserung von Symptomen und Belastbarkeit bei HFpEF unter GLP1-RA Behandlung korreliert mit Gewichtsreduktion

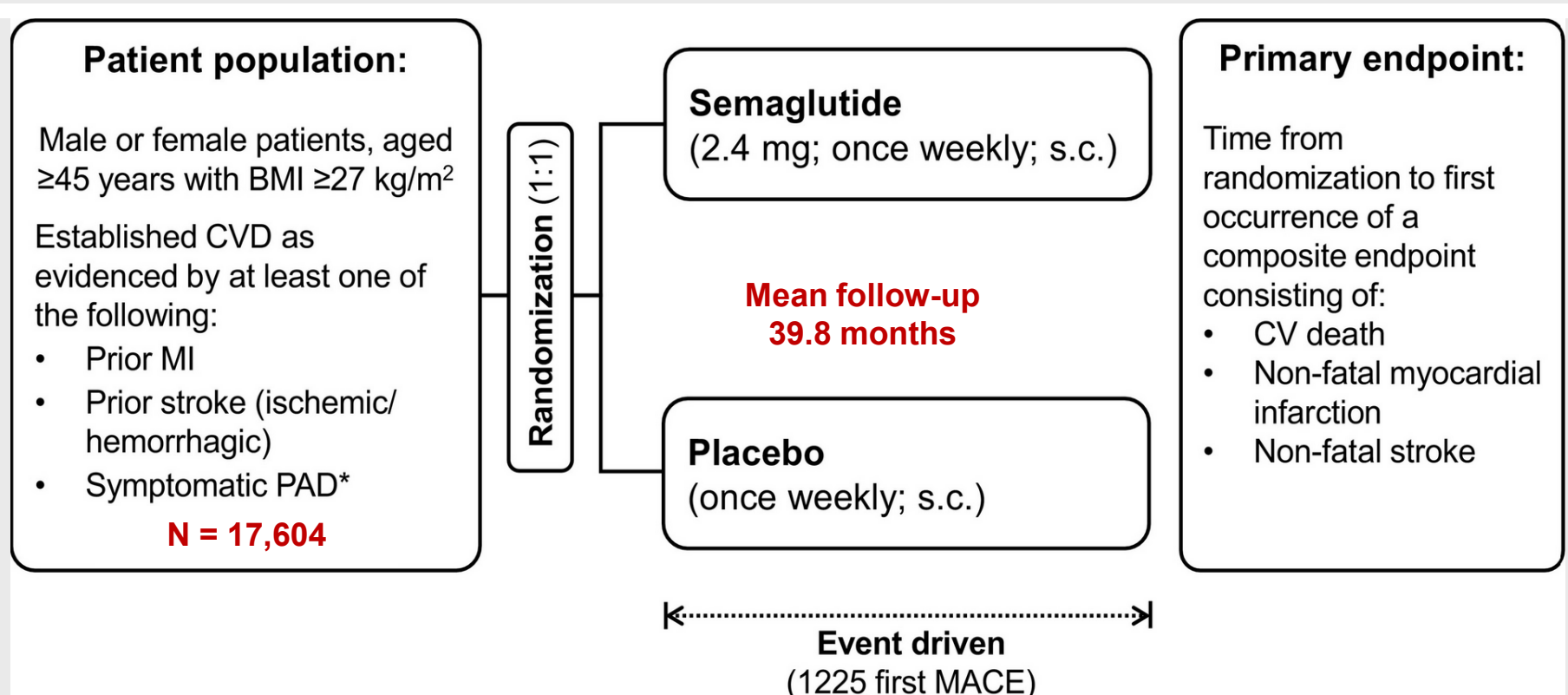
Relationship between weight loss with semaglutide and change in KCCQ-CSS



STEP-HFpEF; Borlaug et al., Nat Med 2023; 29(9):2358-65

SELECT

Semaglutide bei Patienten mit kardiovaskulärem Risiko und Adipositas ohne Diabetes



SELECT Design. Ryan et al., AHJ 2020;229:61-9
Lincoff et al., NEJM 2023;389(24):2221-32

Baseline Characteristics

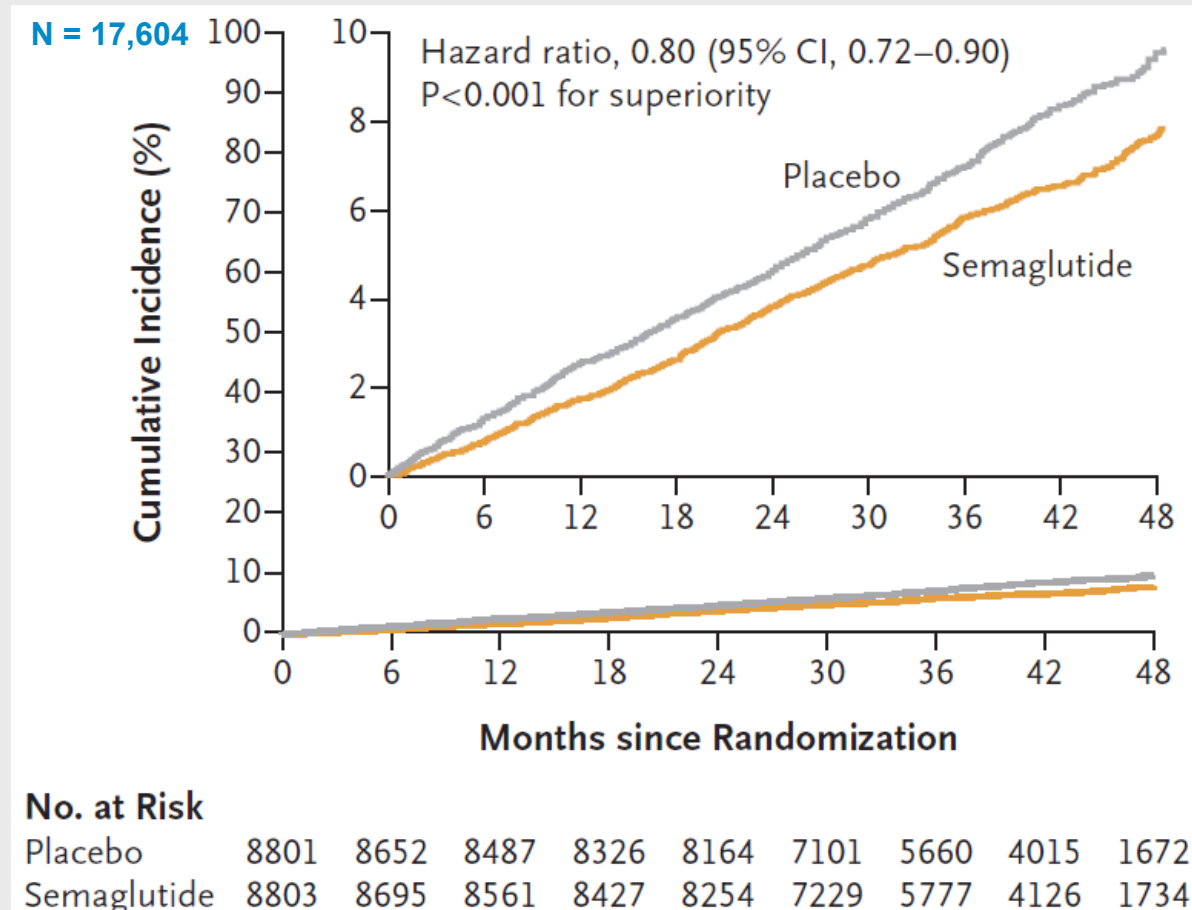
SELECT

semaglutide | effects on cardiovascular outcomes in people with overweight or obesity

(Percent of patients unless otherwise noted)	Semaglutide (N = 8803)	Placebo (N = 8801)
Age (yrs) – mean $\pm$ SD	61.6 $\pm$ 8.9	61.6 $\pm$ 8.8
Female sex	27.8	27.5
Body Mass Index (BMI, kg/m ²) – mean $\pm$ SD	33.3 $\pm$ 5.0	33.4 $\pm$ 5.0
BMI $\geq$ 30 kg/m ²	71.0	71.9
HbA _{1c} (%) – mean $\pm$ SD	5.78 $\pm$ 0.34	5.78 $\pm$ 0.33
HbA _{1c} 5.7-6.4%	66.8	66.1
Prior MI	76.4	76.2
Prior heart failure	24.5	24.2
Systolic BP (mm Hg) – mean $\pm$ SD	131.0 $\pm$ 15.6	130.9 $\pm$ 15.3
Statin therapy	87.7	87.6
LDL Cholesterol (mg/dL) – median (IQR)	78 (61 - 102)	78 (61 - 102)
Triglycerides (mg/dL) – median (IQR)	134 (99 - 188)	135 (100 - 190)

Lincoff et al., hotline AHA 11.11.23 & NEJM 2023 DOI: 10.1056/NEJMoa2307563

SELECT primary end point: CV death, MI or stroke



701 (8.0%)
569 (6.5%)

20 % RRR

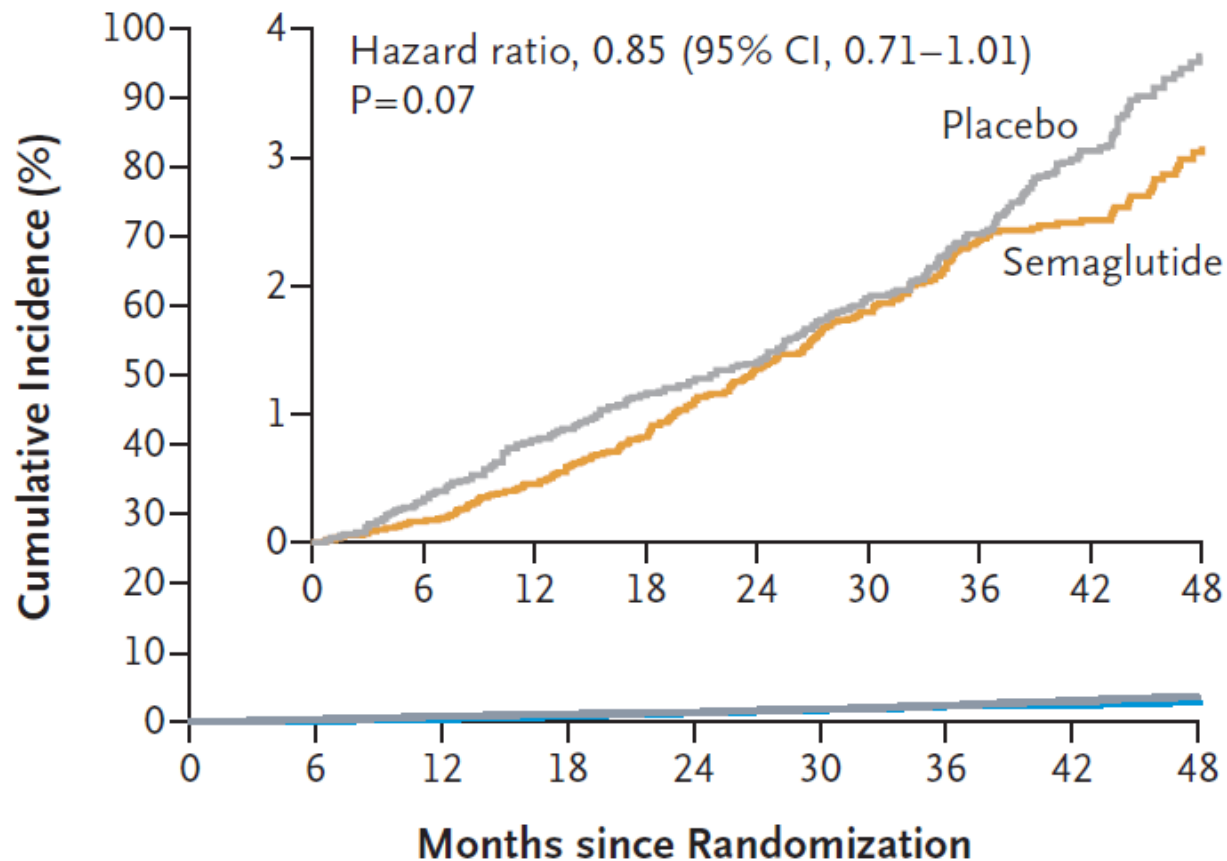
Change in Body Weight
Semaglutide – 9.4%
Placebo: -0.9%

Lincoff et al., NEJM 2023;389(24):2221-32

First confirmatory secondary end point: Death from cardiovascular causes

N = 17,604

Death from Cardiovascular Causes



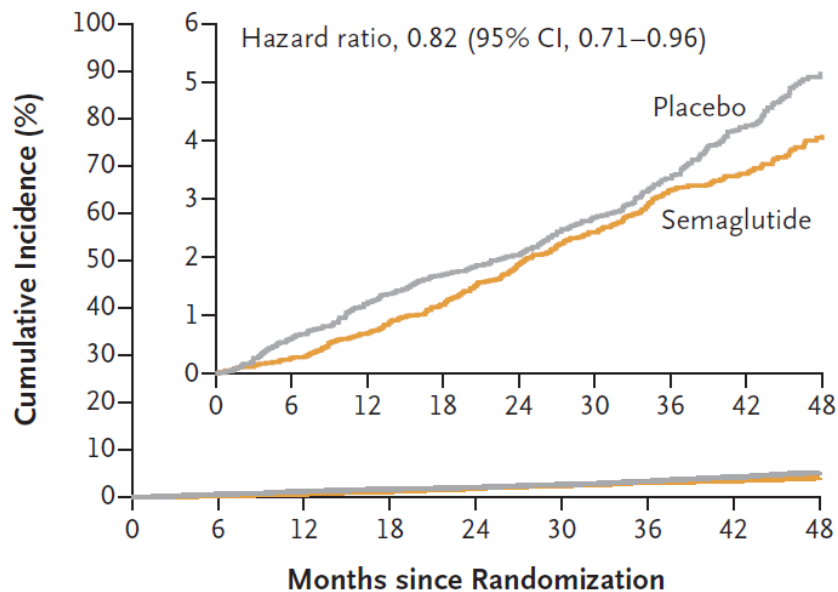
Lincoff et al., NEJM 2023;389(24):2221-32

Secondary end points

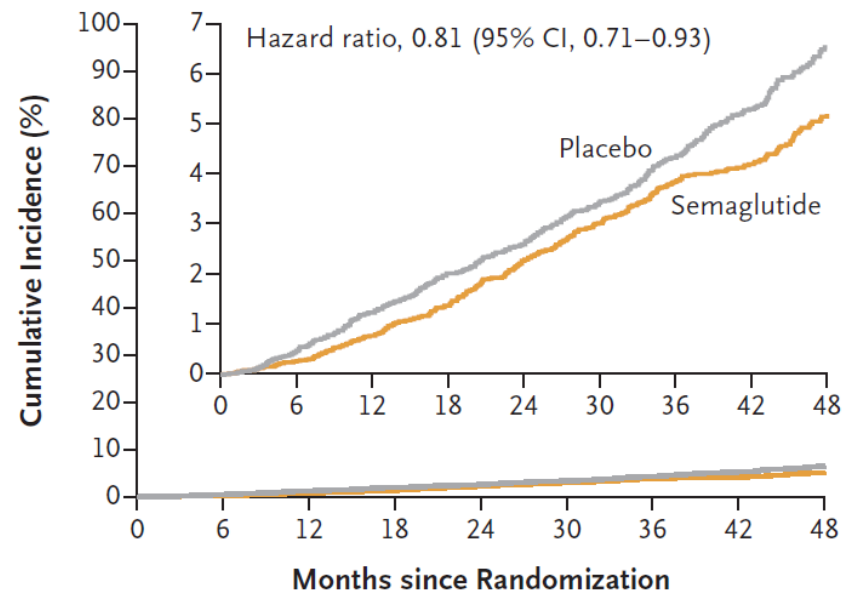
Heart Failure and total Death

N = 17,604

Heart Failure Composite End Point



Death from Any Cause

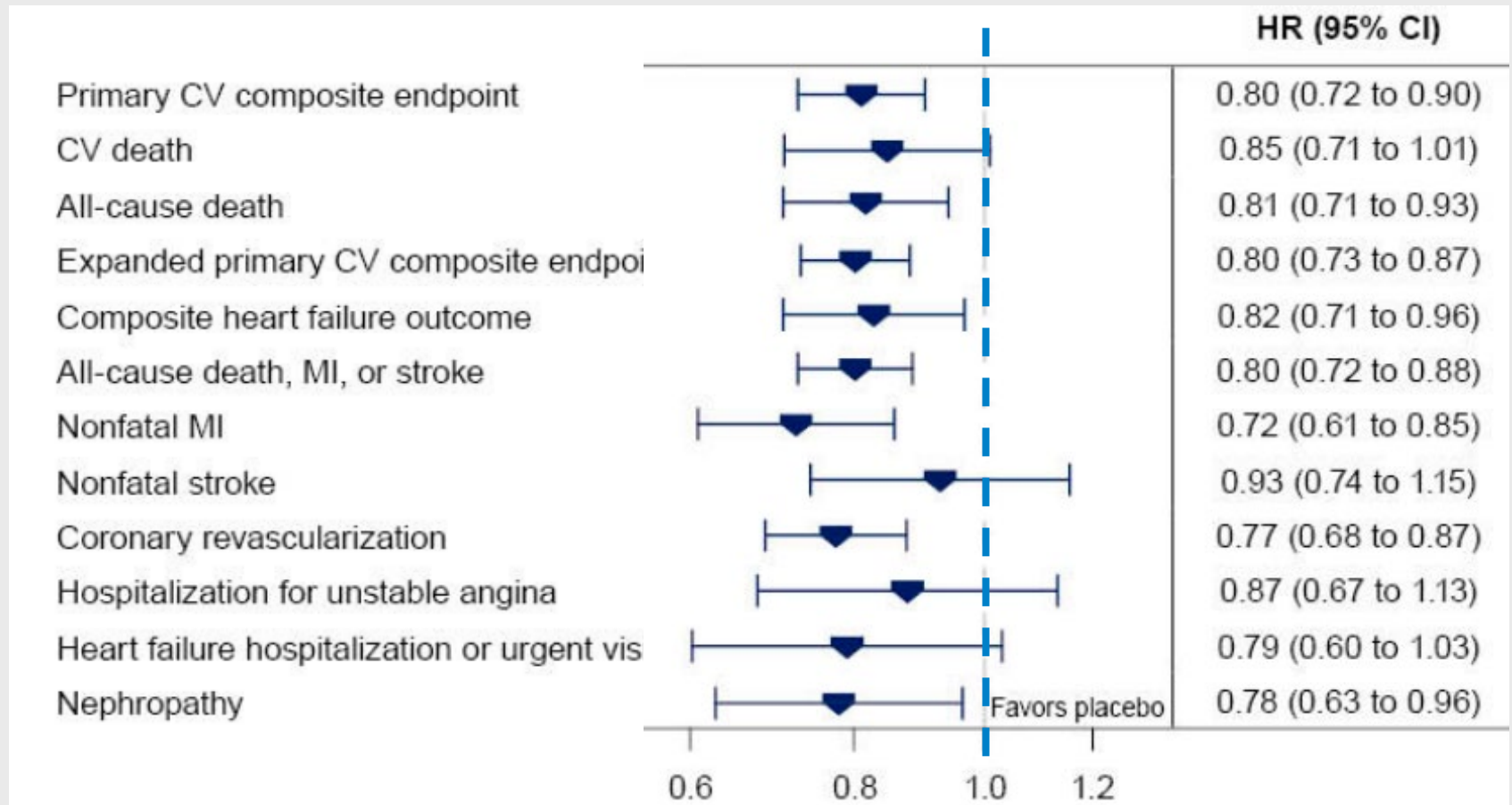


SELECT; Lincoff et al., NEJM 2023;389(24):2221-32

SELECT

Secondary End Points

SELECT; Lincoff et al., NEJM 2023;389(24):2221-32



Selected Adverse Events

(Percent of patients)	Semaglutide	Placebo	P-Value
Serious adverse event (SAE)	33.4	36.4	<0.001
Cardiac disorders	11.5	13.5	<0.001
Infections / infestations	7.1	8.4	0.001
Nervous system	5.0	5.6	0.08
Gastrointestinal	3.9	3.7	0.48
Adverse event leading to drug D/C	16.6	8.2	<0.001
Gastrointestinal	10.0	2.0	<0.001
Metabolism / nutritional	1.2	0.3	<0.001
Adverse events of special interest			
Acute pancreatitis	0.2	0.3	0.28
Gallbladder-related	2.8	2.3	0.04
COVID-19 related	23.9	24.4	0.46
Malignant neoplasms	4.8	4.7	0.92

Lincoff et al., hotline AHA 11.11.23 & NEJM 2023 DOI: 10.1056/NEJMoa2307563

Selected Supportive Secondary Endpoints

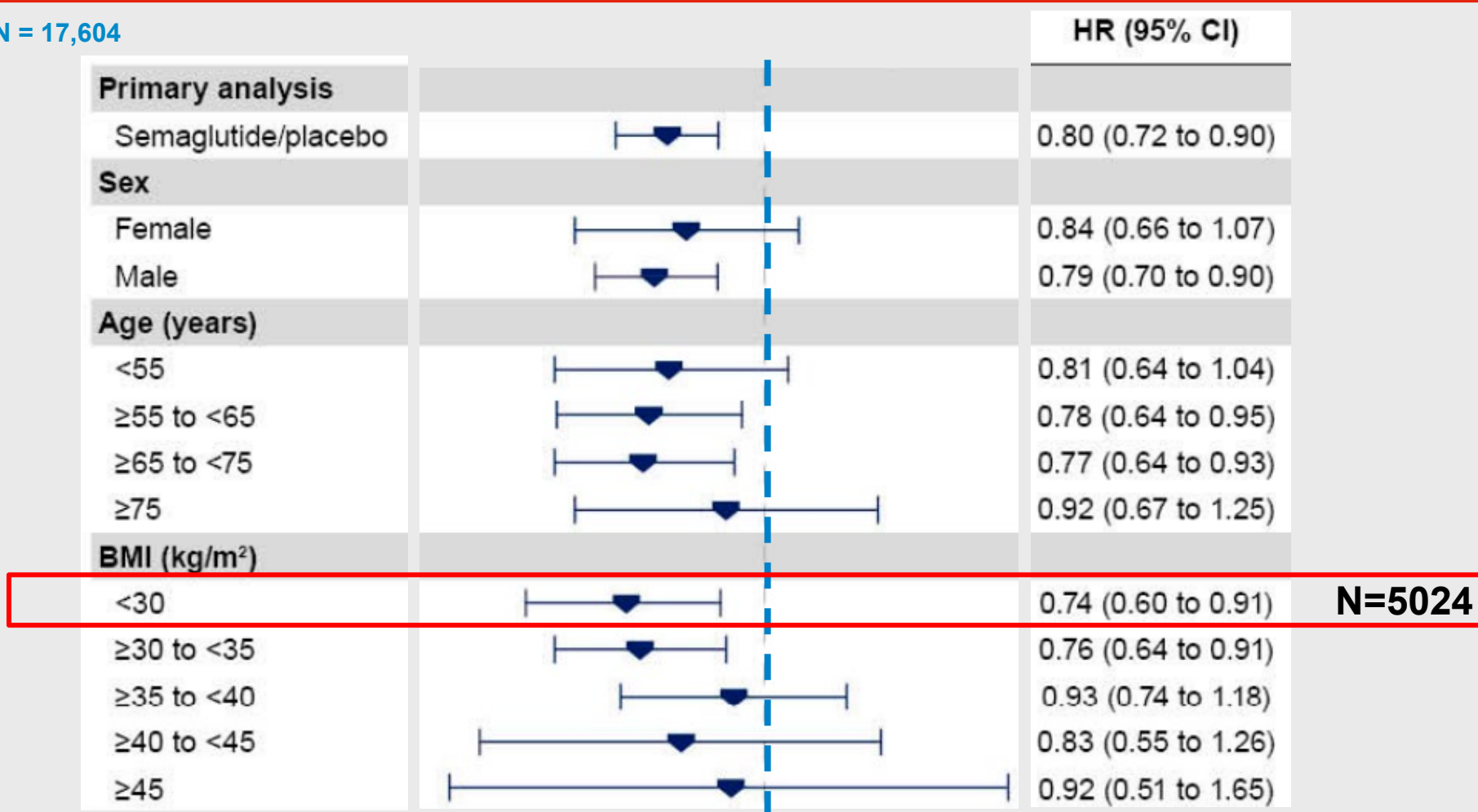
Time to first event	Semaglutide N = 8803	Placebo N = 8801	HR (95% CI)
HbA _{1c} ≥ 6.5% – % pts	3.5	12.0	0.27 (0.24 to 0.31)
HbA _{1c} ≥ 5.7% (pts with baseline <5.7%) – % pts	21.3	50.4	0.33 (0.30 to 0.36)
Change from randomization to week 104			Difference (95% CI)
Systolic BP – mm Hg	–3.8 (0.2)	–0.5 (0.2)	–3.3 (–3.8 to –2.9)
HbA _{1c} – percentage point	–0.3 (0.0)	0.0 (0.0)	–0.3 (–0.3 to –0.3)
hs C-reactive protein – relative change (%)	–39.1	–2.1	–37.8 (–39.7 to –35.9)
LDL-cholesterol – relative change (%)	–5.3	–3.1	–2.2 (–3.2 to –1.1)
Triglycerides – relative change (%)	–18.3	–3.2	–15.6 (–16.7 to –14.6)

SELECT

Prespecified Subgroup Analyses

SELECT; Lincoff et al., NEJM 2023;389(24):2221-32

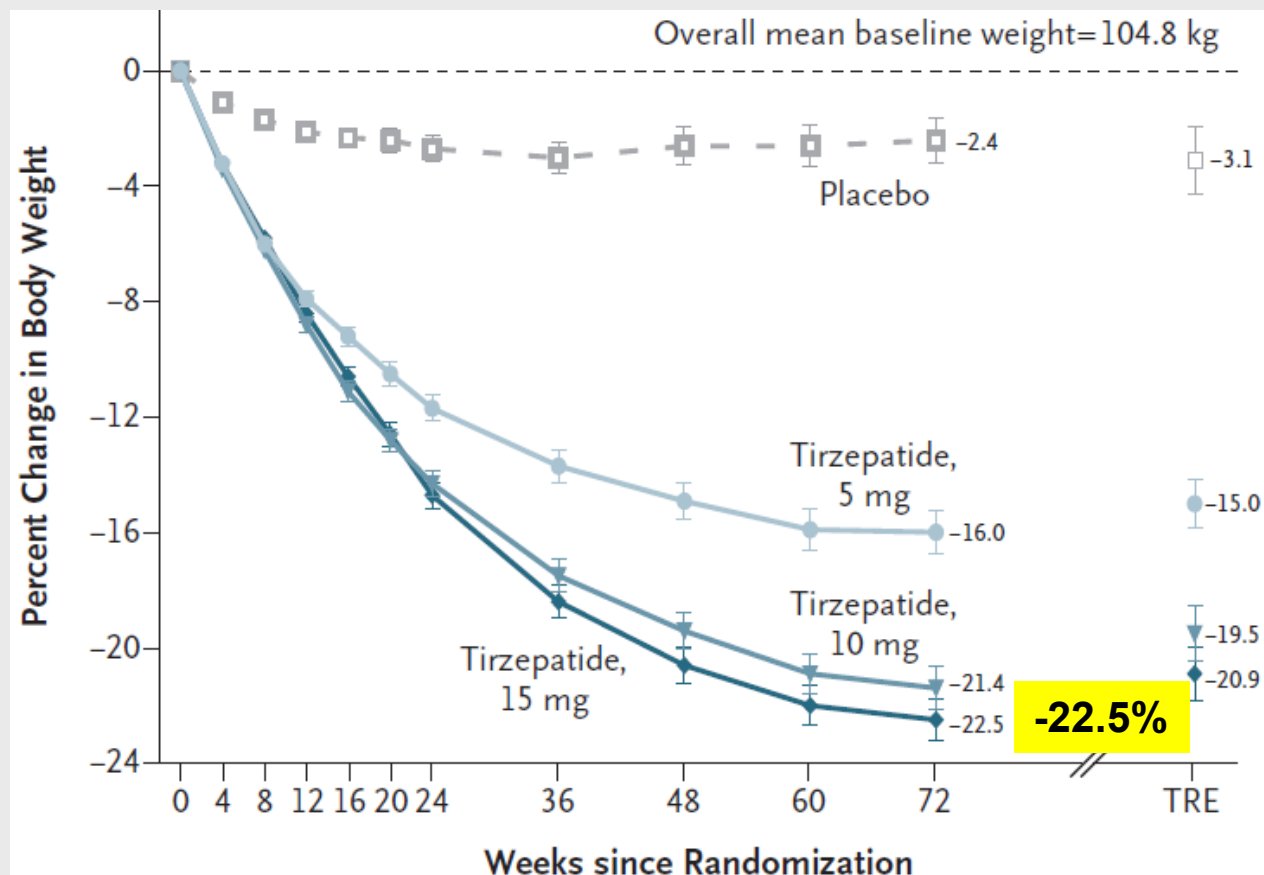
N = 17,604



Dual GLP1- and GIP-Agonist Tirzepatide

SURMOUNT-1; Jastreboff et al. NEJM 2022; 387(3):205-16

glucose-dependent insulinotropic polypeptide and glucagon-like peptide-1 receptor agonist
BMI >30, n=2539, 1:1:1:1, tirzepatide 5 mg, 10 mg, or 15 mg or placebo; 72-wk,



Heart rate

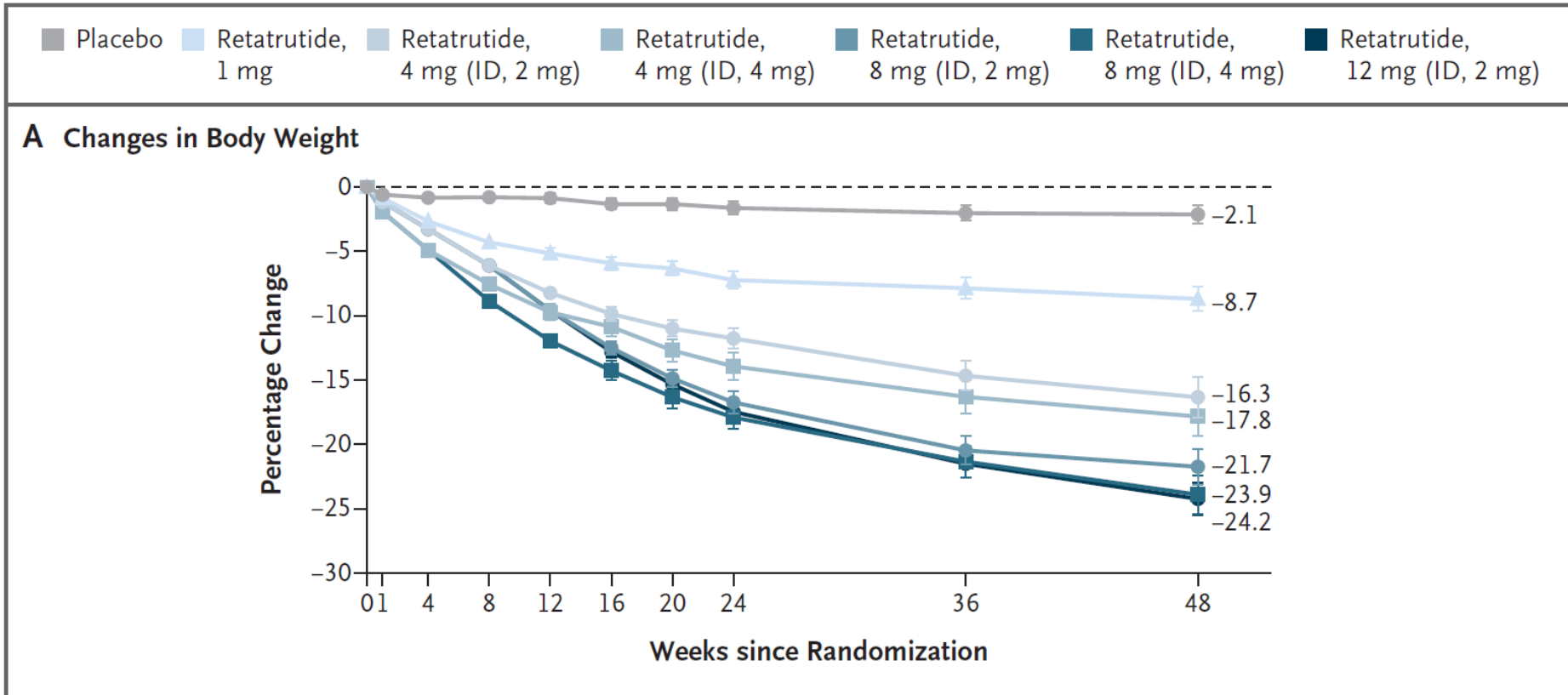
+ 2.1 / min

+ 2.3 / min

+ 5.4 / min

Triple–Hormone-Receptor Agonist Retatrutide

agonist of glucose-dependent insulinotropic polypeptide, glucagon-like peptide 1, and glucagon receptors



Retatrutide Phase 2 Obesity Trial Investigators; Jastreboff et al., NEJM 2023; 389(6):514-26

Gliederung

**Chronisches
Koronarsyndrom**

**Lebensstil:
körperliche Aktivität
Ernährung**

DISKUSSION

Diabetes

Adipositas

Lipide

Bemepedolsäure

PCSK9-Hemmer

Lipoprotein(a)

Screening

Winterschlaf

Alkohol & Zigaretten

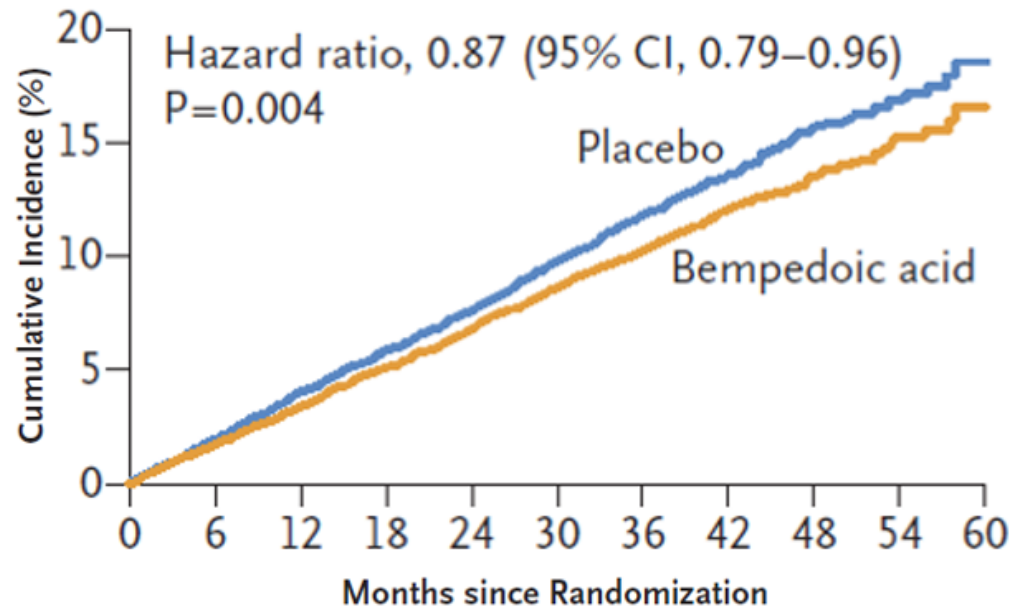
Positive Endpunktstudie für Bempedoinsäure

CLEAR Outcomes; Nissen et al. NEJM 2023; DOI: 10.1056/NEJMoa2215024

N=13,970 statin-intolerant patients; high and very high risk; unable or unwilling to take statins
bempedoic acid monotherapy vs placebo; 40.6 months; delta LDL-C -15.9 %

Kardiovaskulärer Tod,
Myokardinfarkt,
Schlaganfall,
koronare
Revaskularisation

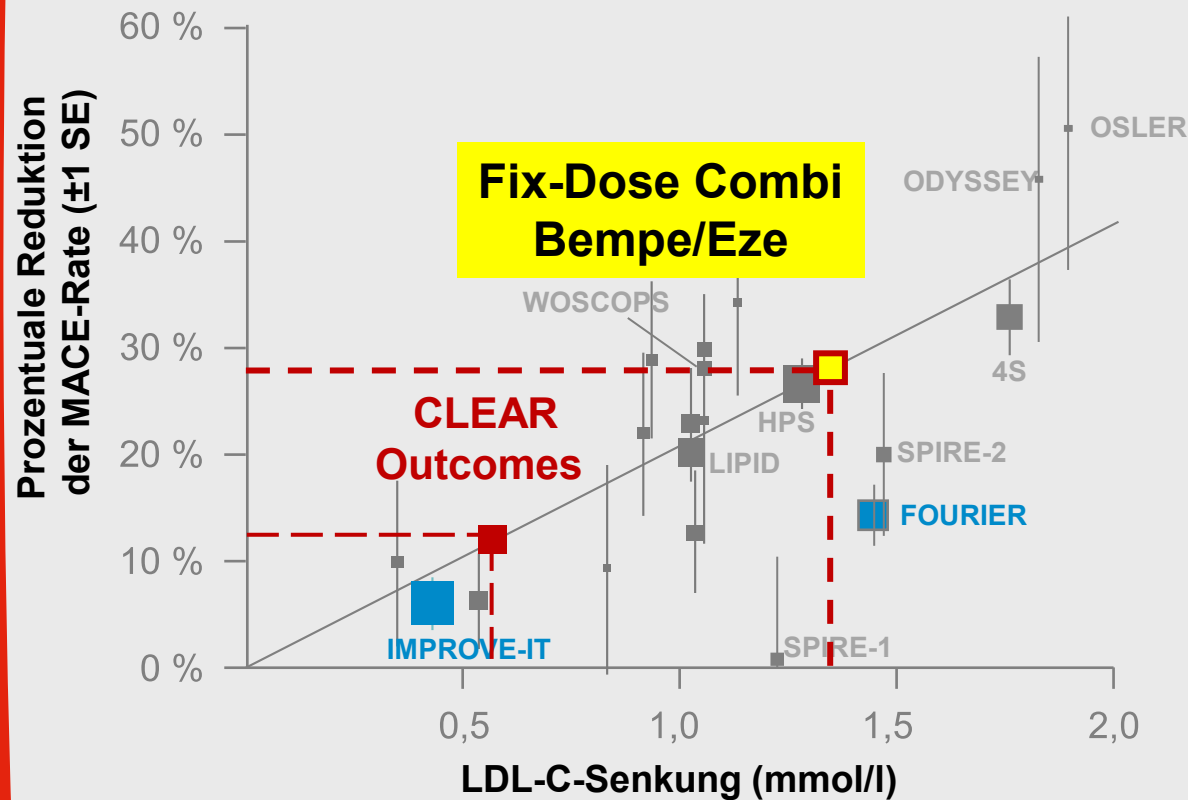
Four-Component MACE (Primary End Point)



No. at Risk

Placebo	6978	6779	6579	6401	6206	5995	5105	2524	1207	513	55
Bempedoic acid	6992	6816	6654	6472	6293	6106	5257	2601	1240	556	74

Extrapolation der CLEAR Outcomes Ergebnisse Bempedoinsäure vs. Bempedoinsäure+Ezetimib



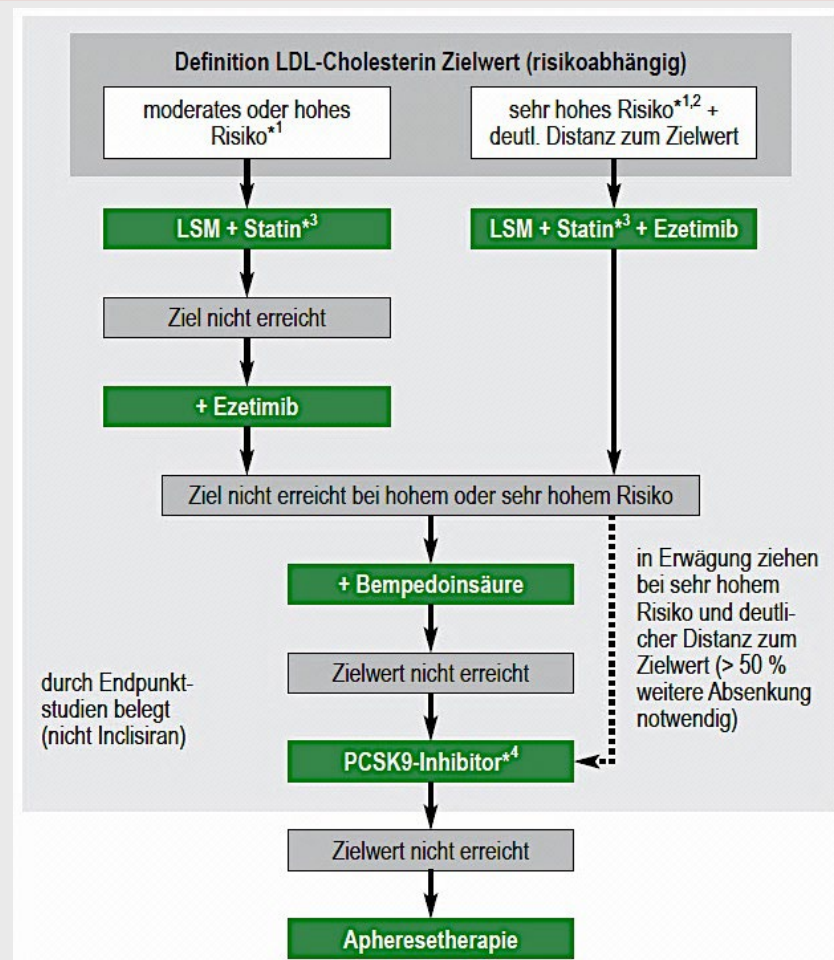
Example:
 60 years, prior MI,
 LDL-C 139 mg/dl (3,59 mmol/l)
 -> 38% LDL-C lowering by
 BA+Eze
 = 52,8 mg/dl (1,37 mmol/l)
 -> RRR for MACE-4: 28%

Baigent C et al. Lancet 2005; 366: 1267-78
 Waters DD et al. Circ Res 2017; 120(10): 1537-9
 Ballantyne CM et al. EJPC 2019 DOI: 10.1177/2047487319864671
 Nissen et al. NEJM 2023; DOI: 10.1056/NEJMoa2215024

State of the Art

LDL-C Senkung – Zielwerte und Strategie

	primärer Zielwert	
kardiovask. Risiko*	LDL-C	
	mg/dL	mmol/L
gering	< 115	< 3,0
moderat	< 100	< 2,6
hoch	< 70	< 1,8
sehr hoch	< 55	< 1,4

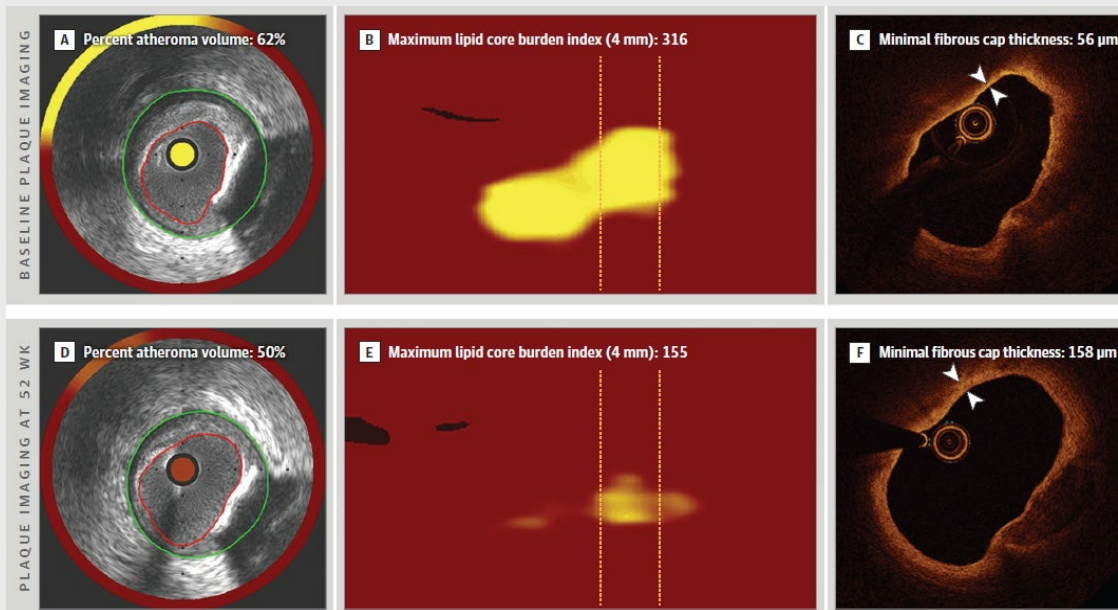


Treatment	Average LDL-C reduction
Moderate-intensity statin	30%
Bempedoic acid plus ezetimibe in statin naive	45%
High-intensity statin	50%
High-intensity statin plus ezetimibe	65%
High-intensity statin plus ezetimibe plus bempedoic acid	70%
PCSK9 inhibitor	60%
PCSK9 inhibitor plus high-intensity statin	75%
PCSK9 inhibitor plus high-intensity statin plus ezetimibe	85%

Katzmann & Laufs, Internist 2022,
doi: 10.1007/s00108-022-01322-y

Intensive LDL-C Senkung nach ACS zusätzlich zu Statinen stabilisiert koronare Plaques

PACMAN-AMI: AMI, n=300, on rosuvastatin 20 mg, alirocumab 150mg q2w vs placebo: achieved LDL-C **24** vs 74 mg/dl
HUYGENS: NSTEMI, n=161, on statin, evolocumab 420 mg sc monthly vs placebo: achieved LDL-C **28** vs 87 mg/dl



Differenz Atherom-
Volumen (IVUS)

Statin+Plazebo -0,92 %
 Statin+Alirocumab **-2,13 %**

Statin+Plazebo -0,06 %
 Statin+Evolocumab **-2,29 %**

Minimale Dicke fibröse
Kappe (OCT)

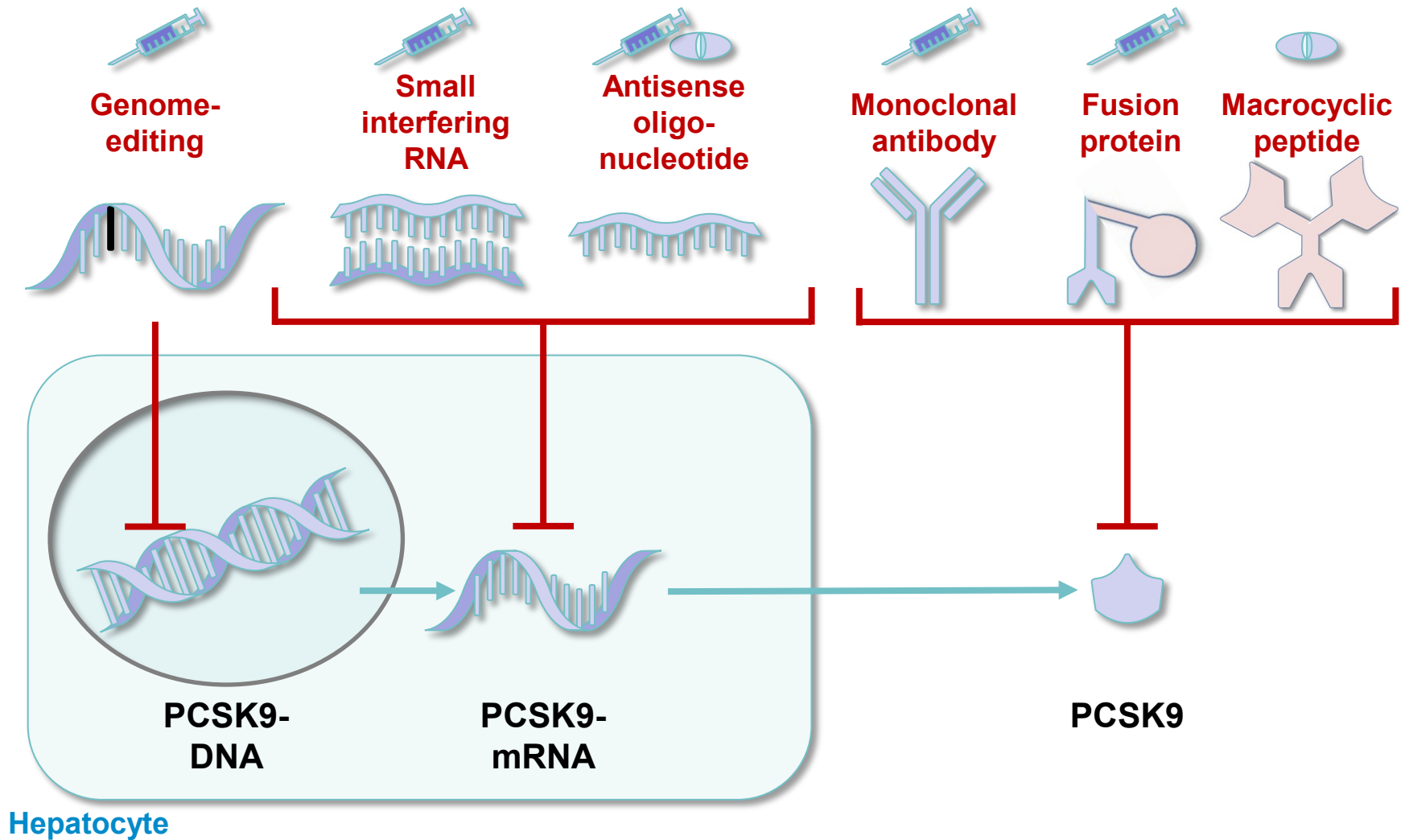
Statin+Plazebo +33,2 μm
 Statin+Alirocumab **+62,7 μm**

Statin+Plazebo +21,5 μm
 Statin+Evolocumab **+42,7 μm**

Räber et al., JAMA 2022,
 doi:10.1001/jama.2022.5218

Nicholls et al., JACC Cardiovasc Imag 2022;
 doi.org/10.1016/j.jcmg.2022.03.002

Strategien zur Hemmung von PCSK9

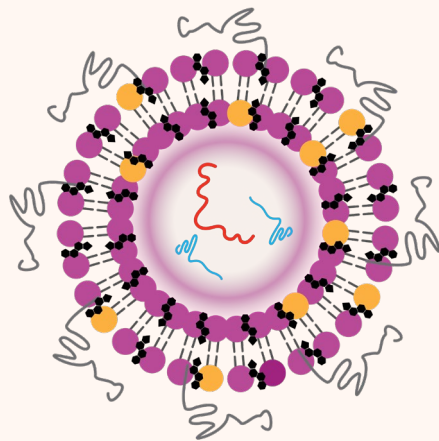


Laufs et al., EHJ 2023; 10.1093/eurheartj/ehad566

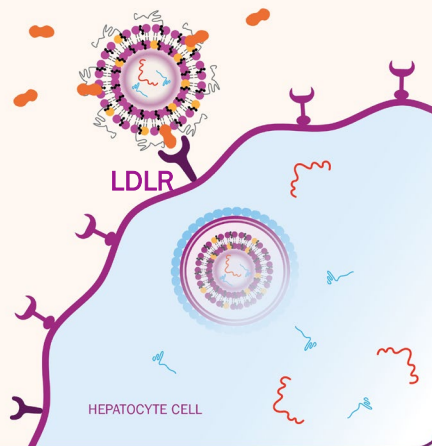
Gentherapie für PCSK9

VERVE-101: CRISPR base editing medicine designed to inactivate hepatic *PCSK9* and lower LDL-C with a single DNA base pair change

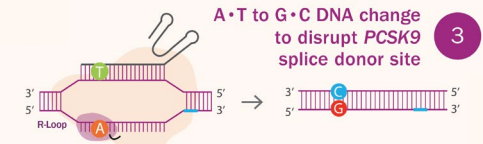
VERVE-101



1 VERVE-101 delivery to the hepatocyte



2 Localization to *PCSK9* gene



3

A to G “spelling” change in DNA to turn off gene



Lipid nanoparticle

Ionizable amino lipid

DSPC

LDL receptor (LDLR)

apoE

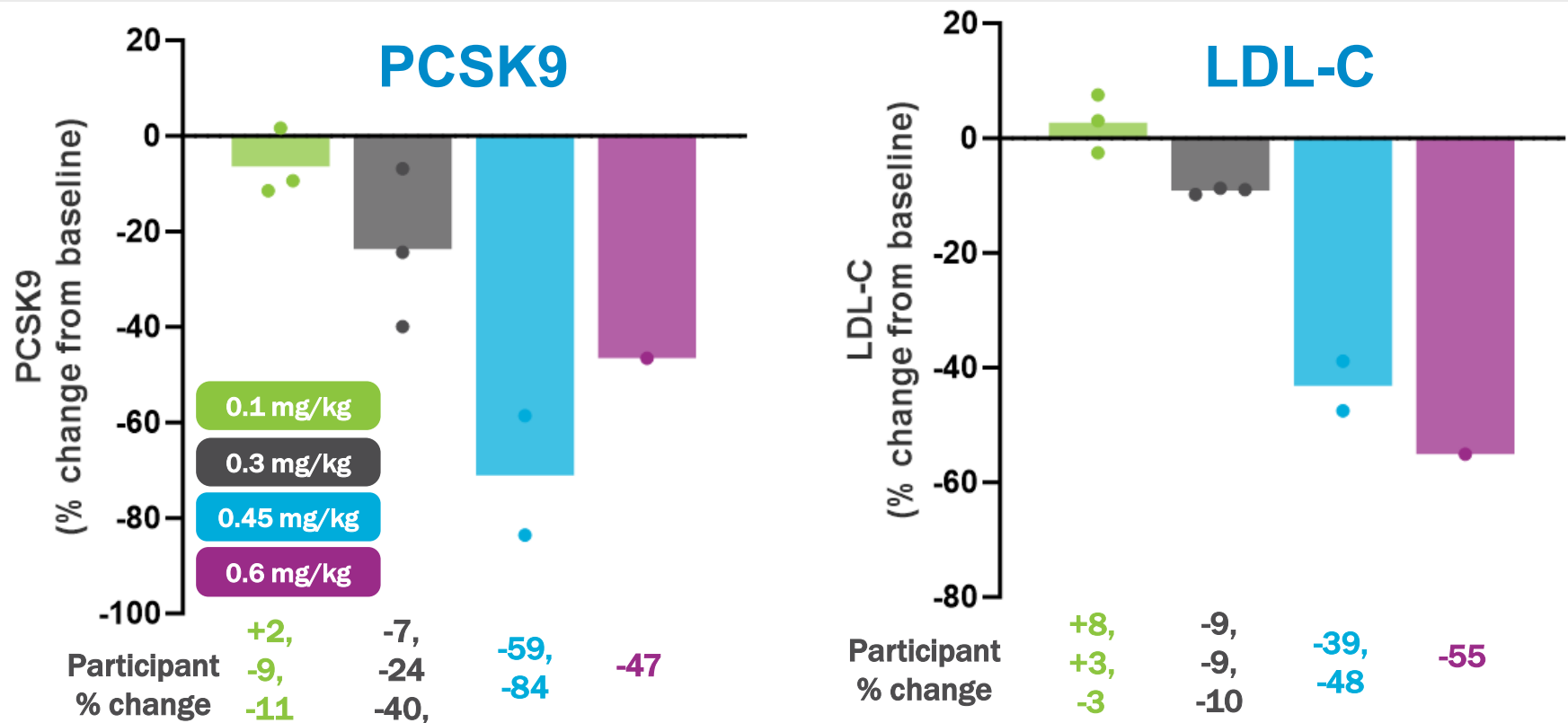
mRNA

gRNA

PEG Lipid

Cholesterol

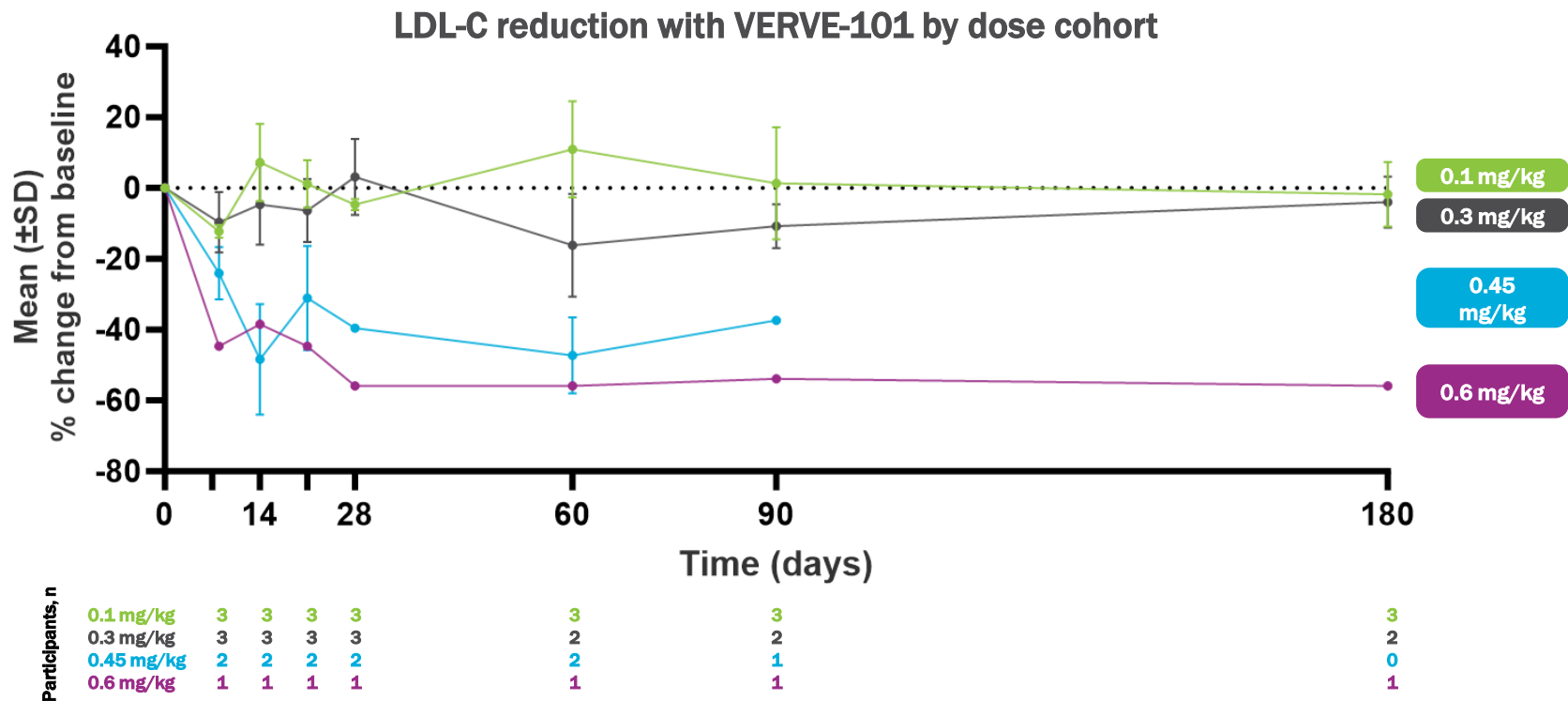
PCSK9 gene modifier VERVE-101 reduziert PCSK9 und LDL-C in Menschen



Andrew Bellinger, AHA Hotline, 12.11.2023

VERVE-101, phase 1, first in men

55% reduction in LDL-C up to 180 days



As of October 16, 2023. Data are from an ongoing study with an open database and have not been fully cleaned
SD, standard deviation

Andrew Bellinger, AHA Hotline, 12.11.2023

SAE in Heart-1

**Herausforderung:
Prüfung der Sicherheit
einer Gen-Therapie**

Fatal cardiac arrest about 5 weeks after infusion **DOSE 0.3 MG/KG**

Myocardial infarction (MI) **on day after infusion**

and non-sustained ventricular tachycardia 4 weeks post infusion

DOSE 0.45 MG/KG

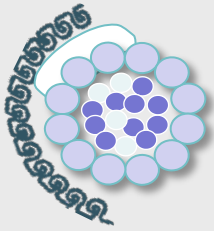
“Independent data and safety monitoring board (DSMB) agreed that SAEs were consistent with a severe, advanced ASCVD patient population and recommended continuing dosing”

Andrew Bellinger, AHA Hotline, 12.11.2023

Gen-Therapie

TARGET	INDICATION	TECHNOLOGY	DEVELOPMENT STATUS			RIGHTS
			Research	IND-enabling	Clinical	
PCSK9 (VERVE-101)	Heterozygous familial hypercholesterolemia ASCVD	Base Editor				
PCSK9 (VERVE-102)	Heterozygous familial hypercholesterolemia ASCVD	Base Editor				
ANGPTL3 (VERVE-201)	Homozygous familial hypercholesterolemia Refractory Hypercholesterolemia	Base Editor				
LPA	ASCVD patients with high blood Lp(a)	Novel Editor				
Undisclosed	Undisclosed ASCVD	Base Editor				
Undisclosed	Undisclosed liver disease	Novel Editor				

A. Bellinger, EAS Hotline, 2023



State of the Art: Lipoprotein(a)

Genetischer Risikomarker für Atherosklerose und Aortenstenose

Aktuelle Empfehlung: Lp(a) einmal im Leben bestimmen

**Konsequenz: Risiko-Stratifizierung, optimale LDL-C Senkung,
Familien-Screening**

Einheit für Lp(a)	Nicht erhöht	Gering erhöht	Stark Erhöht
mg/dL	< 30 mg/dL	< 50 mg/dL	> 50 mg/dL
nmol/L	< 75 nmol/L	< 125 nmol/L	> 125 nmol/L

Pelacarsen

NEJM 2020;382(3):244–55

Olpasiran, Zerlasiran, Lepodisiran

NEJM 2022;387:1855–64

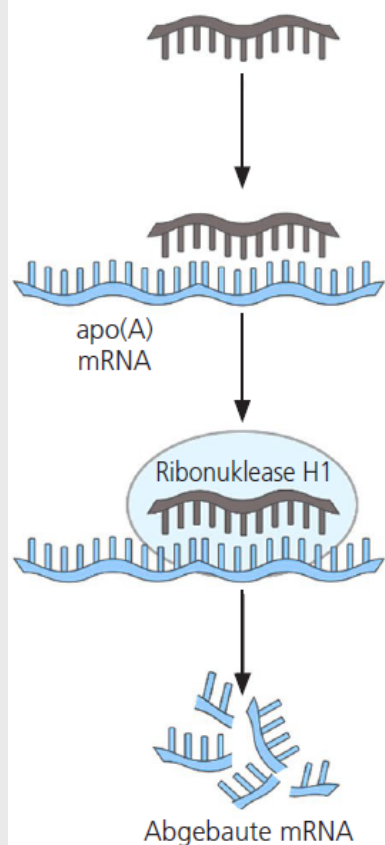
JAMA 2023;330:2075–83

JAMA 2022;327:1679–87

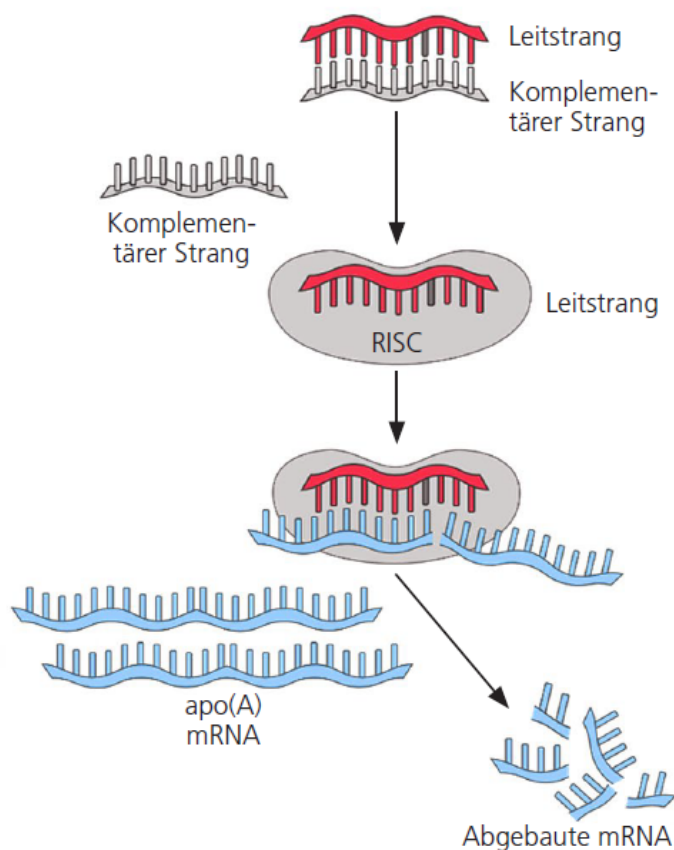
Muvalaplin

JAMA 2023; 330:1042–53

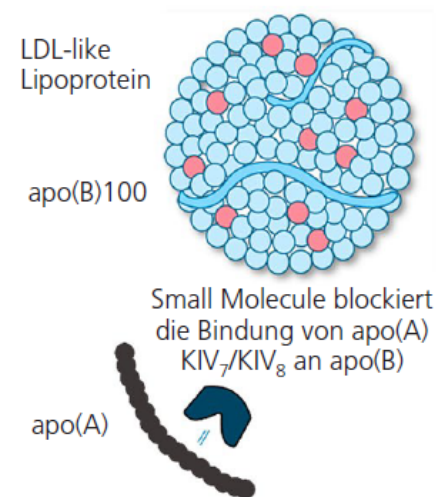
Antisense-Oligonukleotid



Small Interfering RNA



Small Molecule



Pelacarsen

NEJM 2020;382(3):244–55

Olpasiran, Zerlasiran, Lepodisiran

NEJM 2022;387:1855–64

JAMA 2023;330:2075–83

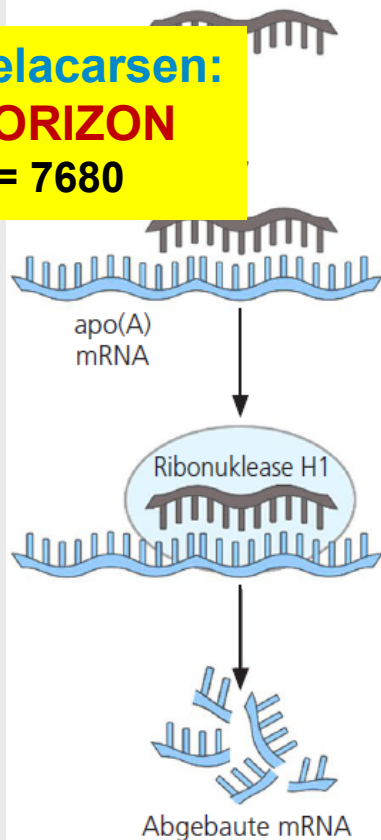
JAMA 2022;327:1679–87

Muvalaplin

JAMA 2023; 330:1042–53

Antisense-Oligonukleotid

Pelacarsen:
HORIZON
n = 7680

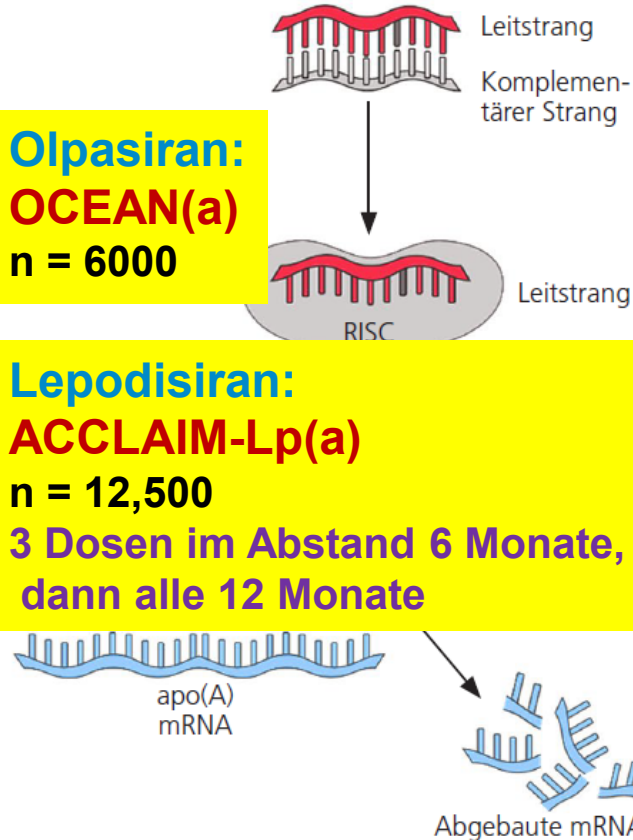


Small Interfering RNA

Olpasiran:
OCEAN(a)
n = 6000

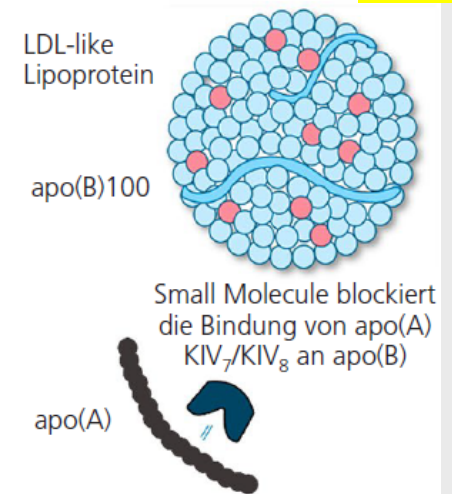
Lepodisiran:
ACCLAIM-Lp(a)
n = 12,500

3 Dosen im Abstand 6 Monate,
dann alle 12 Monate



Small Molecule

oral



Gliederung

**Chronisches
Koronarsyndrom**

**Lebensstil:
körperliche Aktivität
Ernährung**

DISKUSSION

**Diabetes
Adipositas**

Lipide

Bemepedolsäure
PCSK9-Hemmer
Lipoprotein(a)

Screening

Winterschlaf

Alkohol & Zigaretten

Screening-Untersuchungen

Aktuell im Rahmen der U2 durchgeführte Screening-Untersuchungen

Erkrankung	Prävalenz	Therapiemöglichkeit
Ahornsirupkrankheit (MSUD)	1 : 160.000	Diät
Phenylketonurie (PKU)	1 : 10.000	Diät
Mukoviszidose	1 : 4.500	Symptomatisch

Bislang nicht durchgeführte Screeninguntersuchungen

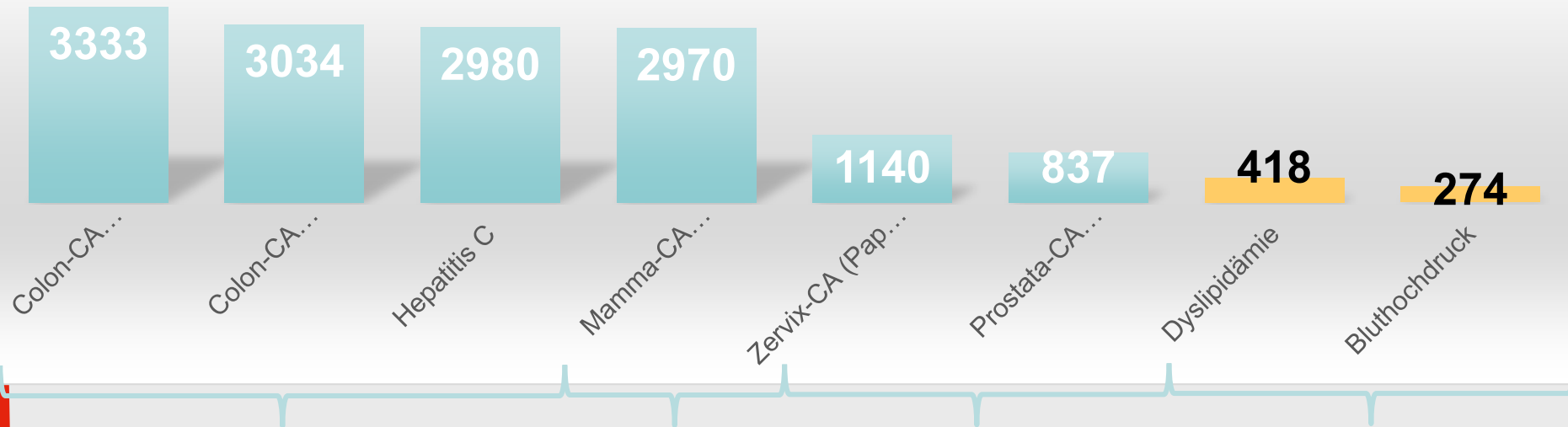
Erkrankung	Prävalenz	Therapiemöglichkeit
Familiäre Hypercholesterinämie	~ 1 : 300	Statin

Folie von S. Baldus – Nationale Herz-Kreislauf-Initiative

Schmidt et al. Familial hypercholesterolemia in primary care in Germany. Diabetes and cardiovascular risk evaluation: Targets and Essential Data for Commitment of Treatment (DETECT) study. Atherosclerosis. 2017;266:24-30. doi:10.1016/j.atherosclerosis.2017.08.019

Rationale für kardiovaskuläres Screening

Number needed to screen über 5-15 Jahre
Verhinderung eines Todesfalls



Folie von S. Baldus

Rembold, BMJ 1998, Tang et al., BMJ 2015,, Wolfram et al., J Hepatol 2015, Omland et al., J Hepatol 2009, Gates, Am J Phys 2001, Loeb et al., J Clin Oncol 2010

Gliederung

**Chronisches
Koronarsyndrom**

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körperliche Aktivität
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DISKUSSION

Diabetes

Adipositas

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Lipoprotein(a)

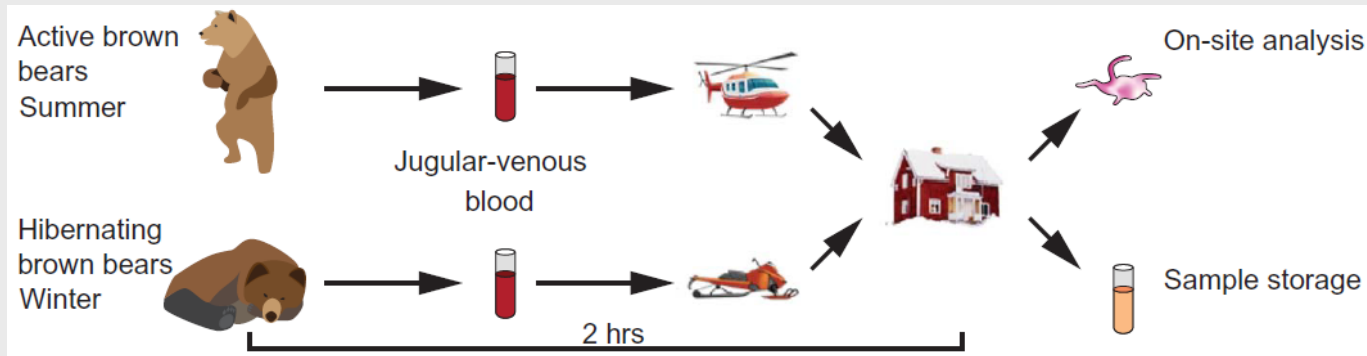
Screening

Winterschlaf

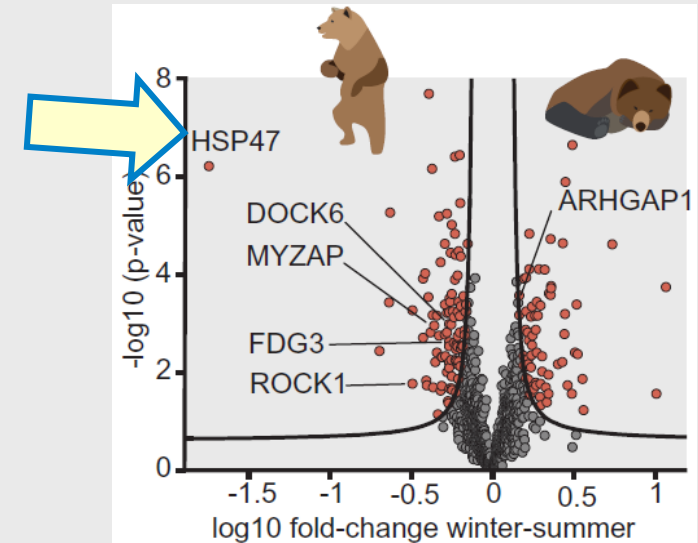
Alkohol & Zigaretten

Winterschlaf von Braunbären gibt Hinweise für Thromboseschutz

Thienel et al., Science 2023; 380:178–87



© LMU Klinikum / Tobias Petzold



Herabregulation von Hitzeschockprotein 47 schützt vor Thrombose bei Immobilität

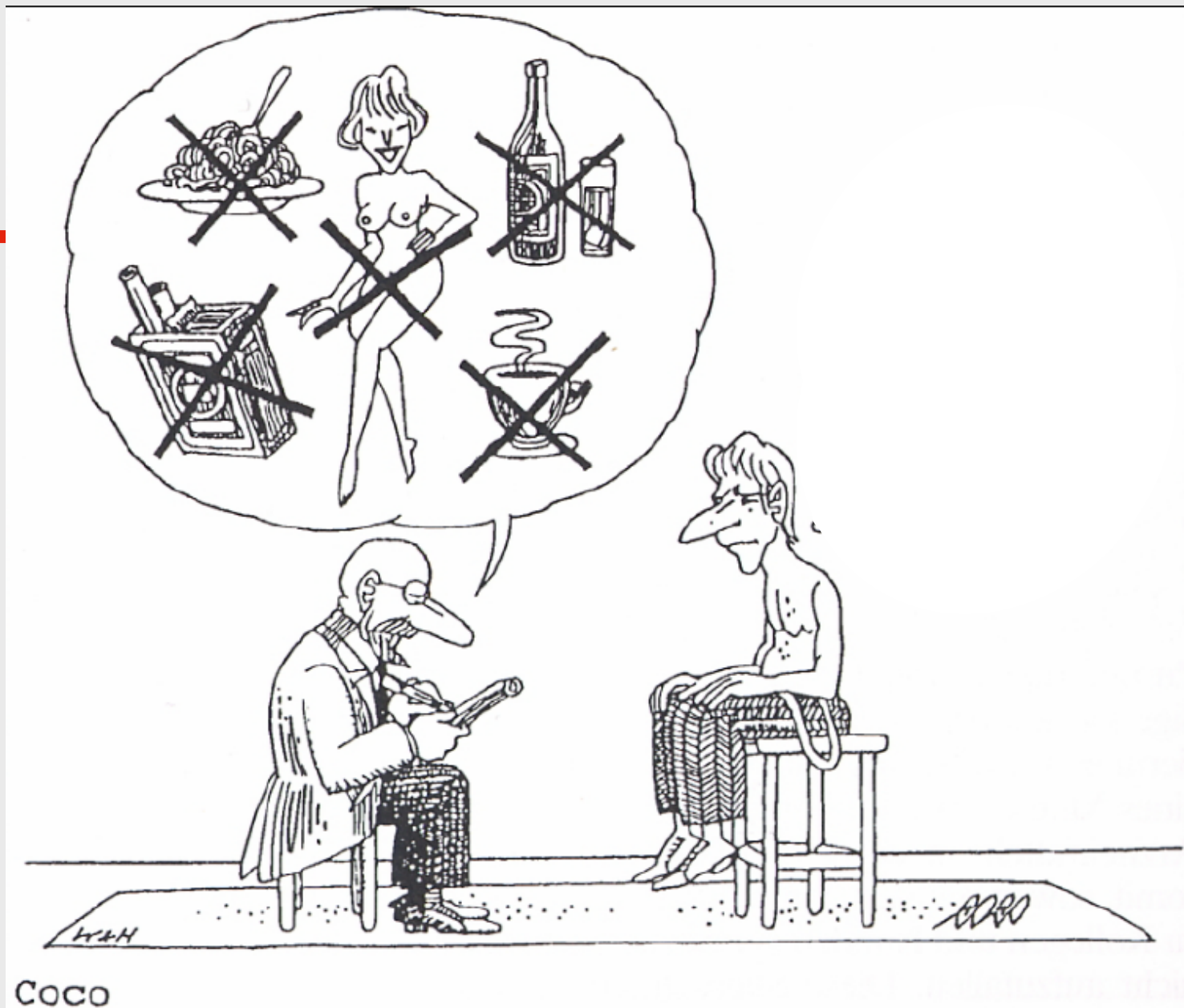
Thienel et al., Science 2023; 380:178–87

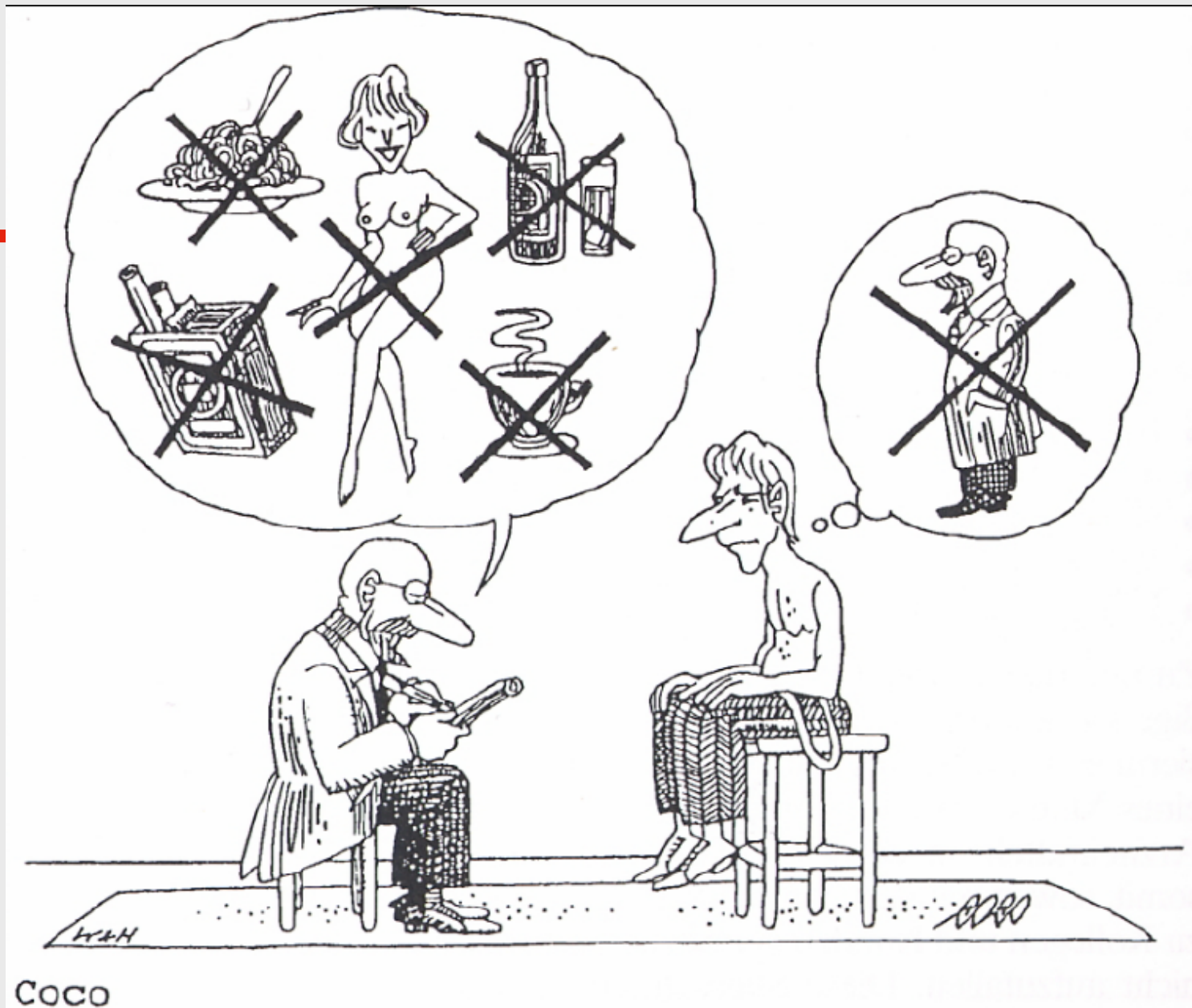
Massenspektroskopie-basierte Proteomik: in Winterruhe wurden gegenüber der Sommeraktivität 71 Proteine hoch- und 80 herunterreguliert

Hitzeschockprotein 47 im Winterschlaf 55-fach herunterreguliert

evolutionär konservierter Mechanismus zur Thromboseprävention in verschiedenen Spezies, parallele Beobachtung bei Querschnittslähmung und Immobilisation (DLR/NASA Studie)

Molekularer Mechanismus: HSP47 wichtig für Interaktion von Blutplättchen und Entzündungszellen









JAMA Intern Med. 2016;176(7):905-12

BRIEF OBSERVATION

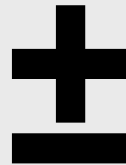
The American Journal of Medicine (2017) 130, 95-100

Red Wine Prevents the Acute Negative Vascular Effects of Smoking

Viktoria Schwarz, MD, Katrin Bachelier, MD, Stephan H. Schirmer, MD, PhD, Christian Werner, MD, Ulrich Laufs, MD, Michael Böhm, MD



Chateau
Haut-Pontet,
Saint-Emilion
Grand Cru,
2005



to reach
0.075%

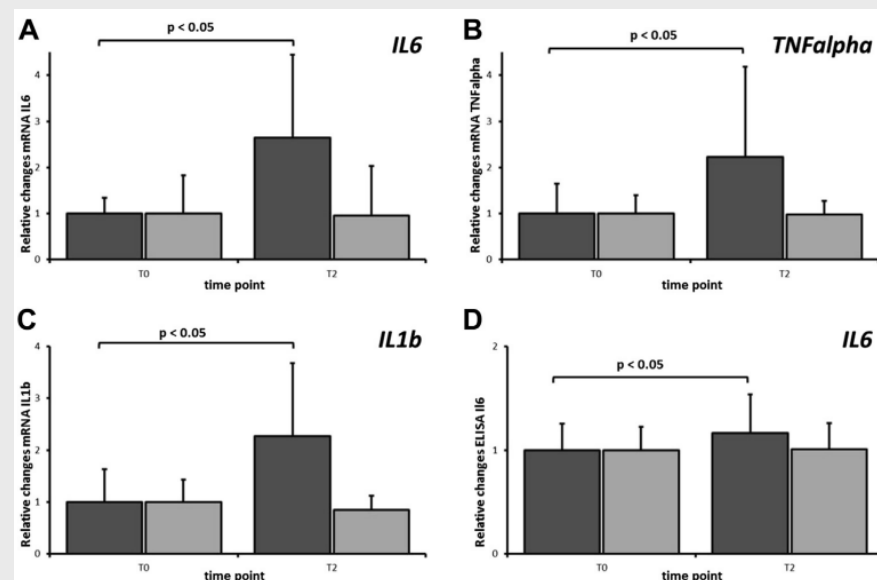
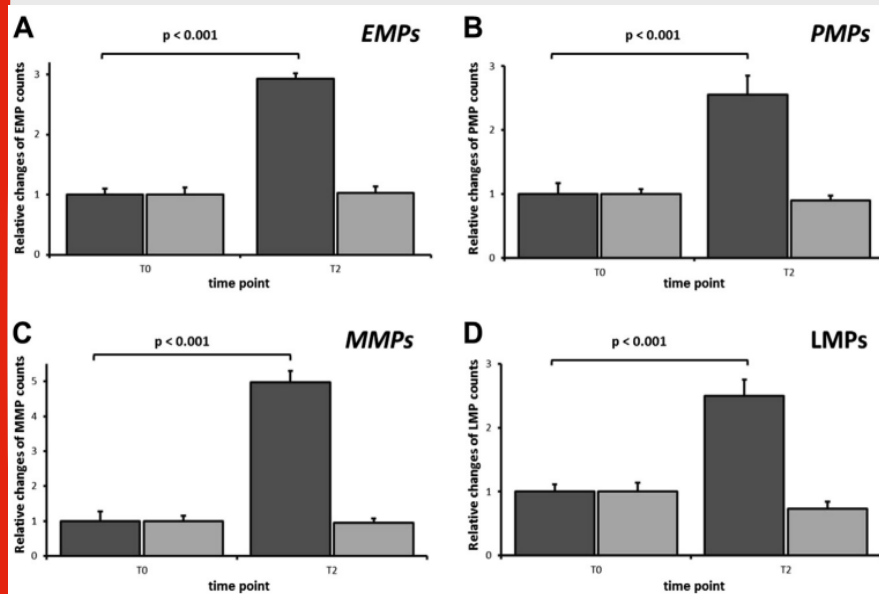
3 Cigarettes
Gauloises Red
45 min after drinking

**Blood + urine sampling
after 100 min and 18 h**

Schwarz et al, Am J Med 2017; 130:95-100

Microparticles

Inflammation



 "Smoking Only"
 "Smoking after Drinking"

Schwarz et al, Am J Med 2017; 130:95-100

Zusammenfassung

CCS: PCI verbessert Symptome
PCI mit intra-koronarer Bildgebung überlegen

Lebensstil: Indikator für Sozialfaktoren
Rezept für körperliche Aktivität
Vorsicht mit Süßstoff und Brausetabletten (NaCl)

Diabetes: Aufwertung von SGLT2i in neuen Leitlinien
Komorbiditäten: CKM-Syndrom, MASLD

Adipositas: Nutrient-Stimulated Hormone-based therapies
GLP1RA verbessern kardiovaskuläre Prognose

Lipide: Screening sinnvoll, 1x für Lipoprotein(a) im Leben