Anti-IL6 Therapie vor und an der Dialyse

Berliner DialyseSeminar 2024

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Conflicts of interest

Consultant and speaker fees
Amgen, Astellas, AstraZeneca, Bayer, Boehringer Ingelheim, GSK, Novartis, Novo Nordisk, Sanofi, Vifor

Years of life lost (YLL) 2016 und 2040

EKFZ Nephrologische Forschung

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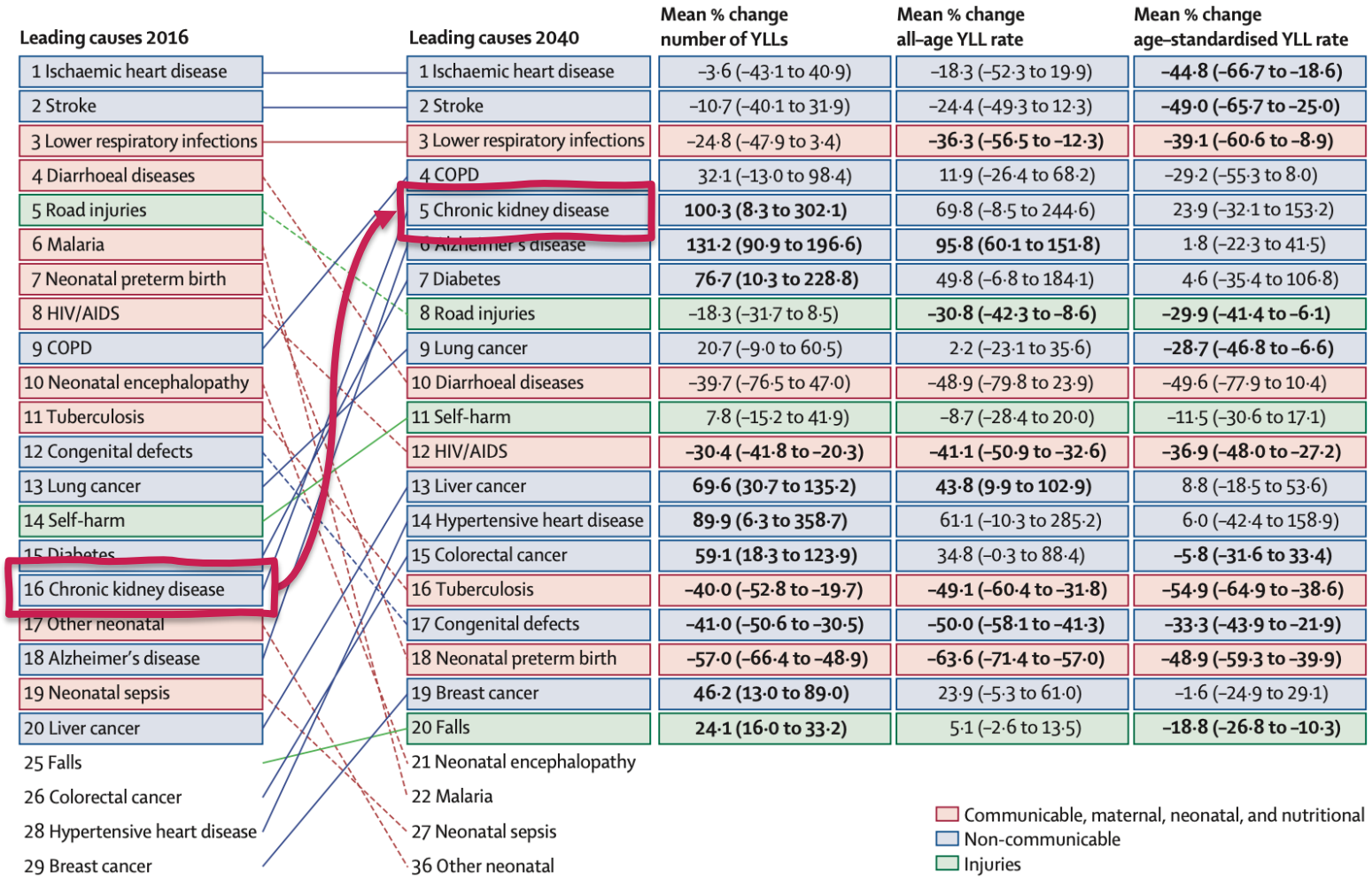
Leading causes 2016

1 Ischaemic heart disease
2 Stroke
3 Lower respiratory infections
4 Diarrhoeal diseases
5 Road injuries
6 Malaria
7 Neonatal preterm birth
8 HIV/AIDS
9 COPD
10 Neonatal encephalopathy
11 Tuberculosis
12 Congenital defects
13 Lung cancer
14 Self-harm
15 Diabetes
16 Chronic kidney disease
17 Other neonatal
18 Alzheimer's disease
19 Neonatal sepsis
20 Liver cancer
25 Falls
26 Colorectal cancer
28 Hypertensive heart disease
29 Breast cancer

Foreman et al. Lancet 2018

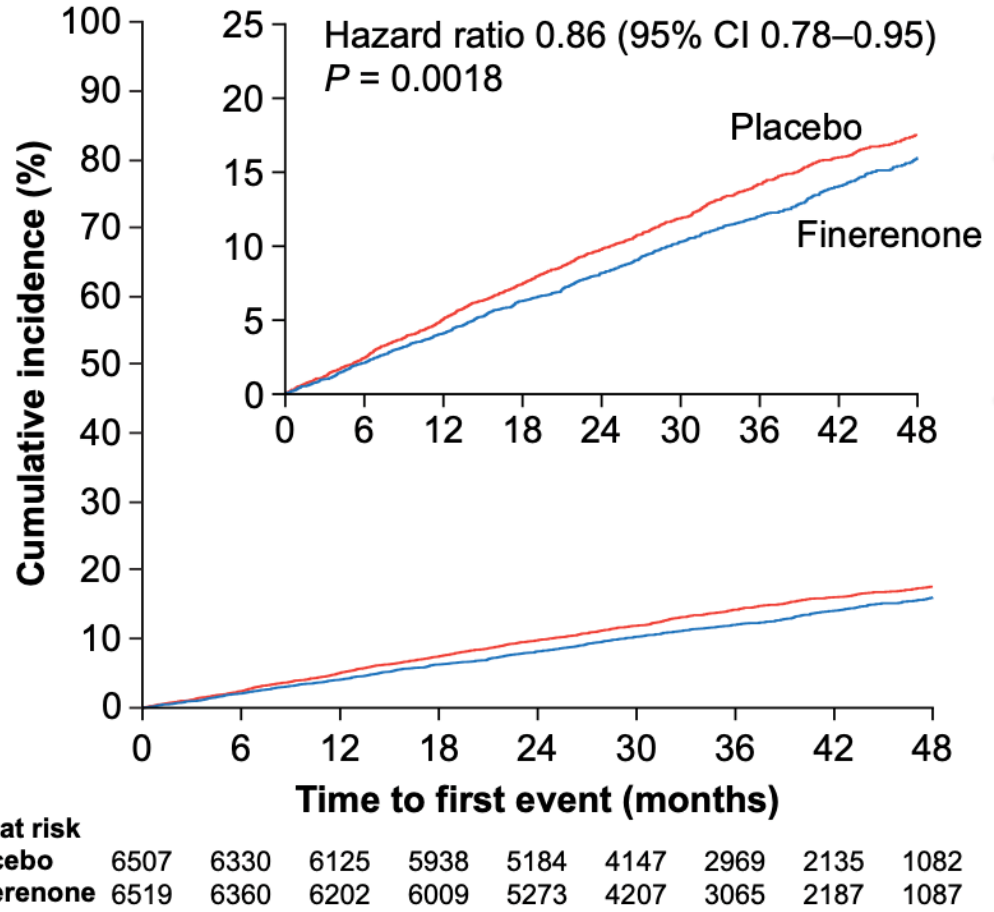
Years of life lost (YLL) 2016 und 2040



Foreman et al. Lancet 2018

FIDELITY Programm

A Composite cardiovascular outcome

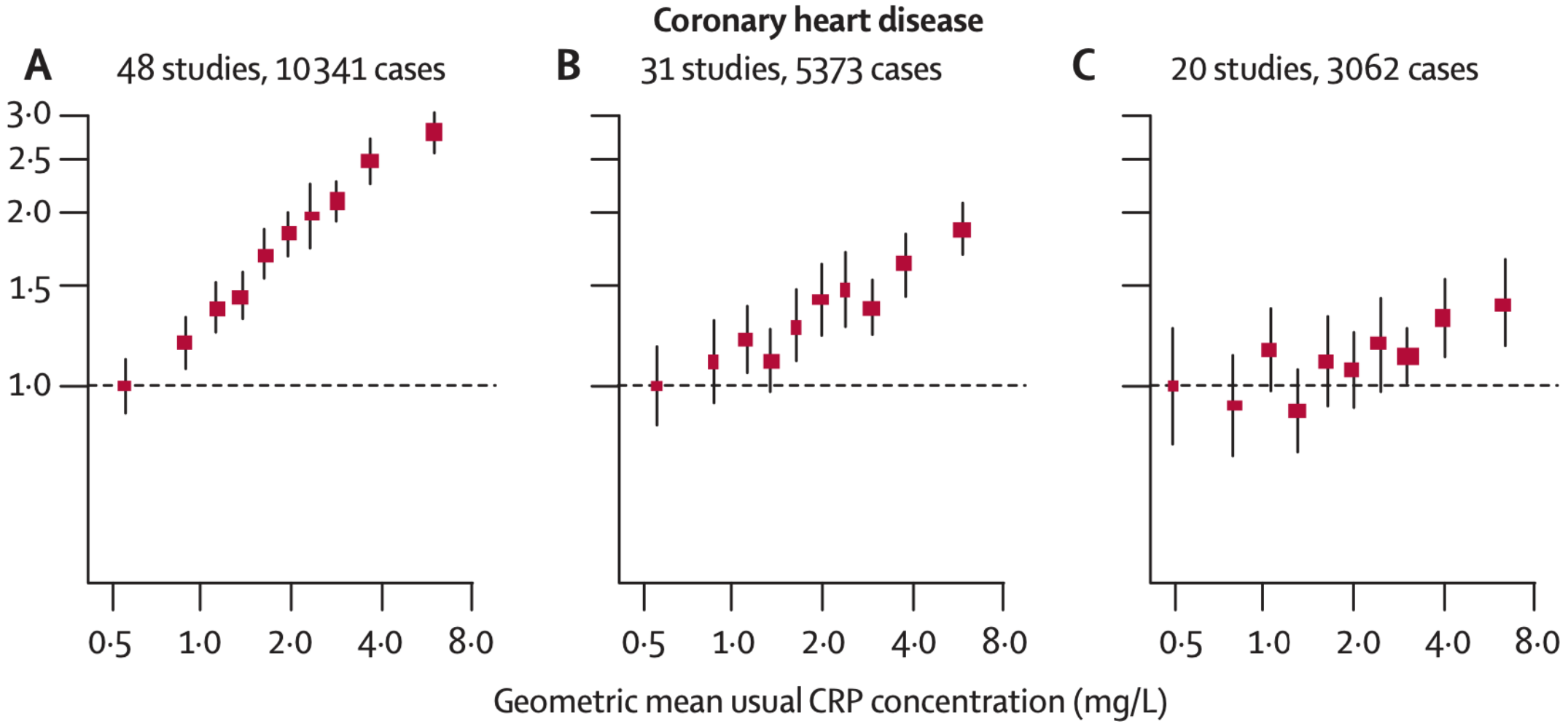


Residuelles Risiko

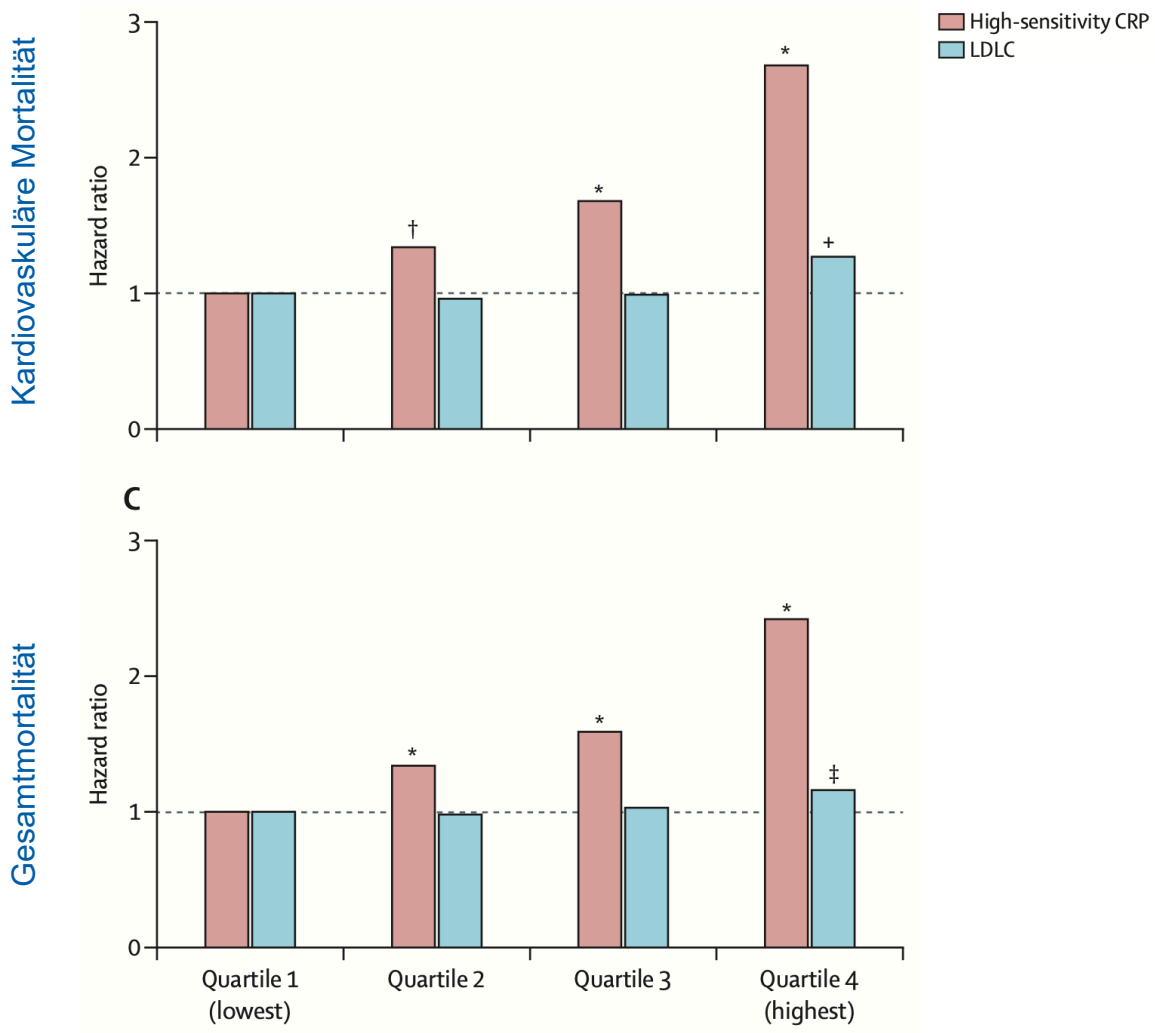
Agarwal et al. Eur Heart J 2021

Inflammation

Inflammation und KHK-Risiko

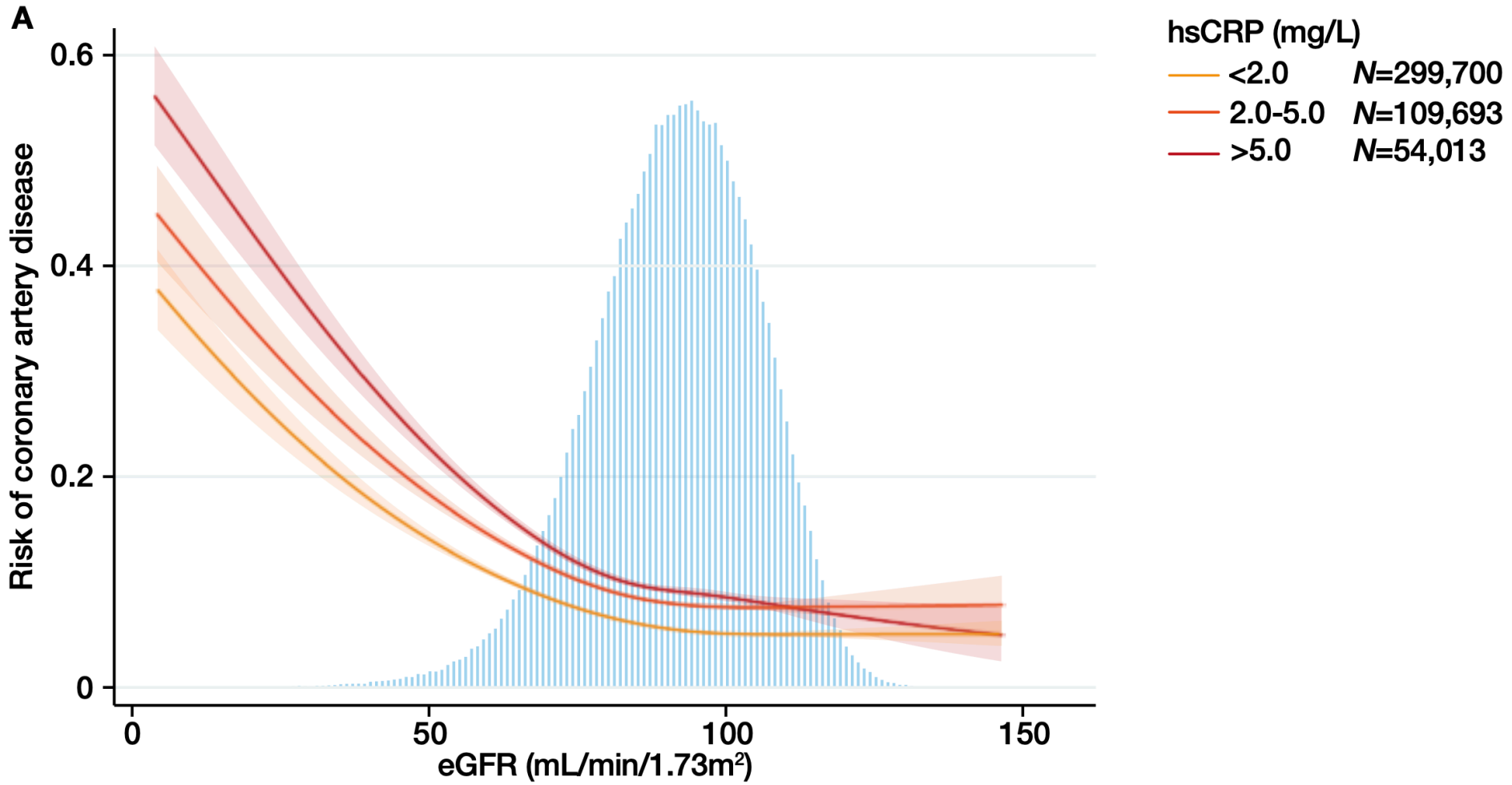


hsCRP und LDL-C unter Statin-Therapie



Ridker et al. Lancet 2023

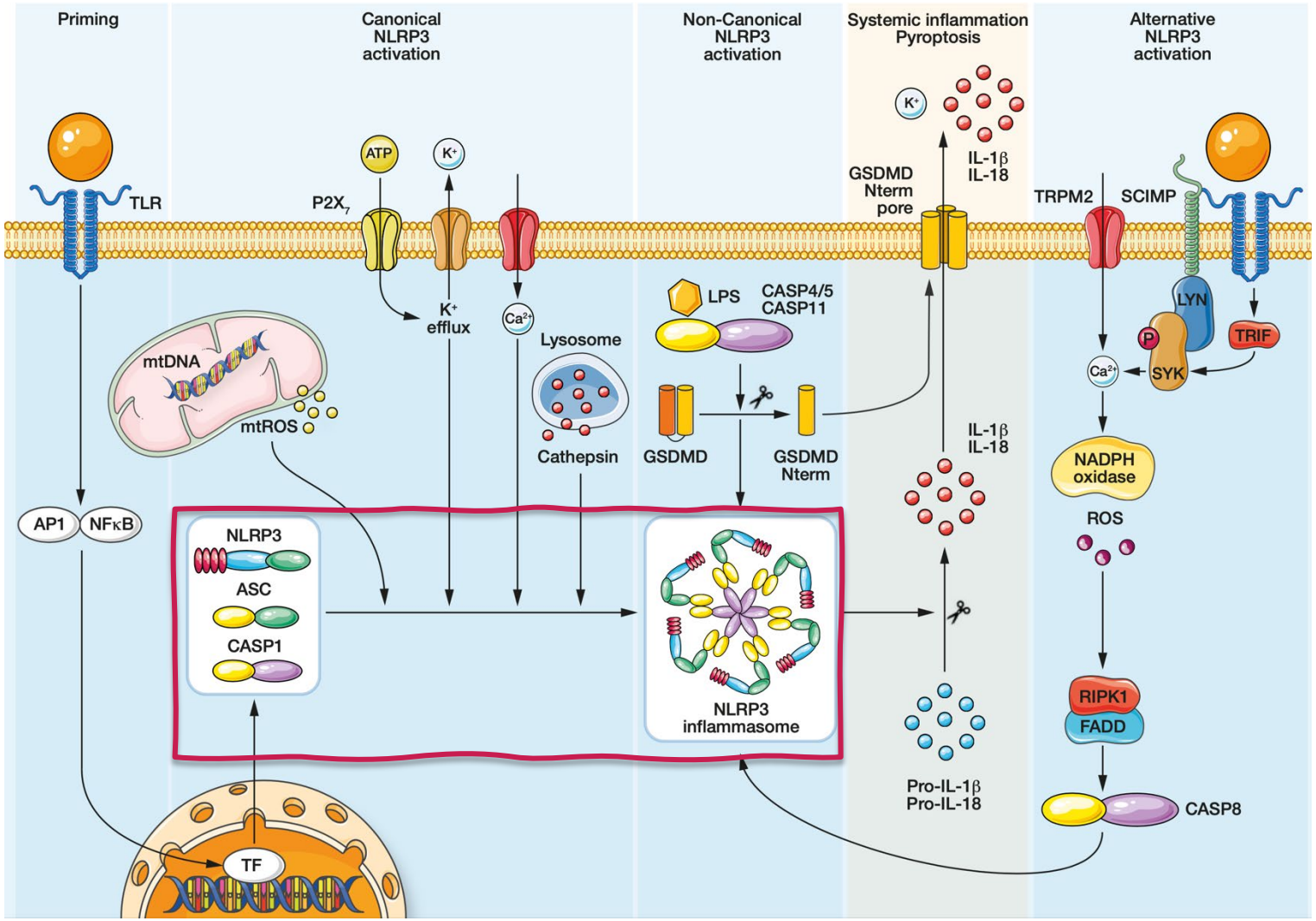
Inflammation und Nierenfunktion



Sarakpi,...,Speer. *In revision*

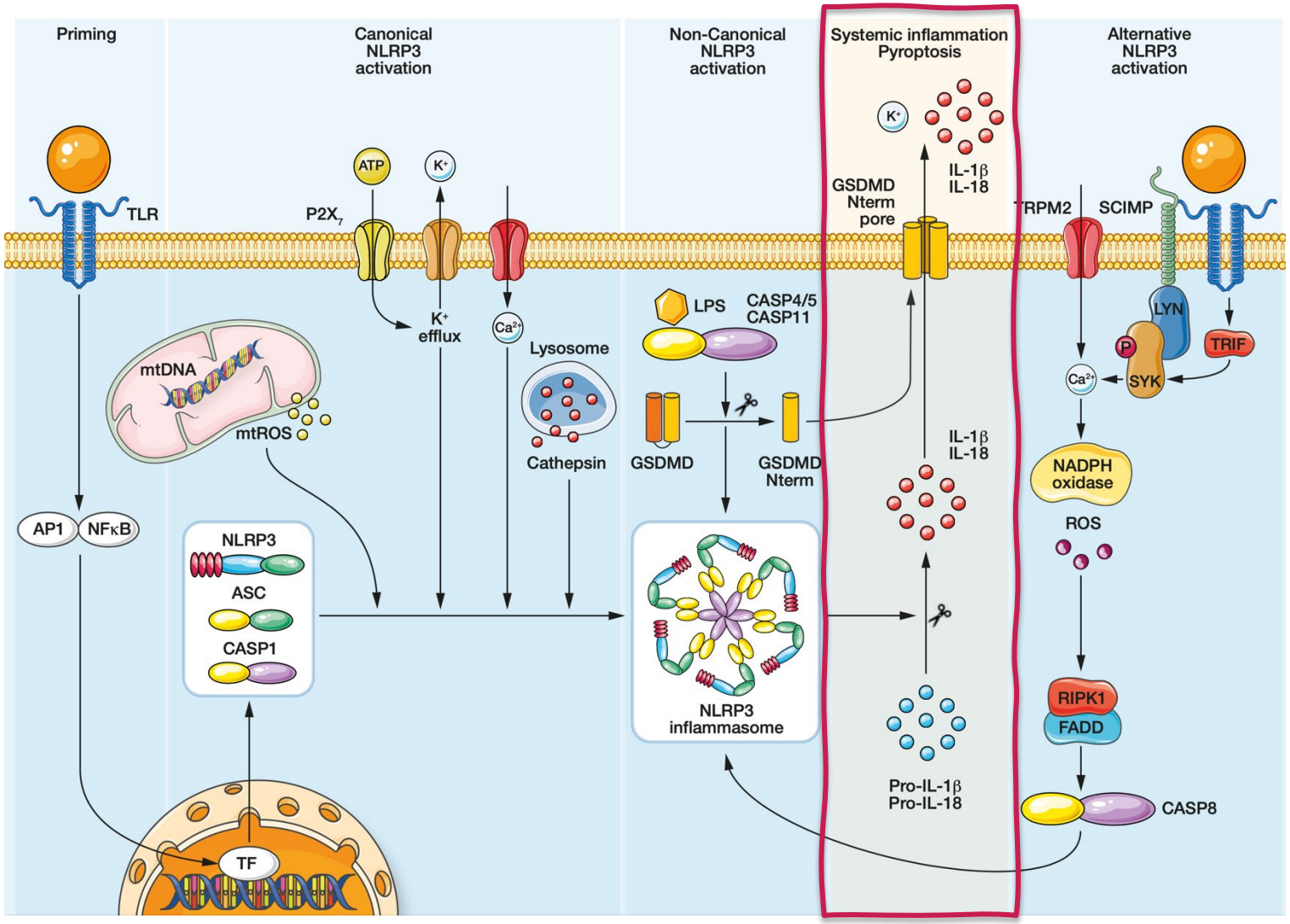
Wie entsteht eine systemische Inflammation?

NLRP3 Inflammasom



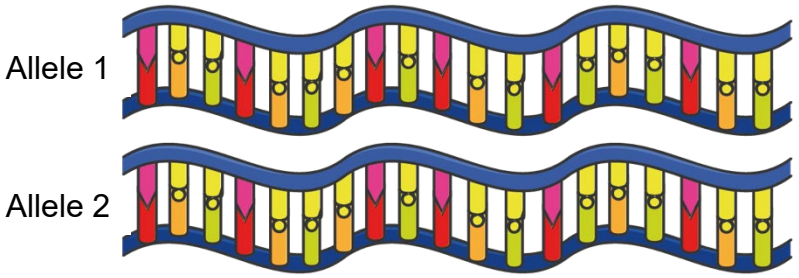
Speer et al. Nat Rev Nephrol 2022

NLRP3 Inflammasom

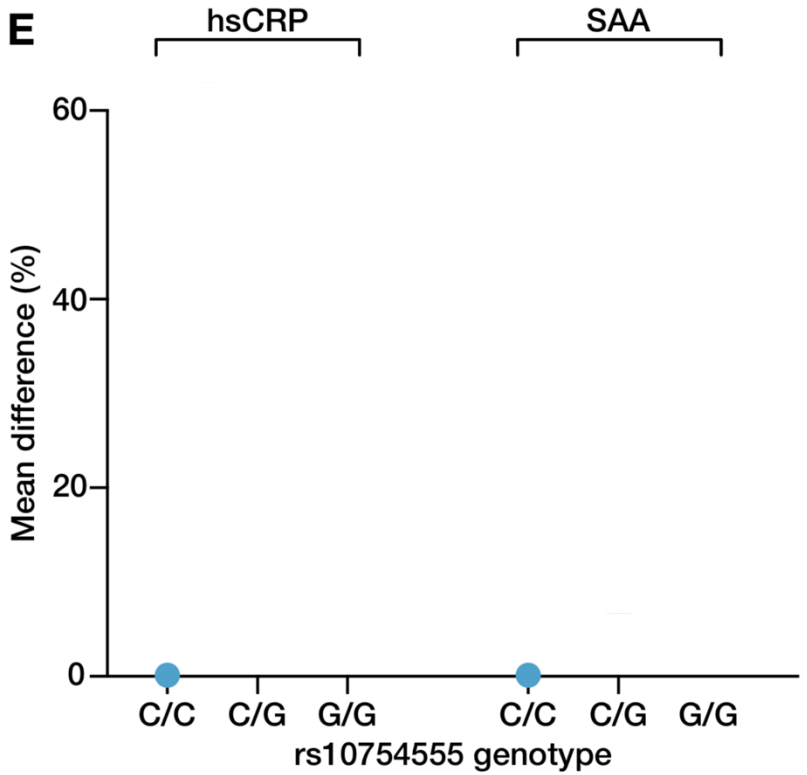


Speer et al. Nat Rev Nephrol 2022

Effekte einer lebenslangen NLRP3-Aktivierung



Wildtype



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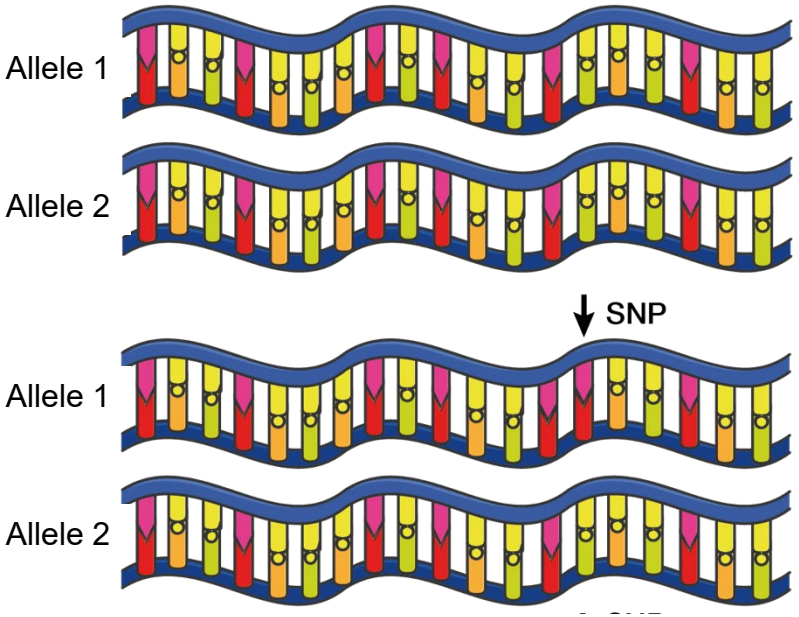
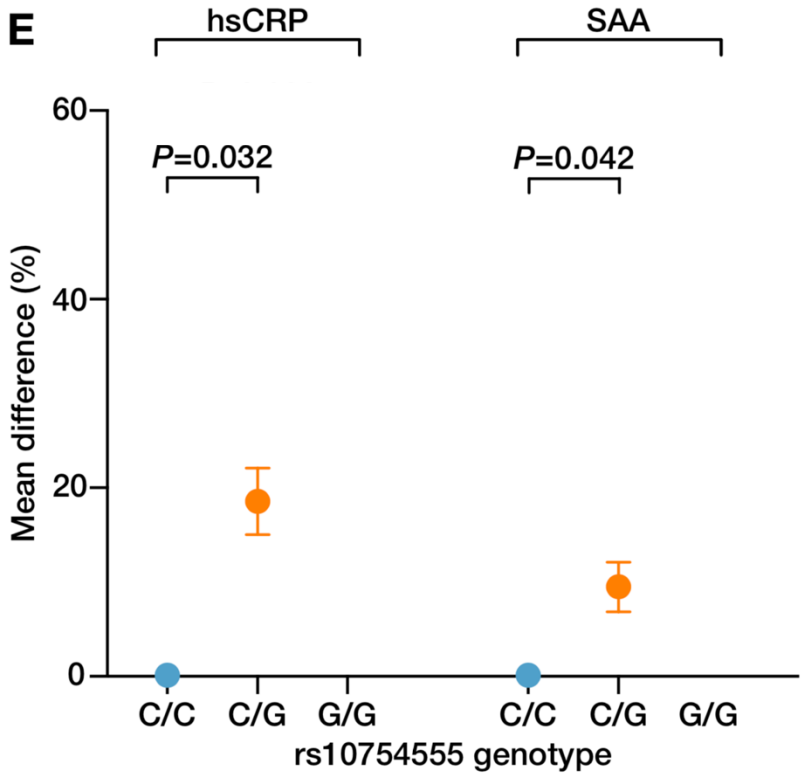


Wildtype

Heterozygous



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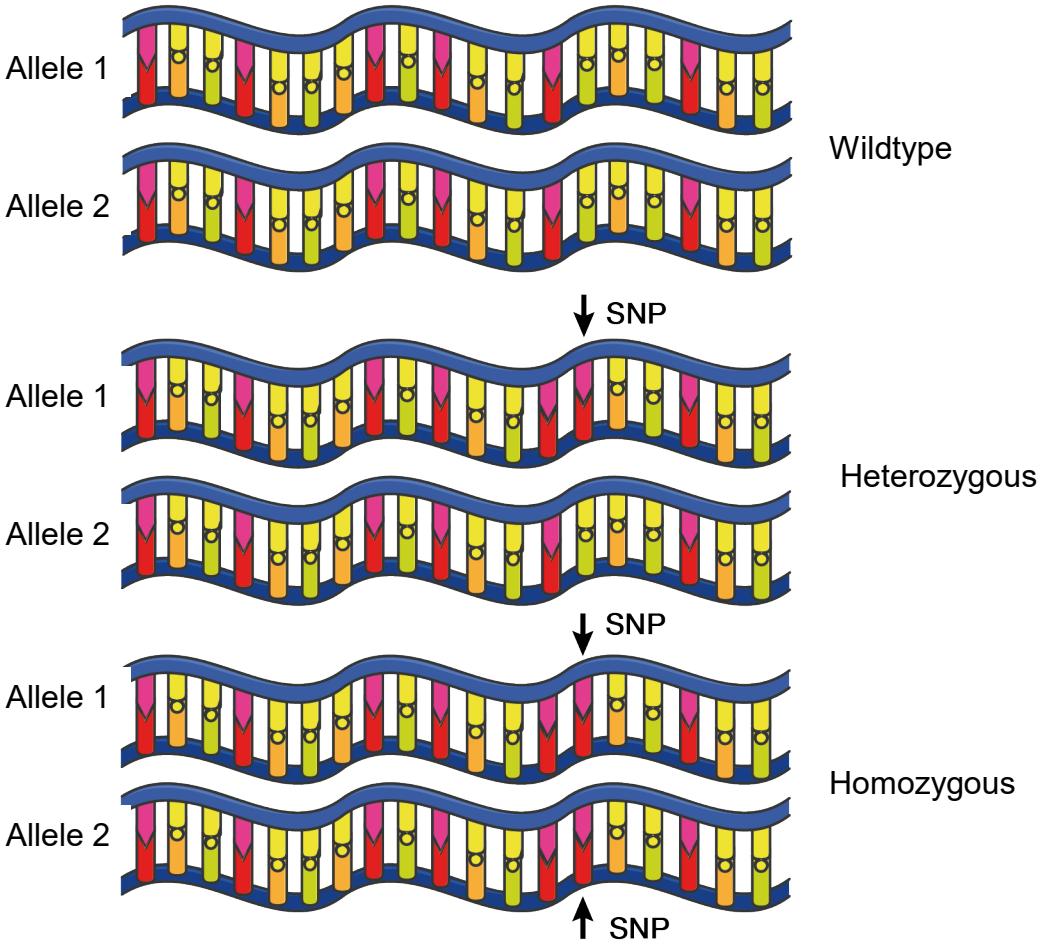

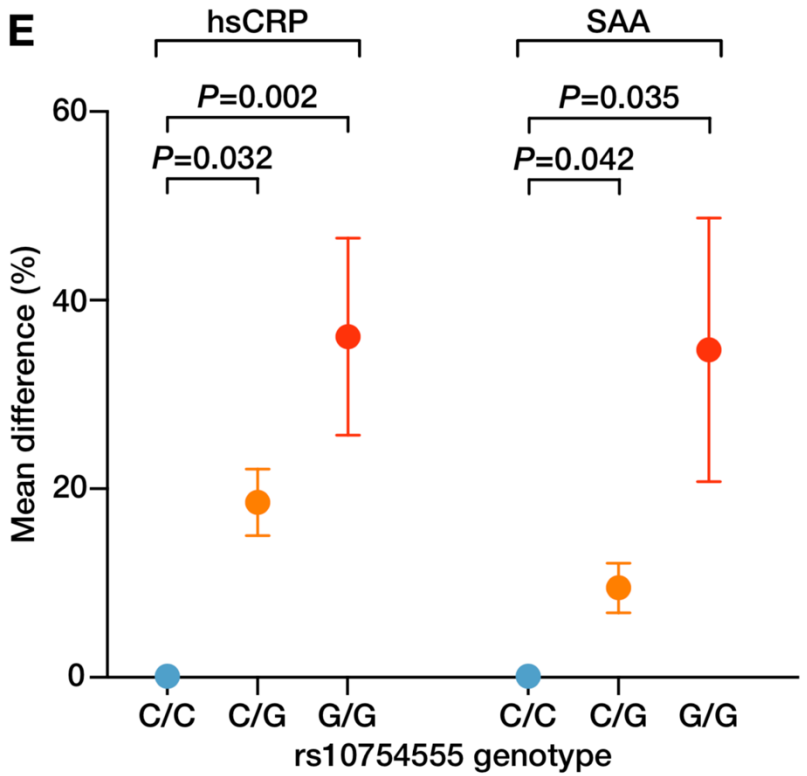

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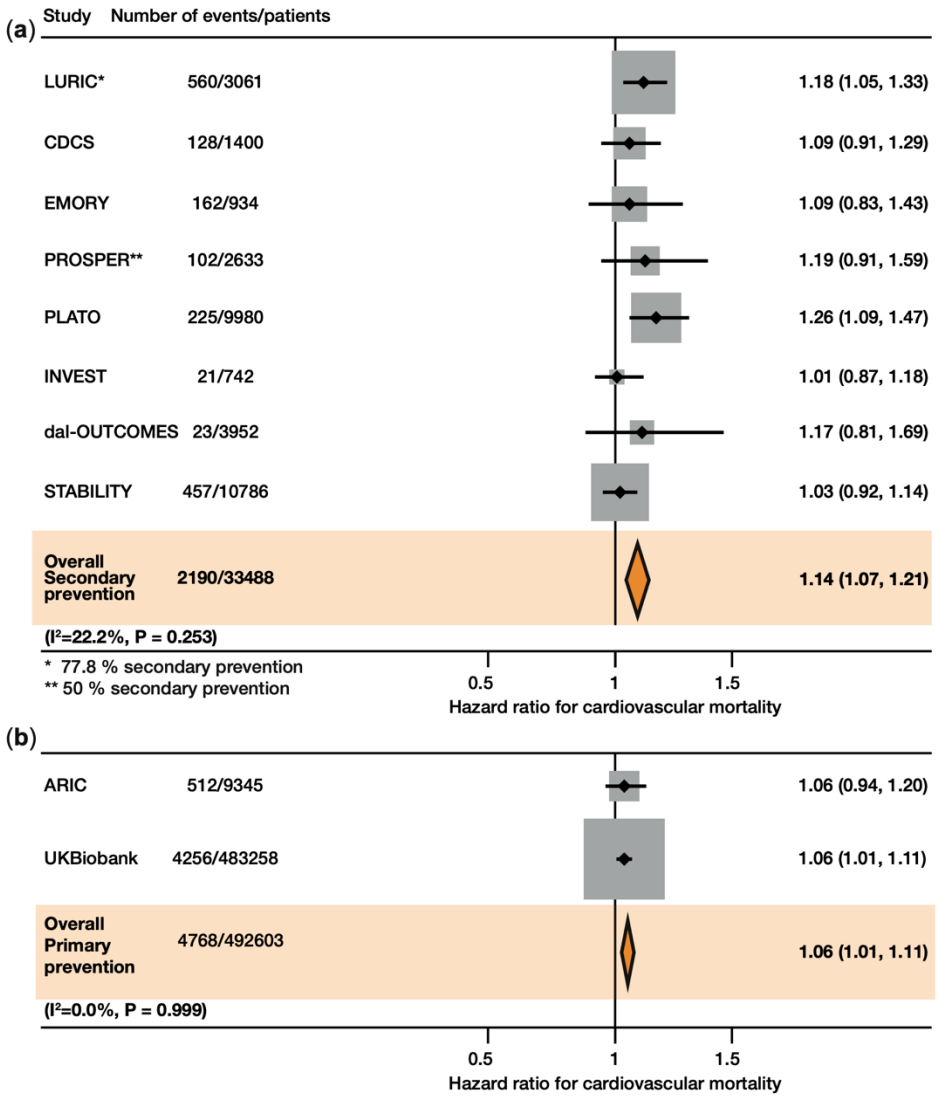


Secondary prevention

Heterozygous: 14 % higher risk

Homozygous: 28 % higher risk

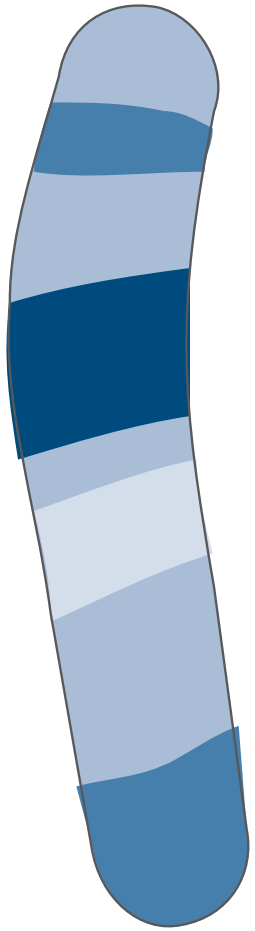
Primary prevention

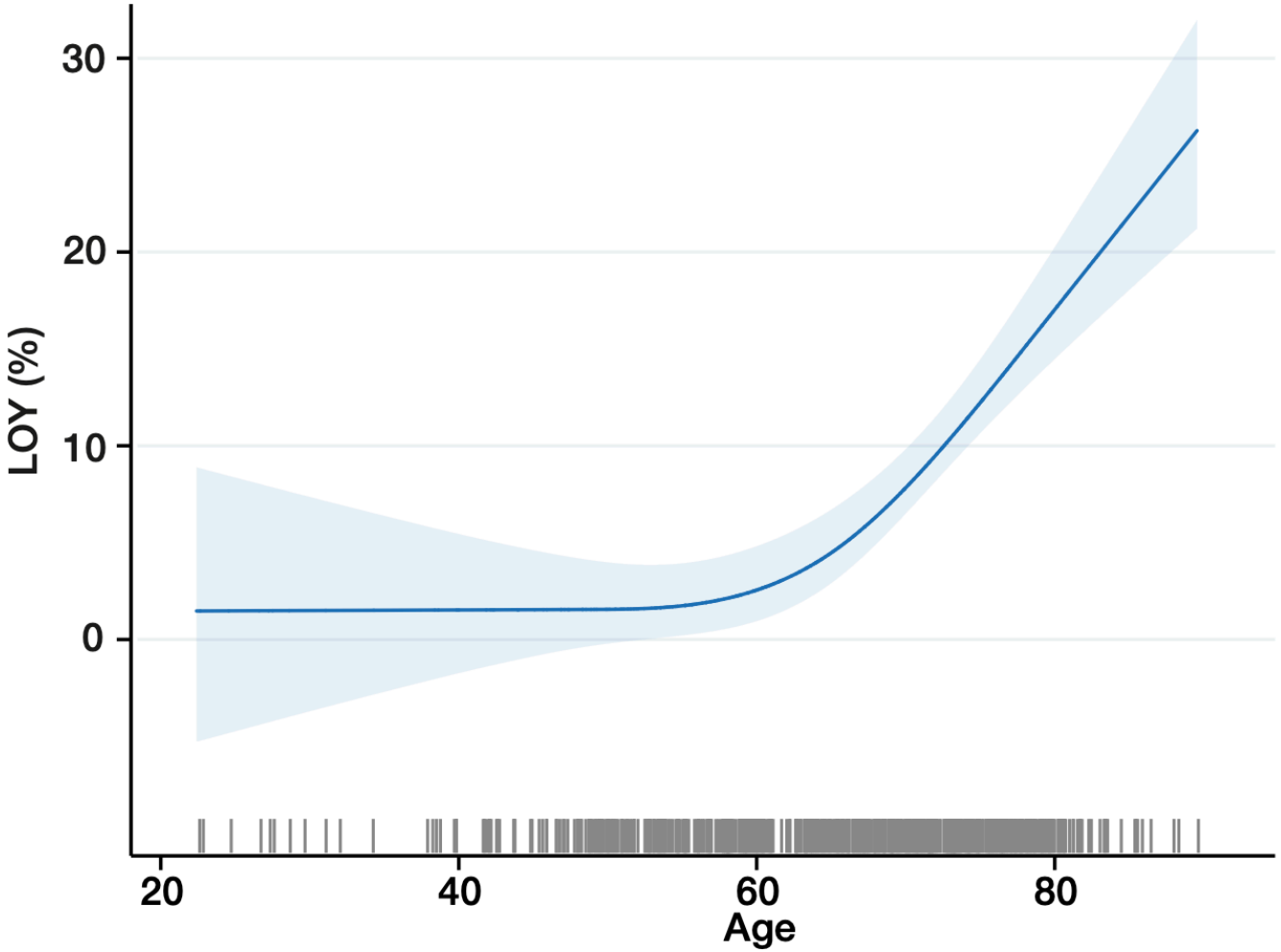
Heterozygous: 6 % higher risk

Homozygous: 12 % higher risk

Schunk,...,Speer. Eur Heart J 2021

Loss of Y-Chromosome (LOY)





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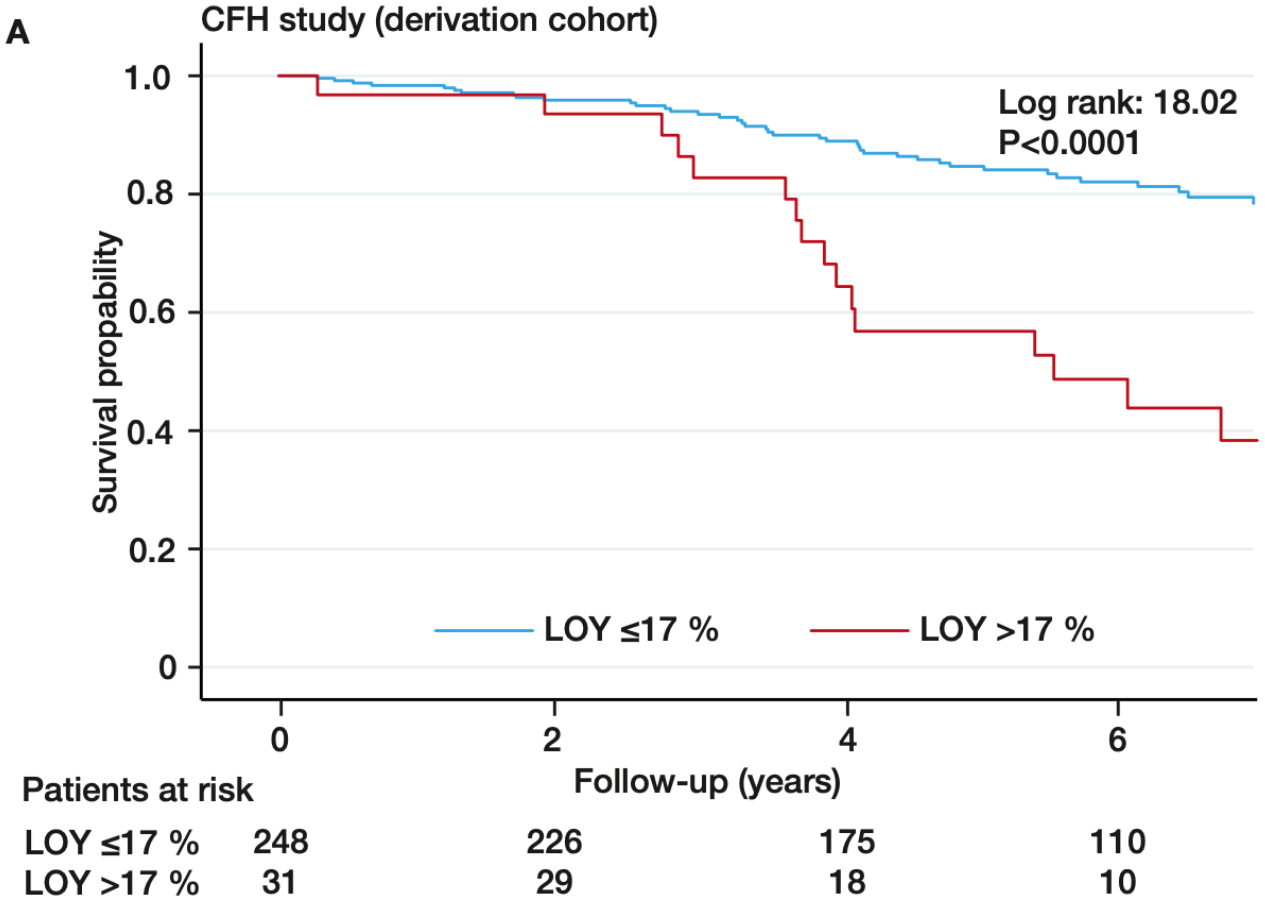
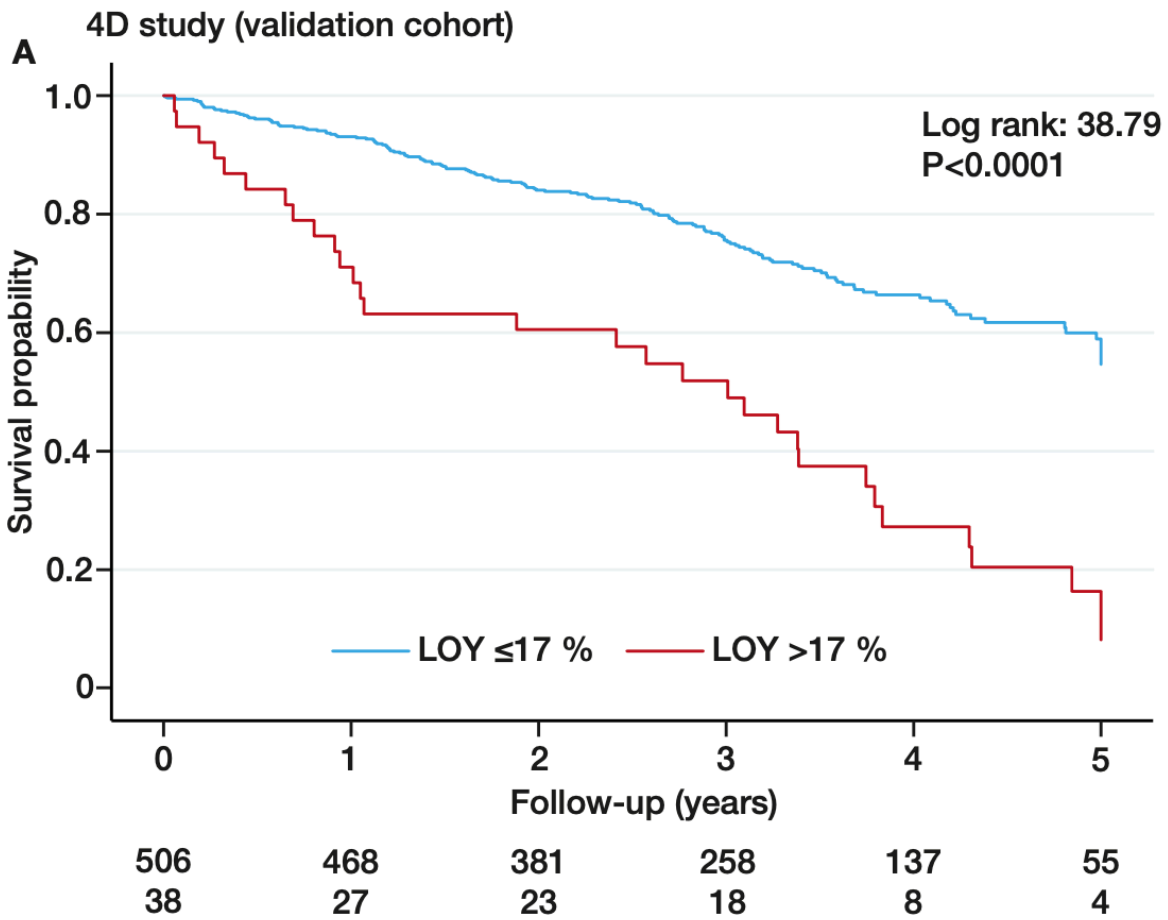




Anti-inflammatorische Therapieansätze

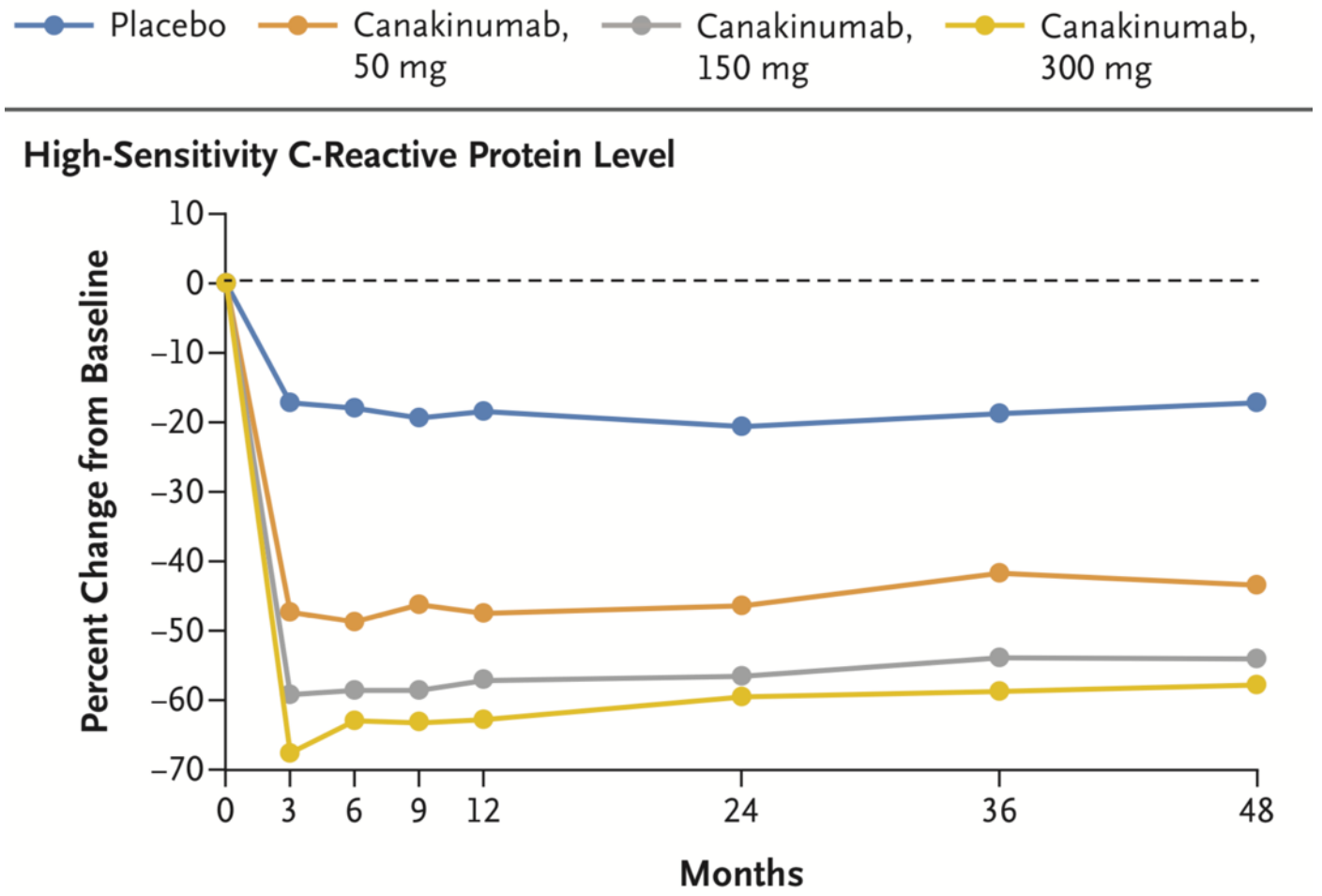
Canakinumab (CANTOS Studie)

Inhibition von IL-1β (CANTOS Studie)

- 10,061 Patienten mit **akutem Myocardinfarkt** (innerhalb 30 Tage vor Randomisierung)
- hsCRP ≥2 mg/L
- eGFR ≥30 ml/ml/1.73m^2

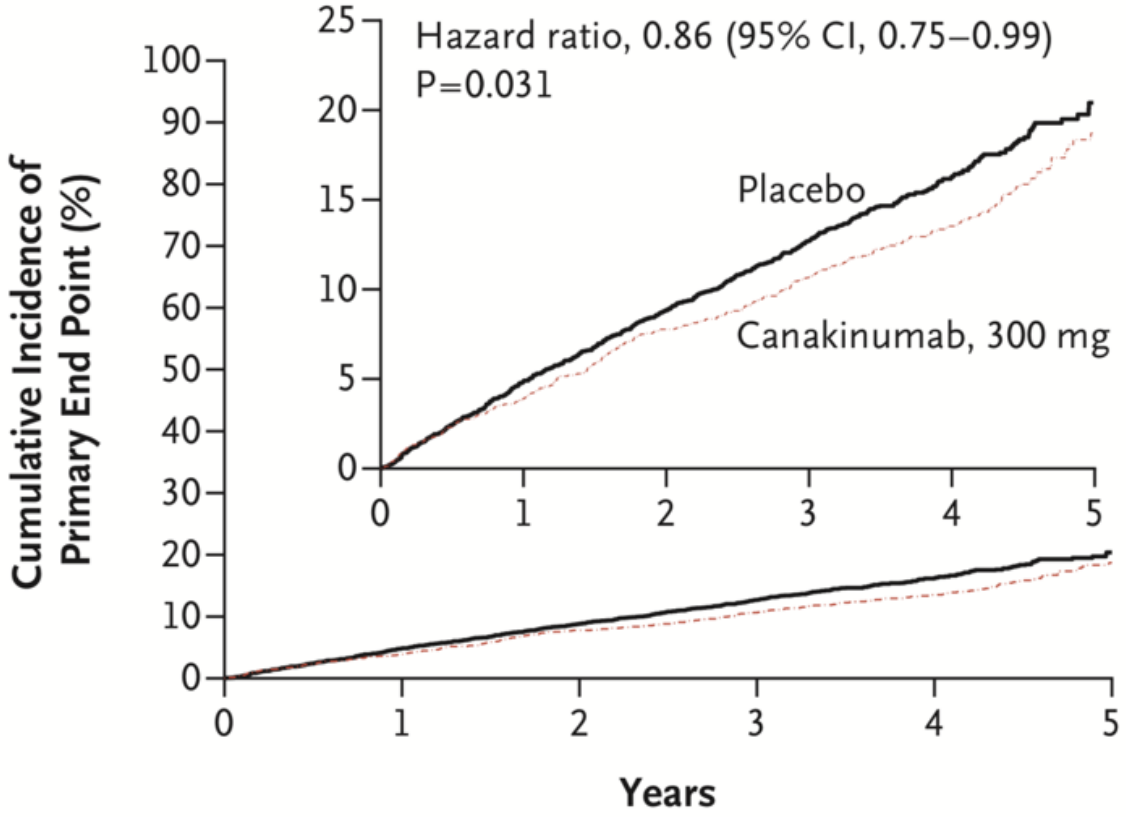
Characteristic	Placebo Group (N=3344)	Canakinumab			
		50-mg Group (N=2170)	150-mg Group (N=2284)	300-mg Group (N=2263)	All Doses (N=6717)
Age — yr	61.1±10.0	61.1±10.1	61.2±10.0	61.1±10.1	61.1±10.1
Female sex — no. (%)	865 (25.9)	541 (24.9)	575 (25.2)	606 (26.8)	1722 (25.6)
Current smoking — no. (%)	765 (22.9)	531 (24.5)	534 (23.4)	536 (23.7)	1601 (23.8)
Median body-mass index (IQR)	29.7 (26.6–33.8)	29.9 (26.6–33.9)	29.8 (26.5–33.7)	29.8 (26.5–33.8)	29.9 (26.6–33.8)
Hypertension — no. (%)	2644 (79.1)	1751 (80.7)	1814 (79.4)	1799 (79.5)	5364 (79.9)
Diabetes — no. (%)	1333 (39.9)	854 (39.4)	954 (41.8)	888 (39.2)	2696 (40.1)
Qualifying myocardial infarction — no. (%)					
STEMI	1807 (54.0)	1231 (56.7)	1231 (53.9)	1213 (53.6)	3675 (54.7)
Non-STEMI	1132 (33.9)	710 (32.7)	781 (34.2)	761 (33.6)	2252 (33.5)
Unknown type or missing data	405 (12.1)	229 (10.6)	272 (11.9)	289 (12.8)	790 (11.8)
History of PCI — no. (%)	2192 (65.6)	1454 (67.0)	1555 (68.1)†	1509 (66.7)	4518 (67.3)
History of CABG — no. (%)	469 (14.0)	302 (13.9)	324 (14.2)	316 (14.0)	942 (14.0)
History of congestive heart failure — no. (%)	721 (21.6)	451 (20.8)	478 (20.9)	523 (23.1)	1452 (21.6)
Lipid-lowering therapy — no./total no. (%)	3132/3344 (93.7)	2038/2169 (94.0)	2114/2280 (92.7)	2113/2259 (93.5)	6265/6708 (93.4)
Statin — no./total no. (%)	3045/3344 (91.1)	1990/2169 (91.7)	2065/2280 (90.6)	2057/2259 (91.1)	6112/6708 (91.1)
Renin–angiotensin inhibitor — no./total no. (%)	2665/3338 (79.8)	1718/2166 (79.3)	1817/2277 (79.8)	1792/2250 (79.6)	5327/6693 (79.6)
Anti-ischemia agent — no./total no. (%)‡	3080/3344 (92.1)	1974/2169 (91.0)	2079/2280 (91.2)	2058/2259 (91.1)	6111/6708 (91.1)
Antithrombotic agent or anticoagulant — no./total no. (%)	3188/3344 (95.3)	2059/2169 (94.9)	2157/2280 (94.6)	2149/2259 (95.1)	6365/6708 (94.9)
Median high-sensitivity CRP level (IQR) — mg/liter	4.10 (2.75–6.85)	4.25 (2.80–7.15)	4.25 (2.85–7.05)	4.15 (2.85–7.15)	4.20 (2.80–7.10)
Median interleukin-6 level (IQR) — ng/liter	2.61 (1.80–4.06)	2.53 (1.80–4.17)	2.56 (1.74–4.11)	2.59 (1.79–4.08)	2.56 (1.77–4.13)
Median total cholesterol level (IQR) — mg/dl	161 (137–190)	159 (136–189)	159 (136–188)	161 (137–189)	160 (136–189)
Median LDL cholesterol level (IQR) — mg/dl	82.8 (64.2–107.5)	81.2 (62.3–106.0)	82.4 (63.4–106.0)	83.5 (64.0–108.0)	82.0 (63.0–106.7)
Median HDL cholesterol level (IQR) — mg/dl	44.5 (37.1–52.6)	43.7 (37.0–52.2)	43.7 (36.3–52.0)†	44.0 (36.7–53.0)	43.7 (36.7–52.2)†

Inhibition von IL-1β (CANTOS Studie)



Inhibition von IL-1β (CANTOS Studie)

C Primary End Point with Canakinumab, 300 mg, vs. Placebo

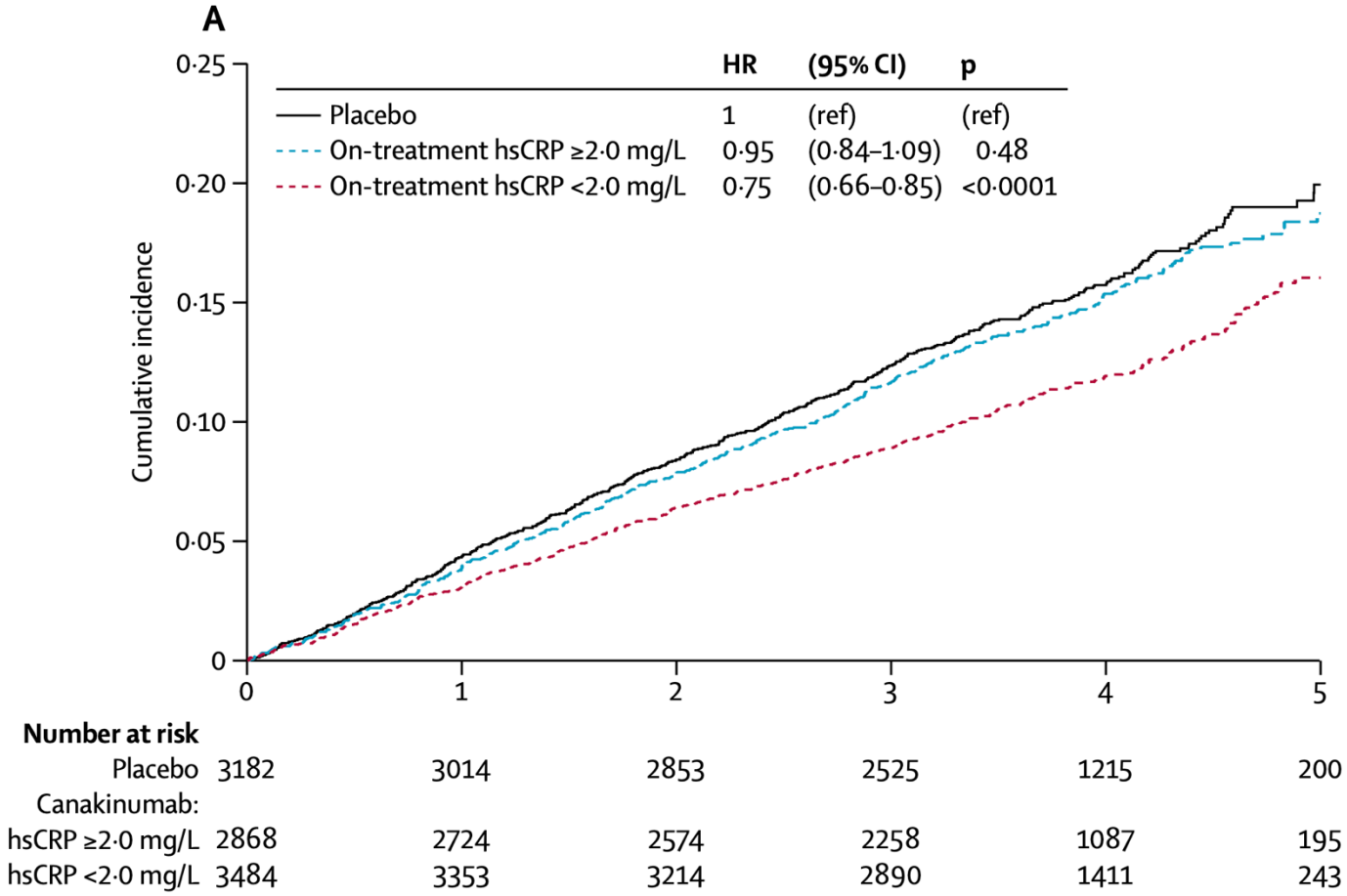


No. at Risk

Placebo	3344	3141	2973	2632	1266	210
Canakinumab	2263	2149	2038	1819	938	199

Ridker et al. N Engl J Med 2017

Inhibition von IL-1β (CANTOS Studie)

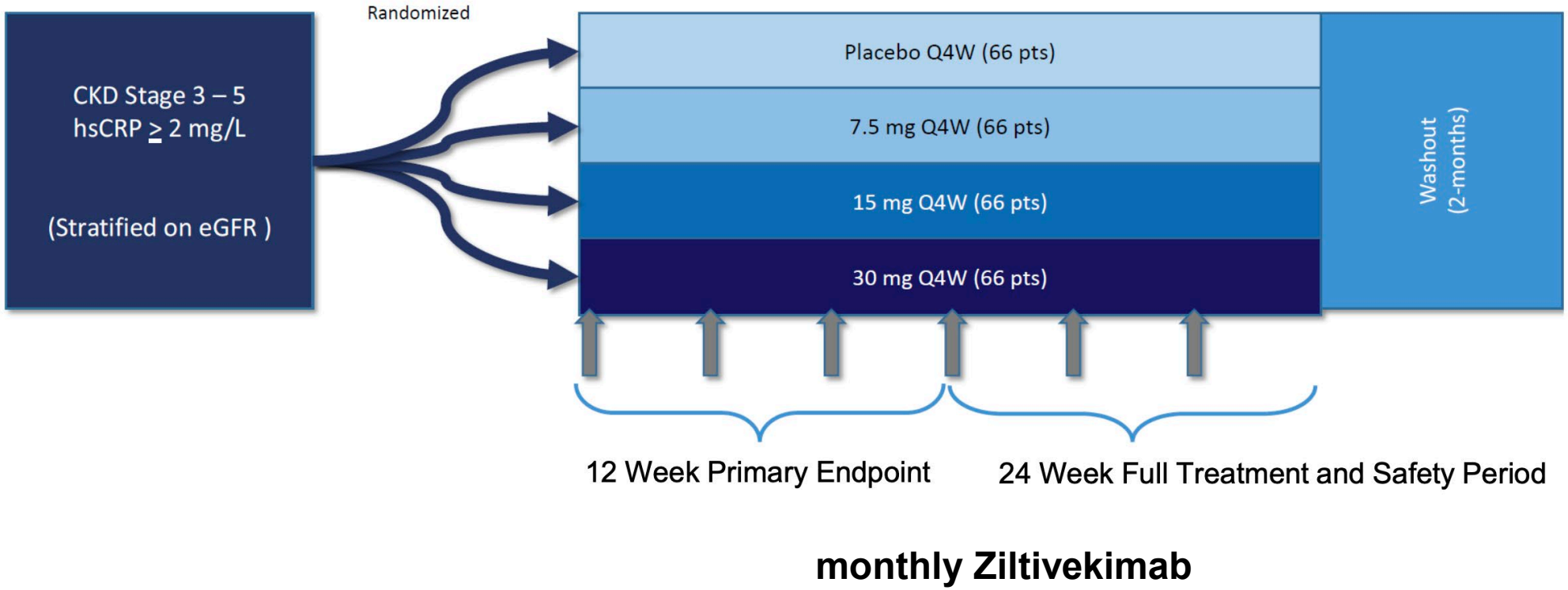


Wer hat auf die Therapie angesprochen?

Ridker et al. Lancet 2017

IL-6 Inhibition (RESCUE Studie)

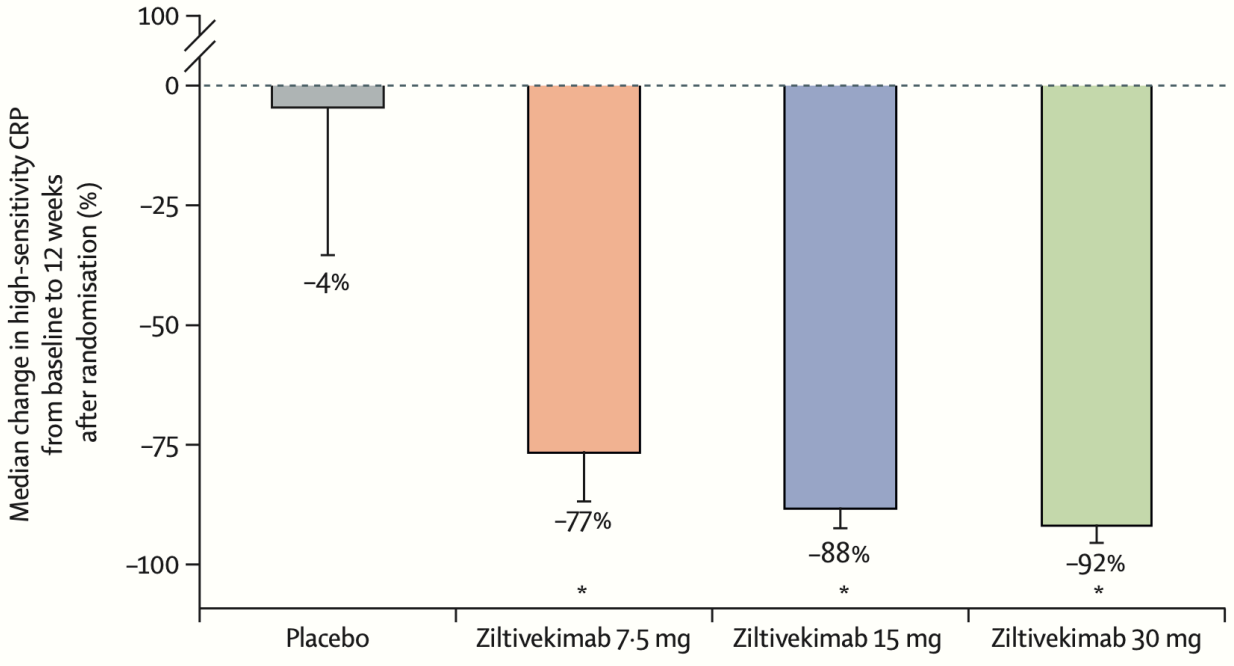
IL-6 Inhibition (RESCUE Studie)

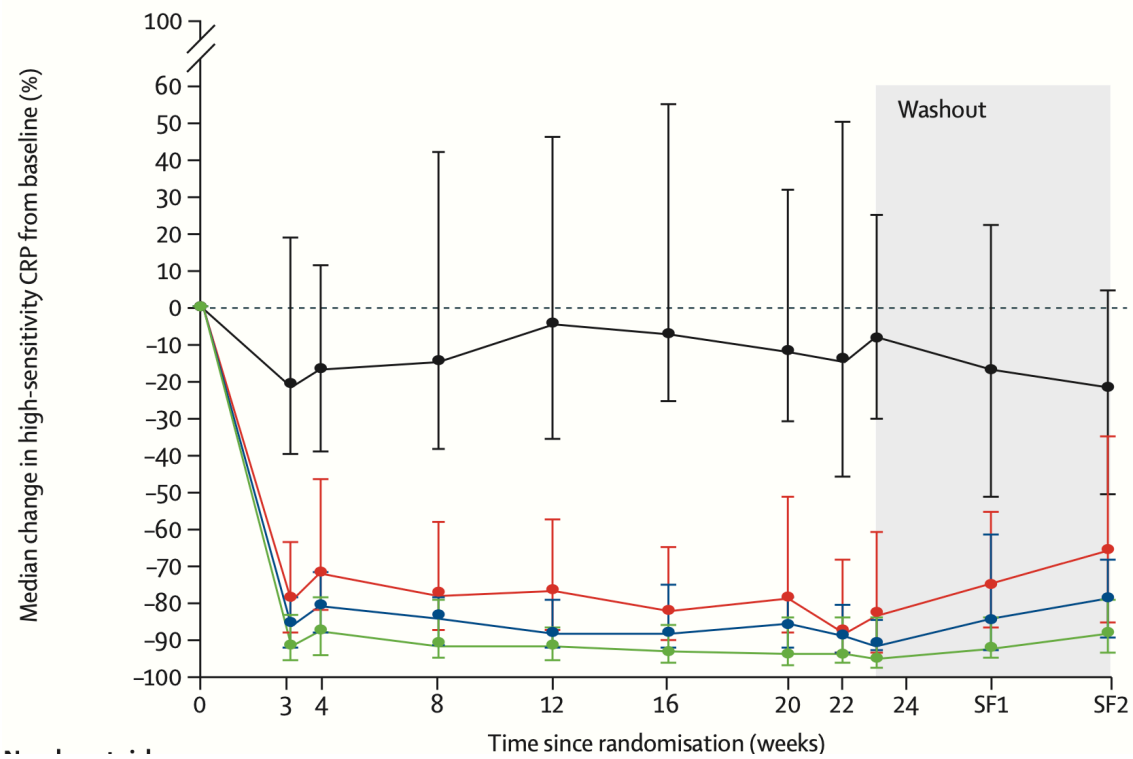


monthly Ziltivekimab

Ridker et al. Lancet 2021

IL-6 Inhibition (RESCUE Studie)





Ridker et al. Lancet 2021

IL-6 Inhibition (ZEUS Studie)

- Phase-3 klinische Studie
- 6,200 Patienten mit CKD, Stadium 3-4
- Prävalente ASCVD
- hsCRP ≥2 mg/L
- Monatlich Ziltivekimab oder Placebo
- Primärer Endpunkt: MACE

IL-6 Inhibition bei Dialysepatienten

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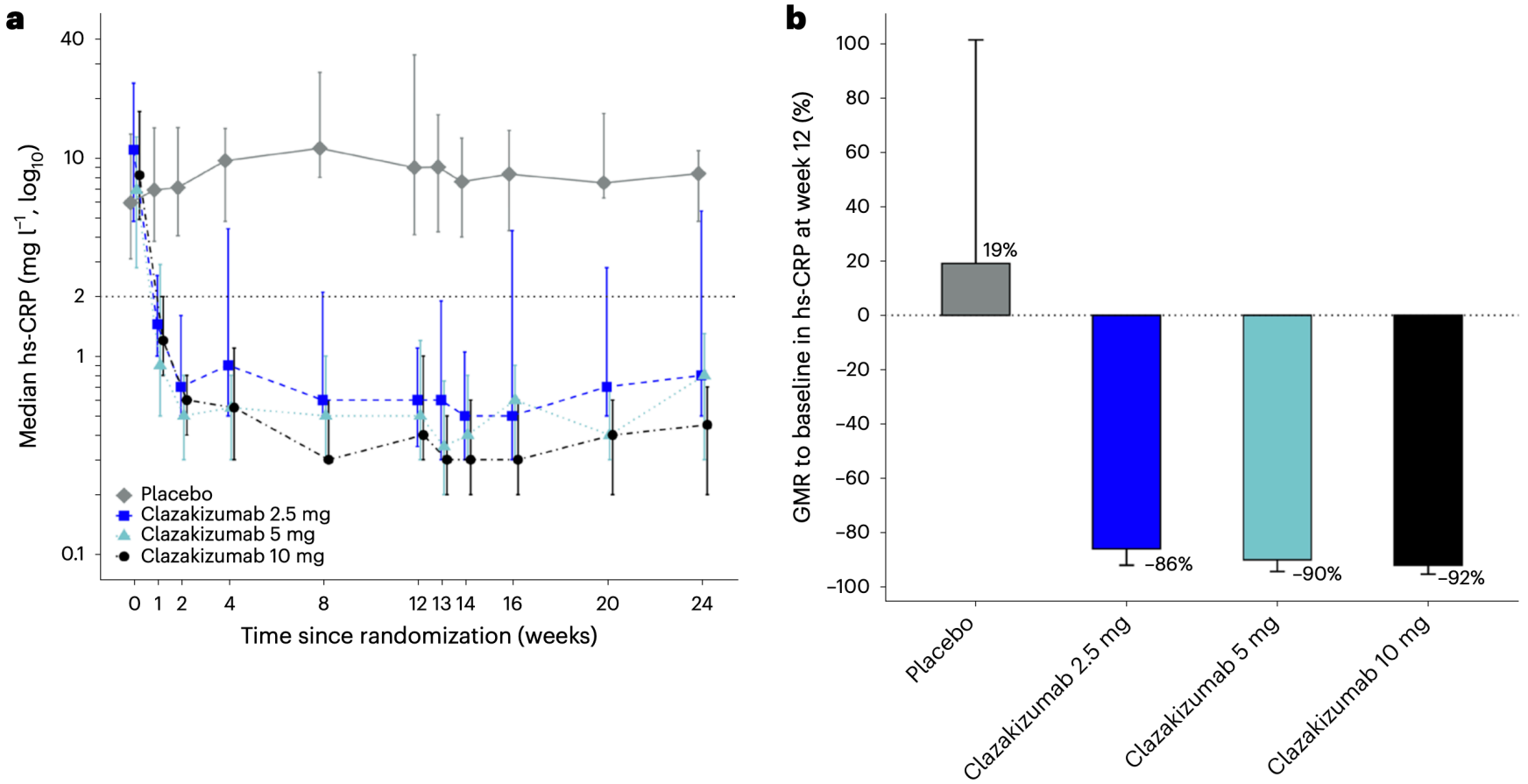
Demographics		Clazakizumab 2.5 mg (*n*=32)	Clazakizumab 5 mg (*n*=32)	Clazakizumab 10 mg (*n*=32)	Placebo (*n*=31)
Age (year), median (range)		63 (39, 83)	67 (36, 82)	63 (31, 83)	69 (36, 86)
Sex	Male, *n* (%)	21 (65.6)	18 (56.3)	25 (78.1)	21 (67.7)
Cardiovascular history	History of CAD	13 (40.6)	22 (68.8)	16 (50.0)	12 (38.7)
	Prior MI	5 (15.6)	2 (6.3)	5 (15.6)	3 (9.7)
	Prior PCI	2 (6.3)	6 (18.8)	2 (6.3)	3 (9.7)
	Prior CABG	3 (9.4)	5 (15.6)	4 (12.5)	3 (9.7)
	Cerebrovascular disease	3 (9.4)	3 (9.4)	6 (18.8)	6 (19.4)
	Diabetes	29 (90.6)	28 (87.5)	30 (93.8)	27 (87.1)
	Hypertension	31 (96.9)	31 (96.9)	32 (100)	30 (96.8)
	Atrial fibrillation	7 (21.9)	5 (15.6)	8 (25.0)	9 (29.0)
	Former or current use of tobacco products	8 (25.0)	11 (34.4)	14 (43.8)	13 (41.9)
Baseline medications	Statins	19 (59.4)	23 (71.9)	19 (59.4)	20 (64.5)
	Antiplatelet agents	12 (37.5)	20 (62.5)	18 (56.3)	13 (41.9)
	ESA use	22 (68.8)	24 (75.0)	23 (71.9)	22 (71.0)
	Parenteral iron	23 (78.1)	18 (56.3)	26 (81.3)	21 (67.7)
	Baseline IL-6 (ng l^{-1}), mean (s.d.)	9.4 (8.2)	9.0 (8.0)	9.7 (8.6)	8.3 (5.6)
	Baseline hs-CRP (mg ml^{-1}) median (25–75%)	9.5 (5.2, 32.3)	7.2 (3.6, 15.0)	8.94 (5.4, 22.9)	7.3 (4.5, 16.2)

Chertow et al. Nat Med 2024

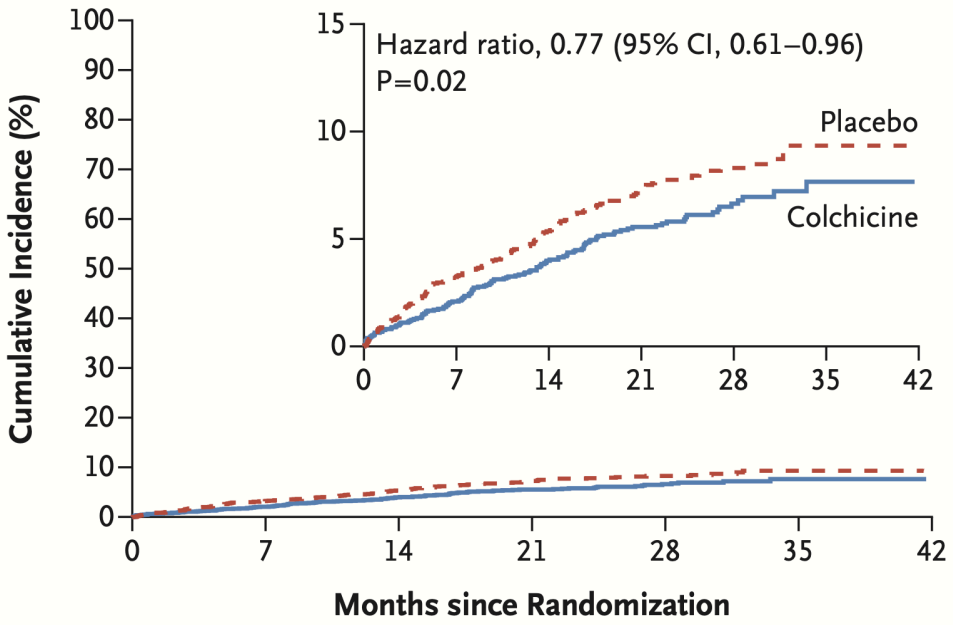
IL-6 Inhibition bei Dialysepatienten



Gibt es schon anti-inflammatorische Therapien?

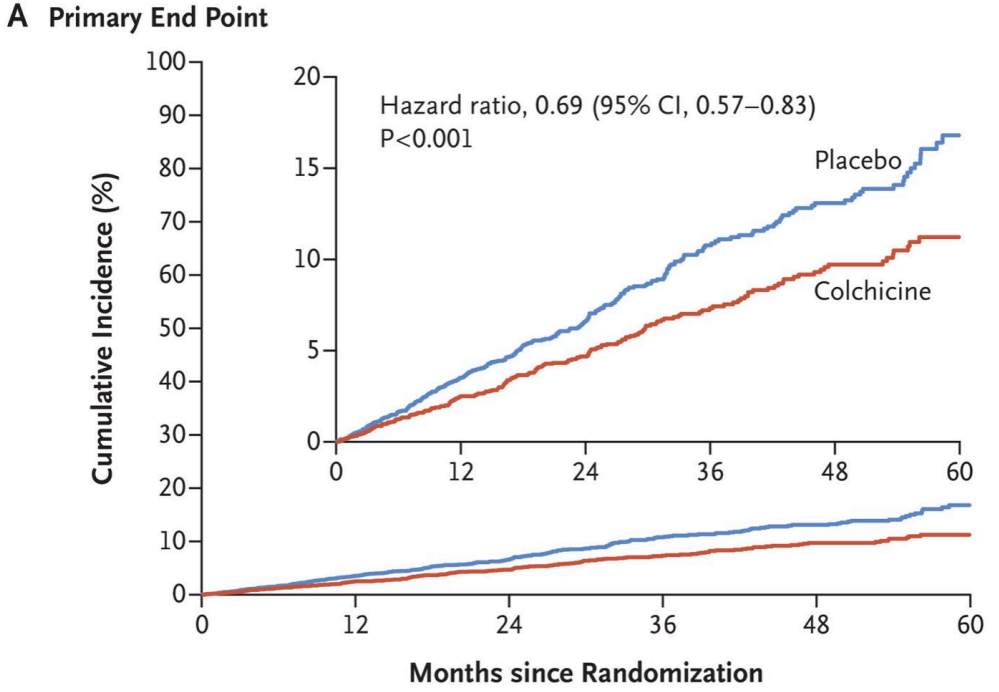
Colchicin

COLCOT trial



No. at Risk							
Placebo	2379	2261	1854	1224	622	144	0
Colchicine	2366	2284	1868	1230	628	153	0

LoDoCo2 trial



No. at Risk						
Placebo	2760	2655	1703	821	590	161
Colchicine	2762	2685	1761	890	629	166

Tardif et al. N Engl J Med 2019

Nidorf et al. N Engl J Med 2020

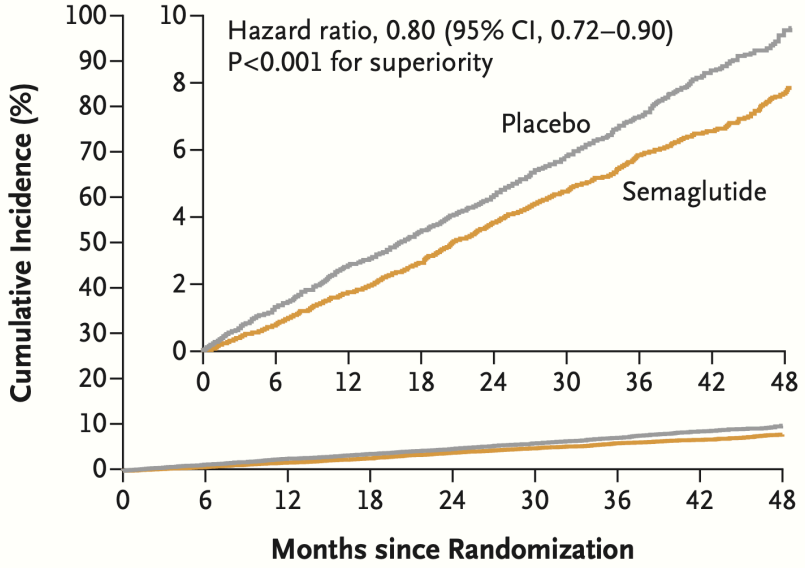
ESC Chronic coronary syndromes guideline

Recommendations	Class[a]	Level[b]
The following blood tests are recommended in all individuals to refine risk stratification, diagnose comorbidities, and guide treatment:		
• lipid profile including LDL-C;[64,128]	I	A
• full blood count (including haemoglobin);[129–133]	I	B
• creatinine with estimation of renal function;[134]	I	B
• glycaemic status with HbA1c and/or fasting plasma glucose.[16,86,135,136]	I	B
In patients with suspected CCS, it is recommended to assess thyroid function at least once.[137,138]	I	B
Additionally, hs-CRP and/or fibrinogen plasma levels should be considered.[109–118,121,125]	IIa	B

Anti-inflammatory drugs in patients with chronic coronary syndrome—*Section 4*		
In CCS patients with atherosclerotic CAD, low-dose colchicine (0.5 mg daily) should be considered to reduce myocardial infarction, stroke, and need for revascularization.	IIa	A

Semaglutid – SELECT trial

A **Primary Cardiovascular Composite End Point**



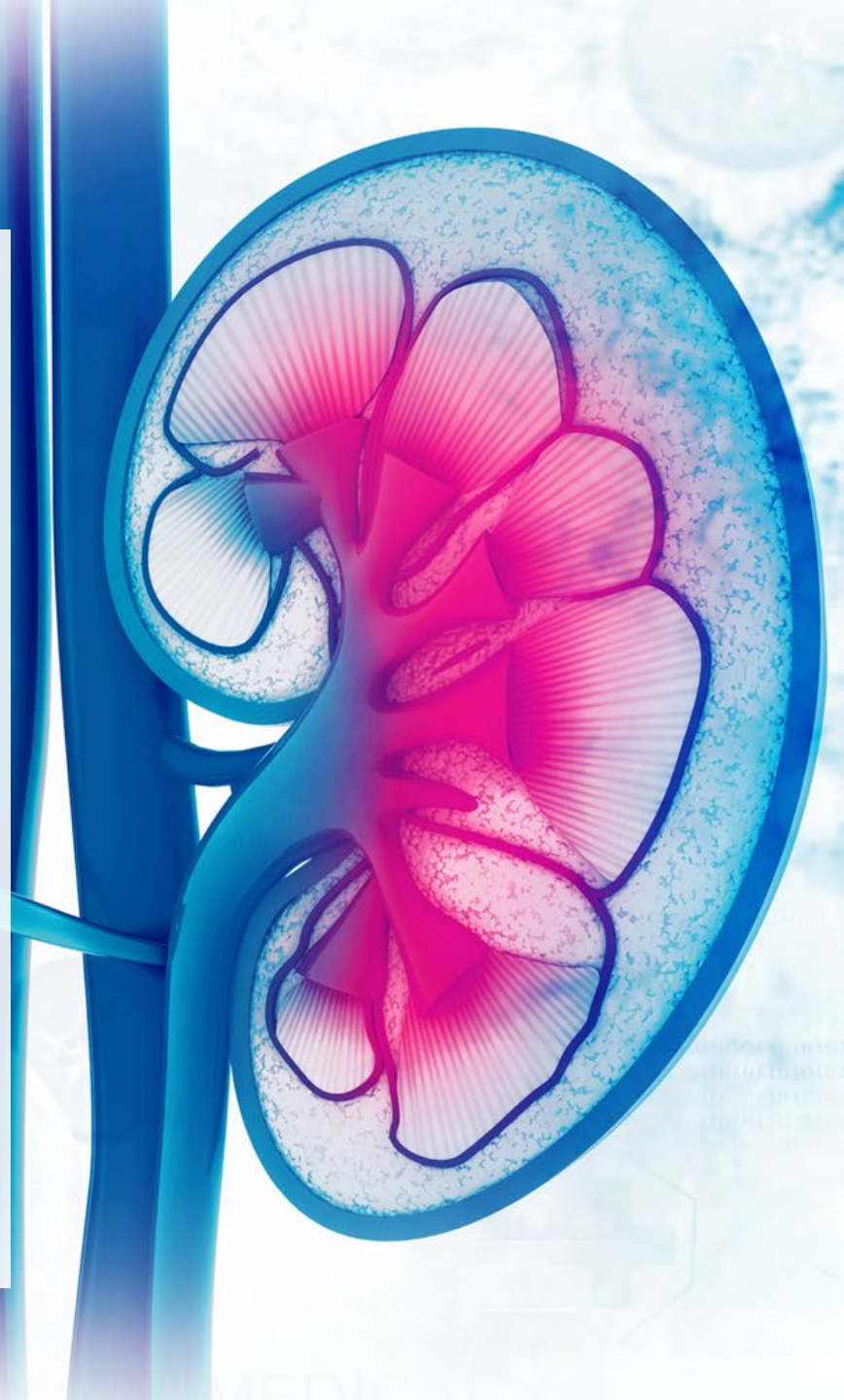
No. at Risk

Placebo	8801	8652	8487	8326	8164	7101	5660	4015	1672
Semaglutide	8803	8695	8561	8427	8254	7229	5777	4126	1734

End Point	Semaglutide (N=8803)	Placebo (N=8801)	Difference (95% CI)†
Glycated hemoglobin level of <5.7% among patients with baseline glycated hemoglobin level of ≥5.7% — no./total no. (%)‡			
At week 52	3848/5831 (66.0)	1136/5748 (19.8)	10.15 (9.18 to 11.23)
At week 104	3775/5750 (65.7)	1211/5663 (21.4)	8.74 (7.91 to 9.65)
Mean change from randomization to week 104			
Body weight — %	−9.39±0.09	−0.88±0.08	−8.51 (−8.75 to −8.27)
Waist circumference — cm	−7.56±0.09	−1.03±0.09	−6.53 (−6.79 to −6.27)
Glycated hemoglobin level — percentage points	−0.31±0.00	0.01±0.00	−0.32 (−0.33 to −0.31)
Systolic blood pressure — mm Hg	−3.82±0.16	−0.51±0.16	−3.31 (−3.75 to −2.88)
Diastolic blood pressure — mm Hg	−1.02±0.10	−0.47±0.10	−0.55 (−0.83 to −0.27)
Heart rate — beats/min	3.79±0.11	0.69±0.11	3.10 (2.80 to 3.39)
EQ-5D-5L index score§	0.01±0.00	−0.01±0.00	0.01 (0.01 to 0.02)
EQ-5D-VAS score§	2.52±0.16	0.92±0.16	1.60 (1.16 to 2.04)
High-sensitivity CRP level — %	−39.12	−2.08	−37.82 (−39.70 to −35.90)
Total cholesterol level — %	−4.63	−1.92	−2.77 (−3.37 to −2.16)
HDL cholesterol level — %	4.86	0.59	4.24 (3.70 to 4.79)
LDL cholesterol level — %	−5.25	−3.14	−2.18 (−3.22 to −1.12)
Triglyceride level — %	−18.34	−3.20	−15.64 (−16.68 to −14.58)

Zusammenfassung

- **Inflammation** spielt eine entscheidende Rolle bei der Entstehung und Progression von **CKD** und **CVD**
- **NLRP3 Inflammasom** ist von besonderer Bedeutung
- **Canakinumab** und **Colchicin** reduzieren kardiovaskuläre Ereignisse bei Patienten mit KHK
- **Ziltivekimab/Clazakizumab** reduziert Inflammation bei CKD-Patienten
- **GLP1RA** zeigen potente **anti-inflammatorische Effekte**
- **Anti-inflammatorische Therapien** werden in der Zukunft unser therapeutisches Spektrum erweitern



EKFZ Nephrologische Forschung

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Vielen Dank

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