Familiäre Hyperlipidämien

Stefan Bilz

St. Gallen, 29. März 2017

Frau R., 18 Jahre, MPA im 3. Lehrjahr

- 2014 Gratischeck: Gesamtcholesterin 5.8 mmol/l, LDL-C 4.8 mmol/l
- 2015 Verlaufskontrolle LDL-C 5.1 mmol/l.
- In den letzten Jahren leichte Gewichtszunahme, Ernährung ausgewogen. Kein Nikotinkonsum.
- Keine Vorerkrankungen

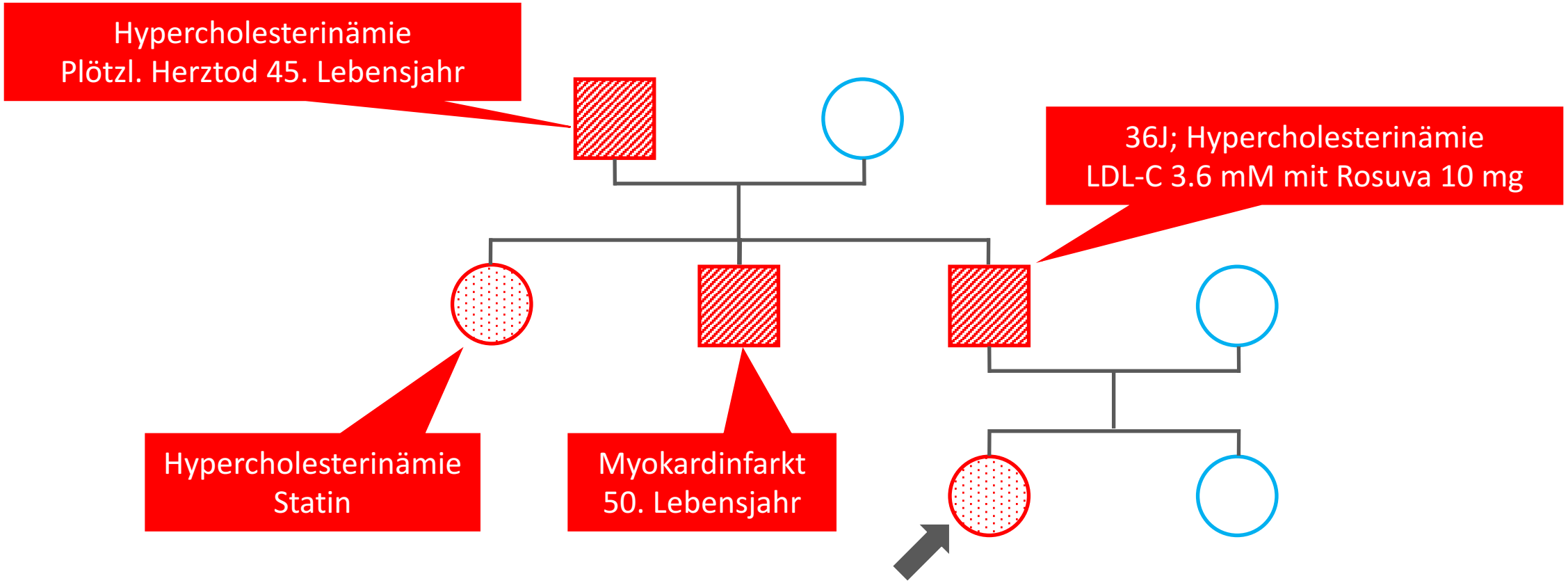
Frau R., 18 Jahre, Zuweisung in die Lipidsprechstunde

BLUT-CHEMIE

		22.9.2015 0121 22.9.2015 09:00	17.12.2015 0112 *17.12.2015 08:40*			
Probenmaterial/Präanalytik:						
Nativ-Blut		x	x			
Cholesterin	[<5.0 mmol/l]	7.1	7.5			
Triglyceride	[<1.7 mmol/l]	1.0	0.7			
Cholesterin/HDL	[<5]	6.5	6.8			
HDL-Cholesterin	[>1.0 mmol/l]	1.1				
HDL-Cholesterin	[>1.0 mmol/l]		1.1			
LDL-Cholesterin	[<2.6 mmol/l]	6.3	6.0			
Lp(a) INA	[<300 mg/l]	110				

- 17jährige Patientin, Grösse 170 cm, Gewicht 73 kg, BMI 25.3 kg/m², Blutdruck 136 / 79 mmHg, Puls 54/min
- Keine lipidspezifischen Stigmata (Xanthome, Arcus lipoides). Pulmonal unauffällig. Kardial: 2/6-Systolikum mit p.m. über Erb ohne Ausstrahlung.

Frau R., 18 Jahre, Familienanamnese



Frau R., 18 Jahre, Genetische Abklärung

Clinical Summary: Suspicion of familial hypercholesterolaemia. LDL 6.3 (without medication). Grandfather sudden death 45y. Dutch Lipid Network criteria 6 points.

Familial Hypercholesterolaemia Results

Sequence Analysis
Gene : *LDLR*
Location : Exon 4
DNA Description : c.[501C>A];[=]
Protein Description : p.[(Cys167*)];[=]

Dosage Analysis
No Mutation Detected

Report Summary
Diagnosis of FH confirmed

***SLCO1B1* polymorphism:** *rs2306283*: Genotype G/G *rs4149056*: Genotype T/T
Please refer to the suggested references below for further guidance

Report
This patient was screened for 4 genes known to be associated with FH by next generation sequencing.

Sequence analysis of the *LDLR* gene has revealed that this patient is heterozygous for the c.501C>A variant in exon 4. This result confirms a diagnosis of familial hypercholesterolemia in this patient.

This sequence change is predicted to cause the cysteine residue at position 167 to be replaced by a stop codon, resulting in premature truncation of the LDLR protein. The mRNA produced may be targeted for nonsense-mediated decay. Functional null alleles have been designated 'severe' (Taylor *et al* 2010 Clin Genet 77: 572-580). This variant has been reported frequently in the literature as a pathogenic mutation causing FH, it has been seen previously in this laboratory, and it has multiple entries on the LDLR database (www.ucl.ac.uk/ldlr/LOVDv1.1.0/).

Any offspring of this patient are at risk of inheriting this pathogenic FH mutation.

Cascade testing is available for relatives if appropriate.

Dutch Lipid Network Score zur Diagnosestellung einer heterozygoten Familiären Hypercholesterinämie

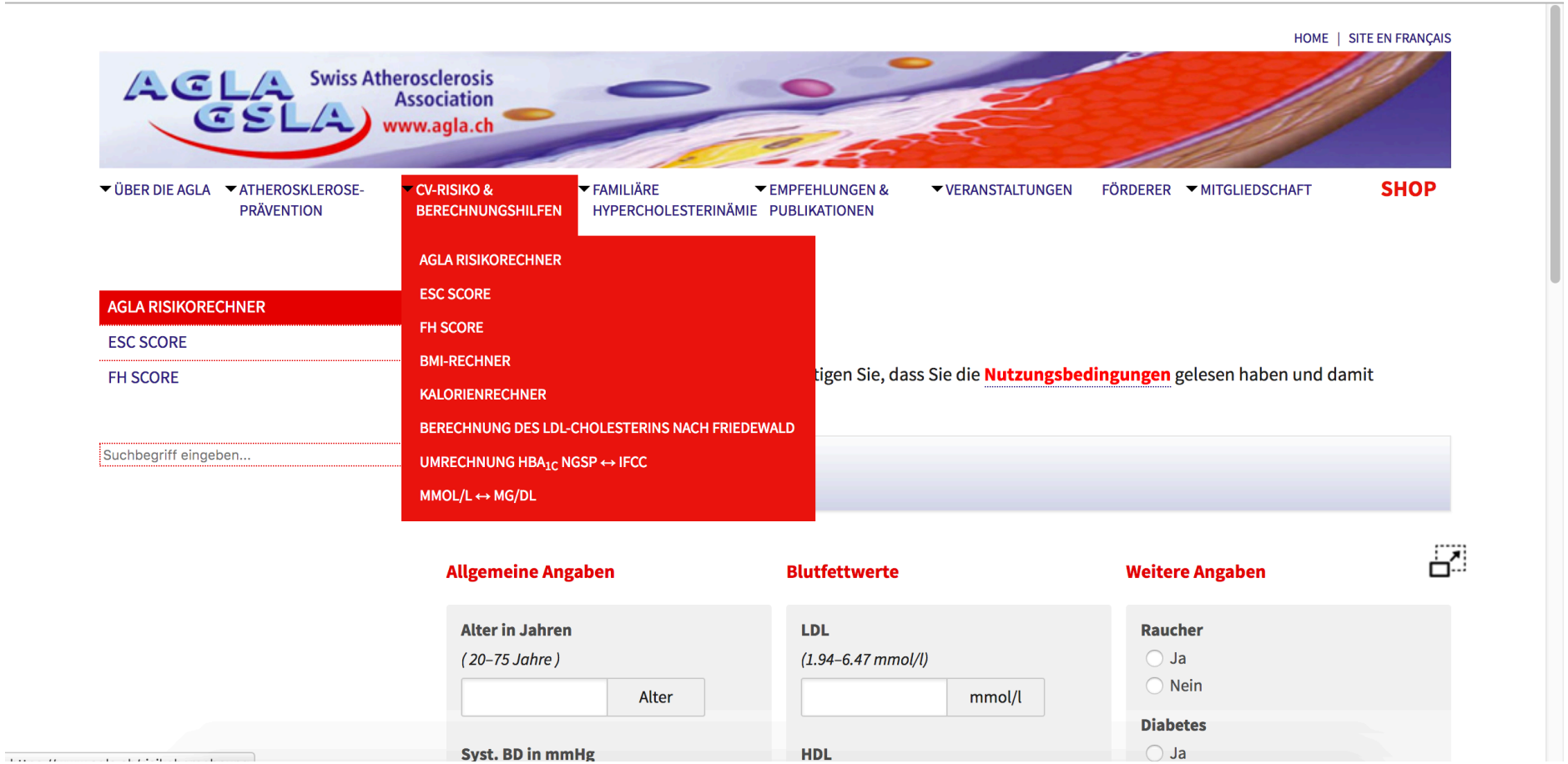
1. Familienanamnese (max. 2 Punkte): Erstgradig Verwandter mit	
a. Frühzeitiger (m < 55 , f < 60) Koronarer Herzkrankheit	1
b. Plasma LDL-C >95. Perzentile	
• Bei Erwachsenen > 18 Jahren (5.5 mmol/l in CH)	1
• Bei < 18 jährigen	2
c. Sehnenscheidenxanthomen oder Arcus lipoides	2
2. Persönliche Anamnese (max. 2 Punkte): Patient mit frühzeitiger (m < 55, f < 60)	
a. Koronarer Herzkrankheit	2
b. PAVK oder zerebrovaskulärer Erkrankung	1
3. Klinische Untersuchung (max. 6 Punkte)	
a. Sehnenscheidenxanthome	6
b. Arcus cornealis (lipoides) vor dem 45. Lebensjahr	4
4. LDL-Cholesterin, mmol/l	
a. > 8.5	8
b. 6.5 – 8.4	5
c. 5.0 – 6.4	3
d. 4.0 – 4.9	1
5. Molekulargentischer Nachweis einer Mutation im LDLR, APOB oder PCSK9-Gen	8

Definitve Di. einer HeFH > 8 Pkte. *Wahrscheinliche Di. HeFH 6-8 Pkte. Mögliche Di. einer HeFH 3-5 Pkte.*

LDL-C > 5 mmol/l bzw. > 3.5 mmol/l unter Statintherapie

→ V.a. Familiäre Hypercholesterinämie → FH-Score

(AGLA-Score nicht geeignet !!!, Diagnosestellung entscheidend !!!)



1. Patienten mit Familiärer Hypercholesterinämie haben ein stark erhöhtes kardiovaskuläres Risiko

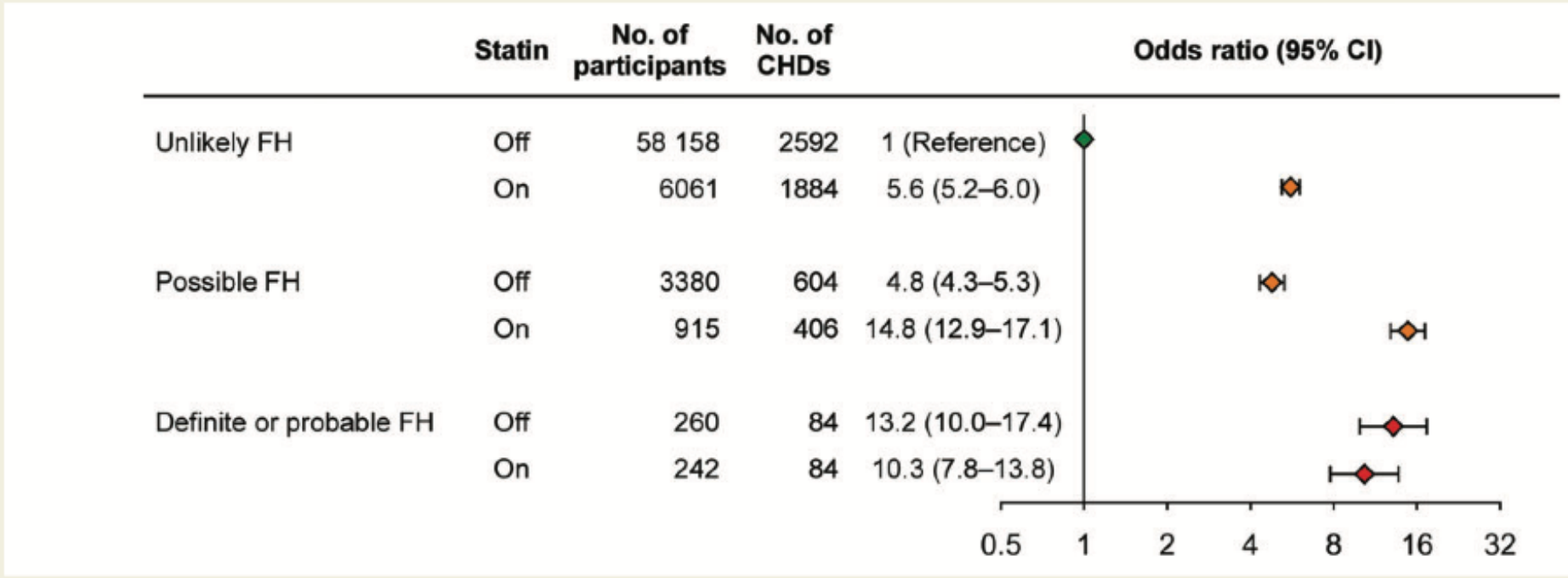


Figure 4 Risk of coronary heart disease as a function of the Dutch Lipid Clinic Network Criteria for a diagnosis of familial hypercholesterolaemia in individuals on or off statin from the general population. Data are based on 69 016 individuals from the Copenhagen General Population Study. CI, confidence interval; FH, familial hypercholesterolaemia; CHD, coronary heart disease = ischaemic heart disease. Adapted from Benn *et al.*[10]

Benn et al., JCEM 97: 3956, 2012
Nordestgaard et al., Eur Heart J 34: 3478, 2013

2. Eine primärpräventive Statintherapie* reduziert das KHK-Risiko bei Heterozygoter FH um 76% !

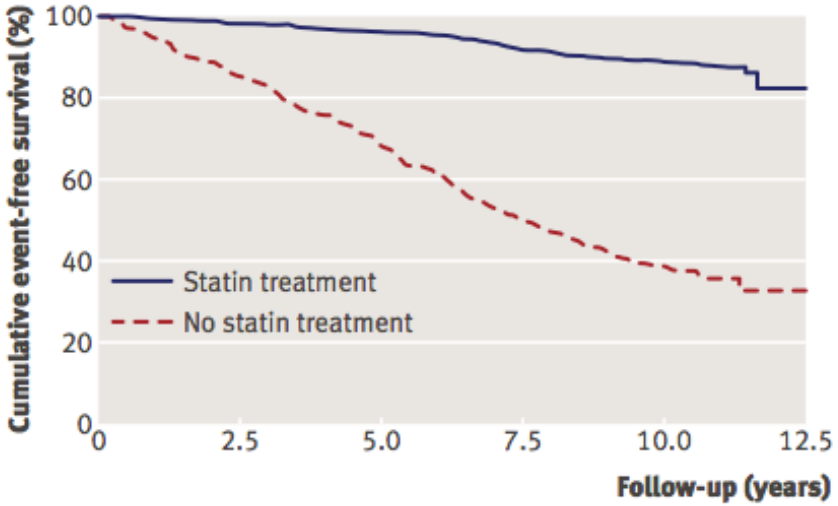


Fig 2 | Kaplan-Meier curve estimates of cumulative coronary heart disease-free survival among patients with familial hypercholesterolaemia according to statin treatment (P<0.001 for difference)

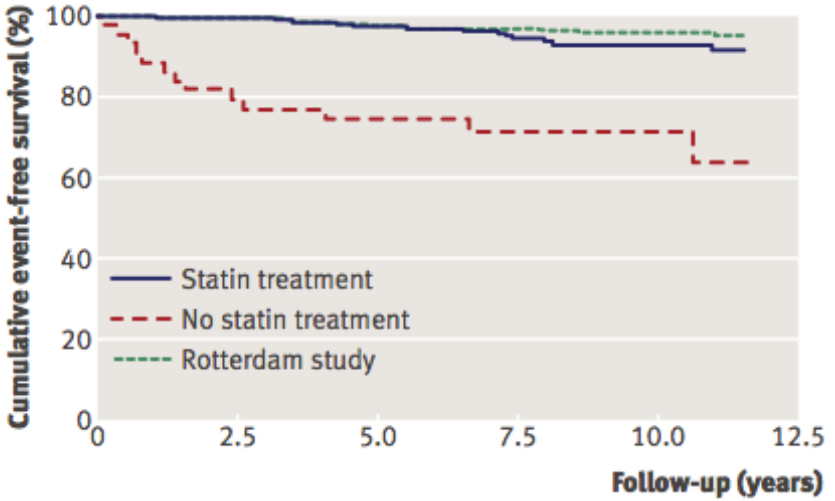
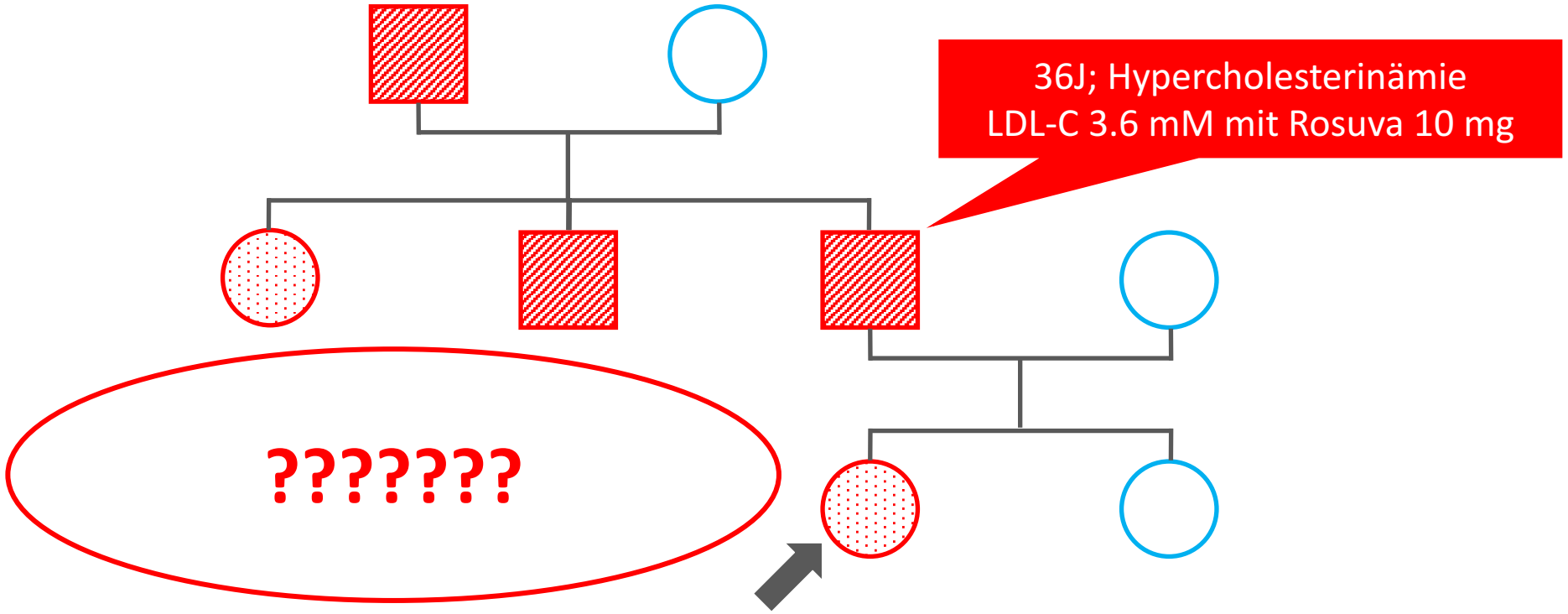


Fig 4 | Kaplan-Meier curve estimates of cumulative myocardial infarct-free survival among patients with familial hypercholesterolaemia older than 55 years according to statin treatment compared with a sample from the general population (Rotterdam study). (P<0.001 for difference between untreated patients and general population; P=0.07 for difference between treated patients and general population)

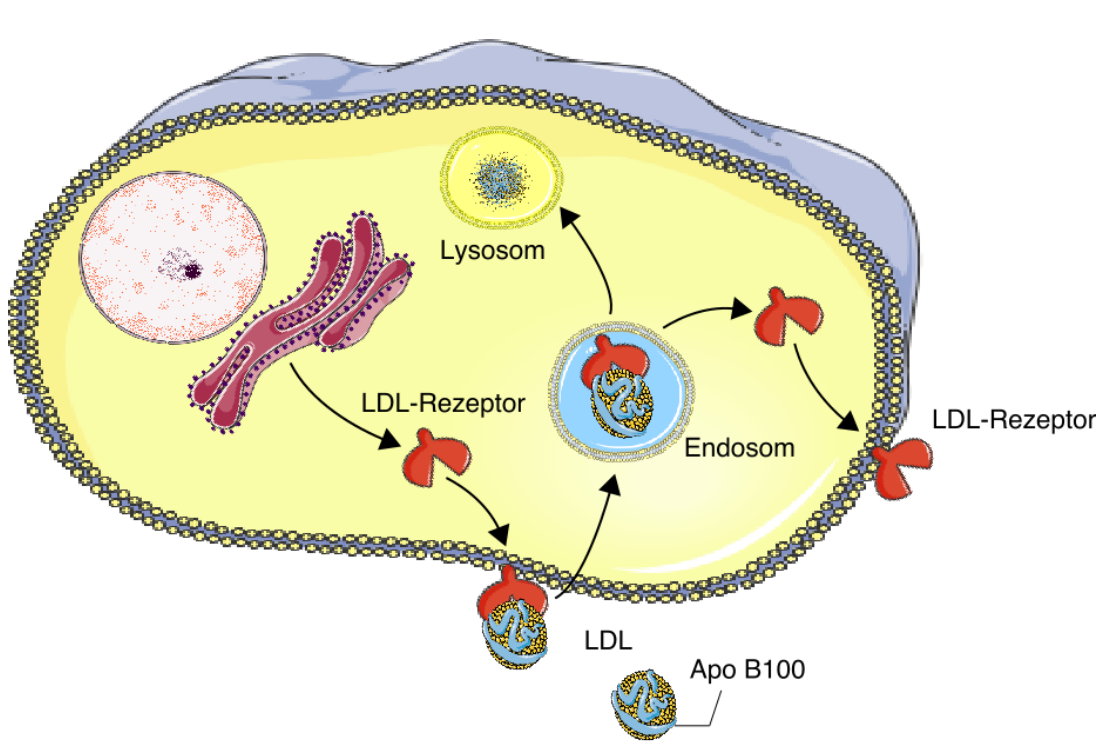
Simva; ⌀ Dosis 33 mg, LDL-C ↓ 44%;
Atorva ⌀ Dosis 49 mg, LDL-C ↓ 49%;

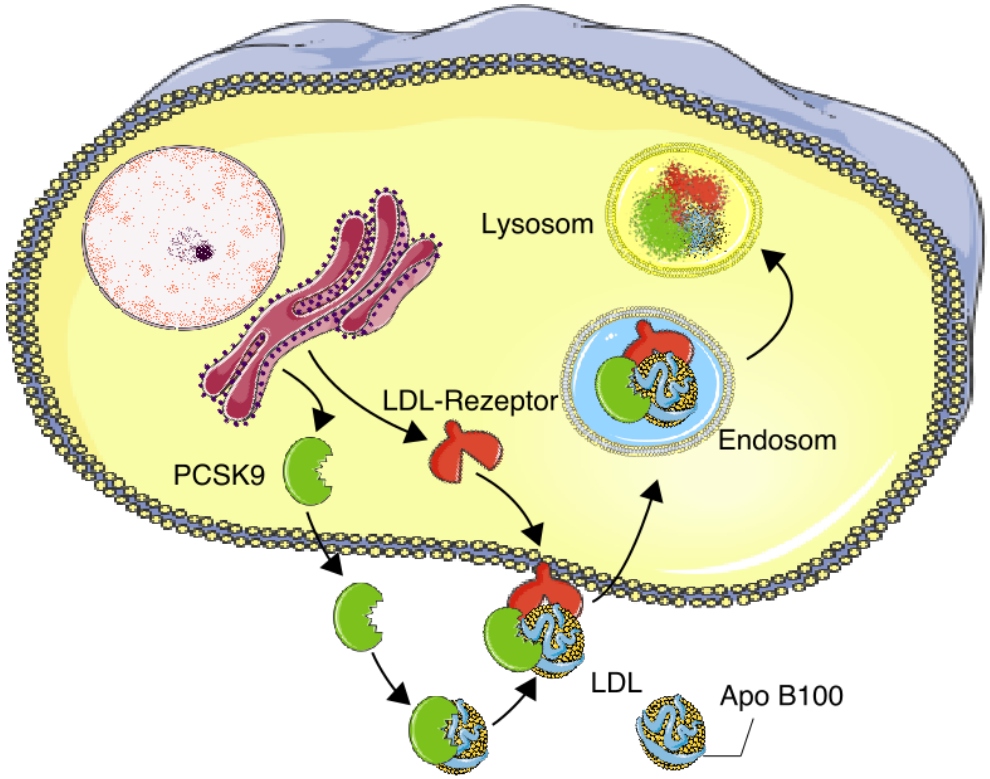
Versmissen et al., BMJ 337: a2423, 2008

3. Autosomal-doninater Erbgang – 50% der erstgradig Verwandten sind betroffen,Familienuntersuchung – Kaskadenscreening obligat !!!



LDL-Rezeptor-Stoffwechsel in der Leberzelle





Mutationen im LDL-Rezeptor-, Apo B und PCSK9-Gen führen zur Familiären Hypercholesterinämie

Familiäre Hypercholesterinämie

Gen	LDLR Familiäre Hypercholesterinämie (FH)		APOB Familiär Defektives ApoB(FDB)		PCSK9 LOF Mutation	ApoE p.Leu167del	Polygene FH
	Het	Hom	Het	Hom	Het	Het	--
Frequency (%)	1:250	selten	1:200	selten	? selten	Wenige Familien	20% der Pat. mit klin. FH
TC (mmol/L)	9-13	15-30	7-10	8.5-12	13-14	ca. 11	⌀ 9.16
LDL-C (mmol/l)	6-11	13-20	5-8	6.7-8.5	11-12	ca. 9	⌀ 5.87
Tendon Xanthoma	30-40% (> 40 J)	>90%	<FH-Het	1/5 Pat	FH-Het	FH-Het	FH-Het
CVD risk	++ 4-8 fach	++++ Kindheit, 40% < 20 J	++	+++	+++	++	++

„Polygene“ FH: Klinische Kriterien einer HeFH erfüllt, aber kein Nachweis einer LDLR-, APOB- PCSK-9 - Mutation

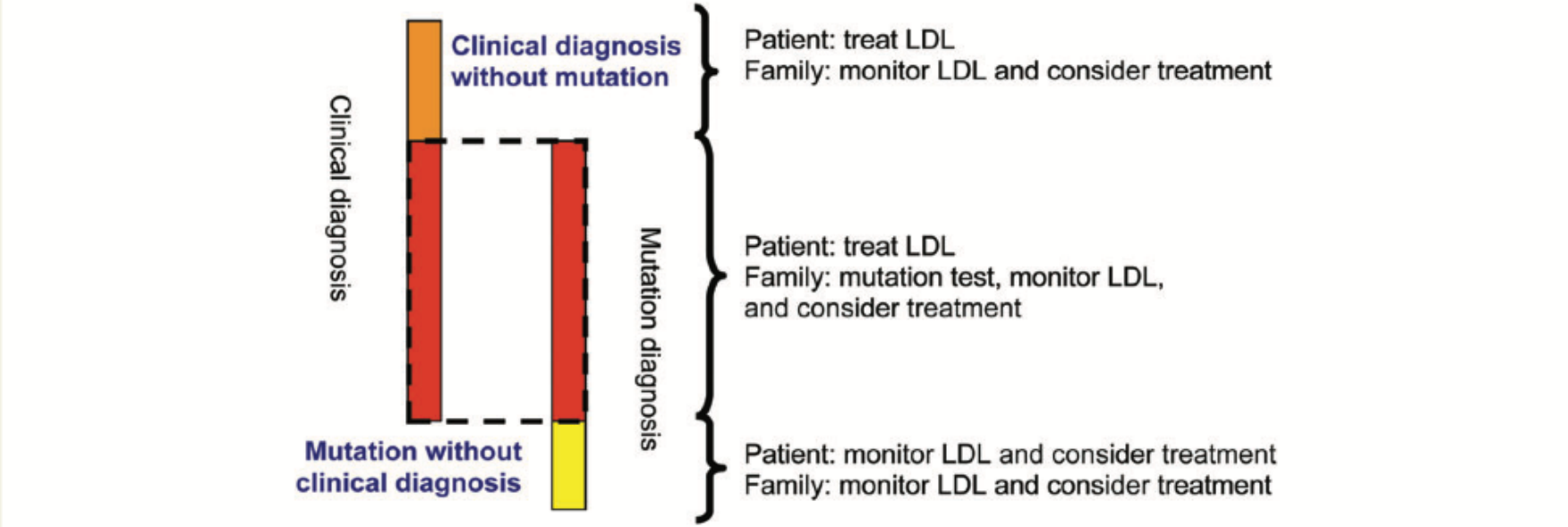
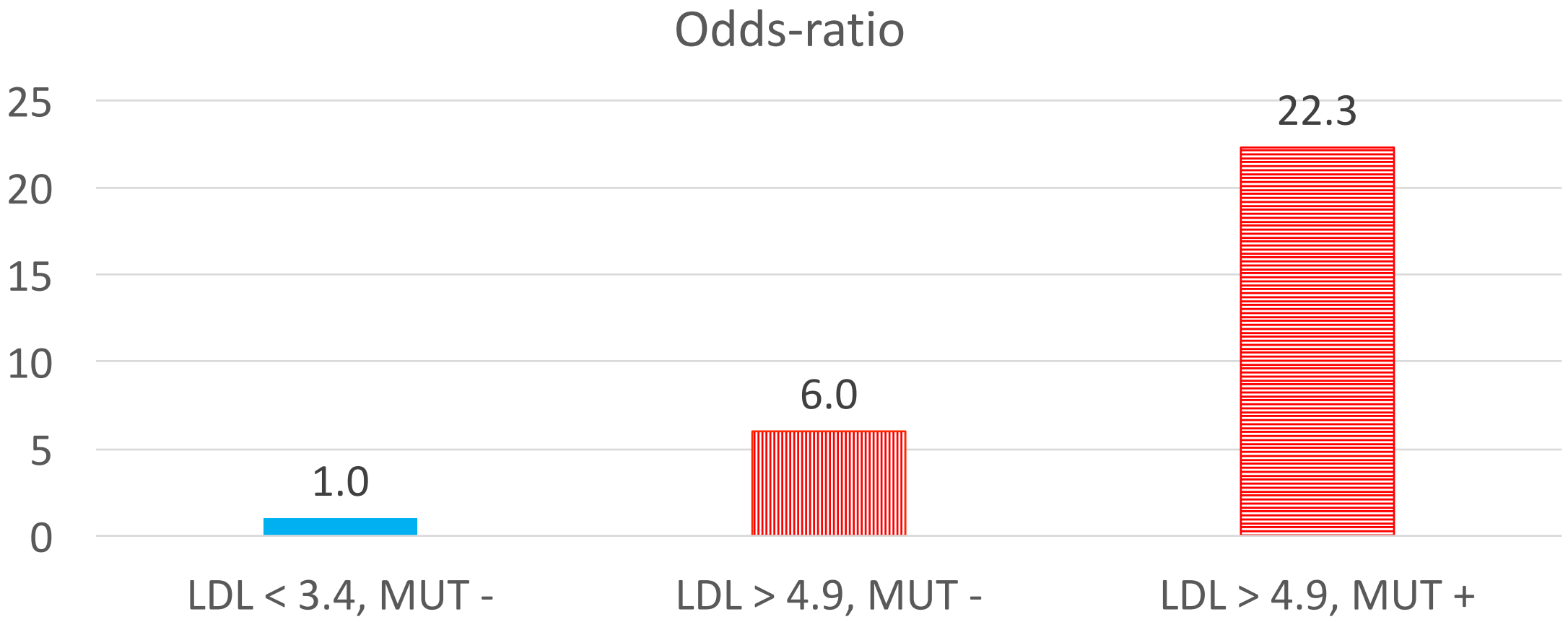


Figure 6 Overlap of clinical and mutation diagnosis of heterozygous familial hypercholesterolaemia. This figure illustrates the fractions of three different clinical scenarios in a study from Spain,[18] and therefore not necessarily the exact proportions for these three groups in other countries. 'Mutation without clinical diagnosis' means definite, probable, or possible familial hypercholesterolaemia with a familial hypercholesterolaemia-causing mutation but with less severely elevated LDL cholesterol (i.e. below the diagnostic threshold). LDL, low-density lipoprotein cholesterol; FH, familial hypercholesterolaemia.

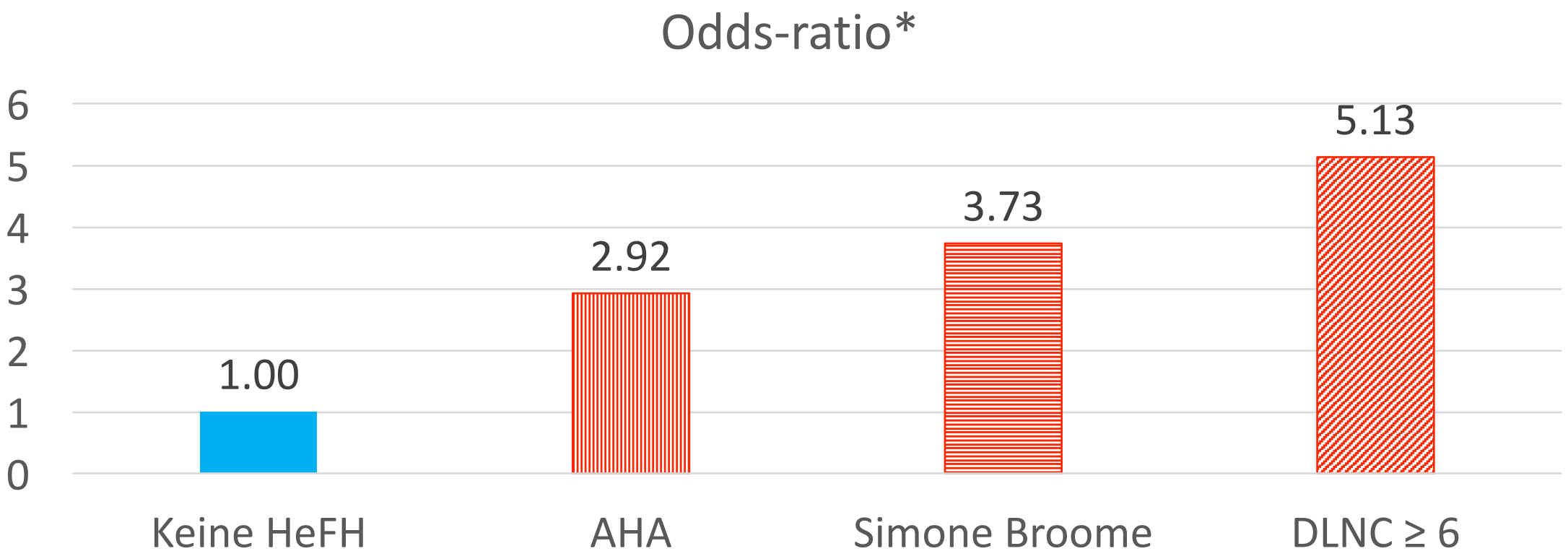
Nordestgaard et al., Eur Heart J 34: 3478, 2013

KHK-Risiko in Abhängigkeit von LDL-C und FH-Mutationsstatus



Khera AV et al., JACC epub 28. März 2016

Risiko für koronare Re-Ereignisse innerhalb eines Jahres nach ACS in Abhängigkeit vom FH-Status (klinische Diagnose)



*Adjustiert für Alter, Geschlecht, Raucherstatus, Hypertonie, DM, Verwendung von hochdosierten Statinen, Teilnahme an kardialer Rehabilitation, KHK-Schweregrad und LDL-C

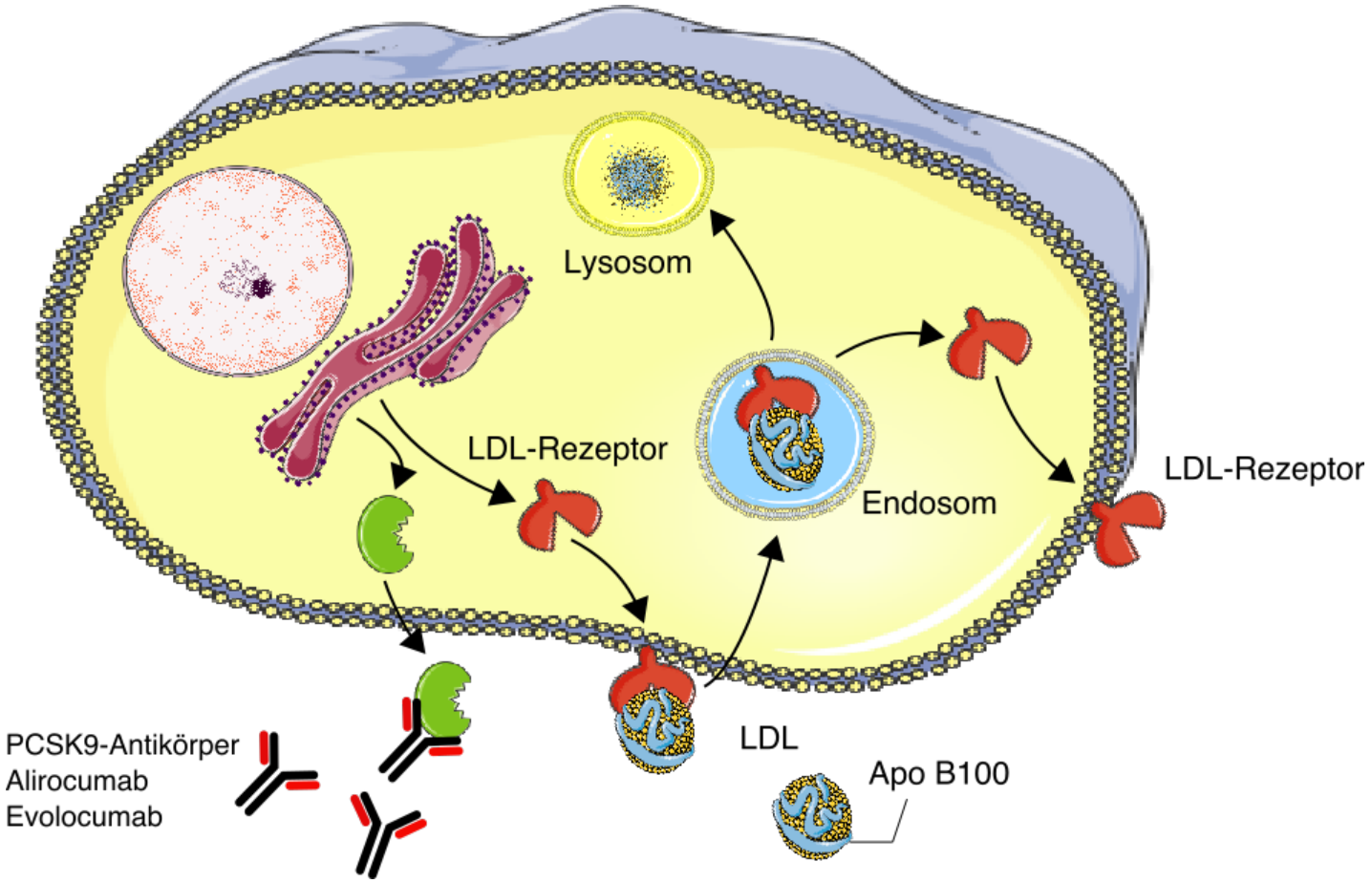
Nanchen D et al., Circulation epub 26. Juli 2016

Risikostratifizierung von Patienten mit HeFH – Definition einer „schweren“ HeFH

Keine bekannte Arteriosklerose	Fortgeschrittene subklinische Arteriosklerose	Klinisch manifeste Arteriosklerose
• LDL-C > 10 mmol/l • LDL-C > 8 mmol/l & 1 RF • LDL-C > 5 mmol/l & 2 RF	• Agatston Score > 100 U • CT-Angio > 50% Stenose oder nicht-obstruktive Plaques in ≥ 1 Gefäss	• Klinisch manifeste KHK (MI, Angina, Revaskularisation) • CVI • PAVK
• **LDL-C-Senkung ≥ 50%** • **Ideal < 2.5 mmol/l**	• **LDL-C-Senkung ≥ 50%** • **Ideal < 1.8 mmol/l**	• **LDL-C-Senkung ≥ 50%** • **Ideal < 1.8 mmol/l**
Risikofaktoren: Alter >40 ohne Therapie; Rauchen; männliches Geschlecht; Lipoprotein(a) >50 mg/dL; HDL-C <1 mmol/L; Hypertonie; Diabetes mellitus; pos FA für frühzeitige KHK (<55 /<60 Männer/Frauen); CKD, eGFR <60 mL/min per 1·73 m^2; BMI >30 kg/m^2		

Santos RD et al., Lancet Diab Endocrinol epub 27. May 2016

PCSK9 - Antikörper



PCSK9-Ak bei Patienten mit HeFH
(Rutherford & Odyssey FH-Studien)

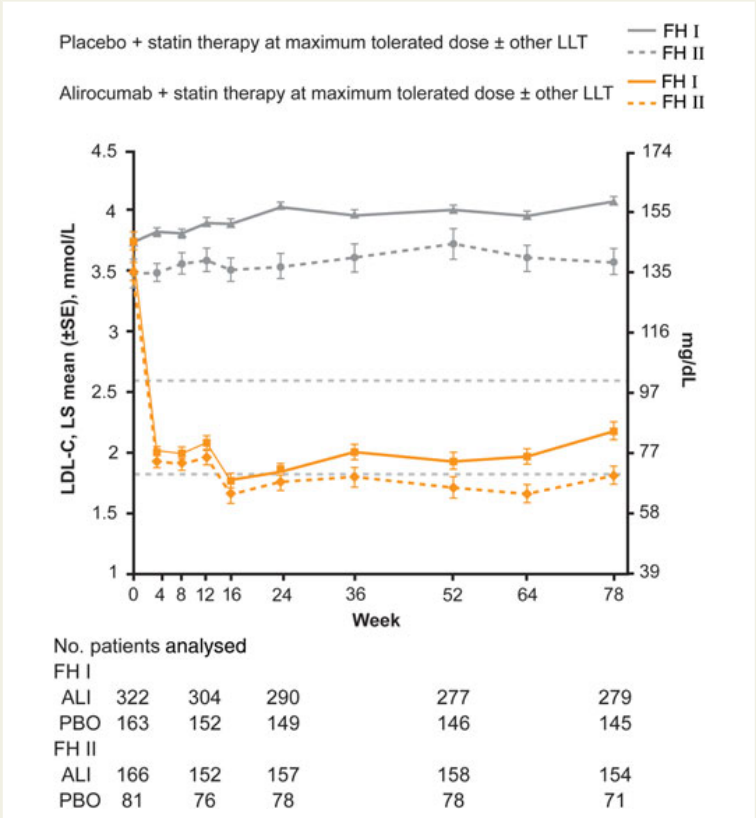


Figure 2 Levels of calculated LDL-C over time (intention-to-treat analysis). ALI, alirocumab; PBO, placebo.

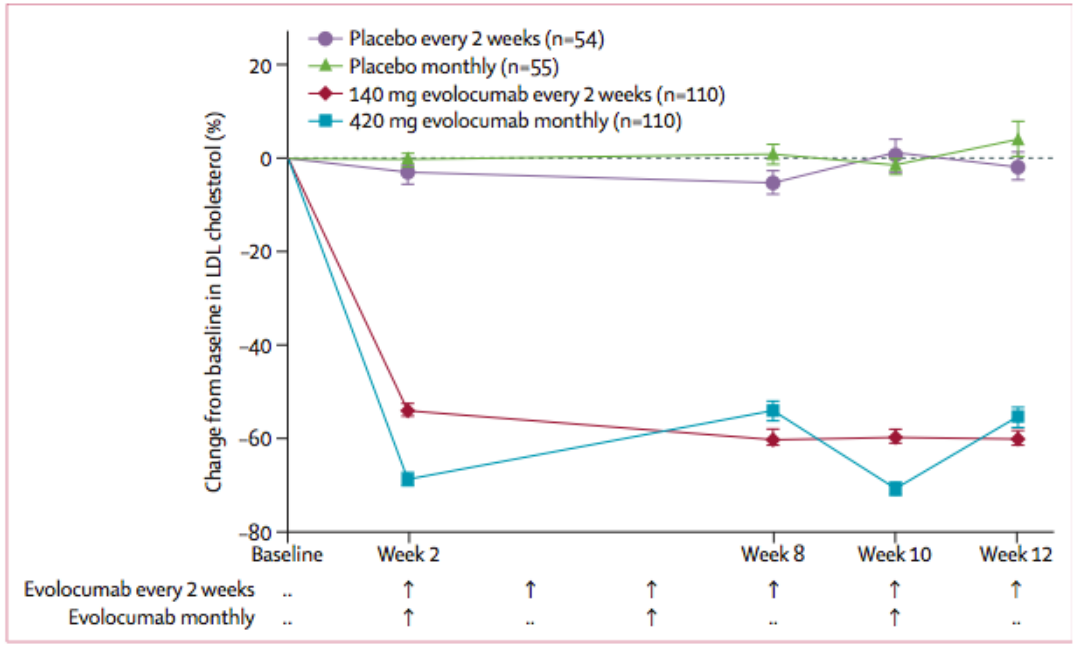


Figure 2: **Mean percentage change from baseline in LDL cholesterol in the four groups**
The arrows underneath the graph represent timepoints of evolocumab administration. Error bars are standard errors. The percentage change in LDL cholesterol was ascertained by the Friedewald formula, with reflexive testing through preparative ultracentrifugation when calculated LDL cholesterol was 1·0 mmol/L or lower or triglyceride concentrations were 4·5 mmol/L or higher.

Raal et al., Lancet epub Oct 2014
Kastelein et al., Eur Heart J, epub Juli 2015

Herr C, 39 Jahre

- Hospitalisation 07/2017 bei subakutem MI und in der Folge kardiogenem Schock, Koro: schwere 3-Gefässerkrankung, EF 25%, PCI mit 7xDES
- Risikofaktoren:
- DM Typ 2, ED 07/2016, HbA1c 7.8%
- Nikotinabusus 10 Zig tgl.

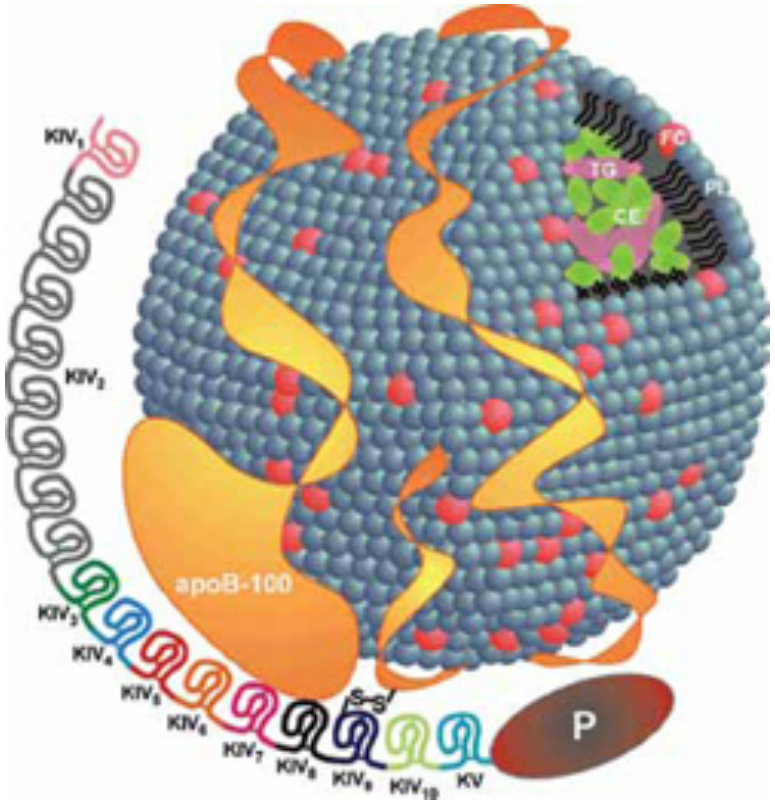
Fragen

TSH (DxI)	[0.25-4 mU/l]	1.58
Cholesterin	[<5.0 mmol/l]	4.7
Triglyceride	[<1.7 mmol/l]	1.4
Cholesterin/HDL	[<5]	5.2
HDL-Cholesterin	[>1.0 mmol/l]	0.9
LDL-Cholesterin	[<2.6 mmol/l]	3.2

- Schwere 3-Gefäss-KHK bei «mildem» Risikofaktorprofil bei einem jungen Patienten
- Wie weiter ?

Glucose (nü)	[3.9-5.6 mmol/l]				8.8			
Ferritin	[25-330 µg/l]				434			
Cholesterin	[<5.0 mmol/l]				4.8			
Triglyceride	[<1.7 mmol/l]				2.3			
Lp(a) INA	[<300 mg/l]						2540	
Apolipoprotein A-I	[1.0-2.0 g/l]						sistiert	
Apolipoprotein A-II	[0.2-0.5 g/l]						sistiert	
Vitamin B12	[180-900 ng/l]				282			
Folsäure (Serum)	[3-20 µg/l]				5.7			
25-OH-Vitamin D Total	[75-250 nmol/l]				27			

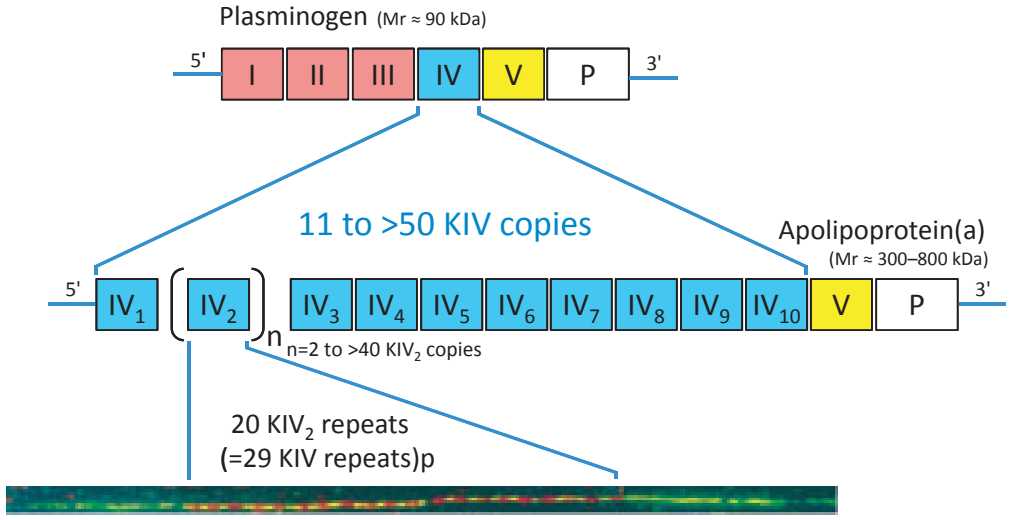
Lipoprotein (a)

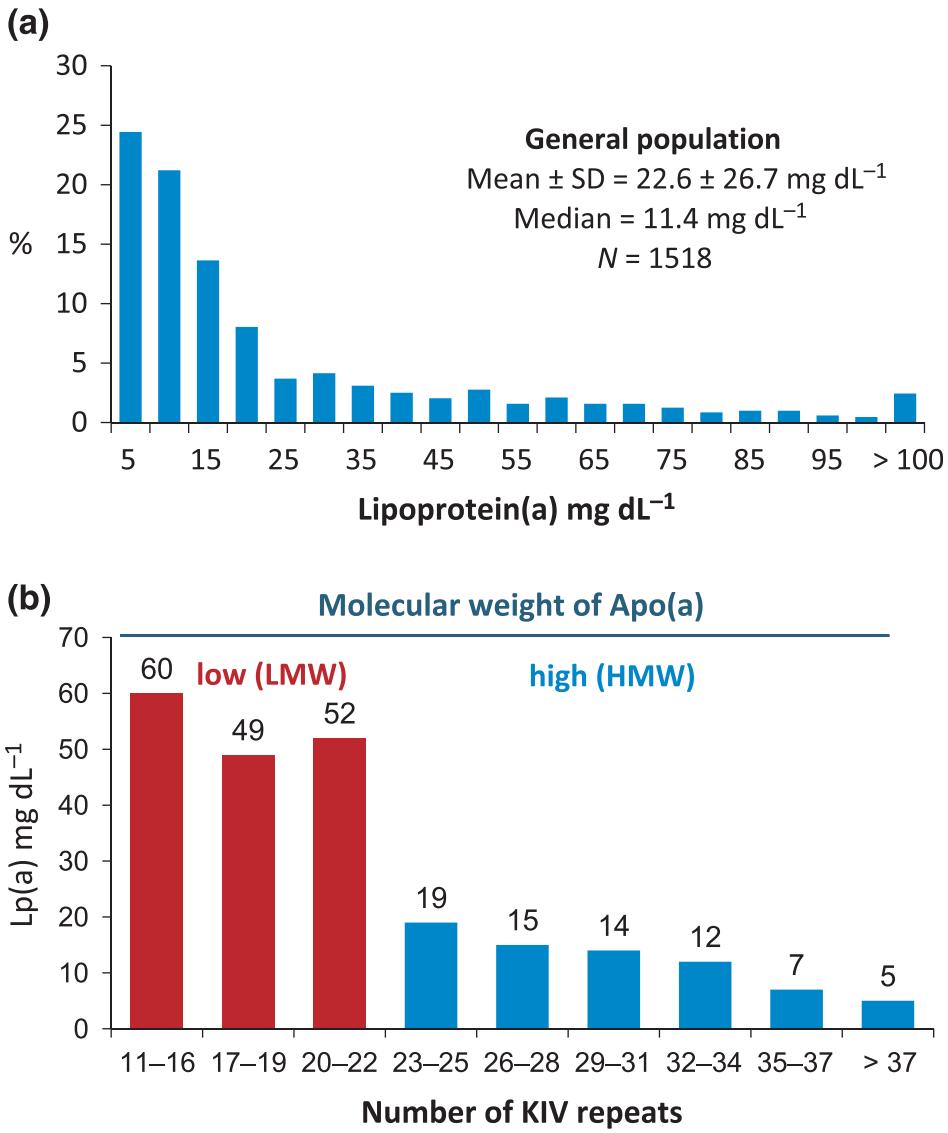


- Komplex aus LDL-Partikel und dem Glykoprotein apo(a), das über eine Disulfidbrücke ans ApoB gebunden ist.
- Apo(a) ist ein Plasminogen-Homolog
- Apo(a) wird vom LPA-Gen kodiert (6q26-q27).
- Es besteht ein Grössenpolymorphismus, der durch die Anzahl der Kopien der Kringel IV-2-Domäne gegeben ist und die Lp(a) Konzentration zu 20-80% bestimmt. Insgesamt ist die Lp(a)-Konzentration zu 70-90% genetisch bedingt
- Inverse Beziehung zwischen apo(a)-Grösse (d.h. KIV-repeats und Lp(a)-Konzentration
- Lp(a)-Konzentration und kleine apo(a) Allele sind mit KHK assoziiert
- Lp(a) ist bei Niereninsuffizienz, HeFH, FDB, Hypothyreose, Postmenopause erhöht
- Lp (a) wird durch Nikotinsäure, E2, anabole Steroide und PCSK-9-Hemmer gesenkt

Kronenberg F., J Intern Med 273: 6, 2013.

Lipoprotein (a)



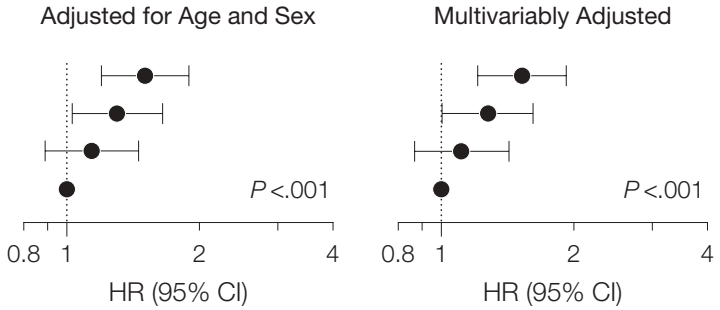


Kronenberg F., J Intern Med 273: 6, 2013.

CCHS

KIV-2 Repeats

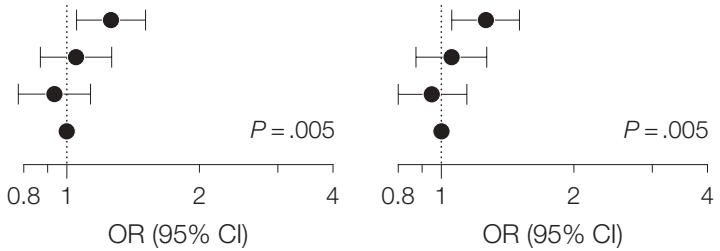
Quartile	No. of Repeats	Participants, No.	Events, No.
1	6-30	2160	181
2	31-35	2159	158
3	36-40	2159	137
4 [Reference]	41-99	2159	123



CGPS

KIV-2 Repeats

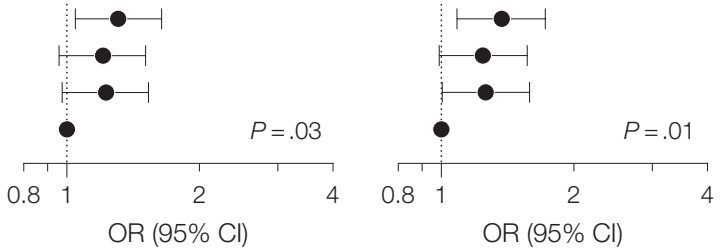
Quartile	No. of Repeats	Controls, No.	Cases, No.
1	6-30	7016	287
2	31-35	7064	246
3	36-40	7095	219
4 [Reference]	41-99	7076	234



CIHDS

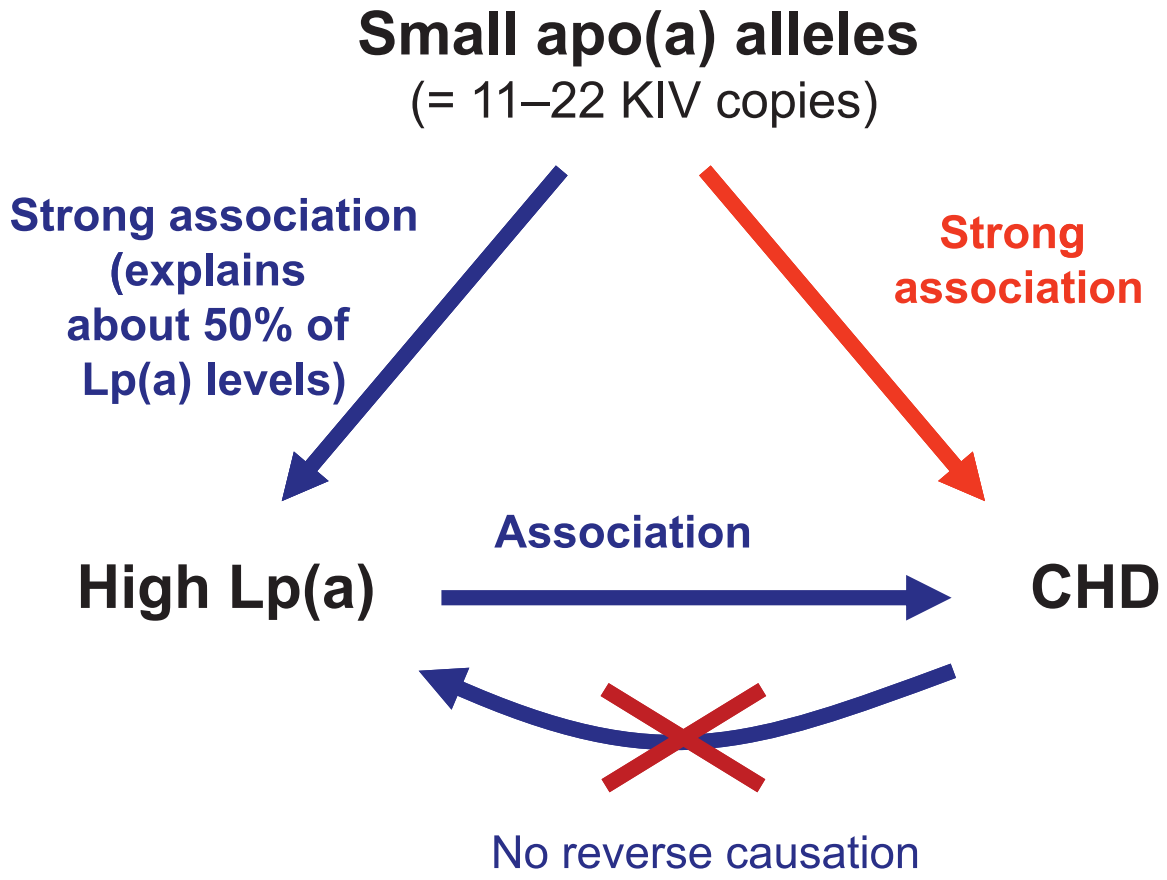
KIV-2 Repeats

Quartile	No. of Repeats	Controls, No.	Cases, No.
1	13-30	291	325
2	31-35	304	311
3	36-40	302	313
4 [Reference]	41-96	333	282



Myokardinfarktrisiko in Abh. vom Kringle IV Polymorphismus in 3 Dänischen Kohorten

Kamstrup PR et al., JAMA 201: 2331, 2009



Kronenberg F., J Intern Med 273: 6, 2013.

Table 2 **Primary and selected secondary efficacy endpoints (intention-to-treat analysis)**

	FH I			FH II		
	Alirocumab (n = 322)	Placebo (n = 163)	% Difference vs. placebo	Alirocumab (n = 166)	Placebo (n = 81)	% Difference vs. placebo
Calculated LDL-C, LS mean ± SE						
Baseline, mmol/L [mg/dL]	3.7 ± 0.1 [144.7 ± 2.9]	3.7 ± 0.1 [144.4 ± 3.7]		3.5 ± 0.1 [134.6 ± 3.2]	3.5 ± 0.1 [134.0 ± 4.6]	
Week 24, mmol/L [mg/dL]	1.8 ± 0.1 [71.3 ± 2.3]	4.0 ± 0.1 [155.6 ± 3.2]		1.8 ± 0.1 [67.7 ± 2.8]	3.5 ± 0.1 [136.6 ± 4.0]	
% Change from baseline to Week 24 (primary endpoint)	−48.8 ± 1.6	9.1 ± 2.2	−57.9 ± 2.7**	−48.7 ± 1.9	2.8 ± 2.8	−51.4 ± 3.4**
95% confidence interval			−63.3 to −52.6			−58.1 to −44.8
Selected secondary efficacy endpoints						
Patients (%) with or without prior CV events achieving LDL-C <1.8 mmol/L (<70 mg/dL) or <2.6 mmol/L (<100 mg/dL), respectively, at Week 24	72.2**	2.4		81.4**	11.3	
Patients (%) achieving LDL-C <1.8 mmol/L at Week 24 (regardless of prior CV events)	59.8**	0.8		68.2**	1.2	
Calculated LDL-C % change from baseline to Week 12, LS mean ± SE	−43.5 ± 1.4	5.7 ± 2.0	−49.2 ± 2.4**	−43.8 ± 1.8	4.6 ± 2.6	−48.4 ± 3.2**
% Change from baseline to Week 24 in secondary lipid variables, LS mean ± SE						
Apolipoprotein B	−41.1 ± 1.2	4.7 ± 1.6	−45.8 ± 2.0**	−42.8 ± 1.4	−3.5 ± 2.0	−39.3 ± 2.4**
Non-HDL-C	−42.8 ± 1.4	9.6 ± 2.0	−52.4 ± 2.4**	−42.6 ± 1.8	3.1 ± 2.5	−45.7 ± 3.1**
Lipoprotein(a)	−25.2 ± 1.4	−7.5 ± 2.0	−17.7 ± 2.5**	−30.3 ± 1.8	−10.0 ± 2.5	−20.3 ± 3.1**
Fasting triglycerides	−9.6 ± 1.6	6.3 ± 2.2	−16.0 ± 2.7**	−10.4 ± 2.0	0.5 ± 2.8	−10.9 ± 3.4*
HDL-C	8.8 ± 0.9	0.8 ± 1.2	8.0 ± 1.5**	6.0 ± 1.2	−0.8 ± 1.6	6.8 ± 2.0*
Apolipoprotein A1	5.0 ± 0.7	0.3 ± 1.0	4.7 ± 1.2*	2.8 ± 0.9	−1.6 ± 1.3	4.4 ± 1.6*

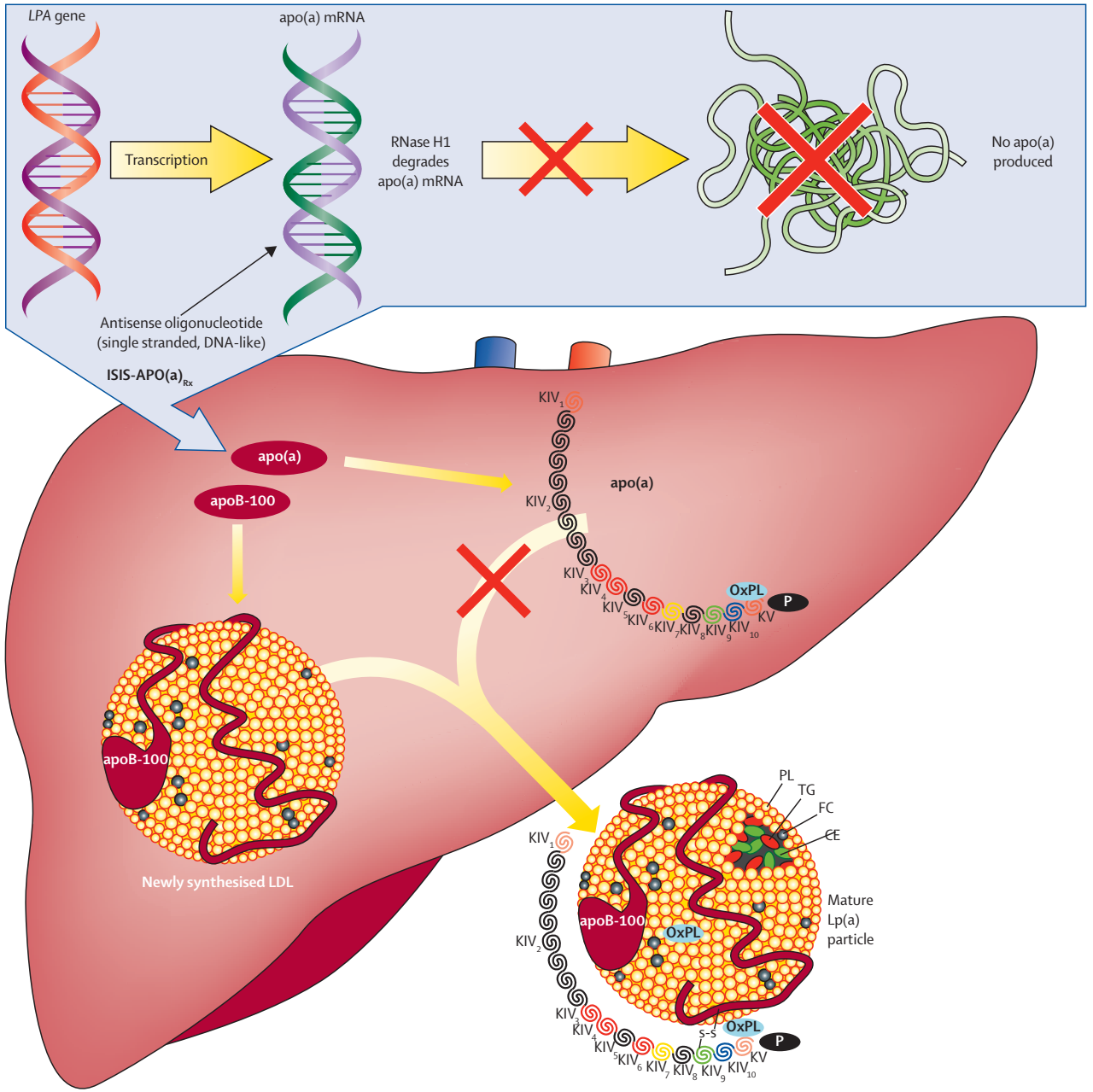
LS, least squares.
*P < 0.05; **P < 0.0001 vs. placebo.

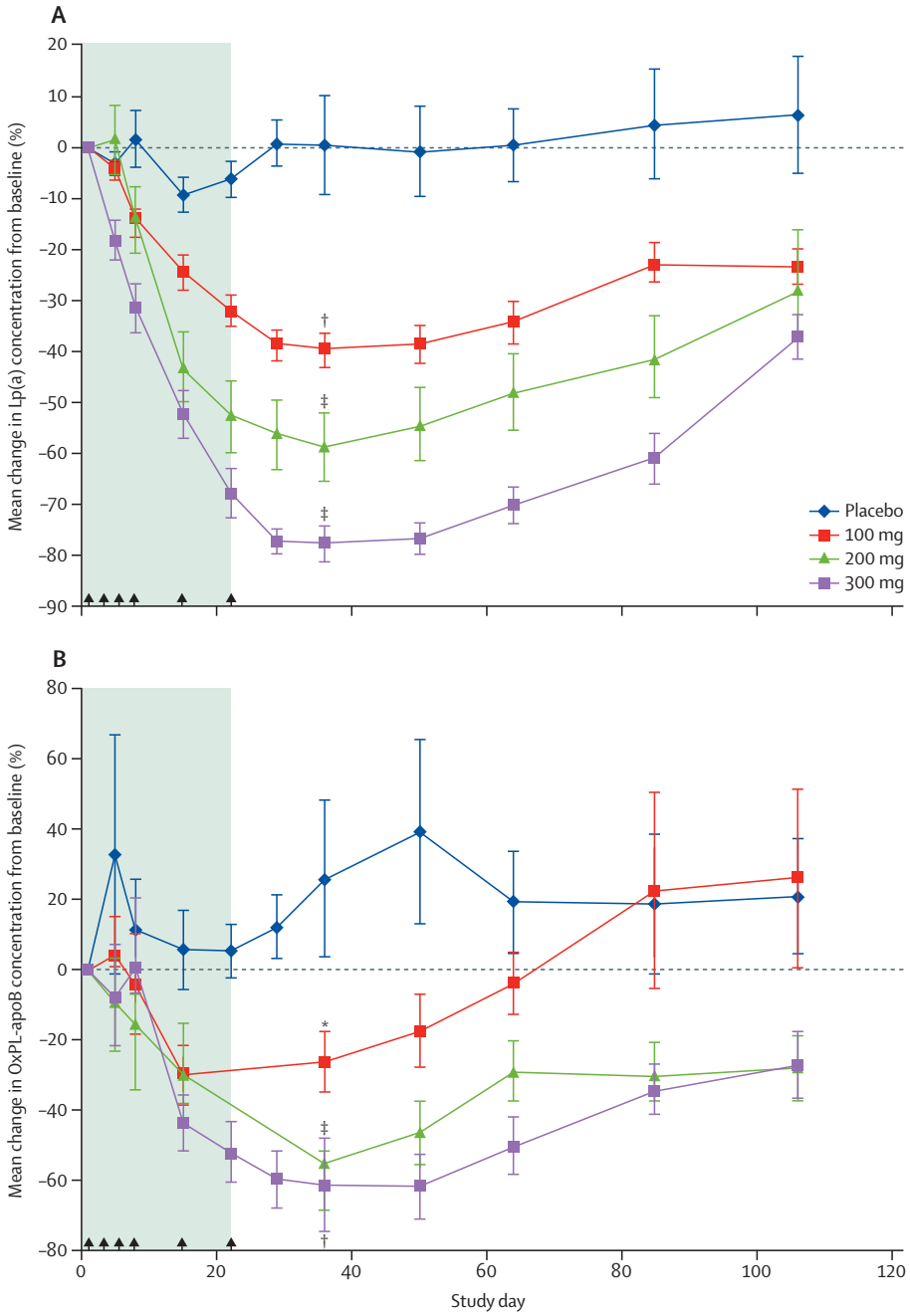
Kastelein et al., Eur Heart J, epub Juli 2015

Antisense therapy targeting apolipoprotein(a): a randomised, double-blind, placebo-controlled phase 1 study

Sotirios Tsimikas, Nicholas J Viney, Steven G Hughes, Walter Singleton, Mark J Graham, Brenda F Baker, Jennifer L Burkey, Qingqing Yang, Santica M Marcovina, Richard S Geary, Rosanne M Crooke, Joseph L Witztum

Lancet **2015; 386: 1472–83**


LPA gene
apo(a) mRNA
Transcription
RNase H1 degrades apo(a) mRNA
No apo(a) produced
Antisense oligonucleotide (single stranded, DNA-like)
ISIS-APO(a)Rx
apo(a)
apoB-100
KIV1
KIV2
KIV3
KIV4
KIV5
KIV6
KIV7
KIV8
KIV9
KIV10
KV
OxPL
P
apo(a)
apoB-100
Newly synthesised LDL
PL
TG
FC
CE
S-S
Mature Lp(a) particle


A
Mean change in Lp(a) concentration from baseline (%)
20
10
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
Placebo
100 mg
200 mg
300 mg
B
Mean change in OxPL-apoB concentration from baseline (%)
80
60
40
20
0
-20
-40
-60
-80
0
20
40
60
80
100
120
Study day

Wichtig !!!

- LDL-C > 5 mmol/l bzw. > 3.5 mmol/l unter Statintherapie → an FH denken
- Klinische Diagnose mit FH-Score, ev. Genetik (nicht vergütet, im ZLM möglich !)
- Therapiebeginn (Statin) mit Diagnosestellung (AGLA-Score verboten !)
  - Statine ab 12. Lebensjahr zugelassen (ggf. OKS, Dr. P. Müller)
- Kaskadenscreening: alle erstgradig Verwandten müssen kontaktiert, informiert und gescreent werden
- Bei schweren Verlaufsformen/sehr hohem Risiko ggf. primärpräventiv PCSK-9-Ak
- Bei frühzeitger KHK und „mildem“ Risikoprofil - an Lp(a) denken !

Vielen Dank !