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Endokrinologie-Kardiologie Kolloquium
23. Oktober 2019

LDL-Cholesterin – je tiefer desto besser ?

Stefan Bilz
Klinik für Endokrinologie, Diabetologie, Osteologie
und Stoffwechselerkrankungen

2019 ESC/EAS Guidelines for the management of dyslipidaemias: *lipid modification to reduce cardiovascular risk*

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The Task Force for the management of dyslipidaemias of the European Society of Cardiology (ESC) and European Atherosclerosis Society (EAS)

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2019 ESC/EAS Guidelines für die Behandlung von Dyslipidämien: LDL-C-Zielwerte

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Recommendations	Class[a]	Level[b]
In secondary prevention for patients at very-high risk,[c] an LDL-C reduction of ≥50% from baseline[d] and an LDL-C goal of <1.4 mmol/L (<55 mg/dL) are recommended.[33–35,119,120]	I	A
In primary prevention for individuals at very-high risk but without FH,[c] an LDL-C reduction of ≥50% from baseline[d] and an LDL-C goal of <1.4 mmol/L (<55 mg/dL) are recommended.[34–36]	I	C
In primary prevention for individuals with FH at very-high risk, an LDL-C reduction of ≥50% from baseline and an LDL-C goal of <1.4 mmol/L (<55 mg/dL) should be considered.	IIa	C
For patients with ASCVD who experience a second vascular event within 2 years (not necessarily of the same type as the first event) while taking maximally tolerated statin-based therapy, an LDL-C goal of <1.0 mmol/L (<40 mg/dL) may be considered.[119,120]	IIb	B
In patients at high risk,[c] an LDL-C reduction of ≥50% from baseline[d] and an LDL-C goal of <1.8 mmol/L (<70 mg/dL) are recommended.[34,35]	I	A
In individuals at moderate risk,[c] an LDL-C goal of <2.6 mmol/L (<100 mg/dL) should be considered.[34]	IIa	A
In individuals at low risk,[c] an LDL-C goal <3.0 mmol/L (<116 mg/dL) may be considered.[36]	IIb	A

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2019 ES… von Dys…

…dlung

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Recommendatio…	Class[a]	Level[b]
In secondary preventi… <1.4 mmol/L (<55 mg… …m baseline[d] and an LDL-C goal of		
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For patients with AS… first event) while tal… considered.[119,120] …ype as the …ay be	IIb	B
In patients at high ri… recommended.[34,35] …g/dL) are	I	A
In individuals at mo…	IIa	A
In individuals at low…	IIb	A

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Very-high-risk

People with any of the following:

Documented ASCVD, either clinical or unequivocal on imaging. Documented ASCVD includes previous ACS (MI or unstable angina), stable angina, coronary revascularization (PCI, CABG, and other arterial revascularization procedures), stroke and TIA, and peripheral arterial disease. Unequivocally documented ASCVD on imaging includes those findings that are known to be predictive of clinical events, such as significant plaque on coronary angiography or CT scan (multivessel coronary disease with two major epicardial arteries having >50% stenosis), or on carotid ultrasound.

DM with target organ damage,[a] or at least three major risk factors, or early onset of T1DM of long duration (>20 years).

Severe CKD (eGFR <30 mL/min/1.73 m^2).

A calculated SCORE ≥10% for 10-year risk of fatal CVD.

FH with ASCVD or with another major risk factor.

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LDL-Cholesterin – je tiefer desto besser !

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LDL-Cholesterin – wieviel besser ist tiefer ?

Stefan Bilz
Klinik für Endokrinologie, Diabetologie, Osteologie
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Kohortenstudien, Mendel‘sche Randomisierungs-studien und randomisierte Studien zeigen: je grösser die LDL-C-Senkung, desto grösser die kardiovaskuläre Risikoreduktion

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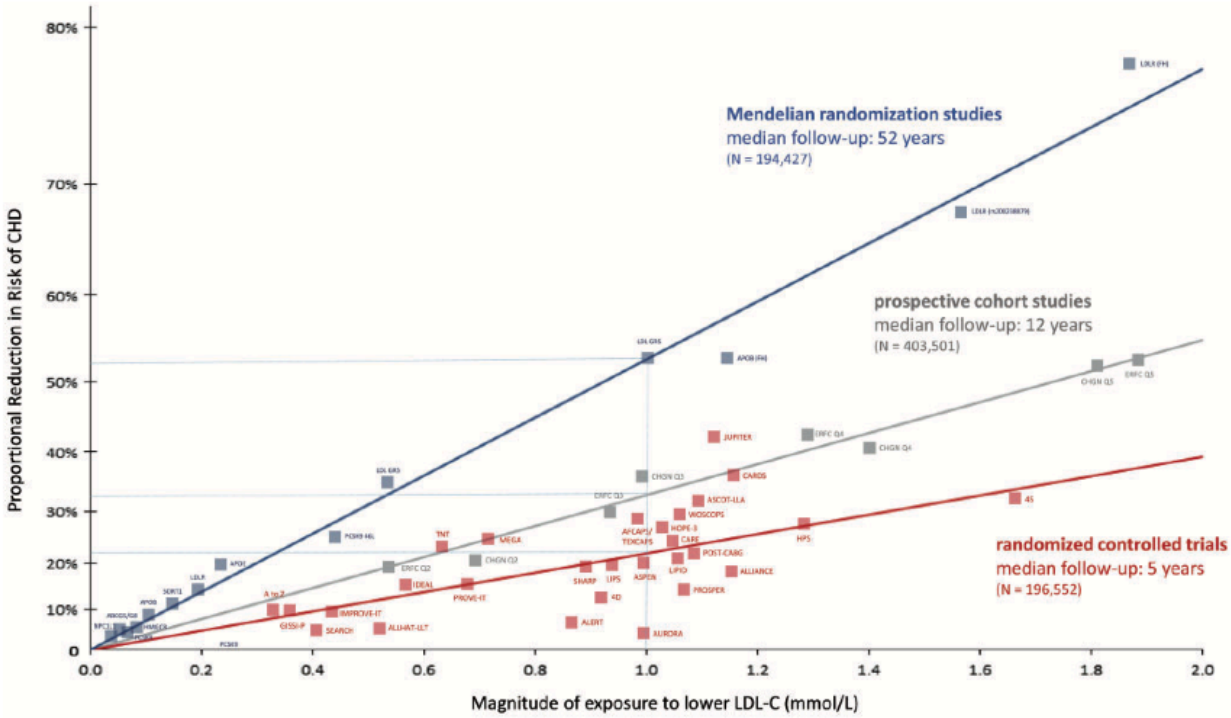
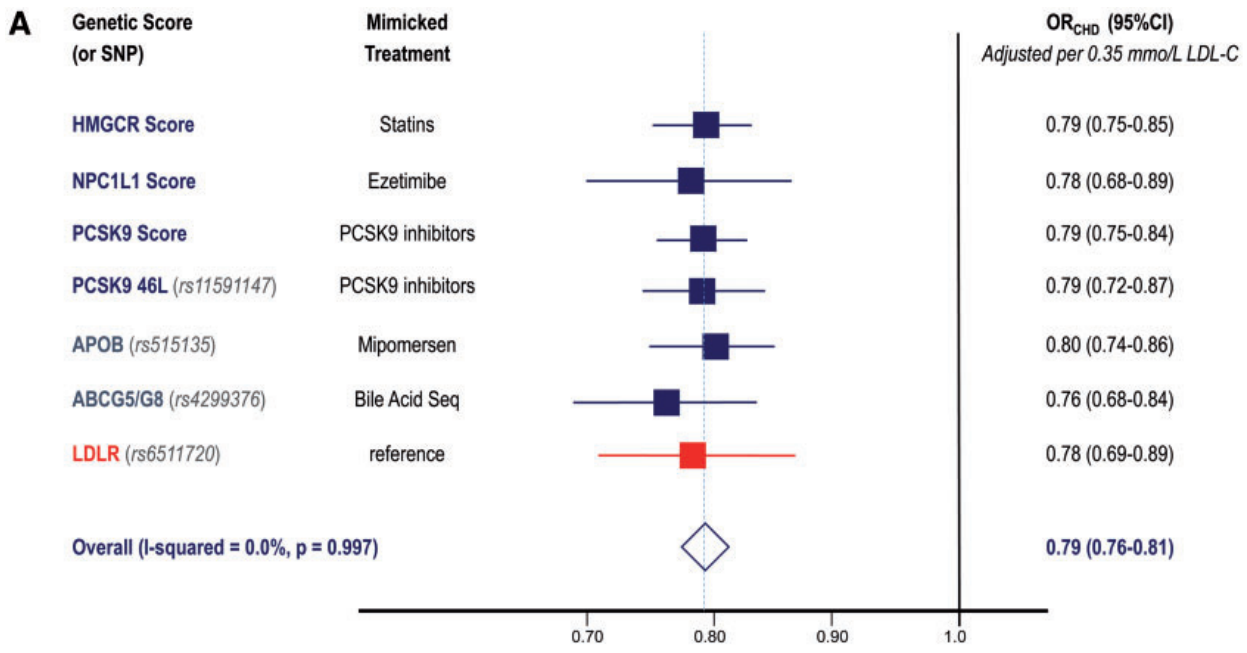


Ference et al., European Heart Journal epub 2017

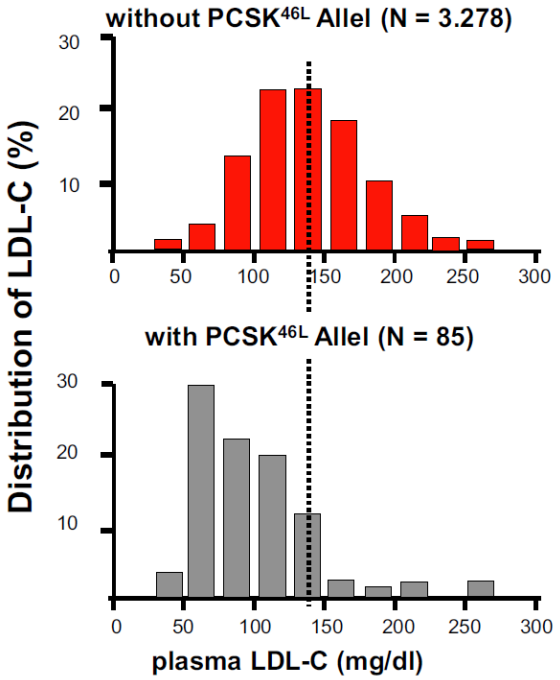
Genetische –Mendel‘sche Randomisierung

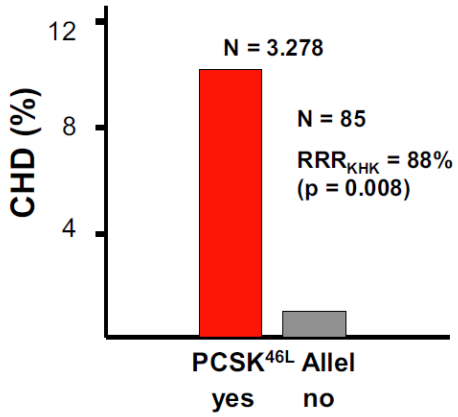
Träger von Genvarianten, die mit lebenslang tieferem LDL-C assoziiert sind, gehen mit einem tieferen KHK-Risiko einher



Ference et al., European Heart Journal epub 2017

PCSK9 „loss-of-function“ Varianten sind mit tiefem LDL-C und tiefem KHK-Risiko assoziiert

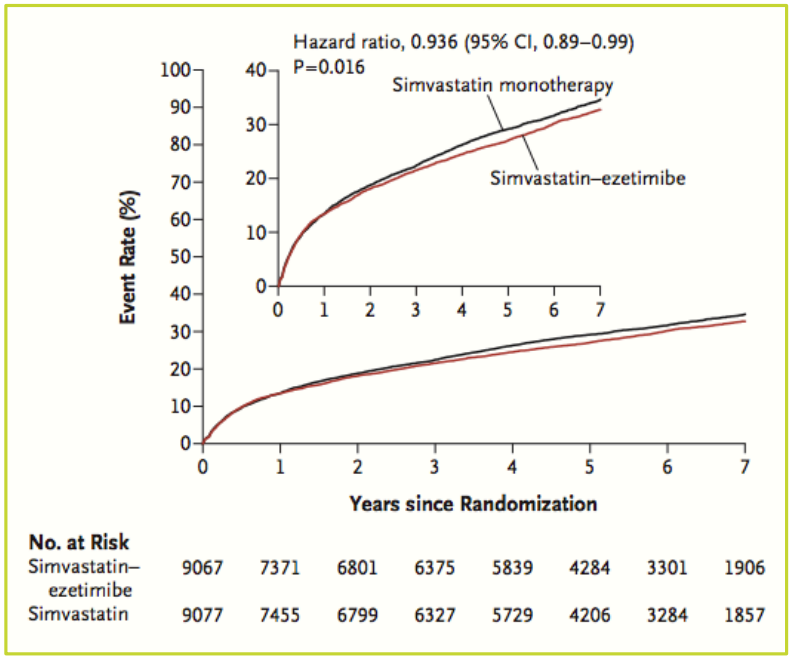




Cohen JC, et al, NEJM 354: 1264, 2006,

IMPROVE-IT Studie: LDL-C 1.8 -> 1.4 mmol/l

Ezetimibe vs. Placebo bei Patienten nach ACS unter Therapie mit Simvastatin



No. at Risk								
Simvastatin–ezetimibe	9067	7371	6801	6375	5839	4284	3301	1906
Simvastatin	9077	7455	6799	6327	5729	4206	3284	1857

Primärer Endpunkt:
Kardiovaskulärer Tod, MI, Instable Angina, Koronare Revaskularisation, oder Stroke
ARR 2%, NNT ca. 50

Cannon et al., N Engl J Med epub Jun 2015

IMPROVE-IT

Simvastatin 40 vs. Simvastatin 40 + Ezetimibe 10 mg bei Patients nach einem akuten Koronarsyndrom

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Endpunkte	Simvastatin n=9077 (%)	Ezetimibe/ Simvastatin, n=9067 (%)	P
Primärer Endpunkt (Kardiovaskulärer Tod, MI, Instable Angina, Koronare Revaskularisation, oder Stroke)	34.7	32.7	0.016
Todesfall	15.3	15.4	0.782
MI	14.8	13.1	0.002
Schlaganfall	4.8	4.2	0.052
Ischämischer Schlaganfall	4.1	3.4	0.008
Instabile Angina	1.9	2.1	0.618
Koronare Revaskularisation	23.4	21.8	0.107
LDL-Cholesterin (mmol/l)	1.80	1.38	

Cannon et al., N Engl J Med epub Jun 2015

FOURIER Studie: LDL-C 2.4 -> 0.8 mmol/l

Evolocumab 140 mg alle 2 Wo oder 420 mg alle w Wo vs. Placebo bei Patienten mit KHK oder multiplen Risikofaktoren (80% KHK, 69% hochdosierte Statintherapie)

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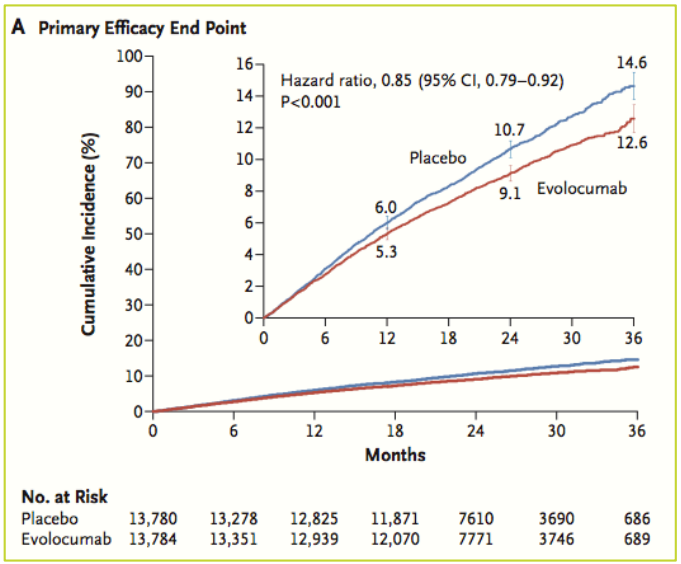

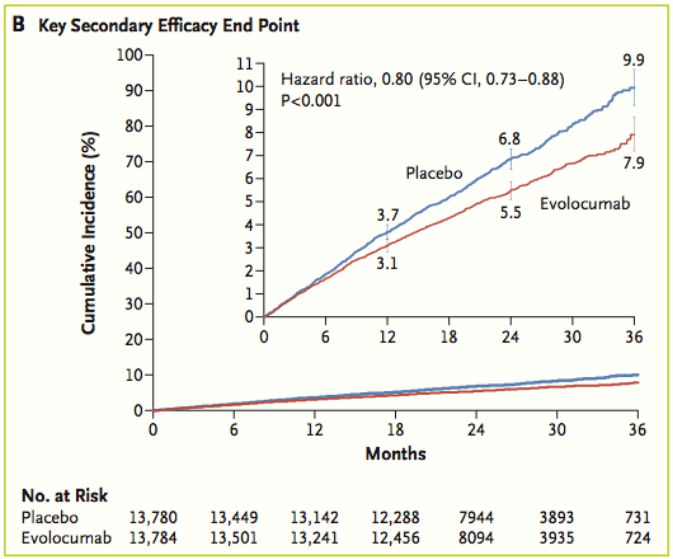

Primärer Endpunkt
Kardiovaskulärer Tod, nicht-tödl. Herzinfarkt oder Schlaganfall, instabile AP, Revaskularisation
ARR 1.6%, NNT = 63

Sekundärer Endpunkt
Kardiovaskulärer Tod, nicht-tödl. Herzinfarkt oder Schlaganfall
ARR 1.4%, NNT=70

Sabatine et al., NEJM 376:1713, 2017

FOURIER Studie

Evolocumab 140 mg alle 2 Wo oder 420 mg alle w Wo vs. Placebo bei Patienten mit KHK oder multiplen Risikofaktoren (80% KHK, 69% intensive Statintherapie)

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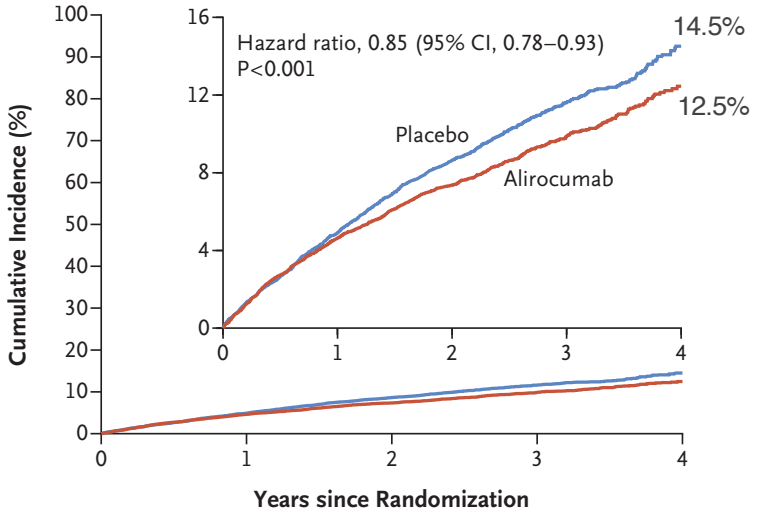
Endpunkt (%)	Placebo n=13‘780	Evolocumab n=13‘784	P
Primärer Endpunkt Kardiovaskulärer Tod, nicht-tödl. Herzinfarkt oder Schlaganfall, instabile AP, Revaskularisation	11.3	9.8	<0.001
Tod	3.1	3.2	0.54
Herzinfarkt	3.6	3.4	<0.001
Schlaganfall	1.9	1.5	0.001
Ischämischer Schlaganfall	2.1	1.7	0.003
Instabile AP	1.7	1.7	ns
Koronare Revaskularisation	7.0	5.5	<0.001
Mittelwert LDL-Cholesterin (mmol/l)	2.40	0.78	

Sabatine et al., NEJM 376:1713, 2017

ODYSSEY Outcomes Studie: LDL-C 2.4 -> 1.2 mmol/l

Alirocumab 75 (150) mg alle 2 Wo (Titration auf LDL-C Ziel of 0.6-1.3 mmol/l) bei Pat. unter hoch dosiertem Statin nach ACS



No. at Risk					
Placebo	9462	8805	8201	3471	629
Alirocumab	9462	8846	8345	3574	653

Primärer Endpunkt
Kardiovaskulärer Tod, nicht-tödl. Herzinfarkt oder Schlaganfall, instabile AP, Revaskularisation
ARR 2.0%, NNT = 49

Zeit nach ACS Median 2.6 Monate hochdosierte Statintherapie 88.8%

Schwarzt et al., NEJM epub Nov 7 2018

ODYSSEY Outcomes Study

Alirocumab 75 (150) mg q 2 weeks (titrated to an LDL-C target of 0.6-1.3 mmol/l) in statin treated post ACS patients

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Endpoint (%)	Placebo n=9'462	Alirocumab n=9'462	P
Primärer Endpunkt: Kardiovaskulärer Tod, nicht-tödl. Herzinfarkt oder Schlaganfall, instabile AP, Revaskularisation	11.1	9.5	<0.001
Koronares Ereignis	14.3	12.7	0.001
Schwerwiegendes koronares Ereignis	9.5	8.4	0.006
Tod, nichttödlicher Herzinfarkt oder Schlaganfall	11.9	10.3	<0.001
Tod infolge KHK	2.3	2.2	0.038
Kardiovaskulärer Tod	2.9	2.5	
Tod	4.1	3.5	
LDL-Cholesterol (mmol/l) @ 12 Monaten	2.5	1.2	

Schwarzt et al., NEJM epub Nov 7 2018

Verteilung der LDL-C-Werte mit Evolocumab vs. Placebo in der FOURIER Studie

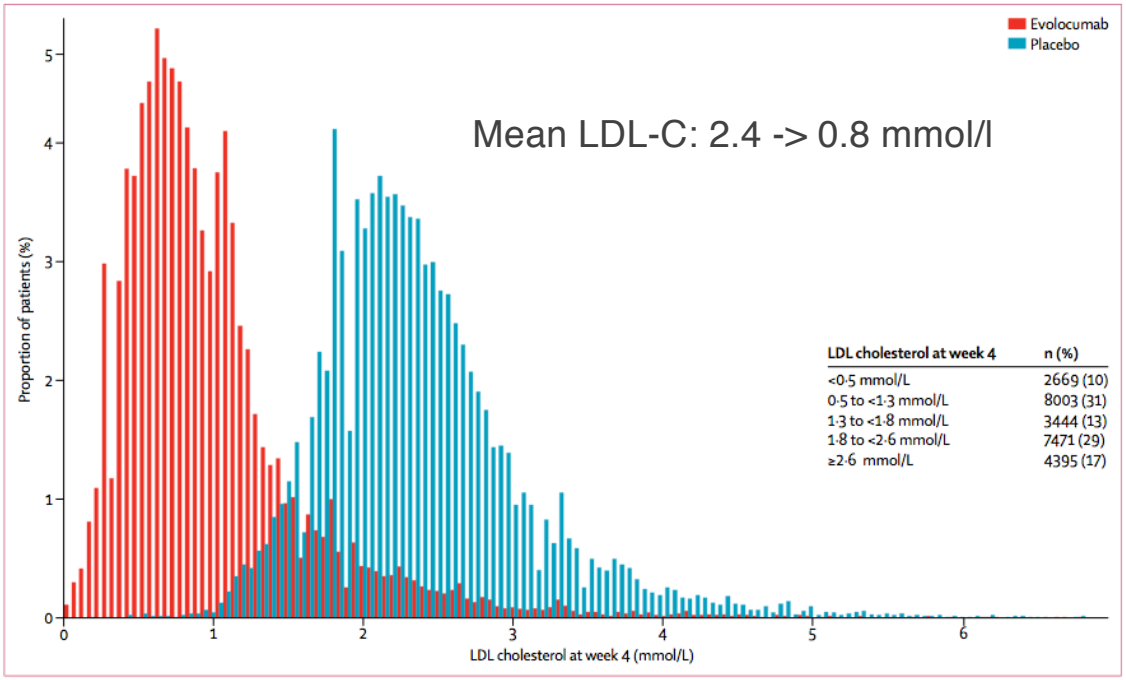

***Figure 1*: Distribution of achieved LDL-cholesterol concentrations at 4 weeks in patients who did not have a primary efficacy or prespecified safety event before the study**

Red bars are evolocumab (median 0·8 mmol/L, IQR 0·5–1·2). Blue bars are placebo (median 2·2 mmol/L, IQR 1·9–2·7).

Giugliano et al., Lancet, epub August 28, 2017

Kardiovaskuläres Risiko und Nebenwirkungen in Abhängigkeit vom Erreichten LDL-C in der FOURIER Studie

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LDL-C (mmol/l) after 4 weeks	< 0.5	0.5 - <1.3	1.3 - <1.8	1.8 - <2.6	≥ 2.6	*p (Trend)*
n	2669	8003	3444	7471	4395	
Evolocumab	99.6	96	41	10	10	
1° endpoint* (%)	10.3	12.4	13.6	13.7	15.5	<0.0001
1° endpoint* (Hazard Ratio, 95% CI)	0.76 (0·64–0·90)	0.85 (0·76–0·96)	0.94 (0·82–1·09)	0.97 (0·86–1·09)	1.0	<0.0001
SAE (Odds-ratio, 95% CI)	0·97 (0·86–1·10)	1·01 (0·92–1·11)	1·01 (0·90–1·13)	0·93 (0·84–1·02)	1.00	0.30
New onset DM (Odds-ratio, 95% CI)	1·06 (0·83–1·35)	1·00 (0·83–1·20)	1·03 (0·83–1·30)	0·95 (0·78–1·14)	1.00	0.48
Neurocognitive event (Odds-ratio, 95% CI)	1·28 (0·84–1·96)	1·10 (0·78–1·55)	1·10 (0·73–1·65)	0·97 (0·68–1·39)	1.00	0.15

*CVD death, MI, stroke, coronary revascularisation, unstable angina

Giugliano et al., Lancet, epub August 28, 2017

Zielwert 1.4 mmol/l – welche Therapie ?

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Potentes Statin

40-50% LDL-C-Reduktion

Potentes Statin + Ezetimibe

60% LDL-C-Reduktion

Potentes Statin + PCSK9i

70% LDL-C-Reduktion

Aktuelle Limitatio für PCSK9i in der Schweiz (Auszug)

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- Im Moment gerade für Praluent und Repatha unterschiedlich
- Klinisch manifestes ischämisches und LDL-C > 2.6 mmol/l trotz max. tolerierter Statintherapie (Repatha)

Was kostet es in der kardiovaskulären Sekundärprävention, 1 Ereignis zu verhindern ?
(3P-MACE: kv Tod, nicht-tödl. MI und CVI)

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Studie	**Präparat**	**ARR (%)**	**NNT**	**Follow-Up** (Monate)	**Kosten/Mo** (CHF)*	**Kosten x FU x NNT**
Odyssey	Alirocumab	1.6	63	34	558	1'195'236
Fourier	Evolocumab	1.5	66	26	450	772'200
Improve-It	Ezetimib	1.6	63	84	26	138'121
Leader	Liraglutide	1.9	52	42	225	491'400
Empa-Reg**	Empagliflozin	6.5	15	37	63	34'965
Compass	Rivaroxaban	2.0	50	21	96	100'800

* Publikumspreis Schweiz gem. SL am 23.10.2019, **Mortalitätsreduktion

Primärer Endpunkt in der Odyssey Outcomes Studie in Abhängigkeit vom Baseline LDL-C

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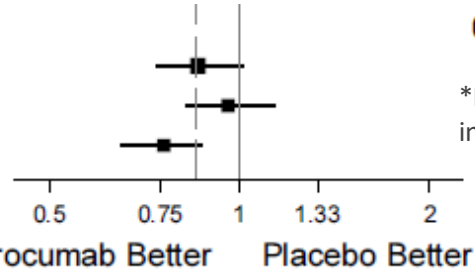
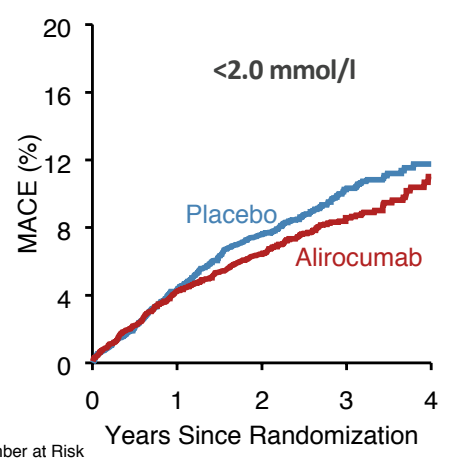
Subgroup	Patients	Incidence (%) Alirocumab	Placebo	HR (95% CI)	p-value*
LDL (mg/dL)					0.09
<80	7164	8.3	9.5	0.86 (0.74, 1.01)	
80 - <100	6128	9.2	9.5	0.96 (0.82, 1.14)	
≥100	5629	11.5	14.9	0.76 (0.65, 0.87)	

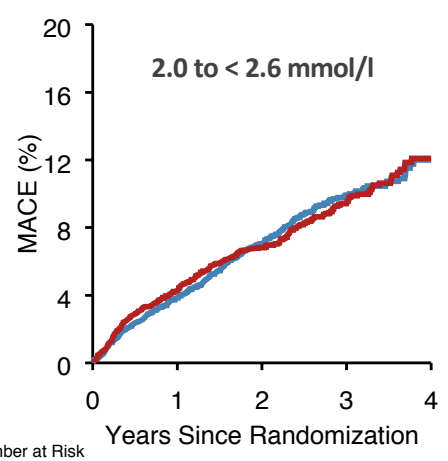
*P-values for interaction





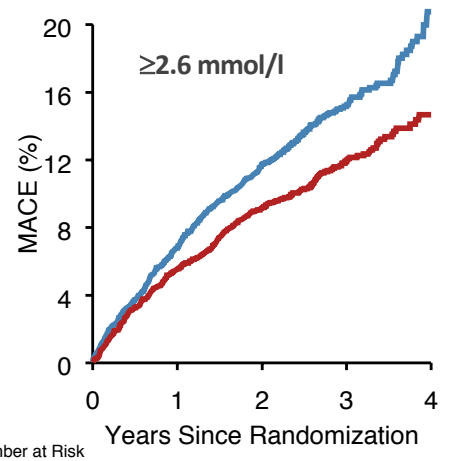
Number at Risk

Placebo	3583	3347	3122	1290	256
Alirocumab	3581	3365	3183	1327	233



Number at Risk

Placebo	3062	2889	2708	1195	195
Alirocumab	3066	2880	2732	1194	213



Number at Risk

Placebo	2815	2568	2371	986	178
Alirocumab	2814	2602	2431	1053	207

14.9%

11.5%

Δ 3.4%
NNT 29

Effekt von Alirocumab in der ODYSSEY Outcomes Studie bei polyvaskulärer Erkrankung (KHK, PAVK, ZVK)

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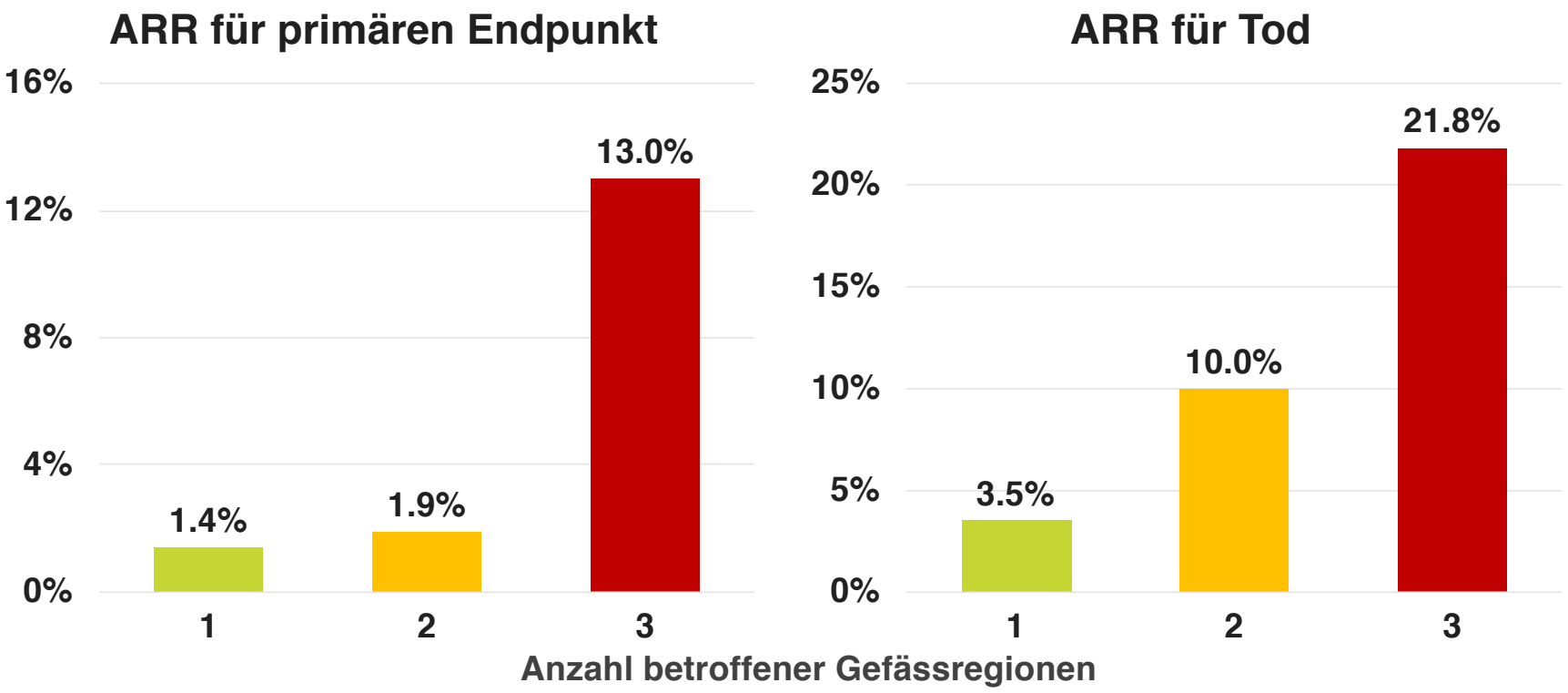

Prozent Patienten pro Gruppe: 1 .. 91.8%, 2 .. 7.4%, 3 .. 0.8%

Jukema et al, JACC epub March 12 2019

Absolute Risikoreduktion und „NNT“ in spezifischen Subgruppen der FOURIER Studie

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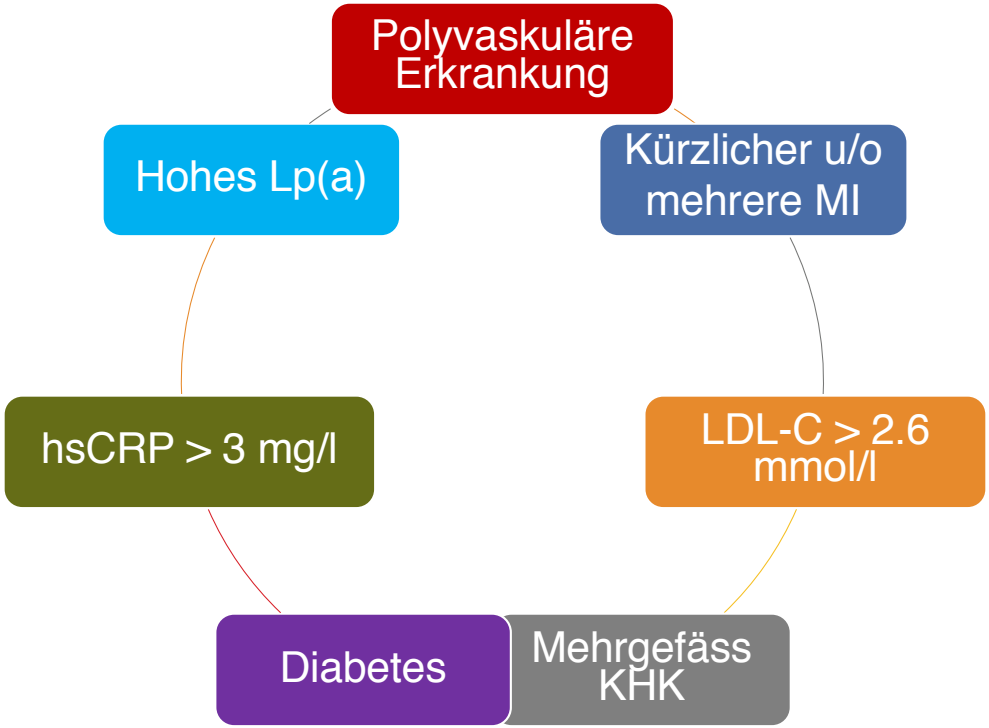
	ARR mit Merkmal	NNT mit Merkmal	ARR ohne Merkmal	NNT ohne Merkmal
Diabetes	2.7	37	1.6	61
hsCRP > 3 mg/l	2.6	36	1.8	58
Lp(a) > 500 mg/l	2.4	41	1.4	71
MI < 2 Jahre	3.4	29	0.8	125
≥ 2 MI	3.7	27	1.3	77
Mehrgefäss KHK	3.6	28	1.2	83

Sabatine et al, Lancet Diab Endo 12: 941, 2017; Bohula et al, Circulation 138: 131, 2018; Sabatine et al, Circulation 138: 756, 2018;O‘Donoghue et al, Circulation 12: 1483, 2019;

Wer profitiert besonders von PCSK9-Hemmern ?



Zusammenfassung

- ESC-Guidelines: neues LDL-C-Ziel in der Sekundärprävention bzw. bei sehr hohem kv Risiko < 1.4 mmol/l.
- Notwendigkeit einer LDL-C-senkenden Kombinationstherapie (Ezetimib/PCSK9-Hemmer) nimmt deutlich zu.
- Limitatio für PCSK9-Hemmer angepasst: klinische ischämische kv Erkrankung und LDL-C > 2.6 mmol/l.
- **Ezetimib/PCSK9i zusätzlich zu einer Statintherapie und eine LDL-C-Senkung < 1.4 mmol/l reduzieren kv Ereignisse, keine Mortalitätsreduktion.**
- PCSK9-Hemmer sind (mE) immer noch sehr (zu) teuer, auch im Vgl. mit anderen Präparaten, die in der kv Prävention eingesetzt werden.
- Das Patientenprofil, das einen bes. Nutzen einer PCSK9-Hemmer-Therapie erwarten lässt, ist gut definiert.

Zu tief ?

Cholesterin	[<5.0 mmol/l]	5.9*	6.2*		sistiert	5.8*	6.5*	1.5
Triglyceride	[<1.7 mmol/l]	1.3	1.7*	1.3	sistiert	1.2	1.5	1.2
Cholesterin/HDL	[<5]	5.9*	6.2*			6.4*	7.2*	1.5
HDL-Cholesterin	[>1.0 mmol/l]	1.0	1.0		sistiert	0.9*	0.9*	1.0
LDL-Cholesterin	[<2.6 mmol/l]	4.7*	4.7*	4.5*	sistiert	4.8*	5.3*	0.3
Lp(a) INA	[<300 mg/l]	175						
Apolipoprotein B	[0.6-1.1 g/l]	1.29*					1.27*	<0.22*

Sicherheit sehr tiefer LDL-C-Werte unter PCSK9i

- Datenquellen
  - Genetische Modelle
    - Familiäre Hypobetalipoproteinemie (APOB-, MTTP- und PCSK9 LOF Mutationen)
    - Familiär kombinierte Hypolipidemie (Agiopoietin like protein 3 mutations)
  - Klinische Studien mit PCSK9i
- Bedenken
  - Neurokognitive Ereignisse – brain function
  - Leber – NAFLD
  - Diabetes
  - Einschränkung der Immunantwort bei Infekten
  - Krebs
- Bisher keine Evidenz für ein mit starker LDL-C-Senkung assoziiertes Risiko

Olsson AG et al, J Int Med 281: 534, 2017
Noto et al, Cardiovasc Res 114: 1595: 2018

Kantonsspital St.Gallen

Danke