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Clinical Shortcuts: **PCSK9-Hemmer**

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Proproteinkonvertase Subtilisin/Kexin Typ 9- (PCSK9-) Inhibitoren

Wirkmechanismus (Abb. 1–3)

- Das Enzym PCSK9 bindet Low-density-Lipoprotein- (LDL-) Rezeptoren.
- Es beschleunigt den irreversiblen Abbau der LDL-Rezeptoren.
- Dadurch gelangen weniger LDL-Rezeptoren wieder an die Zelloberfläche von Hepatozyten (Recycling).

Hemmung von PCSK9

- begünstigt Recycling von LDL-Rezeptoren
- vermehrt zirkulierendes LDL-Cholesterin (LDL-C) wird gebunden
- Verminderung des LDL-C

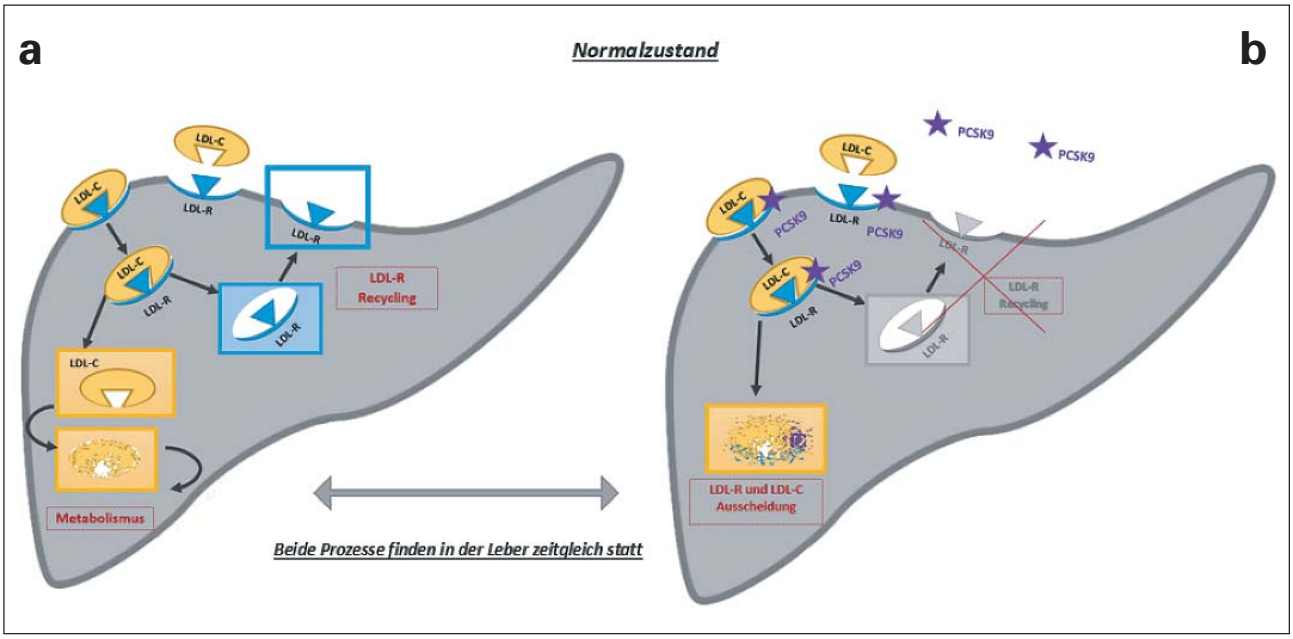

Abbildung 1: (a): Im Blut zirkulierendes LDL-Cholesterin (LDL-C) wird nach Bindung an den LDL-Rezeptor (LDL-R) nach intrazellulär transportiert und metabolisiert. Durch Recycling des LDL-R wird dieser einer Wiederverwendung zugeführt und zurück an die Zelloberfläche transportiert. **(b):** Durch Bindung des PCSK9 an den LDL-R-/LDL-C-Komplex ist ein Recycling des LDL-R nicht mehr möglich. Dieser wird gemeinsam mit dem LDL-C metabolisiert und ausgeschieden. © R. Berent.

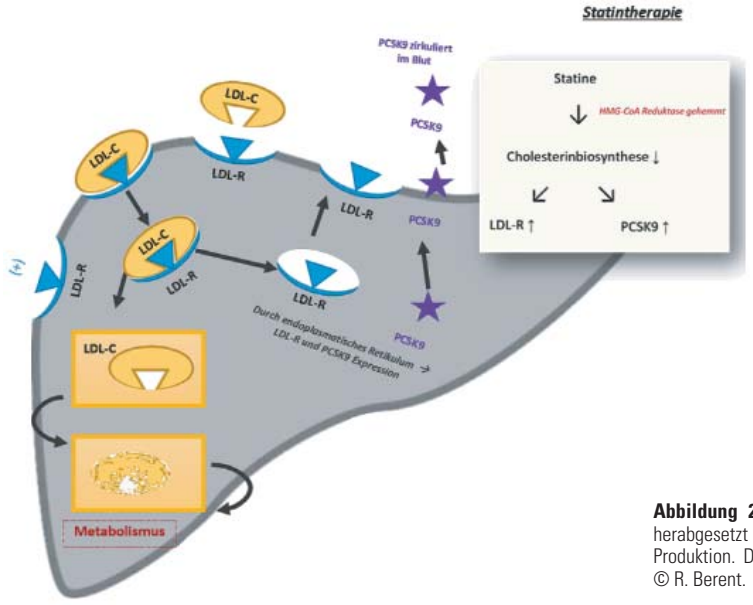

Abbildung 2: Durch Statine wird die körpereigene Cholesterinbiosynthese herabgesetzt und es kommt es zu einer gesteigerten LDL-R-, aber auch PCSK9-Produktion. Die relative Anzahl an LDL-R nimmt an der Zelloberfläche zu (+). © R. Berent.

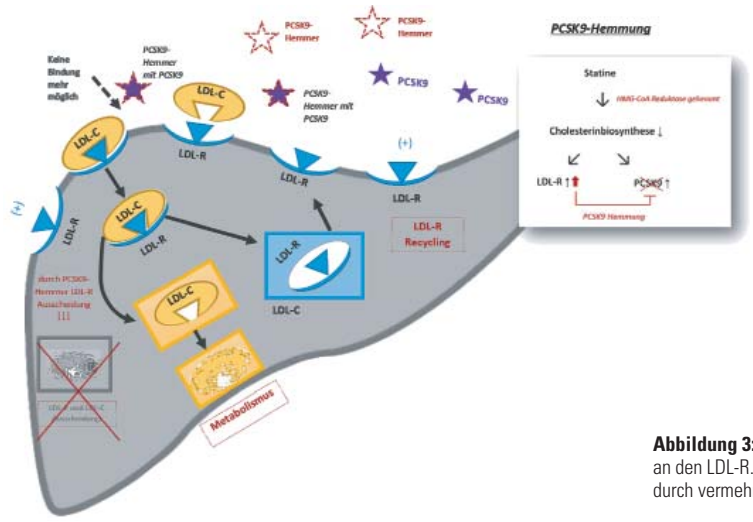

Abbildung 3: PCSK9-Hemmer verhindern durch Bindung des PCSK9 die Bindung an den LDL-R. Das LDL-R-Recycling wird dadurch intrazellulär gewährleistet, wodurch vermehrt LDL-R an der Zelloberfläche zu finden sind (++). © R. Berent.

Therapie mit PCSK9-Inhibitoren (Tab. 1, Tab. 2)

- monoklonale Antikörper gegen PCSK9 (Evolocumab, Alirocumab, Bococizumab)
- jeweils subkutan zu applizieren

Stoffwechselkontrolle

- unter einer lipidsenkenden Therapie (meist Statine) zusammen mit PCSK9-Hemmern ca. 50–60%ige zusätzliche Reduktion von LDL-C
- Senkung des Lipoprotein(a) (Lp[a]) um ca. 25 %
- Senkung von Triglyzeriden um 12–17 %

Senkung kardiovaskulärer Ereignisse

- Erste Ergebnisse (*Post-hoc*-Analysen für Evolocumab und Alirocumab) zeigen eine ca. 50%ige Reduktion kardiovaskulärer Ereignisse.
- Abschließende Bewertung erst nach Publikation der großen klinischen Endpunktstudien möglich (voraussichtlich 2017).

Nebenwirkungen

- mit Ausnahme der Myalgien nicht signifikant unterschiedlich zu den Kontrollgruppen
- lokale Reaktion an der Injektionsstelle (bis zu 6 % der Betroffenen)
- Infektionen der oberen Atemwege (bis zu 5 %)
- grippeähnliche Symptome (bis zu 3 %)
- Muskelbeschwerden (bis zu 5 %)
- neurokognitive Ereignisse (bis zu 1 %)

Tabelle 1: Klinische Phase-III-Studien zu Alirocumab (SAR236553 [REGN727], Regeneron/Sanofi, November 2015) © R. Berent

	Study description/Population	Purpose	Statin	Ezetemibe	Pats. (n)	Dose (mg)	Main results				FU (w)	Status
							LDL-C	HDL-C	Non-HDL-C	Lp(a)		
Lipid lowering												
ODYSSEY Mono [1]	Efficacy and safety vs. ezetimibe in patients with HC	To demonstrate the reductio in LDL-C level vs. ezetimibe	No	Yes	103	75 mg Q2W	–47%	+6%	–40.6%	–16.7%	24	Completed
Odyssey Alternative [2]	Patients with HC and moderate, high, or very high cardiovascular risk, who are intolerant to S	Efficacy and safety vs. ezetimibe and vs. atorvastatin	No	Yes	314	75 mg Q2W up-titrated to 150 mg Q2W	–45%	+7.7%		–21.7%	24	Active, not recruiting, has results
ODYSSEY OPTIONS I [3, 9]	HC (heterozygous FH or non-FH) not adequately controlled with atorvastatin ± ezetimibe and high CVD risk	Reduction in LDL-C level by A as an add-on therapy to atorvastatin ± ezetimibe as an add-on therapy to atorvastatin, vs. doubling the atorvastatin dose, and vs. switching from atorvastatin to rosuvastatin	Nonintensive	Yes	354	75 mg Q2W up-titrated to 150 mg Q2W	–44.1% to –54%	+4.1% to +8.5%	–40.6% to –42.3%	–24% to –27.9%	24	Completed, has results
ODYSSEY OPTIONS II [4, 9]	HC not adequately controlled (rosuvastatin ± ezetimibe), and high CVD risk	Reduction in LDL-C level by A as an add-on therapy to rosuvastatin ± ezetimibe as an add-on therapy to rosuvastatin, and vs. doubling the rosuvastatin dose	Intensive	Yes	305	75 mg Q2W up-titrated to 150 mg Q2W	–36.3% to –50.6%	+7.2% to +9.1%	–31.4% to –42.7%	–22.7% to –27.9%	24	Completed, has results
ODYSSEY Combo I [5]	HC not adequately controlled (with maximum dose of a S ± ezetimibe), and high CVD risk	Reduction in LDL-C level by A vs. P as an add-on therapy to stable, maximally tolerated daily S ± ezetimibe, after 24 wk of treatment	Intensive	No	316	75 mg Q2W up-titrated to 150 mg Q2W	–50,9% to –41.4%	+1.4% to +5.6%	–42.6% to –35.6%	–24.4% to –16.6%	52	Completed, has results
ODYSSEY Combo II [6]	Efficacy and safety vs. ezetimibe on top of S in high cardiovascular risk patients with HC	Reduction in LDL-C level by A vs. ezetimibe as an add-on therapy to stable, maximally tolerated daily S therapy in comparison with ezetimibe, after 24 wk of treatment	Intensive	Yes	720	75 mg Q2W up-titrated to 150 mg Q2W	–50.6% ± 1.4%	+8.6% ± 0.8%	–42.1% ± 1.2%	–27.8% ± 1.4%	52	Completed, has results
ODYSSEY CHOICE 1 [7]	HC	Efficacy and safety every 4 wk vs. P ± S-therapy, after 24 wk of treatment	Nonintensive		803	75 mg Q2W or 150 mg Q4W					56	Completed
ODYSSEY CHOICE II [8, 9]	HC not adequately controlled with their non S-lipid modifying therapy or diet	Reduction of LDL-C as add-on to non-S lipid modifying background therapy (intolerant to S, receiving fenofibrate, ezetimibe or diet alone) or as mono-therapy in comparison with P in patients with HC not treated with a S	No	Yes	233	75 mg Q2W or 150 mg Q4W					24	Active, not recruiting
ODYSSEY FH I [10, 11]	Efficacy and safety vs. P on top of lipid-modifying therapy in patients with heterozygous familial HC not adequately controlled with their lipid-modifying therapy	To evaluate LDL-C level after 24 wk of treatment including background lipid-modifying therapy	Intensive	No	486	75 mg Q2W up-titrated to 150 mg Q2W	–48.8 ± 1.6%	+8.8% ± 0.9%	–42.8% ± 1.4%	–25.2% ± 1.4%	78	Completed, has results
ODYSSEY FH II [10, 11]	Efficacy and safety vs. P on top of lipid-modifying therapy in patients with heterozygous familial HC not adequately controlled with their lipid-modifying therapy	To evaluate LDL-C level after 24 wk of treatment including background lipid-modifying therapy	Intensive	No	249	75 mg Q2W up-titrated to 150 mg Q2W	–48.7% ± 1.9%	+6.0% ± 1.2%	–42.6% ± 1.8%	–30.3% ± 1.8%	78	Completed, has results
ODYSSEY High FH [10, 12, 13]	Efficacy and safety vs. P on top of lipid-modifying therapy in patients with heterozygous familial HC (LDL > 160 mg/dl)	To evaluate LDL-C level after 24 wk of treatment including background lipid-modifying therapy	Nonintensive and intensive	No	105	150 mg Q2W	–45.7% ± 3.5%				78	Completed
NCT02107898 [14]	Japanese patients with hetero-zygous familial HC or high cardio-vascular risk patients with HC on lipid modifying therapy	Efficacy and safety evaluation as add-on therapy to stable daily S-therapy ± other lipid modifying therapy in comparison with P	Nonintensive and intensive	Yes	217						24	Completed
ODYSSEY ESCAPE [15]	Patients with heterozygous familial hypercholesterolemia (HeFH) under-going low-density lipoprotein (LDL) apheresis	Evaluate the effect of A in comparison with placebo on the frequency of LDL apheresis treatments	Nonintensive and intensive	Yes	63	150 mg Q2W					12	Recruiting
Safety												
ODYSSEY OLE [16]	Open label study of long term safety evaluation of A	To assess the long-term safety of A when added to lipid-lowering therapy in patients with hetero-zygous familial HC (heFH)	nonintensive and intensive	No	1000						120	Active, not recruiting
ODYSSEY Long Term [17]	HC not adequately controlled with current lipid-modifying therapy, and high CVD risk	To evaluate the long-term safety and tolerability vs. placebo	Intensive	No	2341	150 mg Q2W	–52.4% ± 0.9%	+4.0% ± 0.4%	–51.6% ± 0.6%	–29.3% ± 0.7%	78	Completed, has results
MACE												
ODYSSEY Outcomes [18]	1–12 mo after an index hospitalization for acute myocardial infarction or unstable angina	To compare the effect vs. P on CVD events (cardiovascular death, nonfatal myocardial infarction, fatal and nonfatal ischaemic stroke, unstable angina requiring hospitalization)	Nonintensive and intensive	Yes	18000	75–150 mg Q2W					64	Recruiting

Intensive statin therapy: rosuvastatin 20/40 mg, atorvastatin 40/80 mg, or simvastatin 80 mg. A: alirocumab; AB: antibody; CHD: coronary heart disease; CVD: cardiovascular disease; E: evolocumab; FH: familial hypercholesterolemia; FU: follow-up; HDL-C: high density lipoprotein cholesterol; Non-HDL-C: non-high density lipoprotein cholesterol; IVUS: intravascular ultrasound; LDL-C: low density lipoprotein cholesterol; Lp: lipoprotein; MI: myocardial infarction; mo: month; n: number; nr: not reported; S: statin; P: placebo; nda: no data available; RF: risk factor; w: week; y: year.

Tabelle 2: Klinische Phase-III-Studien zu Evolocumab (AMG 145, Amgen, November 2015) © R. Berent

							Main results					
	Study description/Population	**Purpose**	**Statin**	**Ezetemibe**	**Pats. (n)**	**Dose (mg)**	**LDL-C**	**HDL-C**	**Non-HDL-C**	**Lp(a)**	**FU (w)**	**Status**
Lipid lowering												
MENDEL-2 [19]	To reduce elevated LDL-C in subjects currently not receiving drug therapy; Framingham Risk Score ≤ 10% and LDL-C ≥ 100 mg/dl	Safety and efficacy vs. ezetimibe and vs. P	No	Yes	614	140 Q2w or 420 Q4w	–56.9% to –58.8%	+3,8%to +3.9%	–50.2% to –52.0%	–18.4% to –19.2%	12	Completed, has results
GAUSS-2 [20]	S-intolerant subjects	Evaluate safety and efficacy vs. ezetimibe	Nonintensive	Yes	160	140 Q2w or 420 Q4w	–53.0% to –56.0%	+5.5% to +7.2%		–23.7% to –26.2%	12	Completed
GAUSS-3 [21]	S- intolerant subjects	Safety and efficacy compared with ezetimibe	No	Yes	519	420 Q4w					24 and 104	Active, not recruiting
DESCARTES [22]	Compared with P study; LDL-C ≥ 75 mg/dl and either at ATP III target with background lipid therapy or taking maximum background lipid therapy (E added to diet alone or to diet + atorvastatin or to diet + atorvastatin plus ezetimibe)	Evaluate efficacy, safety and tolerability every 4 wk vs. P, when added to assigned background lipid-lowering therapy	Nonintensive and intensive	Yes	901	420 Q4w	–48.5% to –61.6%	+3.9% to +11.3%	–41.2% to +54.5%	–9.7% to –29.3%	52	Completed, has results
LAPLACE-2 [23]	HC or mixed dyslipidemia, taking S-therapy ± ezetimibe	Safety, tolerability, and efficacy every 2 or 4 wk + a S vs. a S + ezetimibe	Nonintensive and intensive	Yes	1899	140 Q2w or 420 Q4w	–63.0% to –75.0%	+5.0% to +10.0%	–52.0% to –59.0%	+24.0% to + 39.0%	12	Completed, has results
RUTHERFORD-2 [24]	Reduction of LDL-C in heterozygous FH and LDL-C level ≥ 100 mg/dl with S-therapy	Safety, tolerability, and efficacy of E vs. P	Intensive	Yes	331 420 Q4w	140 Q2w or –59.2%	–55.7% to +8.1%	+5.4% to –56.2%	–49.7% to –22.9%	–21.6% to	12	Completed, has results
YUKAWA-2 [25]	HC, S-treated, high cardiovascular risk Japanese adults	Evaluate efficacy, safety and tolerability of E every 2 or 4 wk + low-dose or high-dose S versus P + low-dose or high-dose S	Nonintensive and intensive	No	409	140 Q2w or 420 Q4w					12	Completed
FLOREY [26]	Effects of treatment ± atorvastatin on Lp-kinetics	% change from baseline in LDL apoB-100 fractional catabolic rate	Nonintensive and intensive	No	89	140 Q2w					10	Completed
TESLA [27]	Homozygous FH and LDL-C level > 130 mg/dl with stable lipid therapy	To determine safety, tolerability, and efficacy	Intensive	Yes	49	420 Q4w	–23.1%	+4.0%	NR	–12.7%	12	Completed, has results
Safety												
EBBINGHAUS [28]	Effect on cognitive function in patients with clinically evident CVD and receiving S-background lipid lowering therapy: a study for subjects enrolled in the FOURIER (Study 20110118) Trial	Change over time in neurocognitive testing in subjects receiving S-therapy + E, compared with subjects receiving S-therapy in combination with P	Nonintensive and intensive	No	1972	140 Q2w or 420 Q4w					208	Active, not recruiting
TAUSSIG [29]	Homozygous FH or PCSK9 mutations; LDL-C level above ATP III target or receiving apheresis; and completion of previous E study	Long-term safety and efficacy on LDL-C level in patients with severe FH	Nonintensive and intensive	Yes	300	140 Q2w or 420 Q4w					260	Active, not recruiting
OSLER-2 [30, 31]	HC or mixed dyslipidaemia; completion of previous E study	Long-term safety, tolerability and efficacy of E vs. usual care	Nonintensive and intensive	Yes	3681	140 Q2w or 420 Q4w					104	Active, not recruiting
Imaging												
GLAGOV [32]	Assessment of plaque regression with a PCSK9 AB as measured by IVUS; CHD; clinical indication for coronary catheterization; and LDL-C ≥ 80 mg/dl LDL-C ≥ 60 to < 80 mg/dl in the presence of one major or three minor risk factors	To determine the effects on atherosclerotic disease burden (% atheroma volume measured by IVUS), at 78 wk	Nonintensive and intensive	Yes	970	420 Q4w					78	Active, not recruiting
MACE												
FOURIER [33]	Subjects with clinical CVD, high risk of recurrent CVD event, and LDL-C ≥ 70 mg/dl or non-HDL-C ≥ 100 mg/dl (no specification regarding S-therapy)	To assess effect of E every 2 or 4 wk + a S vs. P + a S on major CVD events (CVD death, nonfatal myocardial infarction, unstable angina requiring hospitalization, stroke, or coronary revascularization), at 5 y	Nonintensive and intensive	No	27564	140 Q2w or 420 Q4w					260	Active, not recruiting

Intensive statin therapy: rosuvastatin 20/40 mg, atorvastatin 40/80 mg, or simvastatin 80 mg. AB: antibody; CHD: coronary heart disease; CVD: cardiovascular disease; E: evolocumab; FH: familial hypercholesterolemia; FU: follow-up; HDL-C: high density lipoprotein cholesterol; Non-HDL-C: non high density lipoprotein cholesterol; IVUS: intravascular ultrasound; LDL-C: low density lipoprotein cholesterol; Lp: lipoprotein; n: number; nr: not reported; S: statin; P: placebo; nda: no data available; RF: risk factor; w: week; y: year.

Indikation für PCSK9-Hemmer: Welche Patienten?

Heterozygote familiäre Hypercholesterinämie (FH) trotz maximaler lipidsenkender Kombinationstherapie

- LDL-C > 100 mg/dl oder
- non-HDL-C[1] > 130 mg/dl oder
- non-HDL-Lp[2] > 160 mg/dl

Nach kardiovaskulärem Ereignis trotz maximaler medikamentöser lipidsenkender Kombinationstherapie (und Lp[a] < 100 mg/dl [< 250 nmol/l]):

- LDL-C > 70 mg/dl oder
- non-HDL-C[1] > 100 mg/dl oder
- non-HDL-Lp[2] > 130 mg/dl

Dokumentierte Unverträglichkeit sämtlicher in Österreich verfügbarer Statine

- Erhöhung der Leberenzyme ≥ 3× über dem oberen Normwert
- Muskel: CK ≥ 5× über dem oberen Normwert; ≥ 2× bestimmt, ohne starke körperliche Aktivität in den letzten 72 Stunden und/oder
- Muskel- und/oder Sehnen- und/oder Gelenksschmerzen (nachweislich und reproduzierbar durch Statine induziert)

Art der Anwendung

- Subkutane Injektion im 14-tägigen Intervall
- Verabreichung der PCSK9-Hemmer bevorzugt durch Arzt
- Selbstapplikation durch Patienten, wenn Compliance sichergestellt ist

[1]non-HDL-C = Gesamtcholesterin – HDL-C; [2]non-HDL-Lp = non-HDL-C + Lp(a)

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