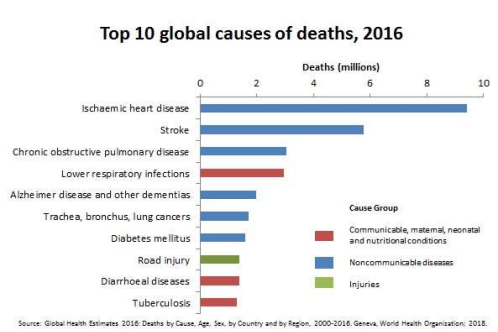
LIPID-THERAPIE IN DER PRAXIS

NISHA ARENJA

Kantonsspital Olten | solothurner spitäler soH

1

Todesursachen



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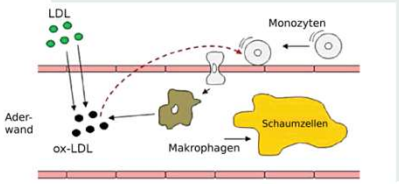
2

Rolle von LDL-Cholesterin

The Nobel Prize in Physiology or Medicine 1985

Michael S. Brown
Prize share: 1/2

Joseph L. Goldstein
Prize share: 1/2



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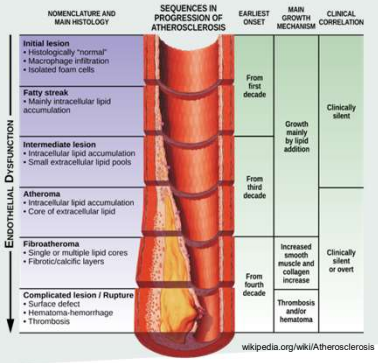
3

Arteriosklerose



wikipedia.org/wiki/Atherosclerosis

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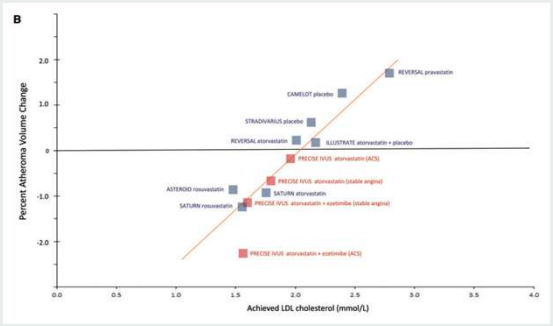
4

Reduktion der Atheromatose



Ference B.A., Eur Heart J. 2017

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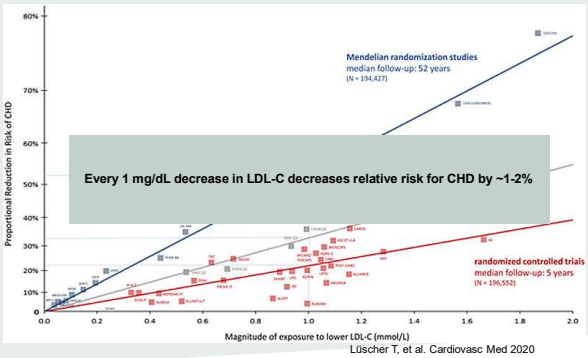
5

Verhältnis LDL-C und CV Events



Lüscher T, et al. Cardiovasc Med 2020

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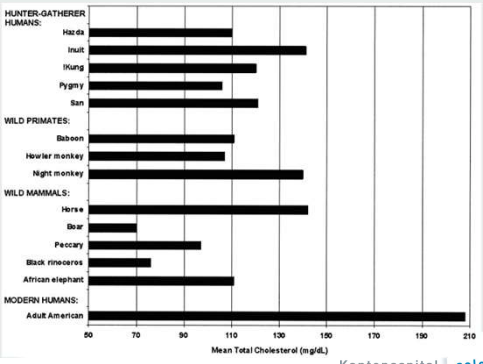
6

LDL Normwerte?



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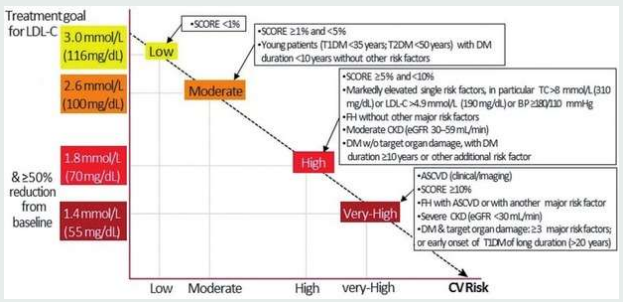
LDL Zielwerte



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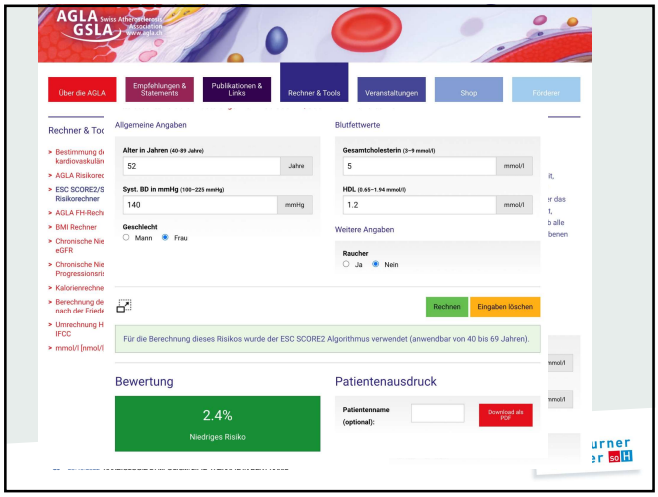
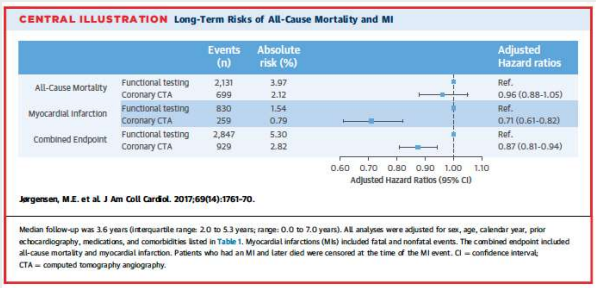


9

Calcium Scoring



Jørgensen et al. J Am Coll Cardiol. 2017

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ZIELSETZUNG:

OPTIMIERUNG LDL-C

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Cholesterin Resorption 20-30%

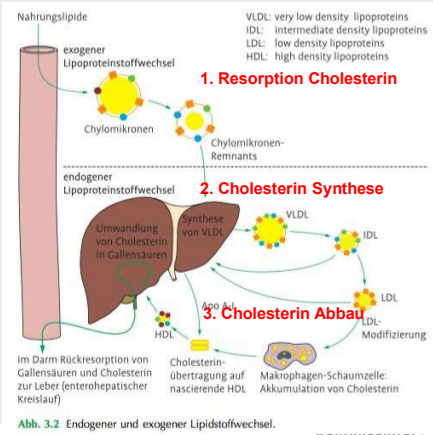

Abb. 3.2 Endogener und exogener Lipidstoffwechsel.

Endogene Synthese 70-80%

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SEVEN COUNTRIES STUDY (SCS)

Ancel Benjamin Keys
26.1.1904 – 20.11.2004

Hypothesis: Apparent epidemic of heart attacks in middle-aged American men related to their mode of life and possibly modifiable physical characteristics

Finding: Coronary deaths in the U.S. and Northern Europe greatly exceeded those in Southern Europe, even when controlled for age, cholesterol, blood pressure, smoking, physical activity, and weight.

Mediterranean diet

13

Empfehlungen Herzstiftung

- Die meisten heutigen Empfehlungen basieren auf Longitudinalstudien und Expertenmeinung, kaum stichhaltige Evidenz
- Kaum Interventionsstudien

Empfehlungen:

- Keine „verbotenen" Lebensmittel (aber mit Mass)
- 5 Portionen Früchte/Gemüse, auch roh
- Geflügel und Fisch statt rotes Fleisch
- Raps-, Olivenöl, Baumnuss-, Weizenkeim-, Sojaöl
- Wenig Zucker, wenig Alkohol, wenig Salz
- Vermeidung gesättigter Fette

14

Diäten im Vergleich

Diet v usual diet	Weight loss (kilograms)	Systolic blood pressure reduction (mm Hg)	Diastolic blood pressure reduction (mm Hg)	Low density lipoprotein reduction (mg/dL)	High density lipoprotein reduction (mg/dL)	C-reactive protein reduction (mg/dL)
Atkins	5.46	5.14	3.30	-2.75	3.41	0.64
Zone	4.07	3.46	2.33	-2.89	-0.33	0.27
DASH	3.63	4.68	2.84	3.93	-1.90	NA
Mediterranean	2.87	2.94	1.03	4.59	-0.61	0.25
Paleolithic	5.31	14.56	3.85	7.27	-2.52	0.52
Low fat	4.87	3.95	2.22	1.92	-2.13	0.33
Jenny Craig	7.77	7.86	7.81	0.21	-2.85	0.19
Volumetrics	5.95	2.93	1.95	7.13	-0.13	NA
Weight Watchers	3.90	2.80	1.03	7.13	-0.88	0.87
Rosemary Conley	3.76	2.39	1.44	7.15	-2.04	NA
Ornish	3.64	0.69	0.20	4.71	-4.87	1.11
Portfolio	3.64	5.97	3.98	21.29	-3.26	-0.37
Biggest Loser	2.88	3.17	2.20	3.90	-0.01	NA
Slimming World	2.15	NA	NA	NA	NA	NA
South Beach	9.86	NA	NA	-0.64	0.36	NA
Dietary advice	0.31	0.58	0.40	-2.01	-1.71	-1.15

"Among the most effective" with moderate to high certainty
"Inferior to the most effective/superior to the least effective" with moderate to high certainty
"Among the least effective" with moderate to high certainty
"Maybe among the most effective" with very low to low certainty
"Inferior to the most effective/superior to the least effective" with very low to low certainty
"Maybe among the least effective" with very low to low certainty
"Maybe worse than usual diet"

Long Ge et al, BMJ 2020

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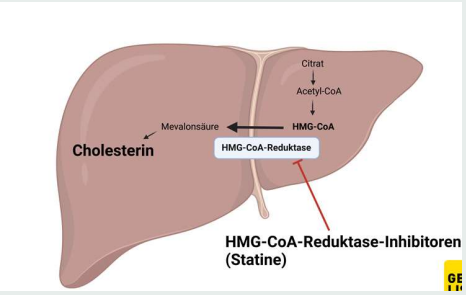
Therapie Strategie: Hemmung Cholesterin Synthese



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Statine: Pleiotrope Effekte

Endothelzellen:
- ↑ eNOS expression and activity
- ↓ Proinflammatory cytokines (IL-1β, IL-6, and cyclooxygenase-2)

Glatte Muskelzellen der Gefässwände
- ↓ AT1 receptor expression

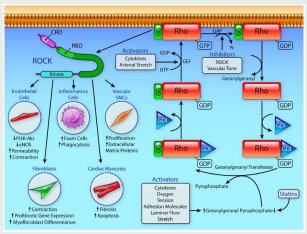
Myokard
- ↓ Left ventricular fibrosis and hypertrophy
- ↑ Nitric oxide
- ↓ Apoptosis

Thrombozyten
- ↓ Platelet reactivity
- ↓ Thromboxane A2 biosynthesis

Monocyte/macrophages
- ↓ Macrophage growth
- ↓ MMP expression and secretion

Vascular inflammation
- ↓ CRP level

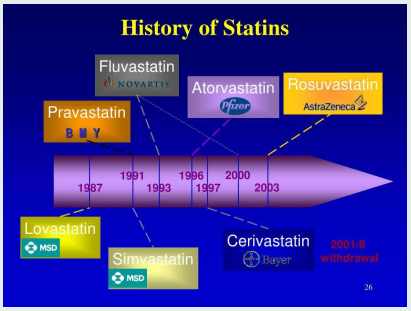
Endothelial progenitor cells
- ↑ Mobilization of stem cells



Oesterle A, Circ Res, 2017

17

Entwicklung Statine



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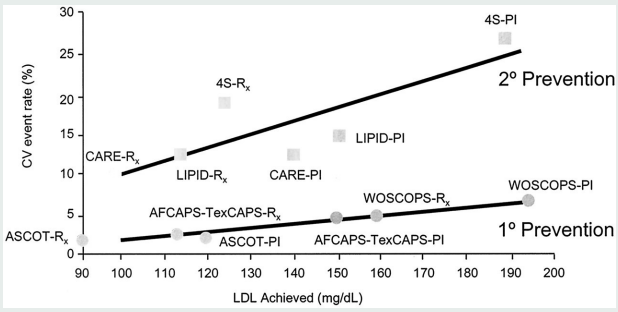
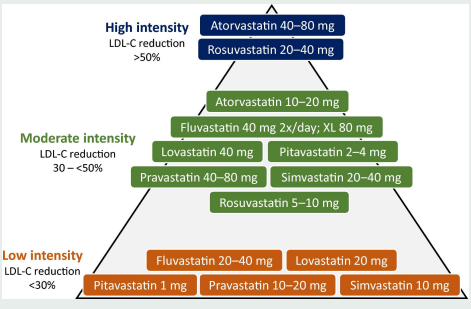
Evidenz Statine



Halcox J, Circulation, 2004

19

Wirkung Statine



McGowan M, et al, JAHA, 2019

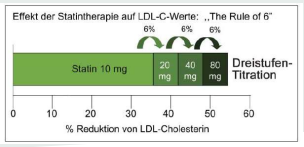
20

Statine: Facts + Caveats

Wichtigste Interaktionen
CYP450 (ausser Rosuvastatin), cave Kombi mit z.B. Amiodaron

Rosuvastatin: cave renale Funktion falls GFR < 30: kontraindiziert, Dosisreduktion bei GFR < 60 auf max. 20 mg

Verdoppelung der Dosis bringt bei Atorvastatin ca 6 % zusätzliche LDL-Senkung, Nebenwirkungen nehmen sprunghaft zu!



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Statine: Myopathie, Rhabdomyolyse

- **Myoalgie = keine CK-Erhöhung**
- **Myopathie = CK-Erhöhung**
- **Rhabdomyolyse = CK-Erhöhung > 10x Norm**

- **Muskelkrämpfe/Myalgien bis zu 5% der Patienten**
  - »run-in phase» in den meisten Statinstudien

- **Rhabdomyolyse-Risiko dosisabhängig und abhängig vom Molekül:**
  - Fibrate 6/10'000
  - Statine 1/10'000
  - Kombitherapie Fibrate/Statin 20/10'000 (Kombi mit Cerivastatin 1/10 (Lipobay©))

22

SAMSON TRIAL

Side Effect Patterns in a Crossover Trial of Statin, Placebo, and No Treatment

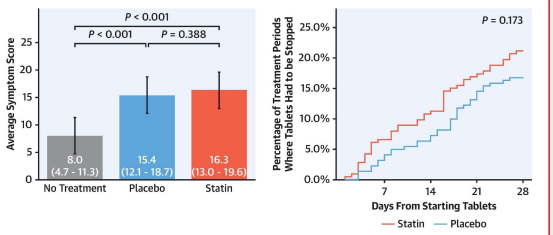
Study design:
- 60 Patienten mit «Statin-Intoleranz» , davon 60 % Myalgien
- während 12 Monaten pro Monat eine Box in zufälliger Reihenfolge
- 4x leer, 4x Placebo, 4x Statin (atorva 20)
- Self-Reporting von Beschwerden jeden Tage, jeden Monat

Results
- 49 Patienten haben 12 Monate absolviert, 11 nur einen Teil
- 71 Unterbrüche wegen Schmerzen während Tabletteneinnahme

Wood F, NEJM 2020

23

CENTRAL ILLUSTRATION: Symptom Scores and Cumulative Early Tablet Stopping Rates by Treatment



Howard, J.P. et al. J Am Coll Cardiol. 2021;78(12):1210–1222.

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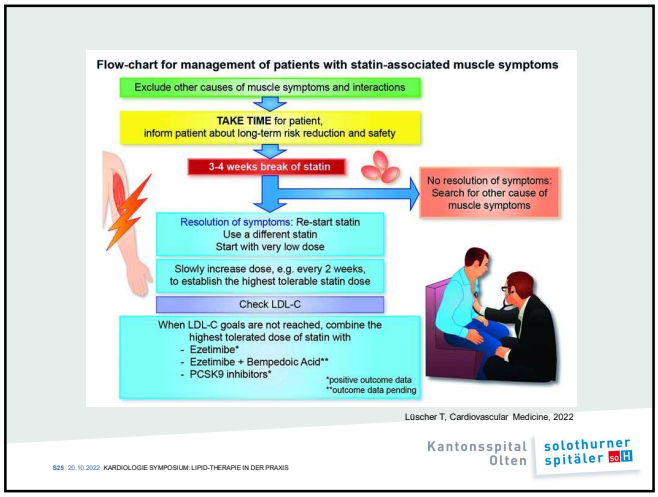
Flow-chart for management of patients with statin-associated muscle symptoms
Exclude other causes of muscle symptoms and interactions
TAKE TIME for patient, inform patient about long-term risk reduction and safety
3-4 weeks break of statin
No resolution of symptoms: Search for other cause of muscle symptoms
Resolution of symptoms: Re-start statin
Use a different statin
Start with very low dose
Slowly increase dose, e.g. every 2 weeks, to establish the highest tolerable statin dose
Check LDL-C
When LDL-C goals are not reached, combine the highest tolerated dose of statin with
- Ezetimibe*
- Ezetimibe + Bempedoic Acid**
- PCSK9 inhibitors*
*positive outcome data
**outcome data pending
Lüscher T, Cardiovascular Medicine, 2022
S25 20.10.2022 KARDIOLOGIE SYMPOSIUM: LIPID-THERAPIE IN DER PRAXIS
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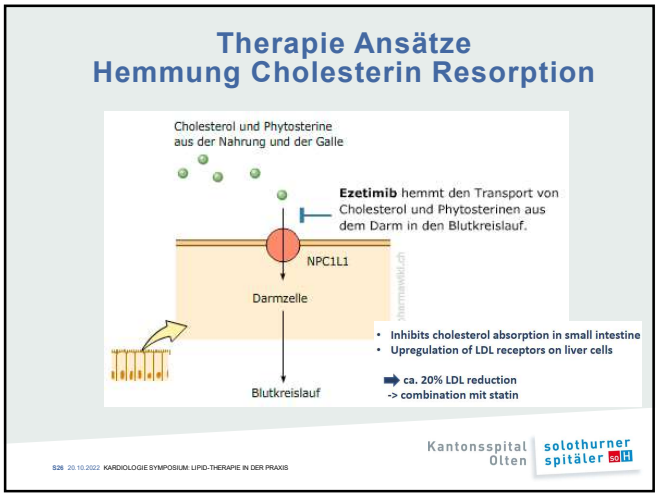
Therapie Ansätze
Hemmung Cholesterin Resorption
Cholesterol und Phytosterine aus der Nahrung und der Galle
Ezetimib hemmt den Transport von Cholesterol und Phytosterinen aus dem Darm in den Blutkreislauf.
NPC1L1
Darmzelle
Blutkreislauf
Inhibits cholesterol absorption in small intestine
Upregulation of LDL receptors on liver cells
ca. 20% LDL reduction
-> combination mit statin
S26 20.10.2022 KARDIOLOGIE SYMPOSIUM: LIPID-THERAPIE IN DER PRAXIS
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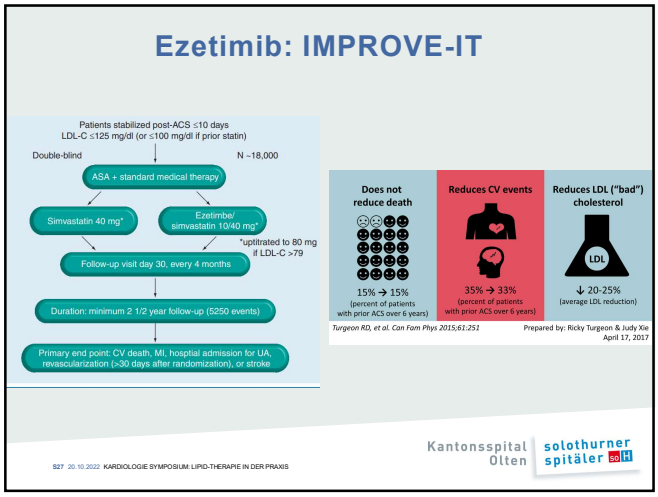
Ezetimib: IMPROVE-IT
Patients stabilized post-ACS ≤10 days
LDL-C ≤125 mg/dl (or ≤100 mg/dl if prior statin)
Double-blind
N ~18,000
ASA + standard medical therapy
Simvastatin 40 mg*
Ezetimibe/ simvastatin 10/40 mg*
*uptitrated to 80 mg if LDL-C >79
Follow-up visit day 30, every 4 months
Duration: minimum 2 1/2 year follow-up (5250 events)
Primary end point: CV death, MI, hosptial admission for UA, revascularization (>30 days after randomization), or stroke
Does not reduce death
15% → 15%
(percent of patients with prior ACS over 6 years)
Reduces CV events
35% → 33%
(percent of patients with prior ACS over 6 years)
Reduces LDL ("bad") cholesterol
LDL
↓ 20-25%
(average LDL reduction)
Turgeon RD, et al. Can Fam Phys 2015;61:251
Prepared by: Ricky Turgeon & Judy Xie
April 17, 2017
S27 20.10.2022 KARDIOLOGIE SYMPOSIUM: LIPID-THERAPIE IN DER PRAXIS
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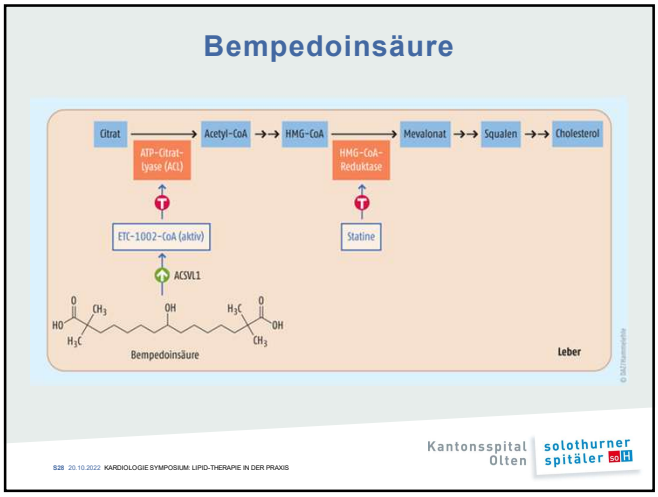
Bempedoinsäure
Citrat
Acetyl-CoA
HMG-CoA
Mevalonat
Squalen
Cholesterol
ATP-Citrat-lyase (ACL)
HMG-CoA-Reduktase
ETC-1002-CoA (aktiv)
Statine
ACSVL1
Bempedoinsäure
Leber
S28 20.10.2022 KARDIOLOGIE SYMPOSIUM: LIPID-THERAPIE IN DER PRAXIS
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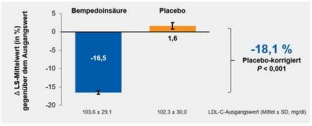
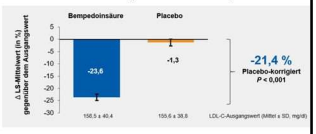
Evidenz: Bempedoinsäure

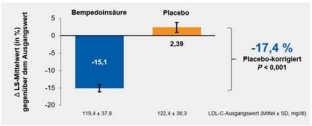
CLEAR Harmony: 93 % unter mäßig-/hochintensiver Statintherapie[3]



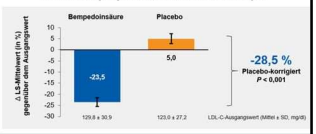
CLEAR Serenity: 8 % unter Statintherapie[5]



CLEAR Wisdom: 85 % unter mäßig-/hochintensiver Statintherapie[4]



CLEAR Tranquility: + EZE; 31 % unter Statintherapie[6]



Ference et al., NEJM 2019;380:1033-42
Ray et al., NEJM 2019;380:1022-32
Goldberg et al., JAMA 2019;322(18):1780-8

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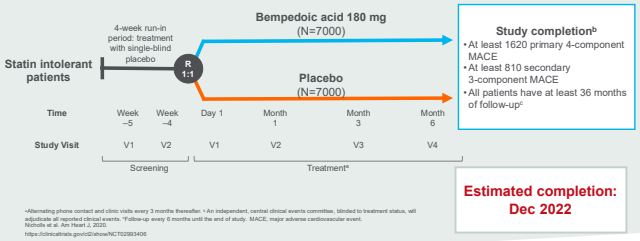
The CLEAR Outcomes Study

Aim: Whether bempedoic acid, added to standard medical therapy, will lower the risk for cardiovascular events in patients with high CV risk and statin intolerance.

Study Design: Phase 3, multi-center, randomized, double-blind, placebo-controlled, event-driven trial ~1,400 sites, 32 countries



Study completion[b]
- At least 1620 primary 4-component MACE
- At least 810 secondary 3-component MACE
- All patients have at least 36 months of follow-up[c]

Estimated completion: Dec 2022

[a]Alternating phone contact and clinic visits every 3 months thereafter. [b]An independent, central clinical events committee, blinded to treatment status, will adjudicate all reported clinical events. [c]Follow-up every 6 months until the end of study. MACE, major adverse cardiovascular event.
Nicholls et al. Am Heart J. 2020.
https://clinicaltrials.gov/ct2/show/NCT02993406

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Steckbrief Bempedoinsäure

Sicherheit
- Gute Verträglichkeit, auch bei Pat. mit "Statin-Intoleranz" Prodrug, wird im Muskel **nicht** aktiviert

CLEAR Outcome Trail, n>12.000, SAMS, 2023

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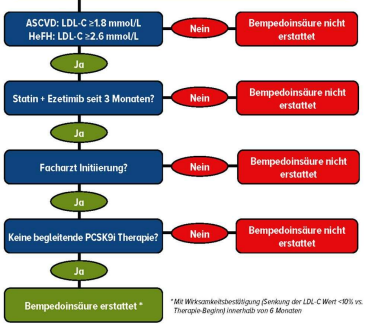
- Erwachsene mit klinisch-manifester ASCVD *(Sekundär-Prävention)* oder
- Erwachsene mit HeFH *(Primär-Prävention)*
- Unter maximal verträglicher Statindosis ± Ezetimib (+ Bempedoinsäure)
- Unerreichtem LDL-C Zielwert
- Zusätzlich zu einer Diät



*Mit Wirksamkeitsbestätigung (Senkung der LDL-C Wert <10% vs. Therapie-Beginn) innerhalb von 6 Monaten

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https://www.universimed.com/__image/a/134712/alias/xd/v/3/c/15/ar/flexible/fn/Abb_1_korr_2.jpg

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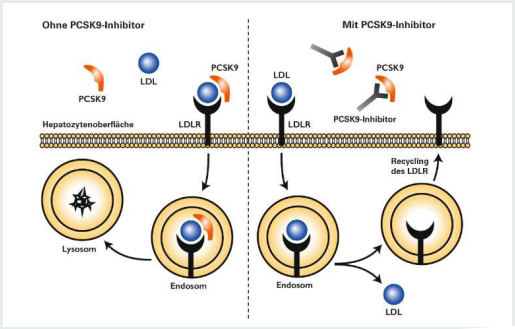
LDL-Abbau und PCSK9



Christina Lyko, SMW, 2017

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PCSK9-Inhibitoren: Outcome Studien

Characteristic	FOURIER	ODYSSEY
Population	**Patients 4 to 52 wks post ACS** • LDL-C ≥70 (1.8) (on atorva 40-80 mg or rosuva 20-40 mg)	**History of clinically evident CVD: MI, stroke or symptomatic PAD and ≥1 major RF or ≥ 2 minor RFs** • LDL-C ≥70 (1.8) or • non-HDL-C ≥100 (2.6) (on atorva 20-80 mg or equivalent)
Primary Endpoints	• CV death, • MI, • All stroke, • Urgent admission with UA, • Revascularization	• Coronary heart disease death, • Non-fatal MI, • Fatal/non-fatal Ischemic stroke, • Unstable Angina requiring hospitalization
No. of Primary EP	3550	1,613
Power	>99% for HR 0.85	90% for HR 0.85
First Secondary Endpoint	• CV death, • MI, • All stroke	• Coronary death, • MI, • Urgent admission with UA, • Ischemia driven revascularization
No. of 1st Secondary EP	1,630	~3,000
Power	~90% for HR 0.85	>90%

Sabatine M, et a. NEJM 2017
Schwartz GG et al, NEJM 2018

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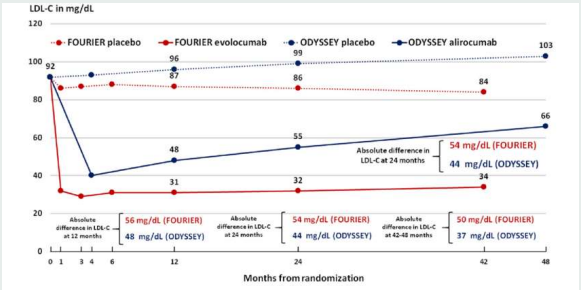
PCSK9-Inhibitoren Outcome Studien



Furtado R et al, 2020 Cardiol. Ther.

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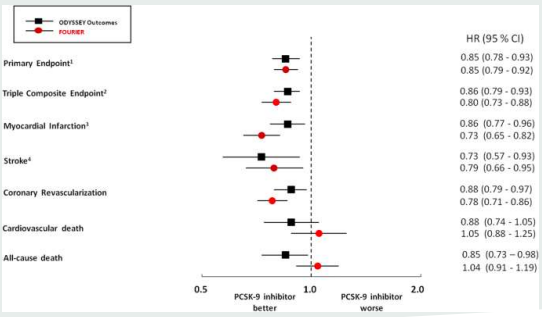
PCSK9-Inhibitoren Outcome Studien



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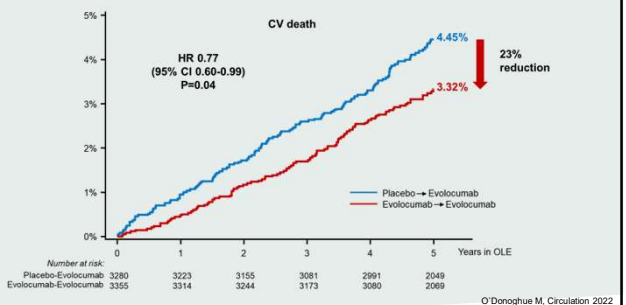
Efficacy during FOURIER-OLE Time Period



O'Donoghue M, Circulation 2022

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Limitatio

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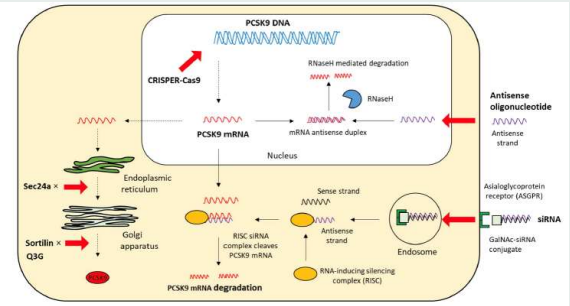
PCSK9 intrazellulär Pathway



Nishikido Frontiers in cardiovascular medicine 01/19

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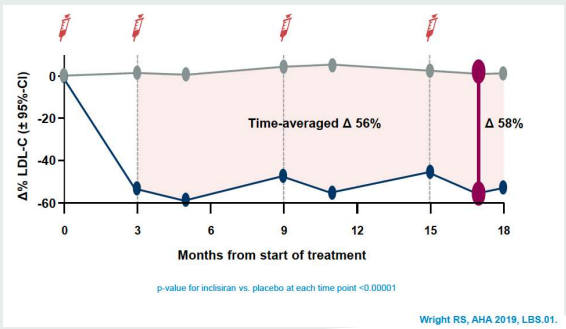
2 Phase und 3 Studien: Inclirisiran ORION 10, 11



Wright RS, AHA 2019, LBS.01.

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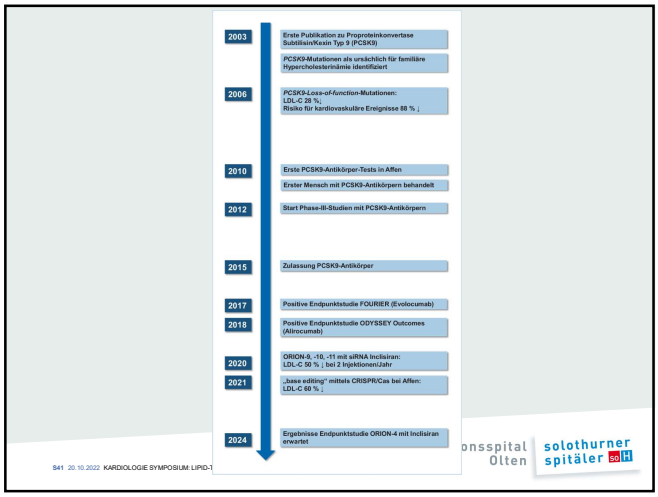
2003
Erste Publikation zu Proproteinkonvertase Subtilisin/Kexin Typ 9 (PCSK9)
PCSK9-Mutationen als ursächlich für familiäre Hypercholesterinämie identifiziert
2006
PCSK9-Loss-of-function-Mutationen: LDL-C 28 %; Risiko für kardiovaskuläre Ereignisse 88 % ↓
2010
Erste PCSK9-Antikörper-Tests in Affen
Erster Mensch mit PCSK9-Antikörpern behandelt
2012
Start Phase-III-Studien mit PCSK9-Antikörpern
2015
Zulassung PCSK9-Antikörper
2017
Positive Endpunktstudie FOURIER (Evolocumab)
2018
Positive Endpunktstudie ODYSSEY Outcomes (Alirocumab)
2020
ORION-9, -10, -11 mit siRNA Inclisiran: LDL-C 50 % ↓ bei 2 Injektionen/Jahr
2021
„base editing" mittels CRISPR/Cas bei Affen: LDL-C 60 % ↓
2024
Ergebnisse Endpunktstudie ORION-4 mit Inclisiran erwartet
S41 20.10.2022 KARDIOLOGIE SYMPOSIUM: LIPID-T
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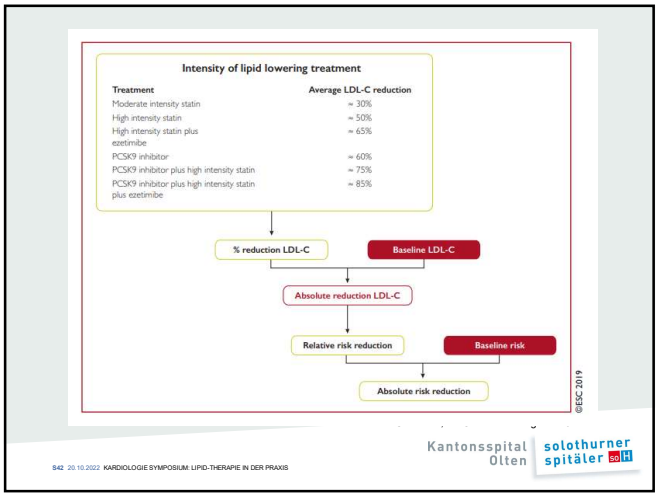
Intensity of lipid lowering treatment
Treatment
Average LDL-C reduction
Moderate intensity statin
≈ 30%
High intensity statin
≈ 50%
High intensity statin plus ezetimibe
≈ 65%
PCSK9 inhibitor
≈ 60%
PCSK9 inhibitor plus high intensity statin
≈ 75%
PCSK9 inhibitor plus high intensity statin plus ezetimibe
≈ 85%
% reduction LDL-C
Baseline LDL-C
Absolute reduction LDL-C
Relative risk reduction
Baseline risk
Absolute risk reduction
©ESC 2019
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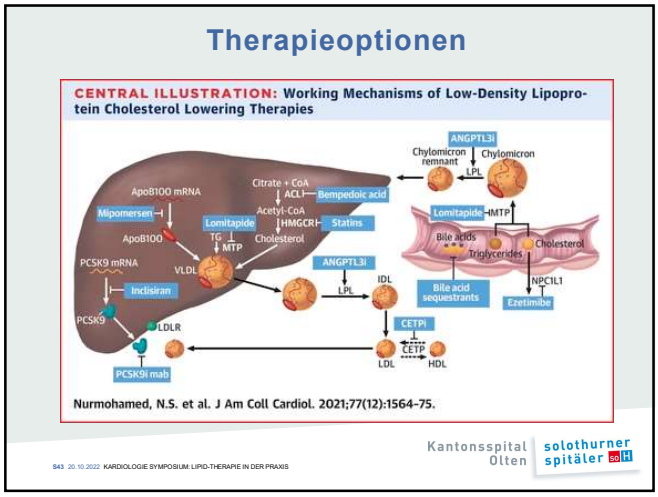
Therapieoptionen
CENTRAL ILLUSTRATION: Working Mechanisms of Low-Density Lipoprotein Cholesterol Lowering Therapies
ANGPTL3i
Chylomicron remnant
Chylomicron
LPL
ApoB100 mRNA
Citrate + CoA
ACL
Bempedoic acid
Mipomersen
Acetyl-CoA
Lomitapide
HMGCR
Statins
ApoB100
TG
MTP
Cholesterol
PCSK9 mRNA
VLDL
Inclisiran
ANGPTL3i
IDL
LPL
Lomitapide
MTP
Bile acids
Cholesterol
Triglycerides
Bile acid sequestrants
NPC1L1
Ezetimibe
PCSK9
LDLR
CETPi
CETP
LDL
HDL
PCSK9i mab
Nurmohamed, N.S. et al. J Am Coll Cardiol. 2021;77(12):1564-75.
S43 20.10.2022 KARDIOLOGIE SYMPOSIUM: LIPID-THERAPIE IN DER PRAXIS
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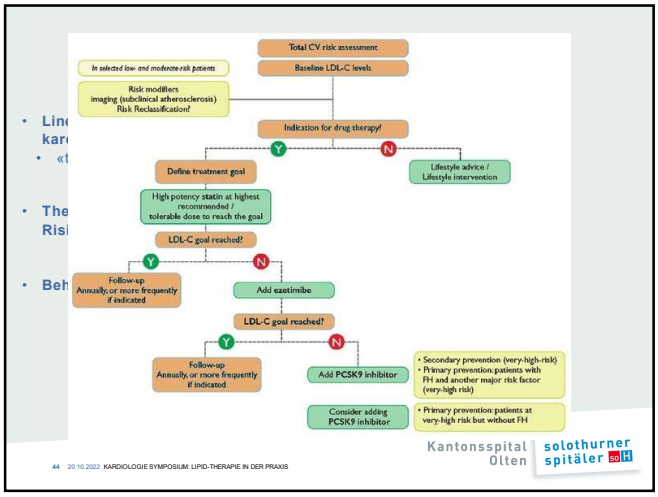
Total CV risk assessment
In selected low- and moderate-risk patients
Baseline LDL-C levels
Risk modifiers
imaging (subclinical atherosclerosis)
Risk Reclassification?
Indication for drug therapy?
Y
N
Define treatment goal
Lifestyle advice / Lifestyle intervention
High potency statin at highest recommended / tolerable dose to reach the goal
LDL-C goal reached?
Y
N
Follow-up Annually, or more frequently if indicated
Add ezetimibe
LDL-C goal reached?
Y
N
Follow-up Annually, or more frequently if indicated
Add PCSK9 inhibitor
Consider adding PCSK9 inhibitor
• Secondary prevention (very-high-risk)
• Primary prevention patients with FH and another major risk factor (very-high risk)
• Primary prevention: patients at very-high risk but without FH
S44 20.10.2022 KARDIOLOGIE SYMPOSIUM: LIPID-THERAPIE IN DER PRAXIS
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