# LDL-C: Wie tief ist tief genug ?

Stefan Bilz
Endokrinologie/Diabetologie, KSSG
stefan.bilz@kssg.ch

1

# LDL-C = 0.3 mmol/l

## Sicher ? Sinnvoll ? Leistbar ?

Stefan Bilz
Endokrinologie/Diabetologie, KSSG
stefan.bilz@kssg.ch

2

# Neue ESC Guidelines 2021 ASCVD

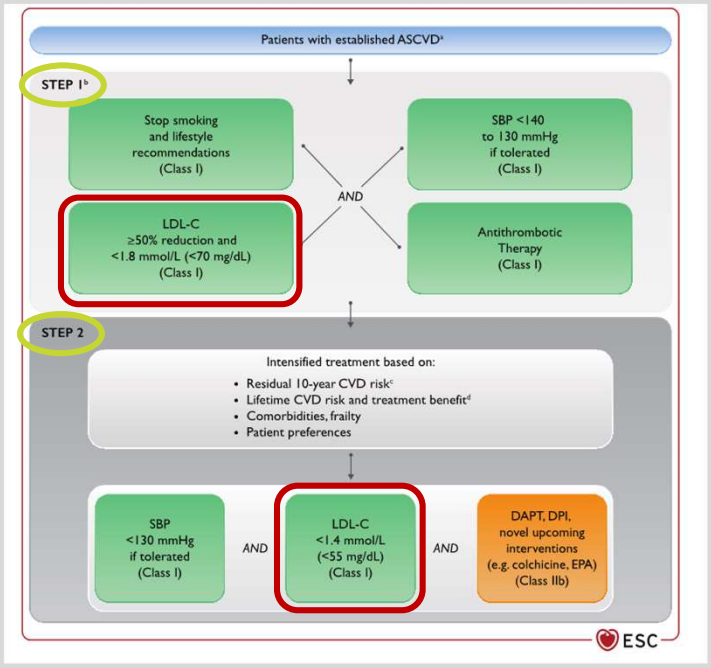
ESC GUIDELINES

**2021 ESC Guidelines on cardiovascular disease prevention in clinical practice**

**Developed by the Task Force for cardiovascular disease prevention in clinical practice with representatives of the European Society of Cardiology and 12 medical societies**

**With the special contribution of the European Association of Preventive Cardiology (EAPC)**

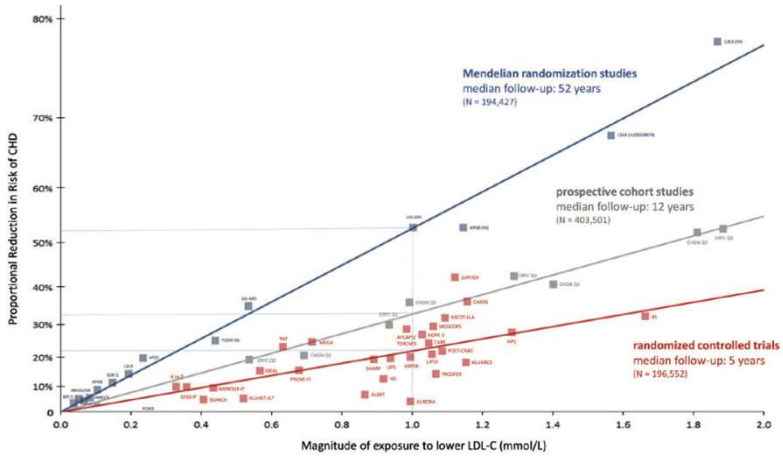
Authors/Task Force Members: Frank L.J. Visseren* (Chairperson) (Netherlands), François Mach* (Chairperson) (Switzerland), Yvo M. Smulders† (Task Force Coordinator) (Netherlands), David Carballo† (Task Force Coordinator) (Switzerland), Konstantinos C. Koskinas (Switzerland), Maria Bäck (Sweden), Athanase Benetos‡ (France), Alessandro Biffi‡,§ (Italy), José-Manuel Boavida‡ (Portugal), Davide Capodanno (Italy), Bernard Cosyns (Belgium), Carolyn Crawford (Northern Ireland), Constantinos H. Davos (Greece), Ileana Desormais (France), Emanuele Di Angelantonio (United Kingdom), Oscar H. Franco (Switzerland), Sigrun Halvorsen (Norway), F. D. Richard Hobbs¶† (United Kingdom), Monika Hollander (Netherlands), Ewa A. Jankowska (Poland), Matthias Michal†† (Germany), Simona Sacco‡ (Italy), Naveed Sattar (United Kingdom), Lale Tokgozoglu‡ (Turkey), Serena Tonstad (Norway), Konstantinos P. Tsioufis‡ (Greece), Ineke van Dis† (Netherlands), Isabelle C. van Gelder (Netherlands), Christoph Wanner‡ (Germany), Bryan Williams (United Kingdom), ESC Scientific Document Group




3

# Kohortenstudien, Mendel'sche Randomisierungs-studien und randomisierte Studien zeigen: je grösser die LDL-C-Senkung, desto grösser die kardiovaskuläre Risikoreduktion

Kantonsspital St.Gallen

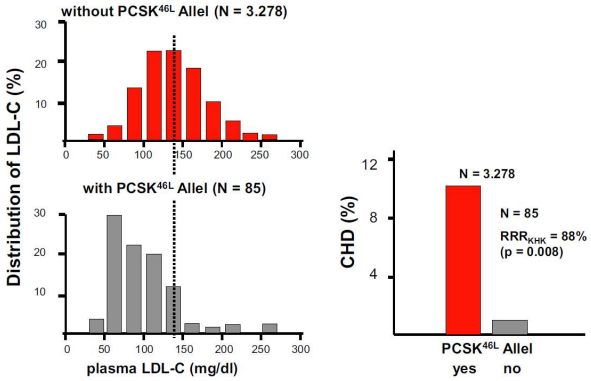



Ference et al., European Heart Journal epub 2017

4

## PCSK9 – "loss of function"-Variante

***Lebenslang tiefes LDL-Cholesterin und Protektion vor Koronarer Herzkrankheit***

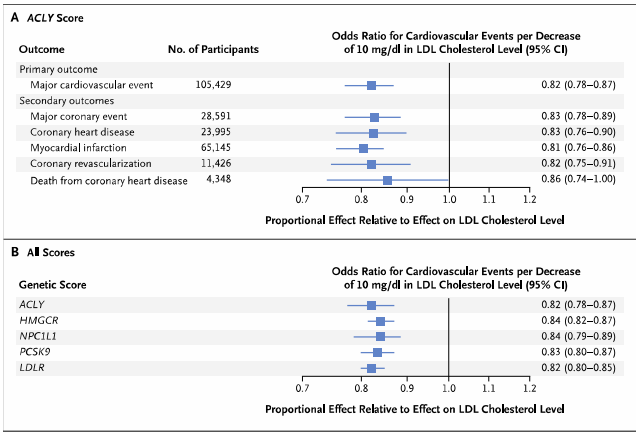



Cohen JC, et al, NEJM 354: 1264, 2006, Schulz R, Basic Res Cardiol 110: 4, 2015

5

## Genetisch bedingte Reduktion der ACLY-Aktivität ist mit tieferem LDL-C und CVD Risiko assoziiert

- **Mendelsche Randomierungsstudie:**
- Zsh. zwischen Varianten in einem/mehreren Genen die mit lebenslang tieferem LDL-C assoziiert sind und CVD-Ereignissen
- "genetisch" bedingt tiefere LDL-C-Werte sind unabh. vom "ursächlichen" Gen mit tieferem CVD-Risiko assoziiert



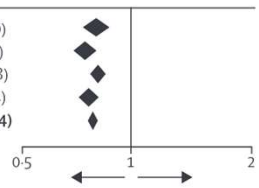

Ference et al., N Engl J Med 380:1033, 2019

6

## Risikoredultion für kardiovaskuläre Ereignisse pro 1 mmol/l LDL-C Senkung in Abhängigkeit vom baseline LDL-C

| Baseline LDL-cholesterol (mmol/L) | Studies | Patients | Events (% per year) | | RR (95% CI) |
|---|---|---|---|---|---|
| | | | More intensive or some LDL cholesterol-lowering therapy | Less intensive or no LDL cholesterol-lowering therapy | |
| ≤ 2·60 | 8 | 116 895 | 7025 (3·4) | 7958 (3·9) | 0·83 (0·75–0·90) |
| 2·61–3·40 | 19 | 115 211 | 5476 (2·5) | 6759 (3·2) | 0·77 (0·71–0·83) |
| 3·41–4·10 | 16 | 77 277 | 5023 (3·2) | 5912 (3·8) | 0·84 (0·79–0·88) |
| 4·10 | 9 | 17 654 | 1133 (2·9) | 1595 (4·1) | 0·79 (0·73–0·84) |
| **Overall** | **52** | **327 037** | **18 657 (3·0)** | **22 224 (3·6)** | **0·81 (0·78–0·84)** |

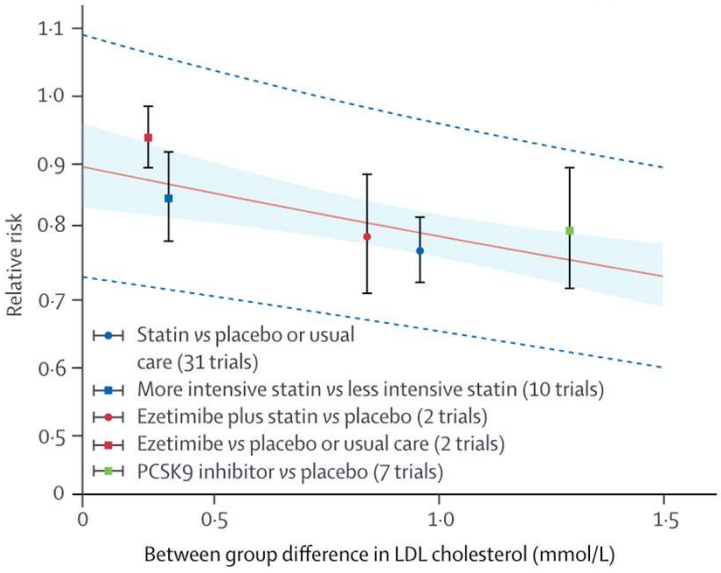
Test for heterogeneity $I^2$=60%, p=0·232




Wang et al., Lancet Diabetes Endocrinol 2020; 8: 36–49

7

## Meta-regression plot showing relative risk of major vascular events according to extent of LDL cholesterol lowering with various drug classes of LDL cholesterol-lowering therapy



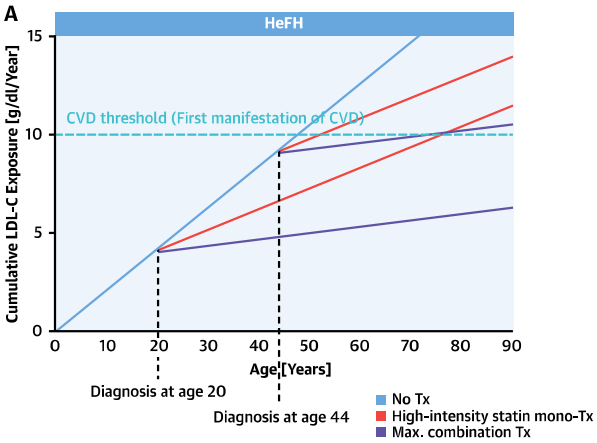

Wang et al., Lancet Diabetes Endocrinol 2020; 8: 36–49

8

## Konzept:
## *Kumulative LDL-Last*
*(cumulative LDL burdon)*

CVD Risiko abh. von kumulativer LDL-Exposition

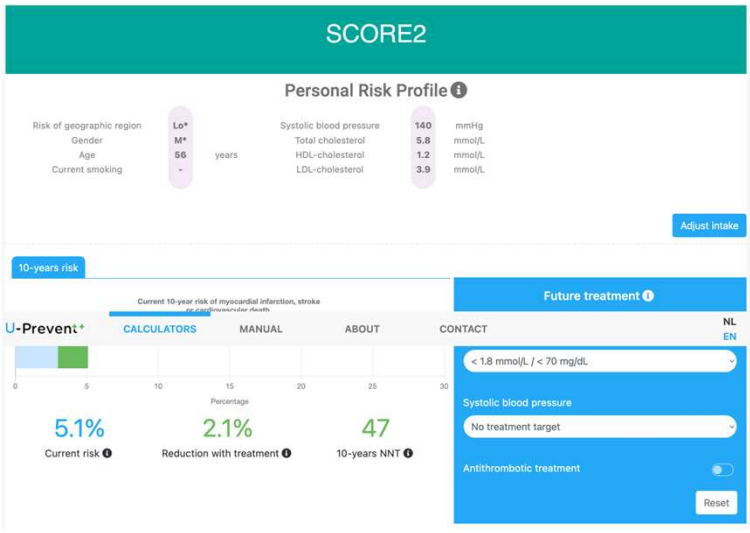
Frühzeitige Statintherapie wirksam !




Brandts & Ray, J Am Coll Cardiol 78:1831, 2021

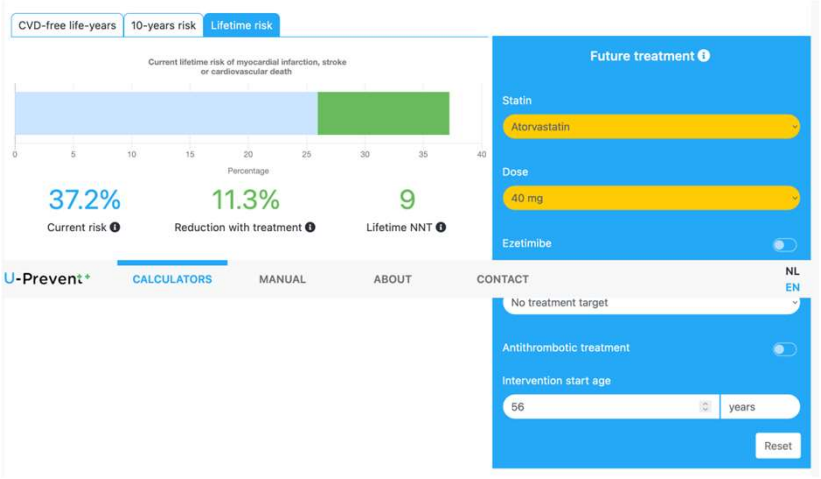
9

## ... Effekt einer LDL-C-senkenden Therapie ... 10 Jahre ...




10

## ... Effekt einer LDL-C-senkenden Therapie ...“life-time“ bei Start mit 56 J




11

## Zusammenfassung

- Genetische (Mendel‘sche) Randomisierungsstudien und Medikamentenstudien sowie deren Metaanalysen zeigen, dass eine LDL-C-Senkung unabhängig von LDL-C Ausgangswert eine zusätzliche kv Risikoreduktion mit sich bringen.
- Neues Konzept der kumulativen LDL-Last suggeriert, dass ein frühzeitiger Therapiebeginn vorteilhaft sein kann.
- V.a. in der 1° Prävention soll das Lebenszeitrisiko zur Entscheidungsfindung herangezogen werden

12

# Association Between Achieved Low-Density Lipoprotein Cholesterol Levels and Long-Term Cardiovascular and Safety Outcomes: An Analysis of FOURIER-OLE

Kantonsspital St.Gallen

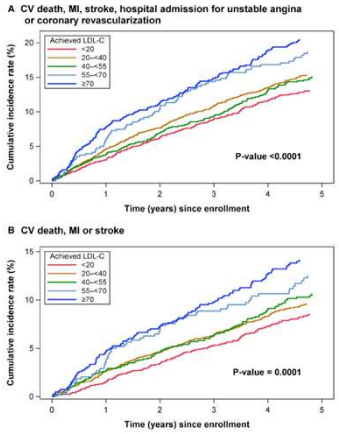



**Table 4. Safety Outcomes According to Achieved LDL-C Level in FOURIER-OLE**

| Safety outcomes | Achieved LDL-C level, mg/dL | | | | | Adjusted *P* trend |
|---|---|---|---|---|---|---|
| | <20 (n=1604) | 20–<40 (n=2627) | 40–<55 (n=1031) | 55–<70 (n=486) | ≥70 (n=811) | |
| Serious adverse events | 12.15 (10.34, 14.27) | 12.64 (10.89, 14.67) | 12.65 (10.70, 14.97) | 12.90 (10.63, 15.65) | 12.18 (10.27, 14.43) | 0.88 |
| Neurocognitive events | 0.50 (0.25, 0.98) | 0.53 (0.28, 1.00) | 0.53 (0.27, 1.07) | 0.30 (0.12, 0.73) | 0.43 (0.21, 0.89) | 0.35 |
| Cataract-related adverse events | 0.82 (0.47, 1.44) | 0.87 (0.51, 1.49) | 0.91 (0.51, 1.62) | 0.33 (0.14, 0.79) | 0.64 (0.35, 1.20) | 0.11 |
| New or progressive malignancy | 1.83 (1.26–2.66) | 1.76 (1.23–2.50) | 1.73 (1.17–2.57) | 1.89 (1.21–2.96) | 1.36 (0.89–2.10) | 0.23 |
| New-onset diabetes* | 0.66 (0.32, 1.39) | 0.52 (0.25, 1.05) | 0.46 (0.20, 1.02) | 0.45 (0.18, 1.12) | 0.43 (0.20, 0.95) | 0.13 |
| Hemorrhagic stroke† | 0.06 (0.02, 0.15) | 0.09 (0.05, 0.17) | 0.07 (0.02, 0.20) | – | 0.06 (0.01, 0.23) | 0.55 |
| Muscle-related events | 0.67 (0.38, 1.18) | 0.62 (0.36, 1.07) | 0.69 (0.38, 1.24) | 0.76 (0.39, 1.46) | 0.56 (0.30, 1.05) | 0.84 |
| Noncardiovascular death | 1.33 (0.87, 2.04) | 1.14 (0.76, 1.71) | 1.65 (1.07, 2.56) | 2.32 (1.46, 3.67) | 1.49 (0.94, 2.36) | 0.04 |
| All-cause mortality | 2.65 (1.98, 3.56) | 2.87 (2.20, 3.76) | 3.72 (2.77, 5.00) | 4.30 (3.10, 5.98) | 3.93 (2.92, 5.29) | 0.0001 |

Gaba et al., Circulation 2023;147:1192

13

# Safety of Very Low Low-Density Lipoprotein Cholesterol Levels With Alirocumab

**TABLE 3 Propensity Analysis of the Risk of Certain Adverse Events of Interest in Alirocumab-Treated Patients With 2 or More Consecutive Low-Density Lipoprotein Cholesterol Values <25 mg/dl (Safety Population; Pool of Phase 3 Studies)**

| | LDL-C ≥25 mg/dl (n = 2,371) | LDL-C <25 mg/dl (n = 811) | HR (95% CI) for LDL-C <25 vs. ≥25 mg/dl |
|---|---|---|---|
| Neurological events | 4.4 (104) | 2.5 (20) | 0.53 (0.30–0.93) |
| Neurocognitive disorders | 1.1 (25) | 0.6 (5) | 0.38 (0.13–1.09) |
| Musculoskeletal events | 17.0 (403) | 14.2 (115) | 0.75 (0.59–0.97) |
| Diabetes mellitus or diabetic complications event (regardless of baseline status) | 4.0 (94) | 6.0 (49) | 1.09 (0.72–1.65) |
| Diabetes mellitus or diabetic complication event (patients with diabetes at baseline) | 9.2 (62) | 12.0 (37) | 1.05 (0.66–1.68) |
| Ophthalmologic events | 2.0 (47) | 1.6 (13) | 0.64 (0.31–1.31) |
| Cataracts | 0.8 (19) | 2.6 (21) | 3.4 (1.58–7.35)* |
| Hepatic disorders | 3.0 (72) | 2.0 (16) | 1.01 (0.54–1.88) |

Values are % (n). *p = 0.0018. All other comparisons were not significant. For definitions of these categories, see Table 2.

CI = confidence interval; HR = hazard ratio; LDL-C = low-density lipoprotein cholesterol.

Robinson et al., J Am Coll Cardiol 2017;69:471

14

## Zusammenfassung

- Genetische Randomsierungsstudien und die randomisierte Medikamentenstudien zeigen keine Hinweise, dass sehr tiefe LDL-C Werte mit unerwünschten Outcomes assoziiert sind

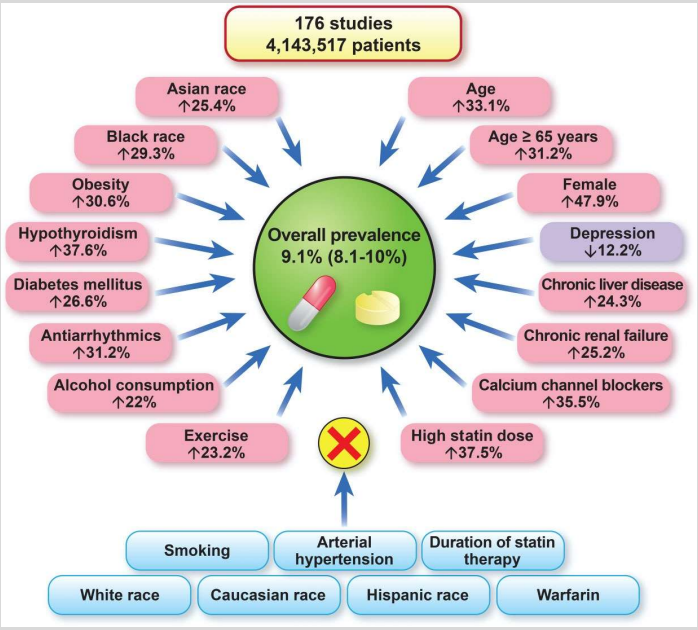
15

## Statinintoleranz Statin assoziierte Muskelsymptome

Nocebo-Effekt

Neg. Auswirkung auf Therapieadhärenz

In Kohortenstudien >> als in RCT

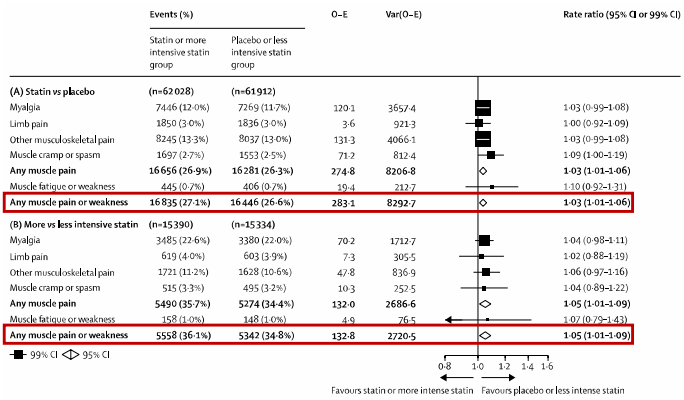



Bytici I. et al., Eur Heart J, epub Feb 16th, 2022

16

# Effect of statin therapy on muscle symptoms: an individual participant data meta-analysis of large-scale, randomised, double-blind trials

Kantonsspital St.Gallen

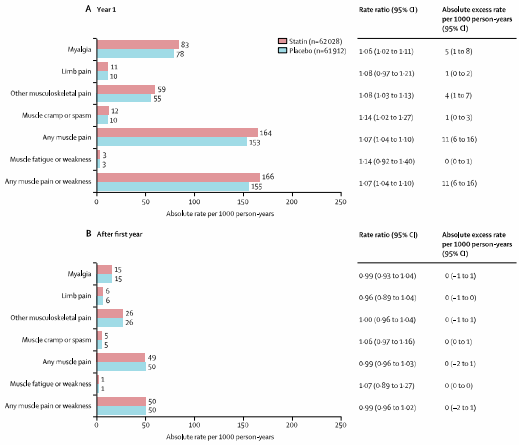


| | Events (%) | | O–E | Var(O–E) | Rate ratio (95% CI or 99% CI) |
|---|---|---|---|---|---|
| | Statin or more intensive statin group | Placebo or less intensive statin group | | | |
| **(A) Statin vs placebo** | **(n=62 028)** | **(n=61 912)** | | | |
| Myalgia | 7446 (12·0%) | 7269 (11·7%) | 120·1 | 3657·4 | 1·03 (0·99–1·08) |
| Limb pain | 1850 (3·0%) | 1836 (3·0%) | 3·6 | 921·3 | 1·00 (0·92–1·09) |
| Other musculoskeletal pain | 8245 (13·3%) | 8037 (13·0%) | 131·3 | 4066·1 | 1·03 (0·99–1·08) |
| Muscle cramp or spasm | 1697 (2·7%) | 1553 (2·5%) | 71·2 | 812·4 | 1·09 (1·00–1·19) |
| **Any muscle pain** | **16 656 (26·9%)** | **16 281 (26·3%)** | **274·8** | **8206·8** | **1·03 (1·01–1·06)** |
| Muscle fatigue or weakness | 445 (0·7%) | 406 (0·7%) | 19·4 | 212·7 | 1·10 (0·92–1·31) |
| **Any muscle pain or weakness** | **16 835 (27·1%)** | **16 446 (26·6%)** | **283·1** | **8292·7** | **1·03 (1·01–1·06)** |
| **(B) More vs less intensive statin** | **(n=15 390)** | **(n=15 334)** | | | |
| Myalgia | 3485 (22·6%) | 3380 (22·0%) | 70·2 | 1712·7 | 1·04 (0·98–1·11) |
| Limb pain | 619 (4·0%) | 603 (3·9%) | 7·3 | 305·5 | 1·02 (0·88–1·19) |
| Other musculoskeletal pain | 1721 (11·2%) | 1628 (10·6%) | 47·8 | 836·9 | 1·06 (0·97–1·16) |
| Muscle cramp or spasm | 515 (3·3%) | 495 (3·2%) | 10·3 | 252·5 | 1·04 (0·89–1·22) |
| **Any muscle pain** | **5490 (35·7%)** | **5274 (34·4%)** | **132·0** | **2686·6** | **1·05 (1·01–1·09)** |
| Muscle fatigue or weakness | 158 (1·0%) | 148 (1·0%) | 4·9 | 76·5 | 1·07 (0·79–1·43) |
| **Any muscle pain or weakness** | **5558 (36·1%)** | **5342 (34·8%)** | **132·8** | **2720·5** | **1·05 (1·01–1·09)** |

99% CI ◇ 95% CI

0·8 1·0 1·2 1·4 1·6

Favours statin or more intense statin | Favours placebo or less intense statin

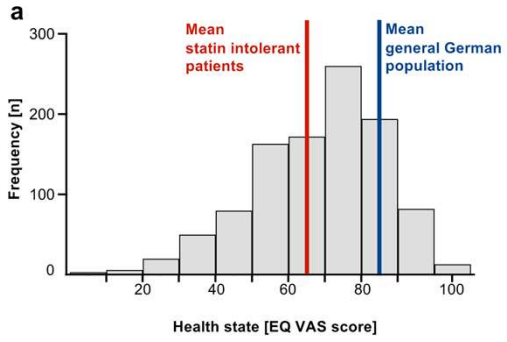


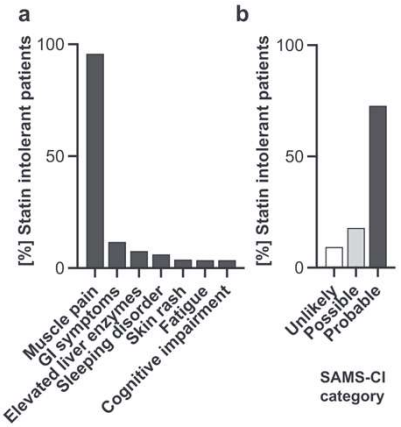

Cholesterol Treatment Trialists' Collaboration, Lancet epub Aug 29th 2022

17

# Statinintolerante Patienten haben eine eingeschränkte Lebensqualität

Kantonsspital St.Gallen



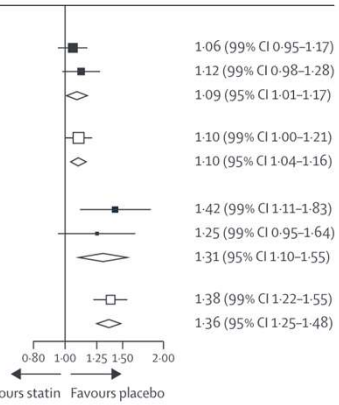

Stürzebecher P et al., Lancet Regional Health - Europe 2024;43: 100981

18

# Effect of statin vs placebo on new-onset diabetes by statin intensity

Kantonsspital St.Gallen

| | Events (% per annum) | | Observed–expected | | Rate ratio (CI) |
|---|---|---|---|---|---|
| | Statin | Placebo | o–e | var(o–e) | |
| **Low-intensity or moderate-intensity statin** | **(n=39179)** | **(n=39266)** | | | |
| Diabetes-related adverse events | 1224 (0·7) | 1153 (0·6) | 32·3 | 594·1 | 1·06 (99% CI 0·95–1·17) |
| Diabetes determined from co-medication | 764 (0·4) | 680 (0·4) | 40·2 | 357·0 | 1·12 (99% CI 0·98–1·28) |
| Subtotal: diabetes-related adverse events and co-medication | 1523 (0·8) | 1396 (0·8) | 60·3 | 728·6 | 1·09 (95% CI 1·01–1·17) |
| Biochemically determined diabetes | 1497 (0·8) | 1369 (0·8) | 67·7 | 715·8 | 1·10 (99% CI 1·00–1·21) |
| Any new-onset diabetes | 2420 (1·3) | 2214 (1·2) | 106·8 | 1156·8 | 1·10 (95% CI 1·04–1·16) |
| **High-intensity statin** | **(n=9935)** | **(n=9859)** | | | |
| Diabetes-related adverse events | 246 (0·9) | 174 (0·7) | 37·0 | 105·0 | 1·42 (99% CI 1·11–1·83) |
| Diabetes determined from co-medication | 198 (0·8) | 159 (0·6) | 20·1 | 89·2 | 1·25 (99% CI 0·95–1·64) |
| Subtotal: diabetes-related adverse events and co-medication | 297 (1·1) | 229 (0·9) | 35·1 | 131·5 | 1·31 (95% CI 1·10–1·55) |
| Biochemically determined diabetes | 1078 (4·1) | 788 (3·0) | 149·3 | 465·7 | 1·38 (99% CI 1·22–1·55) |
| Any new-onset diabetes | 1221 (4·8) | 905 (3·5) | 163·9 | 530·8 | 1·36 (95% CI 1·25–1·48) |

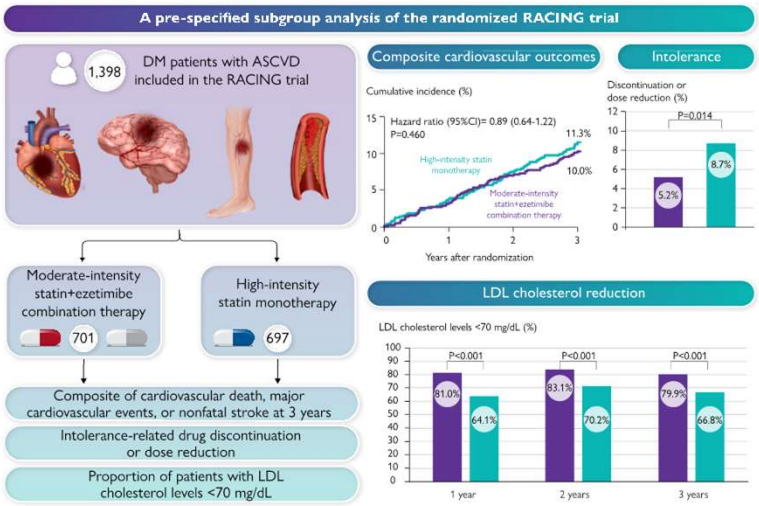



CTT Lancet Diabetes Endocrinol 2024; 12: 306–19

19

# Non-inferiority von „moderate intensity statin + eze“ (Rosuva 10/Eze 10) vs. „high intensity statin“ (Rosuva 20)

Kantonsspital St.Gallen

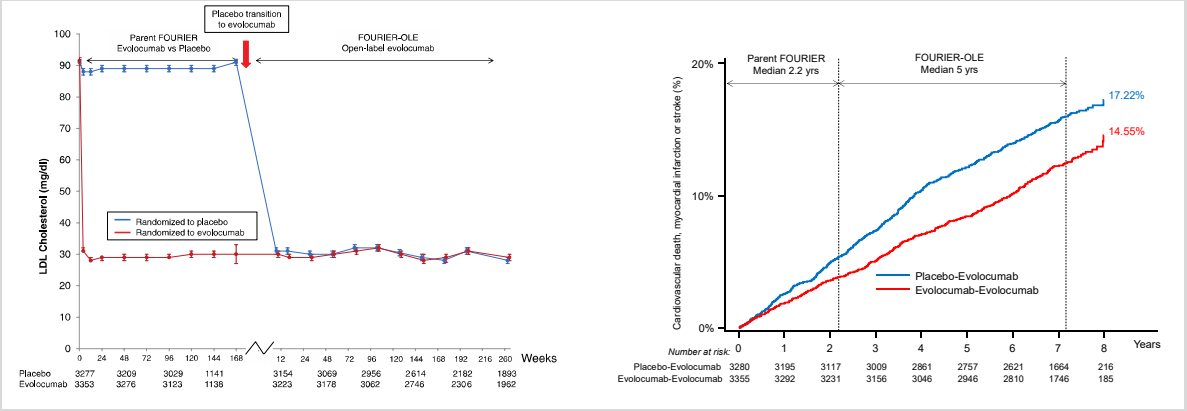



Lee et al., European Heart Journal 44, 972, 2023; Kim et al., Lancet 400: 380, 2022

20

# Fourier open label extension study

(Evolocumab vs. Placebo bei mit intensiver Statintherapie behandelten Patienten mit ASCVD/hohem Risiko)




O'Donoghue et al., Circulation 146: 1109, 2022

21

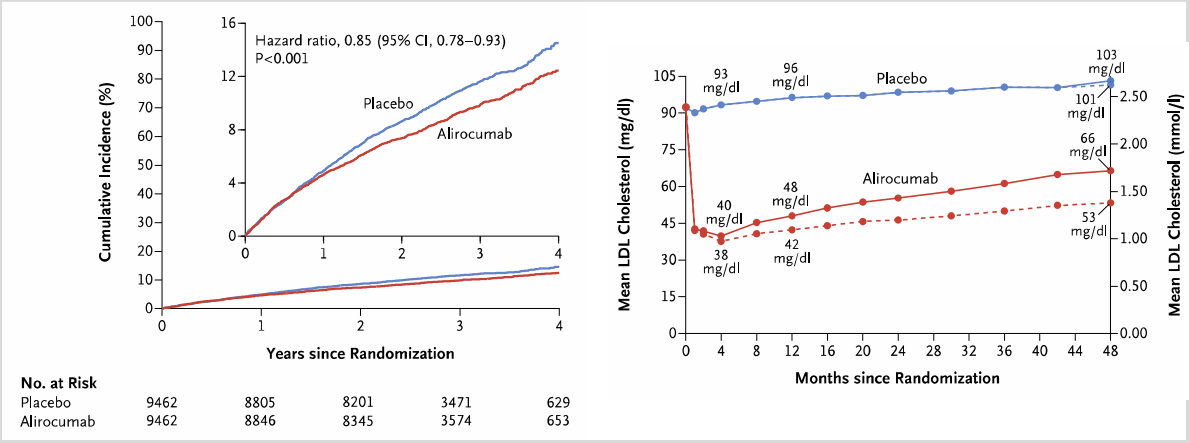
# Relatives Risiko – Absolutes Risiko

- **Absolute Risikoreduktion 2.67% für den primären Endpunkt:**
  - cardiovascular death, myocardial infarction, stroke, hospital admission for unstable angina or coronary revascularization)
- **Number needed to treat: 37 Patienten über 7.2 Jahre**

22

# Odyssey outcomes – time to benefit

**- Alirocumab vs. placebo on top of high intensity statin post ACS**
**- on-treatment LDL-C 1.0-1.4 mmol/l, 50-60% reduction vs. placebo**

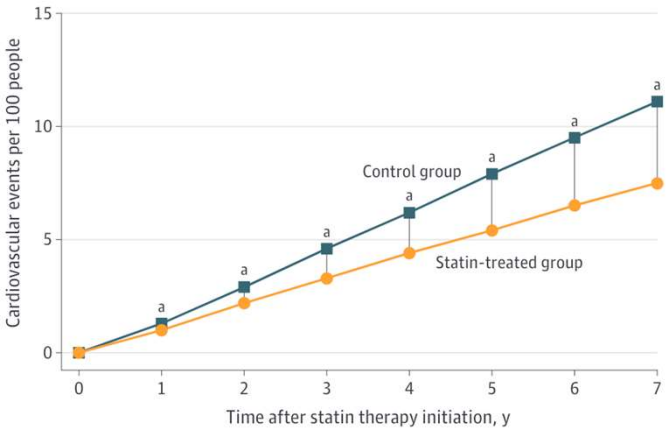



Schwartz et al., N Engl J Med 379: 2097, 2018

23

# TTB to prevent 1 MACE for 100 adults aged 50-75 years treated with statins was 2.5 years

Figure 2. Pooled Mortality Curves for Major Adverse Cardiovascular Events (MACE)




24

# Neue ESC Guidelines 2021 ASCVD

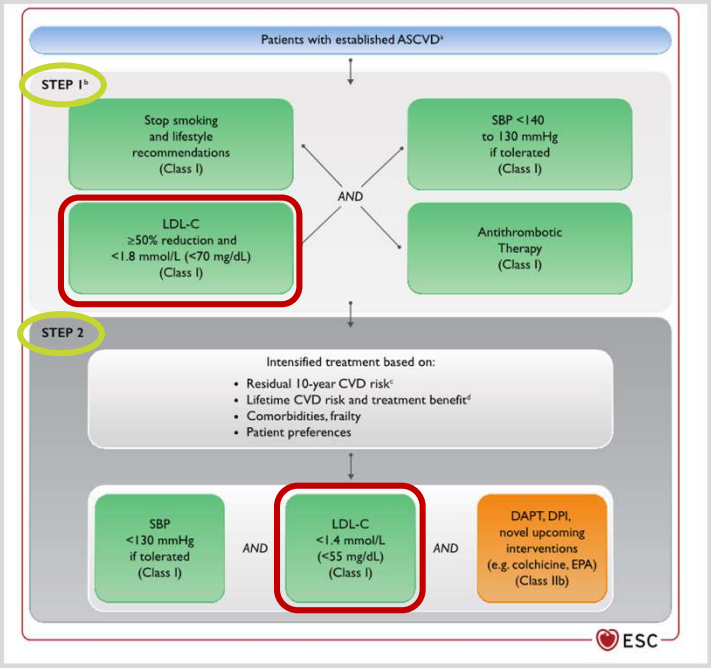
ESC GUIDELINES

**2021 ESC Guidelines on cardiovascular disease prevention in clinical practice**

**Developed by the Task Force for cardiovascular disease prevention in clinical practice with representatives of the European Society of Cardiology and 12 medical societies**

**With the special contribution of the European Association of Preventive Cardiology (EAPC)**

Authors/Task Force Members: Frank L.J. Visseren* (Chairperson) (Netherlands), François Mach* (Chairperson) (Switzerland), Yvo M. Smulders† (Task Force Coordinator) (Netherlands), David Carballo† (Task Force Coordinator) (Switzerland), Konstantinos C. Koskinas (Switzerland), Maria Bäck (Sweden), Athanase Benetos‡ (France), Alessandro Biffi‡,§ (Italy), José-Manuel Boavida‡ (Portugal), Davide Capodanno (Italy), Bernard Cosyns (Belgium), Carolyn Crawford (Northern Ireland), Constantinos H. Davos (Greece), Ileana Desormais (France), Emanuele Di Angelantonio (United Kingdom), Oscar H. Franco (Switzerland), Sigrun Halvorsen (Norway), F. D. Richard Hobbs¶† (United Kingdom), Monika Hollander (Netherlands), Ewa A. Jankowska (Poland), Matthias Michal†† (Germany), Simona Sacco‡ (Italy), Naveed Sattar (United Kingdom), Lale Tokgozoglu‡ (Turkey), Serena Tonstad (Norway), Konstantinos P. Tsioufis‡ (Greece), Ineke van Dis† (Netherlands), Isabelle C. van Gelder (Netherlands), Christoph Wanner‡ (Germany), Bryan Williams (United Kingdom), ESC Scientific Document Group




25

## Numbers needed to treat (needlessly?)

Kantonsspital St.Gallen

- NNT puts the emphasis on the positive side of therapeutic intervention. "To save one life" is a powerful driving force in clinical medicine. However, it tends to obscure the reality that, too often, very large numbers of patients are being treated without benefit.

Bogaty P, Lancet 365: 1307, 20025

26

## Shared decision making …

- **Impact of reporting the number treated needlesslyon perceived effectiveness and decision to adopt an intervention**
- The percentage of participants who decided to adopt the intervention was 92.4%, 87.8%, 67.7%, and 26.2% when RRR, NNT, ARR, and NTN were used, respectively

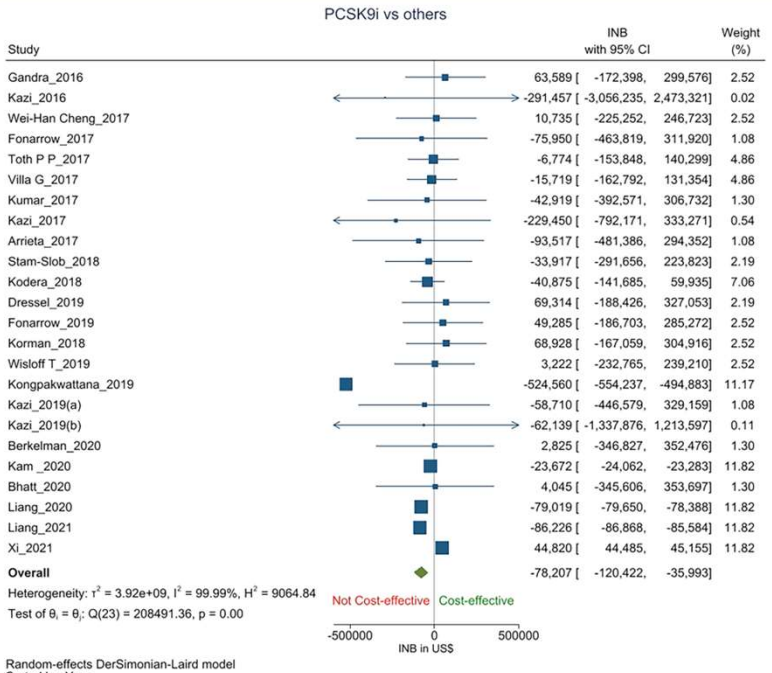
https://abstracts.cochrane.org/2011-madrid/impact-reporting-number-treated-needlesslyon-perceived-effectiveness-and-decision-adopt

27

# Kosten

28

## „Cost effectiveness“ von PCSK9-Hemmern:




Bagepally et al., European Journal of Clinical Pharmacology (2022) 78:351)

29

Kantonsspital St.Gallen

# LDL-C = 0.3 mmol/l

## Sicher - Ja
## Sinnvoll – meistens - je nachdem
## Leistbar – noch, aber nicht kosten-effektiv

30

Kantonsspital St.Gallen

# Vielen Dank !

31