Conflicts of Interest Rahul Mohan

Pharmaceutical and other medical companies for which you have attended an Advisory Board in the past 3 years- Abbott,

Pharmaceutical and other medical companies for which you have delivered or received sponsored education in the past 3 years-) Novo Nordisk, Abbott, Astra Zeneca, Eli Lilly, Janssen, Grunenthal, A.Menarini Pharma, Shionogi, Boehringer-Ingelheim, Bayer, Daiichi Sankyo

Roles that you hold a professional contract with (i.e. for which you earn a salary/fee-Not in receipt of any retainer from any Pharmaceutical Company

Professional non-financial roles- PCDS Committee Member (currently co-opted)

SAHF

Other relevant potential conflicts of interest

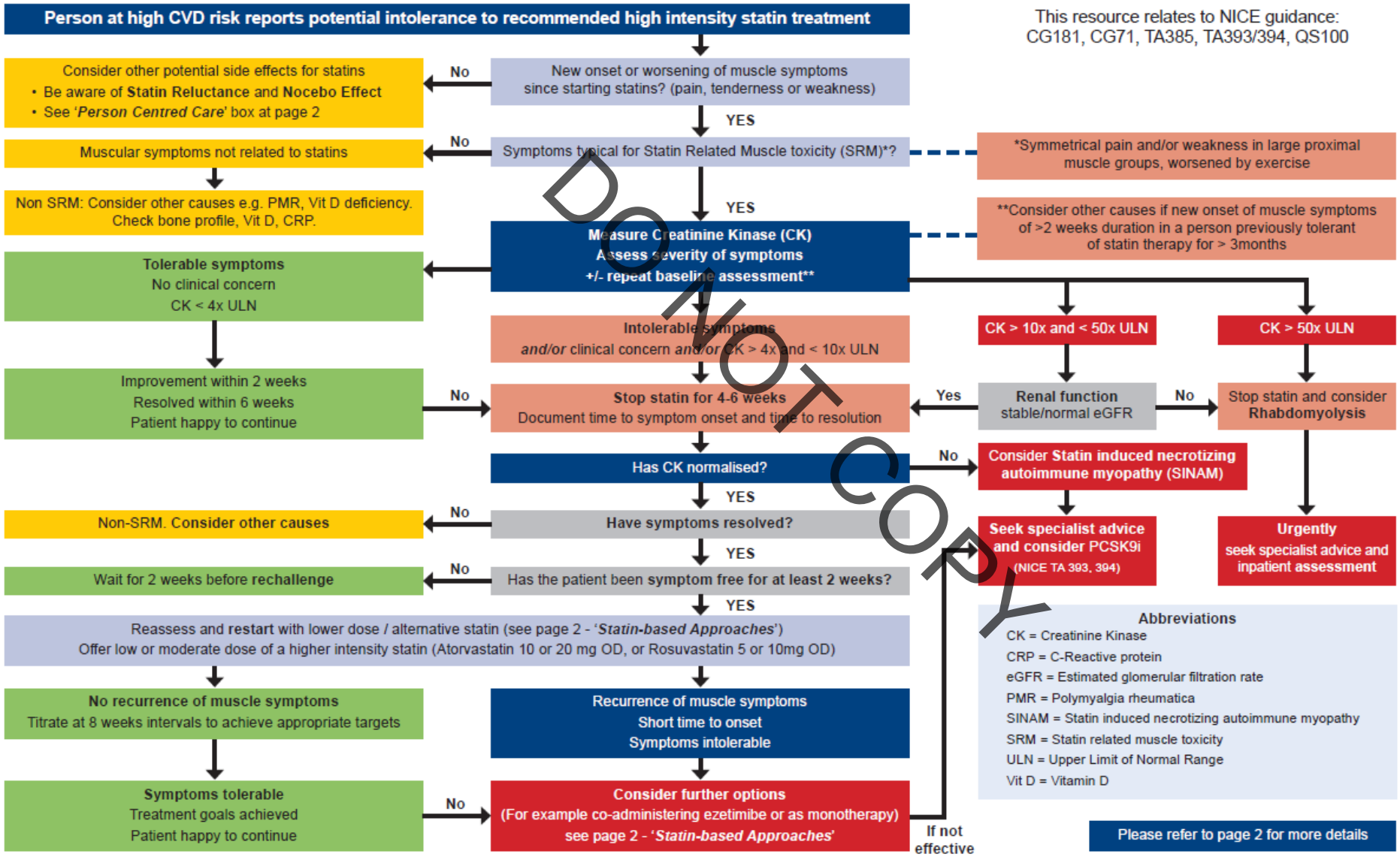
GP- West Bridgford Medical Centre, Nottingham

Nottingham and Nottinghamshire ICB- Chair of Task and Finish group, EDEN trainer

Statin Intolerance Pathway

ACCELERATED ACCESS COLLABORATIVE

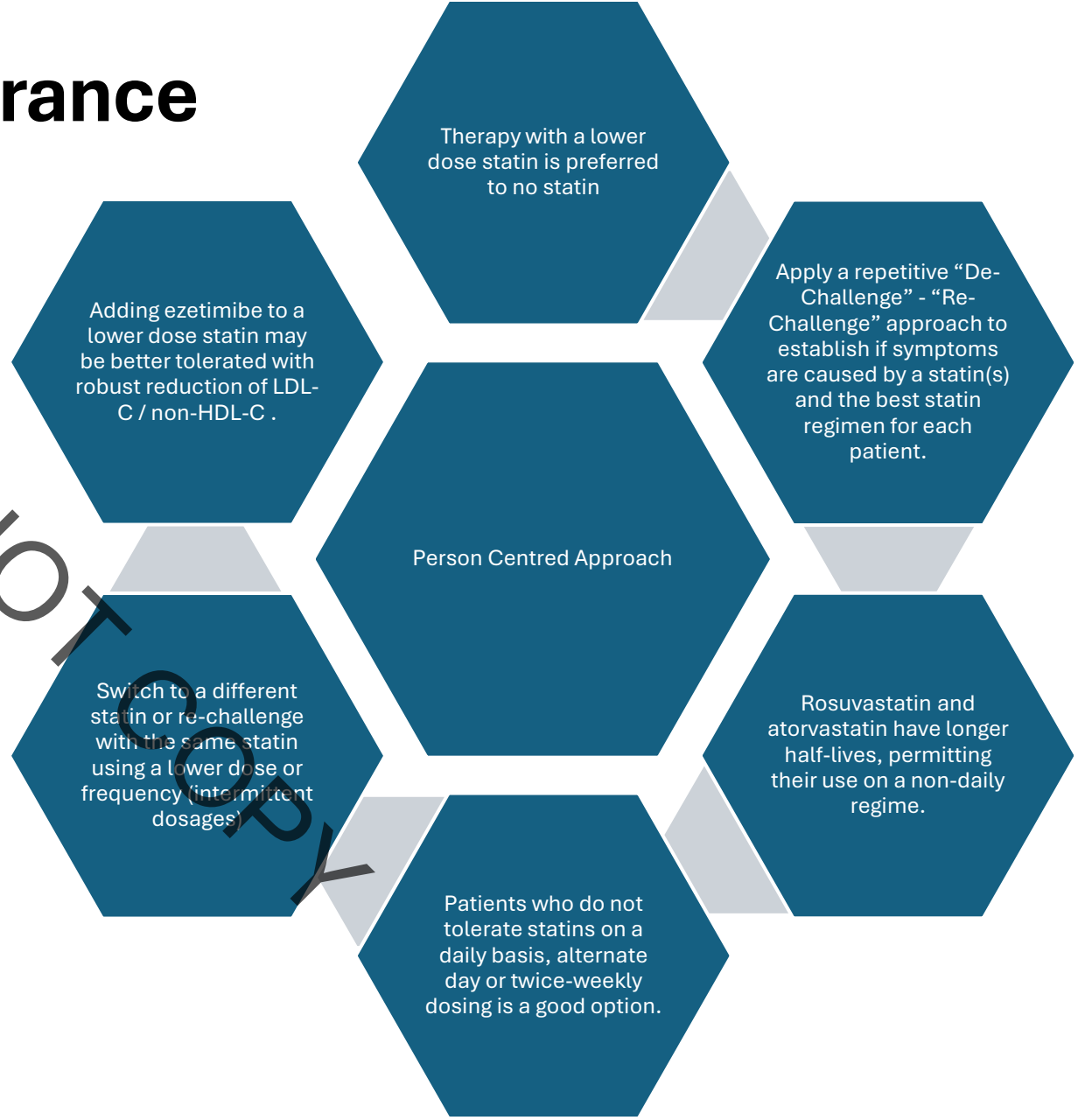
NHS England



https://www.england.nhs.uk/aac/wp-content/uploads/sites/50/2020/09/statin-intolerance-pathway-03092020.pdf

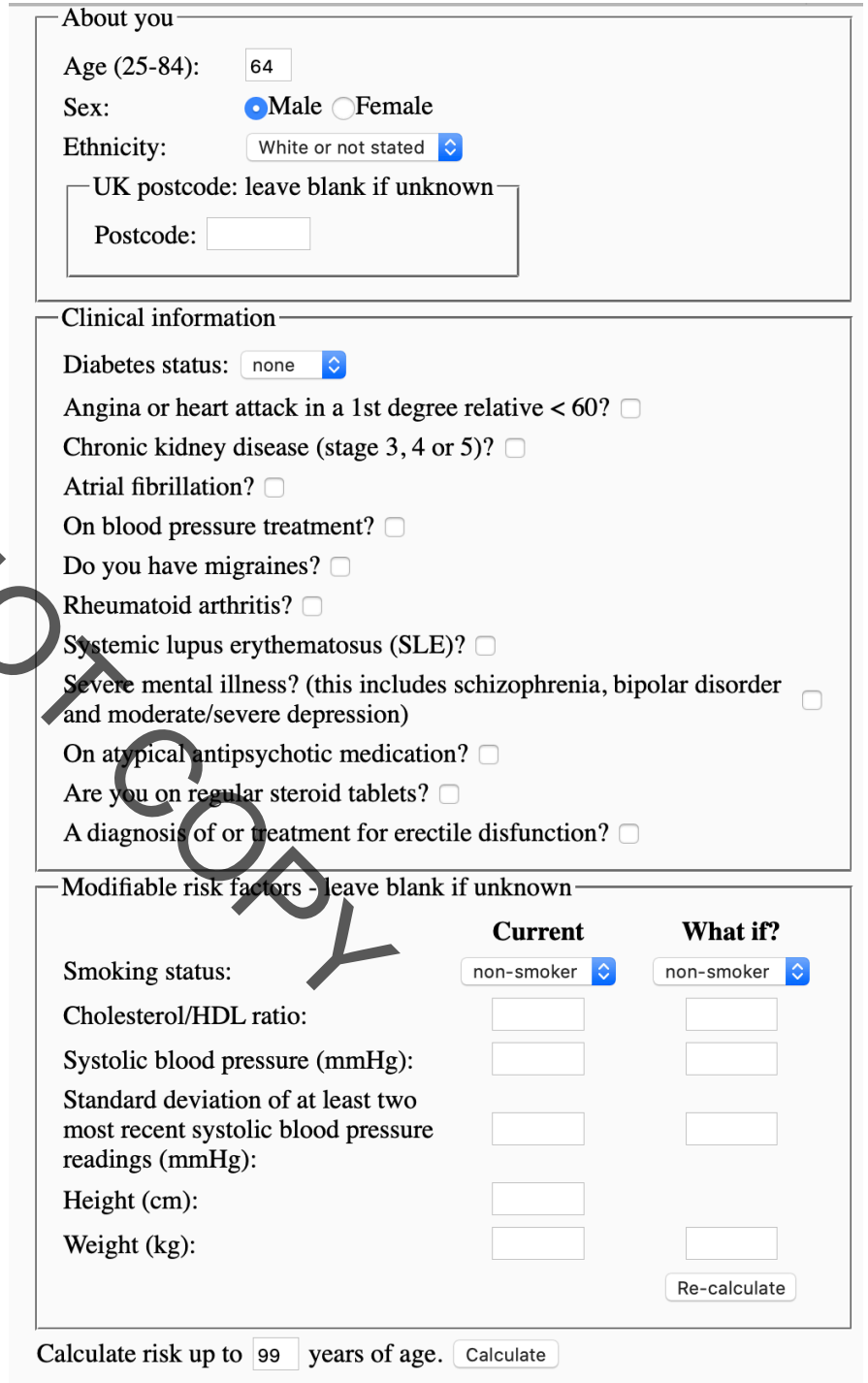
Tips to tackle Statin Intolerance

- **Confirm with history-Statin Related Muscle toxicity (SRM)-** Symmetrical pain and/or weakness in large proximal muscle groups, worsened by exercise
- **Nocebo effect, Statin reluctance**
- **Consider other causes** if new onset of muscle symptoms of >2 weeks duration in a person previously tolerant of statin therapy for > 3months
- **Consider low dose or alternate day** or twice weekly Atorvastatin or Rosuvastatin



https://www.england.nhs.uk/aac/wp-content/uploads/sites/50/2020/09/statin-intolerance-pathway-03092020.pdf

QRISK3-lifetime cardiovascular risk calculator



About you

Age (25-84): 64

Sex: Male Female

Ethnicity: White or not stated

UK postcode: leave blank if unknown

Postcode:

Clinical information

Diabetes status: none

Angina or heart attack in a 1st degree relative < 60?

Chronic kidney disease (stage 3, 4 or 5)?

Atrial fibrillation?

On blood pressure treatment?

Do you have migraines?

Rheumatoid arthritis?

Systemic lupus erythematosus (SLE)?

Severe mental illness? (this includes schizophrenia, bipolar disorder and moderate/severe depression)

On atypical antipsychotic medication?

Are you on regular steroid tablets?

A diagnosis of or treatment for erectile disfunction?

Modifiable risk factors - leave blank if unknown

	Current	What if?
Smoking status:	non-smoker	non-smoker
Cholesterol/HDL ratio:		
Systolic blood pressure (mmHg):		
Standard deviation of at least two most recent systolic blood pressure readings (mmHg):		
Height (cm):		
Weight (kg):		

Re-calculate

Calculate risk up to 99 years of age. Calculate

10 years Q2risk-3.1% Qrisk -3 lifetime 32.6%

https://www.qrisk.org/lifetime/index.php

For quick access, place your favourites here on the favourites bar. Manage favourites now

Reset | UKCA

About you

Age (25-84): 31

Sex: (•) Male ( ) Female

Ethnicity: White or not stated

UK postcode: leave blank if unknown

Postcode: NG2 7QJ

Clinical information

Diabetes status: type 2

Angina or heart attack in a 1st degree relative < 60? ☐

Chronic kidney disease (stage 3, 4 or 5)? ☐

Atrial fibrillation? ☐

On blood pressure treatment? ☐

Do you have migraines? ☐

Rheumatoid arthritis? ☐

Systemic lupus erythematosus (SLE)? ☐

Severe mental illness? (this includes schizophrenia, bipolar disorder and moderate/severe depression) ☑

On atypical antipsychotic medication? ☑

Are you on regular steroid tablets? ☐

A diagnosis of or treatment for erectile disfunction? ☐

Modifiable risk factors - leave blank if unknown

	Current	What if?
Smoking status:	non-smoker	non-smoker
Cholesterol/HDL ratio:	6.1	
Systolic blood pressure (mmHg):	142	
Standard deviation of at least two most recent systolic blood pressure readings (mmHg):	6	
Height (cm):	165	
Weight (kg):	98	

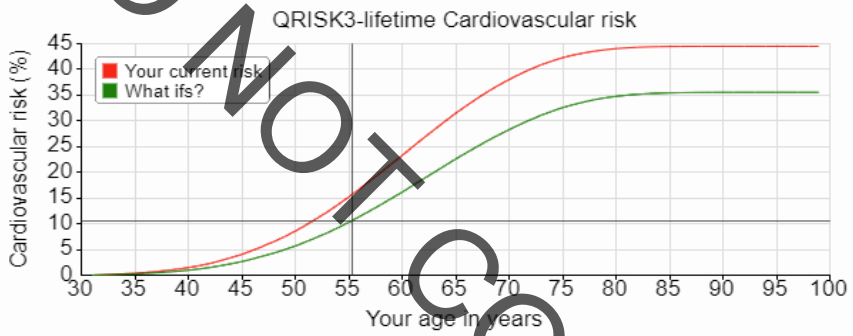
Re-calculate

Calculate risk up to 75 years of age. Calculate

Your results

Your QRISK3-lifetime score

	Current	What if?
Your lifetime risk (i.e. by the time you are 99)	44.5%	35.5%
Your risk up to age 75	42.3%	32.6%



In other words, in a crowd of 100 people like you,

- 42 will develop heart disease or have a stroke/TIA by the time they are 75, and
- 44 will do so by the time they reach 99.

Your score has been calculated using the data you entered.

(If you can only see one line in the graph, that's because the risk profiles are the same, and one line has been drawn on top of the other.)

The NEW ENGLAND JOURNAL of MEDICINE

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Bempedoic Acid and Cardiovascular Outcomes in Statin-Intolerant Patients

S.E. Nissen, A.M. Lincoff, D. Brennan, K.K. Ray, D. Mason, J.J.P. Kastelein, P.D. Thompson, P. Libby, L. Cho, J. Plutzky, H.E. Bays, P.M. Moriarty, V. Menon, D.E. Grobbee, M.J. Louie, C.-F. Chen, N. Li, L.A. Bloedon, P. Robinson, M. Horner, W.J. Sasiela, J. McCluskey, D. Davey, P. Fajardo-Campos, P. Petrovic, J. Fedacko, W. Zmuda, Y. Lukyanov, and S.J. Nicholls, for the CLEAR Outcomes Investigators*

ABSTRACT

BACKGROUND

Bempedoic acid, an ATP citrate lyase inhibitor, reduces low-density lipoprotein (LDL) cholesterol levels and is associated with a low incidence of muscle-related adverse events; its effects on cardiovascular outcomes remain uncertain.

METHODS

We conducted a double-blind, randomized, placebo-controlled trial involving patients who were unable or unwilling to take statins owing to unacceptable adverse effects ("statin-intolerant" patients) and had, or were at high risk for, cardiovascular disease. The patients were assigned to receive oral bempedoic acid, 180 mg daily, or placebo. The primary end point was a four-component composite of major adverse cardiovascular events, defined as death from cardiovascular causes, nonfatal myocardial infarction, nonfatal stroke, or coronary revascularization.

RESULTS

A total of 13,970 patients underwent randomization; 6992 were assigned to the

The authors' full names, academic degrees, and affiliations are listed in the Appendix. Dr. Nissen can be contacted at nissens@ccf.org or at the Department of Cardiovascular Medicine, Cleveland Clinic, Rm. JB-820, 9500 Euclid Ave., Cleveland, OH 44195.

*A list of the investigators in the CLEAR Outcomes trial is provided in the Supplementary Appendix, available at NEJM.org.

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DOI: 10.1056/NEJMoa2215024

Bempedoic Acid significantly reduced MACE-CLEAR outcomes

Three-component MACE (nonfatal MI, nonfatal stroke, CV death): 8.2% vs. 9.5% (p = 0.006)
- Fatal or nonfatal MI: 3.7% vs. 4.8% (p = 0.002)
- Coronary revascularization: 6.2% vs. 7.6% (p = 0.001)
- Fatal or nonfatal stroke: 1.9% vs. 2.3% (p = 0.16)
- All-cause mortality: 6.2% vs. 6.0%
- **Change in LDL-C at 6 months:** -21.1 vs. -0.8 mg/dL (p < 0.06)
- **Change in hsCRP from baseline at 12 months**: -20.6% vs. 0% (p < 0.05)
- **Any muscle disorder:** 15.0% vs. 15.4%
- Hyperuricemia: 10.9% vs. 5.6%
- Gout: 3.1% vs. 2.1%
- Cholelithiasis: 2.2% vs. 1.2%

Is there a LDL-C level that is too low?

ESC European Society of Cardiology
European Heart Journal (2021) **42**, 2154–2169
doi:10.1093/eurheartj/ehaa1080

STATE OF THE ART REVIEW
Dyslipidaemias

How low is safe? The frontier of very low (<30 mg/dL) LDL cholesterol

Angelos D. Karagiannis [1], Anurag Mehta [2], Devinder S. Dhindsa[2], Salim S. Virani[3,4], Carl E. Orringer [5], Roger S. Blumenthal [6], Neil J. Stone[7], and Laurence S. Sperling [2]*

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Low-density lipoprotein cholesterol (LDL-C) is a proven causative factor for developing atherosclerotic cardiovascular disease. Individuals with genetic conditions associated with lifelong very low LDL-C levels can be healthy. We now possess the pharmacological armamentarium (statins, ezetimibe, PCSK9 inhibitors) to reduce LDL-C to an unprecedented extent. Increasing numbers of patients are expected to achieve very low (<30 mg/dL) LDL-C. Cardiovascular event reduction increases log linearly in association with lowering LDL-C, without reaching any clear plateau even when very low LDL-C levels are achieved. It is still controversial whether lower LDL-C levels are associated with significant clinical adverse effects (e.g. new-onset diabetes mellitus or possibly haemorrhagic stroke) and long-term data are needed to address safety concerns. This review presents the familial conditions characterized by very low LDL-C, analyses trials with lipid-lowering agents where patients attained very low LDL-C, and summarizes the benefits and potential adverse effects associated with achieving very low LDL-C. Given the potential for cardiovascular benefit and short-term safe profile of very low LDL-C, it may be advantageous to attain such low levels in specific high-risk populations. Further studies are needed to compare the net clinical benefit of non-LDL-C-lowering interventions with very low LDL-C approaches, in addition to comparing the efficacy and safety of very low LDL-C levels vs. current recommended targets.

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- Given the potential for cardiovascular benefit and short-term safe profile of very low LDL-C, it may be advantageous to attain such low levels in specific high-risk populations
- Individuals with genetic conditions associated with lifelong very low LDL-C levels can be healthy
- Cardiovascular event reduction increases log linearly in association with lowering LDL-C, without reaching any clear plateau even when very low LDL-C levels are achieved.