



LDL-C does not cause cardiovascular disease: a comprehensive review of the current literature

Uffe Ravnskov, Michel de Lorgeril, David M Diamond, Rokuro Hama, Tomohito Hamazaki, Björn Hammarskjöld, Niamh Hynes, Malcolm Kendrick, Peter H Langsjoen, Luca Mascitelli, Kilmer S McCully, Harumi Okuyama, Paul J Rosch, Tore Schersten, Sherif Sultan & Ralf Sundberg

To cite this article: Uffe Ravnskov, Michel de Lorgeril, David M Diamond, Rokuro Hama, Tomohito Hamazaki, Björn Hammarskjöld, Niamh Hynes, Malcolm Kendrick, Peter H Langsjoen, Luca Mascitelli, Kilmer S McCully, Harumi Okuyama, Paul J Rosch, Tore Schersten, Sherif Sultan & Ralf Sundberg (2018) LDL-C does not cause cardiovascular disease: a comprehensive review of the current literature, *Expert Review of Clinical Pharmacology*, 11:10, 959-970, DOI: [10.1080/17512433.2018.1519391](https://doi.org/10.1080/17512433.2018.1519391)

To link to this article: <https://doi.org/10.1080/17512433.2018.1519391>



© 2018 The Author(s). Published by Informa UK Limited, trading as Taylor & Francis Group.



Accepted author version posted online: 10 Sep 2018.
Published online: 11 Oct 2018.



Submit your article to this journal [↗](#)




Article views: 61208



View Crossmark data [↗](#)

LDL-C does not cause cardiovascular disease: a comprehensive review of the current literature

Uffe Ravnskov^a, Michel de Lorgeril^b, David M Diamond^{c,d}, Rokuro Hama^e, Tomohito Hamazaki^f, Björn Hammarskjöld^g, Niamh Hynes^h, Malcolm Kendrickⁱ, Peter H Langsjoen^j, Luca Mascitelli^k, Kilmer S McCully^l, Harumi Okuyama ^m, Paul J Roschⁿ, Tore Schersten^{o,p}, Sherif Sultan^h and Ralf Sundberg^q

^aIndependent investigator, Lund, Sweden; ^bLaboratoire Coeur et Nutrition, TIMC-IMAG, School of Medicine, University of Grenoble-Alpes, Grenoble, France; ^cDepartment of Molecular Pharmacology and Physiology, Center for Preclinical and Clinical Research on PTSD, University of South Florida, Tampa, FL, USA; ^dDepartment of Psychology, Center for Preclinical and Clinical Research on PTSD, University of South Florida, Tampa, FL, USA; ^eJapan Institute of Pharmacovigilance, Osaka, Japan; ^fDepartment of Internal Medicine, Toyama Jonan Onsen Daini Hospital, University of Toyama, Toyama, Japan; ^gStrömstad Academy, Strömstad, Sweden; ^hWestern Vascular Institute, University Hospital Galway & Galway Clinic, National University of Ireland & Royal college of Surgeons of Ireland affiliated Hospital, Galway, Ireland; ⁱEast Cheshire Trust, Macclesfield District General Hospital, Macclesfield, UK; ^jPrivate Practice in Cardiology, Tyler, Texas, USA; ^kMedical Service, Comando Brigata Alpina “Julia”/Multinational Land Force, Udine, Italy; ^lPathology and Laboratory Medicine Service, VA Boston Healthcare System West Roxbury, Harvard Medical School, Boston, MA, USA; ^mFaculty of Pharmaceutical Science, Nagoya City University, Mizuhoku, Nagoya, Japan; ⁿNew York Medical College, The American Institute of Stress, New York, NY, USA; ^oWallenberg Laboratory for Cardiovascular and Metabolic Research, Sahlgren’s Academy, University of Gothenburg, Gothenburg, Sweden; ^pDepartment of Metabolism, Columbia University, New York, NY, USA; ^qIndependent Researcher, Lidingö, Sweden

ABSTRACT

Introduction: For half a century, a high level of total cholesterol (TC) or low-density lipoprotein cholesterol (LDL-C) has been considered to be the major cause of atherosclerosis and cardiovascular disease (CVD), and statin treatment has been widely promoted for cardiovascular prevention. However, there is an increasing understanding that the mechanisms are more complicated and that statin treatment, in particular when used as primary prevention, is of doubtful benefit.

Areas covered: The authors of three large reviews recently published by statin advocates have attempted to validate the current dogma. This article delineates the serious errors in these three reviews as well as other obvious falsifications of the cholesterol hypothesis.

Expert commentary: Our search for falsifications of the cholesterol hypothesis confirms that it is unable to satisfy any of the Bradford Hill criteria for causality and that the conclusions of the authors of the three reviews are based on misleading statistics, exclusion of unsuccessful trials and by ignoring numerous contradictory observations.

ARTICLE HISTORY

Received 11 January 2018
Accepted 31 August 2018

KEYWORDS

Atherosclerosis; cardiovascular; cholesterol lowering; coronary heart disease; exposure–response; mortality; statin

1. Introduction

According to the British-Austrian philosopher Karl Popper, a theory in the empirical sciences can never be proven, but it can be shown to be false. If it cannot be falsified, it is not a scientific hypothesis. In the following, we have followed Popper’s principle to see whether it is possible to falsify the cholesterol hypothesis. We have also assessed whether the conclusions from three recent reviews by its supporters [1–3] are based on an accurate and comprehensive review of the research on lipids and cardiovascular disease (CVD).

2. Does high total cholesterol cause atherosclerosis?

2.1. No association between total cholesterol and degree of atherosclerosis

If high total cholesterol (TC) causes atherosclerosis, people with high TC should have more atherosclerosis than people with low TC. In 1936, Landé and Sperry found that corrected for age, unselected people with low TC were just as

atherosclerotic as people with high TC [4]. Since then, their seminal observation has been confirmed in at least a dozen studies [5]. A weak association between TC and degree of atherosclerosis has been found in some studies [5], but the authors only studied patients admitted to a hospital and may, therefore, have included patients with familial hypercholesterolemia (FH). As the percentage of such patients in a cardiology department is much higher than in the general population, a bias may have been introduced. In accordance, the positive association between TC and degree of atherosclerosis noted in the study by Solberg et al. disappeared when those with TC above 350 mg/l (9 mmol/l) were excluded [5,6].

2.2. No exposure–response

If high TC were the major cause of atherosclerosis, there should be exposure–response in cholesterol-lowering drug trials; for example, the arteries of those whose lipid values are lowered the most should benefit the most. However, in a review of 16 angiographic cholesterol-lowering trials, where

the authors had calculated exposure–response, this correlation was only present in one of them, and in that trial, the only treatment was exercise [5].

3. Does high TC cause CVD?

3.1. An idea supported by fraudulent reviews of the literature

If high TC was the major cause of CVD, people with high TC should have a higher risk of dying from CVD. The hypothesis that high TC causes CVD was introduced in the 1960s by the authors of the Framingham Heart Study. However, in their 30-year follow-up study published in 1987 [7], the authors reported that *'For each 1 mg/dl drop in TC per year, there was an eleven percent increase in coronary and total mortality'*. Three years later, the American Heart Association and the U. S. National Heart, Lung and Blood Institute published a joint summary [8] concluding, *'a one percent reduction in an individual's TC results in an approximate two percent reduction in CHD risk'*. The authors fraudulently referred to the Framingham publication to support this widely quoted false conclusion.

In two additional reviews written by authoritative supporters of the cholesterol hypothesis [9,10], more misleading information was reported. To see how these proponents explained results discordant with the cholesterol hypothesis, quotations from 12 articles with such findings were searched for in the three reviews [11]. Only two of the articles were quoted correctly and only in one of the reviews. About half of the contradictory articles were ignored. In the rest, statistically nonsignificant findings in favor of the cholesterol hypothesis were inflated, and unsupportive results were quoted as if they were supportive. Only one of the six randomized cholesterol-lowering trials with a negative outcome was cited and only in one of the reviews [11].

3.2. The association between TC and CVD is weak, absent or inverse in many studies

During the years following the report of the Framingham Heart Study, numerous studies revealed that high TC is not associated with future CVD. with the strongest evidence of a lack of relation between TC and CVD in elderly people. For instance, a review published in 2002 included references to 12 such studies [12]. A 2004 Austrian study [13] published 2004 including 67,413 men and 82,237 women who had been followed up for many years found that TC was weakly associated with coronary heart disease (CHD) mortality for men, except for those between age 50 and 64 years. For women, it was weakly associated among those below the age of 50 years, and no association was present after that age. No association was found between TC and mortality caused by other CVDs, except that low TC was inversely associated with CVD mortality for women above the age of 60 years.

In 2007, the Prospective Studies Collaboration [14], the writing committee of which included the same authors as those for Collins et al. [1], published a meta-analysis including 61 prospective observational studies consisting of

almost 900,000 adults, which concluded that TC was associated with CHD mortality in all ages and both sexes. We have not been able to obtain the original data [15]. However, the authors had ignored at least a dozen studies, including the Austrian one, where no association or an inverse association was noted, and in several studies, the number of participants deviated from the number reported by the Prospective Studies Collaboration.

Today, the general opinion is that TC is not the most useful or accurate predictor of CVD, and interest has increasingly focused on low-density lipoprotein cholesterol (LDL-C).

4. Does high LDL-C cause atherosclerosis?

4.1. An idea based on selected patient groups

If LDL-C is atherogenic, people with high LDL-C should have more atherosclerosis than those with low LDL-C. At least four studies have shown a lack of an association between LDL-C and degree of atherosclerosis [5], and in a study of 304 women, no association was found between LDL-C and coronary calcification [16]. One exception is a study of 1779 healthy individuals without conventional risk factors for CVD [17]. Here, the authors found that LDL-C was significantly higher among those with subclinical atherosclerosis (125.7 vs. 117.4 mg/dl). However, association does not prove causation. Mental stress, for instance, is able to raise cholesterol by 10–50% in the course of half an hour [18,19], and mental stress may cause atherosclerosis by mechanisms other than an increase in LDL-C; for instance, via hypertension and increased platelet aggregation.

5. Does high LDL-C cause CVD?

5.1. LDL-C of patients with acute myocardial infarction is lower than normal

If high LDL-C causes CVD, LDL-C of untreated patients with CVD should be higher than normal. However, in a large American study [20] including almost 140,000 patients with acute myocardial infarction (AMI), their LDL-C at the time of admission to hospital was actually lower than normal. In another study with the same finding [21], the authors decided to lower the patients' LDL-C even more, but at a follow-up 3 years later, total mortality among those with LDL-C below 105 mg/dl (2 mmol/l) was twice as high compared to those with a higher LDL-C, even after adjustment for confounding variables (14.8% vs. 7.1%, $p = 0.005$).

It has been suggested that inverse causation explains the inverse association between mortality and LDL-C; for example, that cancer and infections lower LDL-C. A more likely explanation is that CVD may be caused by infections and that LDL directly inactivates almost all types of microorganisms and their toxic products [12,22,23]. Consistent with that finding is the observation that healthy individuals with low LDL-C have a significantly increased risk of both infectious diseases [23] and cancer [24]; the latter possibly because microorganisms have been linked to almost 20% of all cancer types [25].

5.2. Elderly people with high LDL-C live the longest

If high LDL-C was the major cause of atherosclerosis and CVD, people with the highest LDL-C should have shorter lives than people with low values. However, in a recent systematic review of 19 cohort studies including more than 68,000 elderly people (>60 years of age), we found the opposite [26]. In the largest cohort study [27], those with the highest LDL-C levels lived even longer than those on statin treatment. In addition, numerous Japanese studies have found that high LDL-C is not a risk factor for CHD mortality in women of any age [28].

5.3. Mendelian randomization

An argument used in the three expert reviews [1–3] is based on Mendelian randomization, which has shown that lower genetically determined LDL-C concentrations are associated with lower all-cause mortality. But again, association does not mean causation. Other genes in the same individual may have opposite effects, and as pointed out by Burgess et al., ‘Power, linkage disequilibrium, pleiotropy, canalization and population stratification have all been recognized as potential flaws in the Mendelian randomization approach’ [29].

6. Does cholesterol-lowering treatment lower the risk of CVD?

6.1. No exposure–response in the statin trials

The strongest proof of causality is that a lowering or elimination of the suspected causal factor is able to lower the incidence of the disease in question. There have been small, but statistically significant, benefits in coronary event outcomes from statin trials. However, are the benefits of statin treatment produced by lowering LDL?

If high LDL-C were the major cause of CVD, the benefit from statin treatment should be better the more LDL-C is lowered; for example, there should be a systematic exposure–response relationship. The authors of the three reviews [1–3] assert that statin trials have demonstrated such dose–responses. As proof, they have compared the outcomes in various trials with the degree of LDL-C lowering, and it is impossible to know whether the greater effect of a trial using a higher statin dose may be caused by its cholesterol-lowering effect or pleiotropic effects. True exposure–response is based on a comparison between the degree of cholesterol lowering in each patient in a single trial and the absolute reduction of their risk. True exposure–response has only been calculated in three clinical statin trials, and it was absent in all three [30–32]. Even a correctly calculated exposure–response does not prove causality, because an innocent risk factor, for instance, LDL-C, may change in the same direction as the real cause, but the absence of exposure–response is a strong argument against causality.

Furthermore, in their calculation, Silverman et al. [2] compared the number of major vascular events (MVEs) with the relative risk reduction (RRR). MVE is of dubious value as a measure of benefit because it is defined very differently in various trials [33]. Using RRR as a measure of benefit is also highly misleading [34], as it inflates the appearance of the rate

of event reduction. For instance, in a trial where 2 of 100 participants in the control group die but only 1 of 100 in the treatment group die, the absolute risk reduction (ARR) is only a 1% benefit. However, if one reports the RRR, then a 50% benefit can be reported, because one is 50% of two.

A preferred way to measure the therapeutic benefit of statin treatment would be to compare the ARR per year of CVD mortality, CHD mortality, and total mortality of each trial with the degree of LDL-C lowering, as we have done in Table 1 and Figures 1 and 2. These data are from the 26 statin trials included in the meta-analysis by Silverman et al. [35–59] and from 11 trials that they excluded [60–69]. As seen from Figures 1 and 2, there was a weak, positive association in the included trials, whereas the association was inverse in the ignored trials.

According to Ference et al. [3], the most compelling clinical evidence for causality is provided by ‘the presence of more than 30 randomized cholesterol-lowering trials that consistently demonstrate that reducing LDL-C reduces the risk of CVD events proportional to the absolute reduction in LDL-C’. As previously noted, this is not true exposure–response. Furthermore, in their Figure 5(a), that illustrates the association, the authors have only included data from 12 of the 30 trials they refer to. If all of the trials in Table 1 are included, as we have done in Figure 3, there is no association between LDL-C lowering and coronary event rate.

Ference et al. [3] claim that short-term follow-up (2 years or less) may be unable to demonstrate an association. We have, therefore, calculated the regression coefficients after having excluded such trials, but they do not differ much (included trials: $r = +2.59$ vs. $+3.39$; excluded trials: $r = -0.1$ vs. $+0.15$).

6.2. The benefit of statin treatment is exaggerated

Collins et al. [1] also used the RRR to quantify the benefit from statin treatment. They claimed that lowering LDL-C by 2 mmol/L will cause an RRR of MVE of about 45%/year, and here, they refer to the meta-analysis performed by the Cholesterol Treatment Trialists [70]. But according to Figures 3 and 4 in that article, the ARR of MVE was only 0.8% (1% for men and 0.2% for women), and the ARR of total mortality was 0.4% (both sexes).

According to the meta-analysis by Silverman et al. [2], reducing LDL-C lowers the risk of MVE in the primary and secondary prevention trials by 0.35 and 1.0%/year/mmol/l reduction of LDL-C, respectively. However, as mentioned, they excluded at least 11 unsuccessful statin trials in which MVE was reported. One of the reasons for the exclusion of a subset of trials may be that they considered trials with fewer than 50 events as unreliable, but in all of the excluded trials, the number of events was higher.

Moreover, neither Collins et al. [1] nor Silverman et al. [2] mentioned that in four statin trials, where a high-degree lowering of LDL-C was compared with a low-degree lowering, no significant difference with respect to the number of MVEs was obtained, although LDL-C was lowered by 0.4–1 mmol/L more in the high-dose groups [53,55,56,61].

Furthermore, the most important outcome – an increase of life expectancy – has never been mentioned in any

Table 1. Mortality in the statin trials included in the meta-analysis by Silverman et al. [2] and in 11 statin trials they have ignored and where the authors have reported coronary and/or total mortality. The figures for LDL-C lowering are the approximate mean differences between the treatment group and the control group. Among the ignored trials only the EXCEL trials [60,61] were primary preventive.

Statin trials	Length (years)	Number of participants		Mortality (%)		ARR per year (%)	ΔLDL-C (mmol/l)
		T/C	T/C	ARR (%)	ARR per year (%)		
Primary-preventive trials included in the meta-analysis by Silverman et al. [2]							
WOSCOPS [35]	CM	4.9	3302/3293	1.15/1.58	-0.43	-0.09	-1.3
	TM			3.21/4.10	-0.89	-0.18	
AFCAPS/TexCAPS [36]	CM	5.2	3304/3301	0.33/0.45	-0.12	-0.02	-1.08
	TM			2.42/2.33	+0.09	+0.02	
ASCOTT-LLA [37]	TM	3.3	5168/5137	3.58/4.13	-0.55	-0.17	-1.20
CARDS [38]	CM	3.95	1428/1410	1.26/1.70	-0.44	-0.11	-1.20
	TM			4.27/5.82	-1.55	-0.39	
MEGA ^a [39]	CM	5.3	3866/3966	0.051/0.076	-0.032	-0.00	-0.59
	TM			1.11/1.66	-0.55*	5-0.10	
ASPEN primary preventive [40]	TM	4	959/946	4.6/4.3	+0.3	+0.08	-0.78
JUPITER [41]	CM	1.9	8901/8901	0.1/0.07	+0.03	+0.02	-1.42
	TM			2.22/2.77	-0.55*	-0.29	
HOPE-3 [42]	TM	5.6	6361/6344	5.25/5.63	-0.38	-0.07	-0.89
Secondary-preventive trials included in the meta-analysis by Silverman et al. [2]							
4S [43]	CM	5.4	2221/2223	1.35/2.83	-1.48***	-0.27	-1.75
	TM			8.19/11.5	-3.33***	-0.62	
CARE [44]	CM	5	2081/2078	4.13/5.73	-1.6	-0.32	-0.98
	TM			8.64/9.43	-0.79	-0.16	
POST-CAB [45]	CM	4.3	676/675	0.89/0.59	+0.30	+0.07	-1.11
	TM			4.73/5.19	-0.46	-0.11	
LIPID [46]	CM	6.1	4512/4502	6.36/8.29	-1.92***	-0.32	-0.97
	TM			11.04/14.06	-3.02***	-0.50	
GISSI-P [47]	CM	2	2138/2133	1.45/2.3	-0.85	-0.43	-0.62
	TM			3.37/4.13	-0.76	-0.38	
LIPS [48]	CM	3.9	844/833	1.5/2.88	-1.34	-0.34	-1.1
	TM			4.27/5.88	-1.62**	-0.41	
HPS [49]	CM	5	10,269/10,267	5.7/6.9	-1.17***	-0.23	-1.0
	TM			12.9/14.68	-1.75***	-0.35	
GREACE ^a [50]	CM	3	800/800	2.5/4.75	-2.25**	-0.75	-1.86
	TM			2.88/5.0	-2.12**	-0.71	
PROSPER [51]	CM	3.2	2891/2913	3.25/4.19	-0.94*	-0.29	-1.0
	TM			10.31/10.50	-0.20	-0.06	
ALLHAT-LLT ^a [52]	CM	4.8	5170/5185	3.09/3.12	-0.03	0	-0.56
	TM			12.21/12.36	-0.15	-0.03	
PROVE-IT [53]	CM	2	2099/2063	1.1/1.41	-0.31	-0.15	-0.85
	TM			2.2/3.2	-1.0	-0.5	
A to Z [54]	TM	2	2265/2232	4.59/5.82	-1.23	-0.62	-0.36
ALLIANCE ^a [55]	CM	4.3	1217/1225	3.53/4.98	-1.45	-0.32	-0.39
	TM			9.94/10.37	-0.43	-0.09	
TNT [56]	CM	4.9	4995/5006	2.02/2.54	-0.52	-0.11	-0.62
	TM			5.69/5.63	+0.06	+0.01	
IDEAL [57]	CM	4.8	4439/4449	4.0/3.94	+0.06	+0.01	-0.56
	TM			8.25/8.41	-0.16	-0.03	
SPARCL [58]	CM	4.9	2365/2366	1.69/1.64	+0.04	+0.01	-1.43
	TM			9.13/8.92	+0.21	+0.04	
ASPEN secondary preventive [40]	TM	4	252/253	10.32/10.67	-0.35	-0.03	-0.67
SEARCH [59]	CM	6.7	6031/6033	7.41/7.28	+0.14	+0.02	-0.35
	TM			15.98/16.08	-0.1	-0.01	
Trials ignored by Silverman et al.							
EXCEL 20 mg/day [60,61]	TM	0.92	1642/1663	0.5/0.2	+0.3	+0.33	-1.14
EXCEL 40 mg/day [60,61]	TM	0.92	3291/1663	0.45/0.2	+0.25	+0.27	-1.51
EXCEL 80 mg/day [60,61]	TM	0.92	1649/1663	0.5/0.2	+0.3	+0.33	-1.88
4D [62]	CM	3.93	619/636	3.72/5.19	-1.47	-0.37	-0.9
	TM			47.98/50.31	-2.33	-0.59	
DEBATE ^a [63]	CM	3.4	199/201	7.5/6.0	+1.5	+0.44	-0.73
	TM			18.1/17.4	+0.07	+0.02	
CORONA [64]	CM	2.7	2514/2497	0.36/0.32	+0.04	+0.01	-1.61
	TM			28.96/30.40	-1.44	-0.53	
SAGE [65]	CM	1	446/445	0.4/1.3	-0.9	-0.9	-0.86
	TM			1.34/4.04	-2.70*	-2.70	
SEAS [66]	CM	4.35	944/929	0.53/1.08	-0.55	-0.13	-1.80
	TM			11.12/10.76	+0.36	-0.08	
GISSI-HF [67]	CM	3.9	2285/2289	0.44/0.66	-0.22	-0.06	-0.95
	TM			28.75/28.13	+0.62	+0.16	
AURORA [68]	CM	3.8	1389/1384	14.69/15.10	-0.41	-0.11	-1
	TM			45.79/47.69	-1.90	-0.50	
IMPROVE-IT [69]	CM	7	9067/9077	0.45/0.54	-0.09	-0.01	-0.43
	TM			13.4/13.56	-0.16	-0.02	
Total number			112,599/110,981				

CM: coronary mortality; TM: total mortality; ARR: absolute risk reduction; T: treatment group or high-dose group; C: control group or low-dose group.

^aProbably unblinded because no placebo-group was included; that is, the treatment group was compared with 'Usual care'.

* $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$.

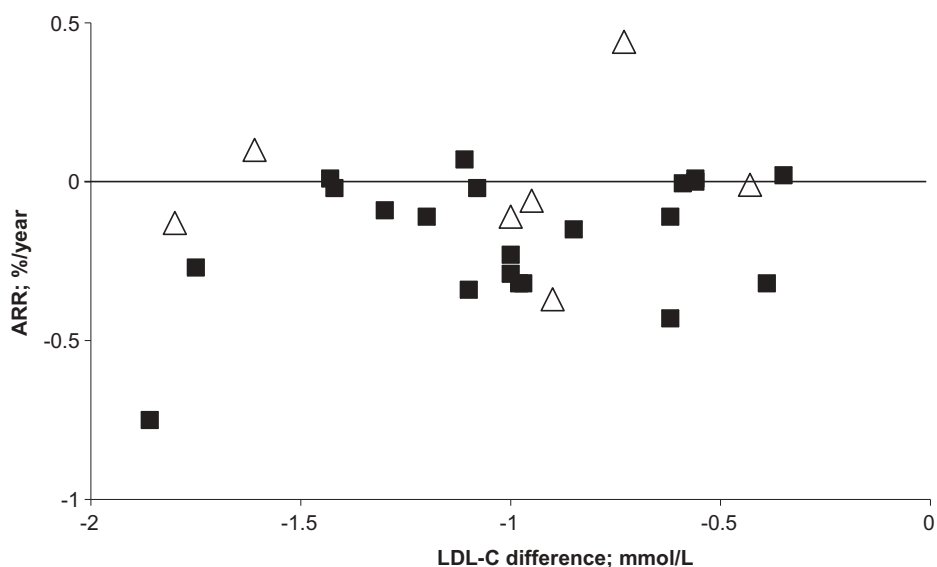


Figure 1. The association between degree of LDL-C lowering and the absolute risk reduction of CHD mortality (%/year) in 21 statin trials, where CHD mortality was recorded and which were included in the study by Silverman et al. and in 8 ignored statin trials ($y = 0.16x - 0.018$) but inversely associated in the ignored trials ($y = 0.08x + 0.062$).

Squares: included trials; triangles: ignored trials.

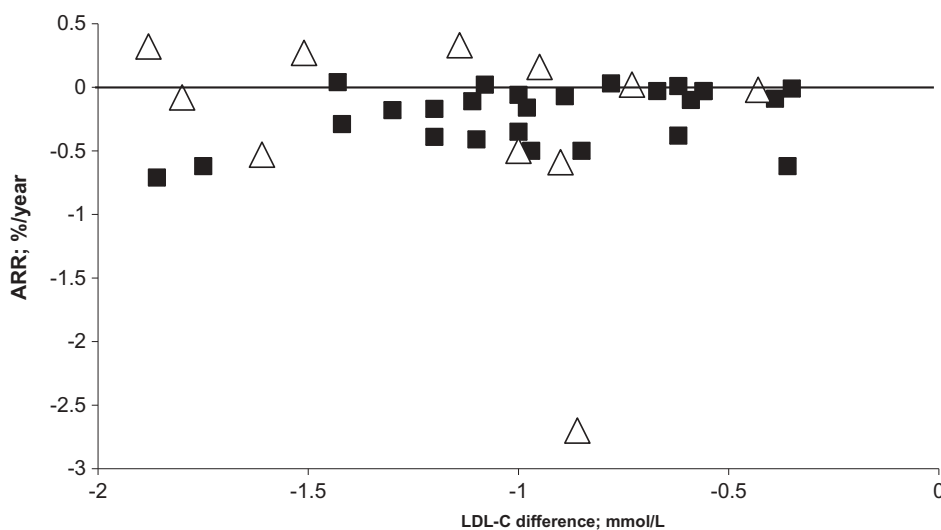


Figure 2. The association between degree of LDL-C lowering and the absolute risk reduction of total mortality (%/year) in 26 statin trials, where total mortality was recorded and which were included in the study by Silverman et al. and in 11 ignored trials. ARR is weakly associated with degree of LDL-C lowering in the included trials ($y = 0.28x + 0.06$) but inversely associated in the excluded trials ($y = -0.49x - 0.81$). Symbols: see Figure 1.

cholesterol-lowering trial, but as calculated recently by Kristensen et al., statin treatment does not prolong lifespan by more than an average of a few days [71].

6.3. The benefit from statin treatment has been questioned

For some years, many researchers have questioned the results from statin trials because they have been denied access to the primary data. In 2004–2005, health authorities in Europe and the United States introduced New Clinical Trial Regulations, which specified that all trial data had to be made public. Since

2005, claims of benefit from statin trials have virtually disappeared [72], see Figures 4 and 5.

6.4. Adverse effects from statin treatment

According to Collins et al. [1], adverse effects from statin treatment are extremely rare, and the incidence of statin adverse effects can only be obtained from randomized controlled trials. However, many drug-related adverse effects in other therapy areas have only emerged from observational studies and post-marketing surveillance. Furthermore, most statin trials have included a run-in period, where participants received the drug for a few weeks, after which those who

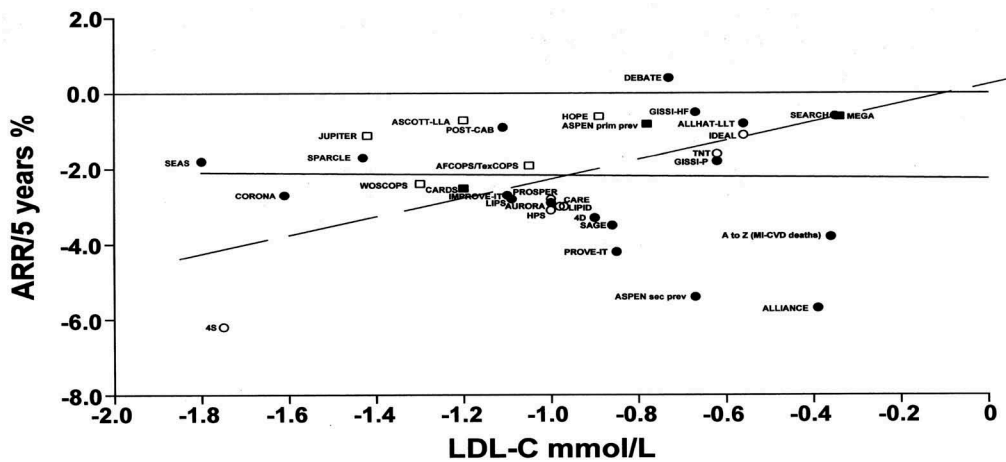


Figure 3. The association between the absolute 5-year risk reduction (ARR) and the degree of LDL-C lowering in 12 trials included in Table 4A in the article by Ference et al. ($r = 2.59$) and from 21 trials they have ignored or excluded ($r = -0.1$).

White symbols: trials included in the analysis by Ference et al.; black symbols: excluded or ignored trials; squares: primary-preventive trials; round symbols: secondary-preventive trials; stippled line: regression line for the included trials; full line: regression line for all trials.

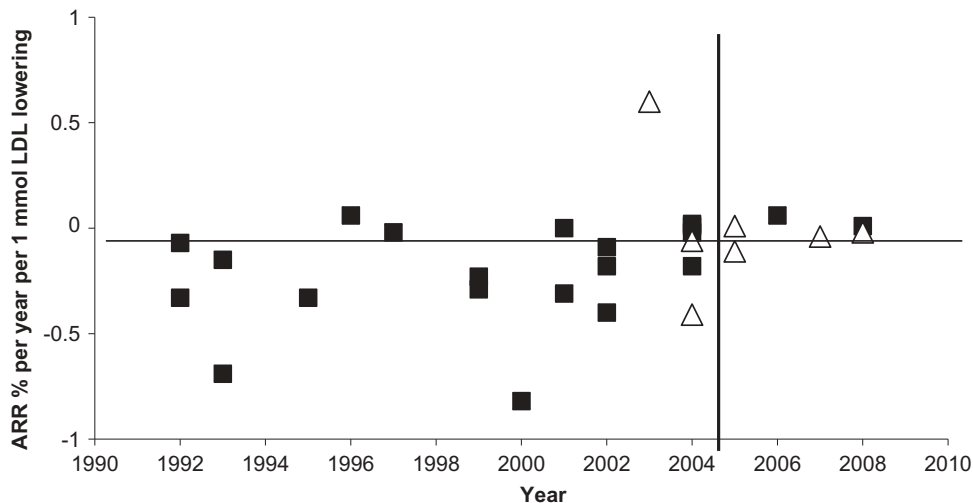


Figure 4. The association between the absolute risk reduction of CHD mortality in 21 statin trials included in the study by Silverman et al. and in 7 ignored trials and the year where the trial protocols were published. The vertical line indicates the year where the new trial regulations were introduced. Symbols: see Figure 1.

suffered adverse effects or who were unwilling to continue were excluded. The results from two trials without a run-in period [55,64] and where a high statin dose was compared with a low dose demonstrated that this is an effective way to minimize the number of reported side effects; in SAGE [64], serious side effects were recorded in more than 20% in both groups, and in IDEAL [55], the number was almost 50%.

According to Collins et al. [1], myopathy occurs in only 0.01% of treated individuals per year, but in most statin trials, myopathy is only recorded if creatine kinase is more than 10 times higher than normal. However, in a study by Phillips et al. [73], microscopic examinations of muscle biopsies from statin-treated patients with muscular symptoms and normal creatine kinase levels showed signs of myopathy. When patients

stopped treatment, their symptoms disappeared, and repeated biopsies showed resolution of the pathological changes.

To reject the frequent occurrence of muscular problems with the argument that muscle symptoms are nocebo effects is also invalid. In a study of 22 statin-treated professional athletes [74], the authors reported that 17 (77%) of the athletes terminated treatment because of muscular symptoms, which disappeared a few days or weeks after drug withdrawal. The explanation for statin-induced adverse muscle effects is probably that statin treatment not only blocks the production of cholesterol but also blocks the production of several other important molecules, for instance, coenzyme Q10, which is indispensable for energy production. As most energy is

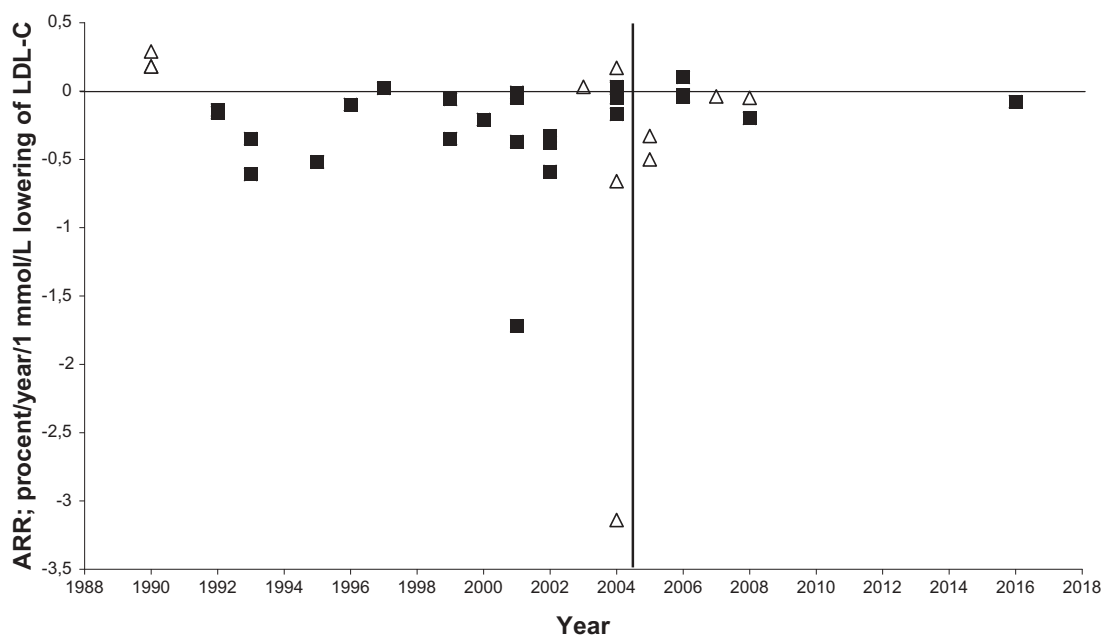


Figure 5. The association between the absolute risk reduction of total mortality in 26 statin trials included in the study by Silverman et al. and in 11 ignored trials and the year where the trial protocols were published. The vertical line indicates the year where the new trial regulations were introduced. Symbols: see Figure 1.

produced in the muscle cells, including those of the heart, the extensive use of statin treatment may explain the epidemics of heart failure that have been observed in many countries [75].

Furthermore, case-control and cross-sectional studies have shown that statin use is observed significantly more often among patients with cataracts [76], hearing loss [77], suicidal ideation [78], peripheral neuropathy [79], depression [80], Parkinson's disease [81], interstitial cystitis [82], herpes zoster [83], impotency [84], cognitive impairments [85–88], and diabetes [89,90]. In some of these studies, the side effects disappeared with discontinuation of the statins and worsened with rechallenge [74,84,85]. As cholesterol is a vital substance for the renewal of all cells, and since statins also block the production of other molecules necessary for normal cell function [75], it is not surprising that statin treatment may result in side effects from many different organs.

According to Collins et al., statin treatment protects against cancer. However, in three trials, cancer occurred significantly more often in the treatment groups [24], and there is much evidence that low cholesterol predisposes to cancer. For instance, several experiments on rodents with lipid-lowering drugs produced cancer [91], and in nine human cohort studies, cancer rates were inversely associated with cholesterol levels measured in healthy people 10 to more than 30 years earlier [24]. Therefore, case-control studies in which the incidence of cancer in statin-treated patients was lower than in controls are invalid because many untreated individuals have low cholesterol, and those on statins have lived most of their lives with high cholesterol that may have provided protection from developing cancer.

The reported incidence of most of the above-mentioned side effects may be relatively small, but taken together, the total number can become substantial, in particular in patients who continue statin treatment for many years.

6.5. Does treatment with proprotein convertase subtilisin-kexin type 9 inhibitors improve the outcome?

A new cholesterol-lowering drug has recently been introduced. It is an antibody that inhibits proprotein convertase subtilisin-kexin type 9 (PCSK-9), which lowers LDL-C by approximately 60%. In FOURIER, the largest and longest PCSK-9 inhibitor trial, evolocumab was compared with placebo in more than 27,000 statin-treated patients with CVD [92]. The trial was stopped after 2.2 years because the number of MVE was reduced with statistical significance (9.8% vs. 11.3%). However, both CVD mortality and total mortality had increased, although not with statistical significance. A relevant question is, therefore, why the trial, the sponsor of which (Amgen) was responsible for data collection, was ended after only 2.2 years. Furthermore, this trial is yet another proof that there is no exposure-response between LDL-C and total or CVD mortality.

7. Does FH prove that high LDL-C causes CVD?

7.1. A low percentage of FH individuals die prematurely

For many years, it has been assumed that high LDL-C was the cause of the increased risk of CVD and premature deaths in individuals with FH, and this argument was used by Collins

et al. [1] and Ference et al. [2] as well. However, many observations are in conflict with this hypothesis.

For instance, according to the Simon Broome registry, only a small percentage of FH individuals die at an early age, and the mortality among the elderly does not differ from the mortality of the general population despite their high LDL-C [93].

In a study by Mundal et al., 4688 individuals aged 0–92 years with FH were followed up for 18 years [94]. During that time, 113 died, whereas the expected number in the general population was 133. The mortality benefit cannot have been due to lipid-lowering treatment because there was no significant difference between the number on such treatment among those who died and those above the age of 18 years who survived (88.2% vs. 89.1%).

7.2. No LDL-C difference between FH individuals with and without CVD

If high LDL-C causes premature CVD in FH, the LDL-C of those with CVD should be higher compared to others, but at least six studies of untreated FH individuals have shown no significant differences in LDL-C or age [95–100]. It has also been shown that FH relatives without FH may have shorter lives than the general population [101]. Most likely, a small subset of FH individuals and their relatives inherit CVD risk factors that are more important than high LDL-C on CVD outcomes.

8. Has CVD mortality decreased after the introduction of statin treatment?

For decades, a decrease in CVD mortality has been observed in many countries, and the presumed reason for the decrease is the increasing use of statin treatment. However, this interpretation is highly questionable [72]. In a Swedish study including 289 of the 290 municipalities, no association was found between statin use and the change in mortality from AMI [102]. Also, the American National Health and Nutrition Examination Survey [103] found that during the period 1999–2006, the number of AMI and strokes increased from 3.4% to 3.7% and from 2.0% to 2.9%, respectively. During the same period, mean LDL-C level decreased from 126.1 to 114.8 mg/dl, and the self-reported use of lipid-lowering drugs increased from 8% to 13.4%. Furthermore, statin utilization in 12 European countries between 2000 and 2012 was not associated with reduced CHD mortality or its rate of change over the years [104].

9. Conclusion

The idea that high cholesterol levels in the blood are the main cause of CVD is impossible because people with low levels become just as atherosclerotic as people with high levels and their risk of suffering from CVD is the same or higher. The cholesterol hypothesis has been kept alive for decades by reviewers who have used misleading statistics, excluded the results from unsuccessful trials and ignored numerous contradictory observations.

10. Expert commentary

In our analysis of three major reviews [1–3], that claim the cholesterol hypothesis is indisputable and that statin treatment is an effective and safe way to lower the risk of CVD, we have found that their statements are invalid, compromised by misleading statistics, excluding unsuccessful trials, minimizing the side effects of cholesterol lowering, and ignoring contradictory observations from independent investigators.

The usual argument in support of the lipid hypothesis is that numerous studies of young and middle-aged people have shown that high TC or LDL-C predict future CVD. This is correct, but association is not the same as causation. Few authors have adjusted for other CVD-promoting factors such as mental stress, coagulation factors, inflammation, infections, and endothelial sensitivity, all of which are closely related to LDL receptor abnormalities [105]. For instance, mental stress can raise TC [17,18] possibly because cholesterol is necessary for the production of cortisol and other steroid stress hormones, and mental stress may cause CVD by an increased production of epinephrine and norepinephrine, which contribute to hypertension and hypercoagulation. The reason why high TC is a risk factor only for young and middle-aged people may be that mental stress is more common among working people than among retired senior citizens.

It is important to emphasize that LDL participates in the immune system by adhering to and inactivating all kinds of microorganisms and their toxic products and that many observations and experiments have incriminated infections as a possible causal factor of CVD [21–23], and our results indicate that there may be better methods than cholesterol lowering to prevent atherosclerosis and CVD.

11. Five-year view

Statin treatment is prescribed for perpetual use, but very few trials have continued for more than a few years. In the longest follow-up study (20 years) [106], the authors claimed that pravastatin used as primary prevention reduced the risk of CHD by 27% and the risk of major adverse cardiovascular events by 25%. However, these figures represented RRR; the ARR was only a few percentage points. A more serious bias is the statement, mentioned only in a supplement, that the authors did not know how many of the participants had used pravastatin during the 20 years of follow-up after the trial [107]. A relevant goal for future research would be to encourage independent investigators to compare the health status of those who have taken statins for many years with the status of untreated individuals with the same risk factors who have lived just as long.

The lipid hypothesis has been perpetuated by the authors who have ignored the results from trials with a negative outcome, who have misused statistics, and who have ignored all contradictions documented by independent researchers. The increased risk of CVD in people with FH has been a primary argument in support of the lipid hypothesis. Surprisingly, several studies of untreated people with FH have shown that LDL-C does not differ significantly between those with and

without CVD [95–100] and that elderly people with FH live just as long as elderly people from the general population despite their high LDL-C [93,94]. FH individuals with significant CVD may have inherited other, more important risk factors than a high LDL-C.

Despite the fact that LDL-C is routinely referred to as the ‘bad cholesterol’, we have shown that high LDL-C levels appear to be unrelated to the risk of CVD, both in FH individuals and in the general population and that the benefit from the use of cholesterol-lowering drugs is questionable. Therefore, a systematic search for other CVD risk factors is an important topic for future research.

Key issues

- The hypothesis that high TC or LDL-C causes atherosclerosis and CVD has been shown to be false by numerous observations and experiments.
- The fact that high LDL-C is beneficial in terms of overall lifespan has been ignored by researchers who support the lipid hypothesis.
- The assertion that statin treatment is beneficial has been kept alive by individuals who have ignored the results from trials with negative outcomes and by using deceptive statistics.
- That statin treatment has many serious side effects has been minimized by individuals who have used a misleading trial design and have ignored reports from independent researchers.
- That high LDL-C is the cause of CVD in FH is questionable because LDL-C does not differ between untreated FH individuals with and without CVD.
- Millions of people all over the world, including many with no history of heart disease, are taking statins, and PCSK-9 inhibitors to lower LDL-C further are now being promoted, despite unproven benefits and serious side effects.
- We suggest that clinicians should abandon the use of statins and PCSK-9 inhibitors and instead identify and target the actual causes of CVD.

Acknowledgments

The WVI board had approved sponsorship for the open access. This is a charitable organisation and not for profit.

Funding

This paper was funded by Western Vascular Institute.

Declaration of Interest

U Ravnskov, M de Lorgeril, R Hama, M Kendrick, H Okuyama and R Sundberg has published books with criticism of the cholesterol hypothesis. PJ Rosch has edited a book with criticism of the cholesterol hypothesis. KS Mccully has a US patent for a homocysteine-lowering protocol. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

Reviewer disclosures

Peer reviewers on this manuscript have no relevant financial or other relationships to disclose.

ORCID

Harumi Okuyama  <http://orcid.org/0000-0003-3332-4565>

References

Papers of special note have been highlighted as either of interest (*) or of considerable interest (***) to readers.

1. Collins R, Reith C, Emberson J, et al. Interpretation of the evidence for the efficacy and safety of statin therapy. *Lancet*. 2016;388:2532–2561.
2. Silverman MG, Ference BA, Im K, et al. Association between lowering LDL-C and cardiovascular risk reduction among different therapeutic interventions: systematic review and meta-analysis. *JAMA*. 2016;316:1289–1297.
3. Ference BA, Ginsberg HN, Graham I, et al. Low-density lipoproteins cause atherosclerotic cardiovascular disease. 1. evidence from genetic, epidemiologic, and clinical studies. A consensus statement from the European atherosclerosis society consensus panel. *Eur Heart J*. 2017;38:2459–2472.
4. Landé KE, Sperry WM. Human atherosclerosis in relation to the cholesterol content of the blood serum. *Arch Pathol*. 1936;22:301–312.
- **This paper shows that for more than 80 years we should have known that high cholesterol is not the cause of atherosclerosis.**
5. Ravnskov U. Is atherosclerosis caused by high cholesterol? *QJM*. 2002;95:397–403.
6. Solberg LA, Hjermand I, Helgeland A, et al. Association between risk factors and atherosclerotic lesions based on autopsy findings in the Oslo study: a preliminary report. In: Schettler G, Goto Y, Hata Y, et al., editors. *Atherosclerosis IV. proc 4. int. symp.* Berlin: Springer Verlag; 1977. p. 98–100.
7. Anderson KM, Castelli WP, Levy D. Cholesterol and mortality. 30 years of follow-up from the framingham study. *JAMA*. 1987;257:2176–2180.
8. LaRosa JC, Hunninghake D, Bush D, et al. The cholesterol facts. A summary of the evidence relating dietary fats, serum cholesterol, and coronary heart disease. A joint statement by the American heart association and the national heart, lung, and blood institute. *Circulation*. 1990;81:1721–1733.
9. Kannel WB, Doyle JT, Ostfeld AM, et al. Optimal resources for primary prevention of atherosclerotic diseases. Atherosclerosis study group. *Circulation*. 1984;70:157A–205A.
10. National Research Council Diet and Health. Implications for reducing chronic disease risk. Washington, DC: National Academy Press; 1989.
11. Ravnskov U. Quotation bias in reviews of the diet-heart idea. *J Clin Epidemiol*. 1995;48:713–719.
12. Ravnskov U. High cholesterol may protect against infections and atherosclerosis. *QJM*. 2003;96:927–934.
13. Ulmer H, Kelleher C, Diem G, et al. Why Eve is not adam: prospective follow-up in 149650 women and men of cholesterol and other risk factors related to cardiovascular and all-cause mortality. *J Womens Health*. 2004;13:41–53.
14. Prospective Studies Collaboration. Blood cholesterol and vascular mortality by age, sex, and blood pressure: a meta-analysis of individual data from 61 prospective studies with 55 000 vascular deaths. *Lancet*. 2007;370:1829–1839.
15. Okuyama H, Hamazaki T, Ogushi Y. New cholesterol guidelines for longevity (2010). *World Rev Nutr Diet*. 2011;102:124–136.
16. Hecht HS, Superko HR. Electron beam tomography and national cholesterol education program guidelines in asymptomatic women. *J Am Coll Cardiol*. 2001;37:1506–1511.

17. Fernández-Friera L, Fuster V, López-Melgar B, et al. Normal LDL-cholesterol levels are associated with subclinical atherosclerosis in the absence of risk factors. *JACC*. 2017;70:2979–2991.
18. Dimsdale JE, Herd A. Variability of plasma lipids in response to emotional arousal. *Psychosom Med*. 1982;44:413–430.
19. Rosenman RH. Relationships of neurogenic and psychological factors to the regulation and variability of serum lipids. *Stress Med*. 1993;9:133–140.
20. Sachdeva A, Cannon CP, Deedwania PC, et al. Lipid levels in patients hospitalized with coronary artery disease: an analysis of 136,905 hospitalizations in get with the guidelines. *Am Heart J*. 2009;157:111–117.
21. Al-Mallah MH, Hatahet H, Cavalcante JL, et al. Low admission LDL-cholesterol is associated with increased 3-year all-cause mortality in patients with non-ST segment elevation myocardial infarction. *Cardiol J*. 2009;16:227–233.
22. Ravnskov U, McCully KS. Vulnerable plaque formation from obstruction of vasa vasorum by homocysteinylated and oxidized lipoprotein aggregates complexed with microbial remnants and LDL autoantibodies. *Ann Clin Lab Sci*. 2009;39:3–16.
23. Ravnskov U, McCully KS. Infections may be causal in the pathogenesis of atherosclerosis. *Am J Med Sci*. 2012;344:391–394.
- **A more likely CVD hypothesis**
24. Ravnskov U, Rosch PJ, McCully KS. The statin-low cholesterol-cancer conundrum. *QJM*. 2012;105:383–388.
25. Parkin DM. The global health burden of infection-associated cancers in the year 2002. *Int J Cancer*. 2006;118:3030–3044.
26. Ravnskov U, Diamond DM, Hama R, et al. Lack of an association or an inverse association between low-density-lipoprotein cholesterol and mortality in the elderly: a systematic review. *BMJ Open*. 2016;6:e010401.
- **This review should have stopped statin treatment of elderly people because in 92% of the participants of 19 observational studies those with the highest LDL-C lived the longest and none of them found the opposite.**
27. Bathum L, Depont Christensen R, Engers Pedersen L, et al. Association of lipoprotein levels with mortality in subjects aged 50+ without previous diabetes or cardiovascular disease: a population-based register study. *Scand J Prim Health Care*. 2013;31:172–180.
28. Hamazaki T, Okuyama H, Ogushi Y, et al. Towards a paradigm shift in cholesterol treatment. A re-examination of the cholesterol issue in Japan. *Ann Nutr Metab*. 2015;66(suppl 4):1–116.
29. Burgess S, Timpson NJ, Ebrahim S, et al. Mendelian randomization: where are we now and where are we going? *Int J Epidemiol*. 2015;44:379–388.
30. West of Scotland Coronary Prevention Study Group. Influence of pravastatin and plasma lipids on clinical events in the West of Scotland Coronary Prevention Study (WOSCOPS). *Circulation*. 1998;97:1440–1445.
31. Sacks FM, Moyé LA, Davis BR, et al. Relationship between plasma LDL concentrations during treatment with pravastatin and recurrent coronary events in the cholesterol and recurrent events trial. *Circulation*. 1998;97:1446–1452.
32. Schwartz GG, Olsson AG, Ezekowitz MD, et al. Effects of atorvastatin on early recurrent ischemic events in acute coronary syndromes: the MIRACL study: a randomized controlled trial. *JAMA*. 2001;285:1711–1718.
33. Cordoba G, Schwartz L, Woloshin S, et al. Definition, reporting and interpretation of composite outcomes in clinical trials: systematic review. *BMJ*. 2010;341:c3920.
34. Diamond DM, Ravnskov U. How statistical deception created the appearance that statins are safe and effective in primary and secondary prevention of cardiovascular disease. *Expert Rev Clin Pharmacol*. 2015;8:201–210.
- **This review demonstrates the many illegitimate ways by which the results from the statin trials are presented.**
35. Shepherd J, Cobbe SM, Ford I, et al. Prevention of coronary heart disease with pravastatin in men with hypercholesterolemia. West of Scotland coronary prevention study group. *N Engl J Med*. 1995;333:1301–1307.
36. Downs JR, Clearfield M, Weis S, et al. Primary prevention of acute coronary events with lovastatin in men and women with average cholesterol levels: results of AFCAPS/TexCAPS. air force/Texas coronary atherosclerosis prevention study. *JAMA*. 1998;279:1615–1622.
37. Sever PS, Dahlof B, Poulter NR, et al. Prevention of coronary and stroke events with atorvastatin in hypertensive patients who have average or lower-than-average cholesterol concentrations, in the Anglo-Scandinavian Cardiac Outcomes Trial—lipid Lowering Arm (ASCOT-LLA): a multicentre randomised controlled trial. *Lancet*. 2003;361:1149–1158.
38. Colhoun HM, Betteridge DJ, Durrington PN, et al. Primary prevention of cardiovascular disease with atorvastatin in type 2 diabetes in the Collaborative Atorvastatin Diabetes Study (CARDS): multicentre randomised placebo-controlled trial. *Lancet*. 2004;364:685–696.
39. Nakamura H, Arakawa K, Itakura H, et al. Primary prevention of cardiovascular disease with pravastatin in Japan (MEGA study): a prospective randomised controlled trial. *Lancet*. 2006;368:1155–1163.
40. Knopp RH, d'Emden M, Smilde JG, et al. Efficacy and safety of atorvastatin in the prevention of cardiovascular end points in subjects with type 2 diabetes: the atorvastatin study for prevention of coronary heart disease endpoints in non-insulin-dependent diabetes mellitus (ASPEN). *Diabetes Care*. 2006;29:1478–1485.
41. Ridker PM, Danielson E, Fonseca FA, et al. Rosuvastatin to prevent vascular events in men and women with elevated C-reactive protein. *N Engl J Med*. 2008;359:2195–2207.
42. Yusuf S, Bosch J, Dagenais G, et al. Cholesterol lowering in intermediate-risk persons without cardiovascular disease. *N Engl J Med*. 2016;374:2021–2031.
43. Scandinavian Simvastatin Survival Study Group. Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian simvastatin survival study (4S). *Lancet*. 1994;344:1383–1389.
44. Sacks FM, Pfeffer MA, Moye LA, et al. The effect of pravastatin on coronary events after myocardial infarction in patients with average cholesterol levels. cholesterol and recurrent events trial investigators. *N Engl J Med*. 1996;335:1001–1009.
45. The Post Coronary Artery Bypass Graft Trial Investigators. The effect of aggressive lowering of low-density lipoprotein cholesterol levels and low-dose anticoagulation on obstructive changes in saphenous-vein coronary-artery bypass grafts. *N Engl J Med*. 1997;336:153–162.
46. Tonkin A, Alyward P, Colquhoun D, et al. Prevention of cardiovascular events and death with pravastatin in patients with coronary heart disease and a broad range of initial cholesterol levels. *N Engl J Med*. 1998;339:1349–1357.
47. GISSI Prevenzione Investigators. Results of the low-dose (20 mg) pravastatin GISSI Prevenzione trial in 4271 patients with recent myocardial infarction: do stopped trials contribute to overall knowledge? GISSI Prevenzione Investigators (Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico). *Ital Heart J*. 2000;1:810–820.
48. Serruys PW, de Feyter P, Macaya C, et al. Fluvastatin for prevention of cardiac events following successful first percutaneous coronary intervention: a randomized controlled trial. *JAMA*. 2002;287:3215–3222.
49. Heart Protection Study Collaborative Group. MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20 536 high-risk individuals: a randomised placebo-controlled trial. *Lancet*. 2002;360:7–22.
50. Athyros VG, Papageorgiou AA, Mercouris BR, et al. Treatment with atorvastatin to the national cholesterol educational program goal versus 'usual' care in secondary coronary heart disease prevention. The GREek Atorvastatin and Coronary-heart-disease Evaluation (GREACE) study. *Curr Med Res Opin*. 2002;18:220–228.
51. Shepherd J, Blauw GJ, Murphy MB, et al. Pravastatin in elderly individuals at risk of vascular disease (PROSPER): a randomised controlled trial. *Lancet*. 2002;360:1623–1630.
52. The Allhat Officers and Coordinators for the ALLHAT collaborative research group. Major outcomes in moderately

- hypercholesterolemic, hypertensive patients randomized to pravastatin vs usual care: the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT-LLT). *JAMA*. 2002;288:2998–3007.
53. Cannon CP, Braunwald E, McCabe CH, et al. Intensive versus moderate lipid lowering with statins after acute coronary syndromes. *N Engl J Med*. 2004;350:1495–1504.
 54. de Lemos JA, Blazing MA, Wiviott SD et al. Early intensive vs a delayed conservative simvastatin strategy in patients with acute coronary syndromes: phase Z of the A to Z trial. *JAMA*. 2004;292:1307–1316.
 55. Koren MJ, Hunninghake DB. ALLIANCE investigators. Clinical outcomes in managed-care patients with coronary heart disease treated aggressively in lipid-lowering disease management clinics: the ALLIANCE study. *J Am Coll Cardiol*. 2004;44:1772–1779.
 56. LaRosa JC, Grundy SM, Waters DD, et al. Intensive lipid lowering with atorvastatin in patients with stable coronary disease. *N Engl J Med*. 2005;352:1425–1435.
 57. Pedersen TR, Faergeman O, Kastelein JJ, et al. High-dose atorvastatin vs usual-dose simvastatin for secondary prevention after myocardial infarction: the IDEAL study: a randomized controlled trial. *JAMA*. 2005;294:2437–2445.
 58. Amarenco P, Bogousslavsky J, Callahan A 3rd, et al. Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) investigators. High-dose atorvastatin after stroke or transient ischemic attack. *N Engl J Med*. 2006;355:549–559.
 59. Study of the Effectiveness of Additional Reductions in Cholesterol and Homocysteine (SEARCH) Collaborative Group. Intensive lowering of LDL cholesterol with 80 mg versus 20 mg simvastatin daily in 12 064 survivors of myocardial infarction: a double-blind randomised trial. *Lancet*. 2010;376:1658–1669.
 60. Bradford RH, Shear CL, Chremos AN, et al. Expanded Clinical Evaluation of Lovastatin (EXCEL) study results. I. Efficacy in modifying plasma lipoproteins and adverse event profile in 8245 patients with moderate hypercholesterolemia. *Arch Intern Med*. 1991;151:43–49.
 61. Dujovne CA, Chremos AN, Pool JL, et al. Expanded clinical evaluation of lovastatin (EXCEL) study results: IV. Additional perspectives on the tolerability of lovastatin. *Am J Med*. 1991;91:255–305.
 62. Wanner C, Krane V, März W, et al. Atorvastatin in patients with type 2 diabetes mellitus undergoing hemodialysis. *N Engl J Med*. 2005;353:238–248. Erratum in: *N Engl J Med* 2005;353:1640
 63. Strandberg TE, Pitkala KH, Berglund S, et al. Multifactorial intervention to prevent recurrent cardiovascular events in patients 75 years or older: the Drugs and Evidence-Based Medicine in the Elderly (DEBATE) study: a randomized, controlled trial. *Am Heart J*. 2006;152:585–592.
 64. Kjekshus J, Apetrei E, Barrios V, et al. Rosuvastatin in older patients with systolic heart failure. *N Engl J Med*. 2007;357:2248–2261.
 65. Deedwania P, Stone PH, Bairey Merz CN, et al. Effects of intensive versus moderate lipid-lowering therapy on myocardial ischemia in older patients with coronary heart disease: results of the Study Assessing Goals in the Elderly (SAGE). *Circulation*. 2007;115:700–707.
 66. Rossebø AB, Pedersen TR, Boman K, et al. Intensive lipid lowering with simvastatin and ezetimibe in aortic stenosis. *N Engl J Med*. 2008;359:1343–1356.
 67. Tavazzi L, Maggioni AP, Marchioli R, et al. Effect of rosuvastatin in patients with chronic heart failure (the GISSI-HF trial): a randomised, double-blind, placebo-controlled trial. *Lancet*. 2008;372:1231–1239.
 68. Fellström BC, Jardine AG, Schmieder RE, et al. Rosuvastatin and cardiovascular events in patients undergoing hemodialysis. *N Engl J Med*. 2009;360:1395–1407. Erratum in: *N Engl J Med*. 2010;362:1450.
 69. Cannon CP, Blazing MA, Giugliano RP, et al. Ezetimibe added to statin therapy after acute coronary syndromes. *N Engl J Med*. 2015;372:2387–2397.
 70. Cholesterol Treatment Trialists' (CTT) Collaboration. Efficacy and safety of LDL-lowering therapy among men and women: meta-analysis of individual data from 174 000 participants in 27 randomised trials. *Lancet*. 2015;385:1397–1405.
 71. Kristensen ML, Christensen PM, Hallas J. The effect of statins on average survival in randomised trials, an analysis of end point postponement. *BMJ Open*. 2015;5:e007118.
- **This study demonstrates that primary prevention with statin treatment is only able to prolong the life with a few days.**
72. de Lorgeril M, Rabaeus M. Beyond confusion and controversy, can we evaluate the real efficacy and safety of cholesterol-lowering with statins? *J Controvers Biomed Res*. 2015;1:67–92.
 73. Phillips PS, Haas RH, Bannykh S, et al. Statin-associated myopathy with normal creatine kinase levels. *Ann Intern Med*. 2002;137:581–585.
 74. Sinzinger H, O'Grady J. Professional athletes suffering from familial hypercholesterolaemia rarely tolerate statin treatment because of muscular problems. *Br J Clin Pharmacol*. 2004;57:525–528.
 75. Okuyama H, Langsjoen PH, Hamazaki T, et al. Statins stimulate atherosclerosis and heart failure: pharmacological mechanisms. *Expert Rev Clin Pharmacol*. 2015;8:189–199.
- **A detailed description of the many ways by which the statins destroy our cells.**
76. Hippisley-Cox J, Coupland C. Unintended effects of statins in men and women in England and Wales: population based cohort study using the QResearch database. *BMJ*. 2010;340:c2197.
 77. Chung SD, Chen CH, Hung SH, et al. A population-based study on the association between statin use and sudden sensorineural hearing loss. *Otolaryngol Head Neck Surg*. 2015;152:319–325.
 78. Davison KM, Kaplan BJ. Lipophilic statin use and suicidal ideation in a sample of adults with mood disorders. *Crisis*. 2014;35:278–282.
 79. Gaist D, Jeppesen U, Andersen M, et al. Statins and risk of polyneuropathy: a case-control study. *Neurology*. 2002;58:1333–1337.
 80. Kang JH, Kao LT, Lin HC, et al. Statin use increases the risk of depressive disorder in stroke patients: a population-based study. *J Neurol Sci*. 2015;348:89–93.
 81. Huang X, Alonso A, Guo X, et al. Statins, plasma cholesterol, and risk of Parkinson's disease: a prospective study. *Mov Disord*. 2015;30:552–559.
 82. Huang CY, Chung SD, Kao LT, et al. Statin use is associated with bladder pain syndrome/interstitial cystitis: a population-based case-control study. *Urol Int*. 2015;95:227–232.
 83. Antoniou T, Zheng H, Singh S, et al. Statins and the risk of herpes zoster: a population-based cohort study. *Clin Infect Dis*. 2014;58:350–356.
 84. Solomon H, Samarasinghe YP, Feher MD, et al. Erectile dysfunction and statin treatment in high cardiovascular risk patients. *Int J Clin Pract*. 2006;60:141–145.
 85. Evans MA, Golomb BA. Statin-associated adverse cognitive effects: survey results from 171 patients. *Pharmacotherapy*. 2009;29:800–811.
 86. Padala KP, Padala PR, McNeilly DP, et al. The effect of HMG-CoA reductase inhibitors on cognition in patients with Alzheimer's dementia: a prospective withdrawal and rechallenge pilot study. *Am J Geriatr Pharmacother*. 2012;10:296–302.
 87. Muldoon MF, Barger SD, Ryan CM, et al. Effects of lovastatin on cognitive function and psychological well-being. *Am J Med*. 2000;108:538–546.
 88. Muldoon MF, Ryan CM, Sereika SM, et al. Randomized trial of the effects of simvastatin on cognitive functioning in hypercholesterolemic adults. *Am J Med*. 2004;117:823–829.
 89. Cederberg H, Stančáková A, Yaluri N, et al. Increased risk of diabetes with statin treatment is associated with impaired insulin sensitivity and insulin secretion: a 6 year follow-up study of the METSIM cohort. *Diabetologia*. 2015;58:1109–1117.
 90. Mansi I, Frei CR, Wang CP, et al. Statins and new-onset diabetes mellitus and diabetic complications: a retrospective cohort study of US healthy adults. *J Gen Intern Med*. 2015;30:1599–1610.
 91. Newman TB, Hulley SB. Carcinogenicity of lipid-lowering drugs. *JAMA*. 1996;275:55–60.
 92. Sabatine MS, Giugliano RP, Keech AC, et al. Evolocumab and clinical outcomes in patients with cardiovascular disease. *N Engl J Med*. 2017;376:1713–1722.

93. Scientific steering committee on behalf of the simon broome register group. Risk of fatal coronary heart disease in familial hypercholesterolaemia. *BMJ*. 1991;303:893–896.
94. Mundal L, Saranic M, Ose L, et al. Mortality among patients with familial hypercholesterolemia: a registry-based study in Norway, 1992–2010. *JAMA*. 2014;3:e001236.
95. Seed M, Hoppichler F, Reaveley D, et al. Relation of serum lipoprotein(a) concentration and apolipoprotein(a) phenotype to coronary heart disease in patients with familial hypercholesterolemia. *N Engl J Med*. 1990;322:1494–1499.
96. Wiklund O, Angelin B, Olofsson SO, et al. Apolipoprotein(a) and ischaemic heart disease in familial hypercholesterolaemia. *Lancet*. 1990;335:1360–1363.
97. Vuorio AF, Turtola H, Piilhti KM, et al. Familial hypercholesterolemia in the finnish north Karelia. A molecular, clinical, and genealogical study. *Arterioscler Thromb Vasc Biol*. 1997;17:3127–3138.
98. Wittekoek ME, de Groot E, Prins MH, et al. Differences in intima-media thickness in the carotid and femoral arteries in familial hypercholesterolemic heterozygotes with and without clinical manifestations of cardiovascular disease. *Atherosclerosis*. 1999;146:271–279.
99. Smilde TJ, Trip MD, Wollersheim H, et al. Rationale, design and baseline characteristics of a clinical trial comparing the effects of robust vs conventional cholesterol lowering and intima media thickness in patients with familial hypercholesterolaemia: the atorvastatin versus simvastatin on atherosclerosis progression (ASAP) study. *Clin Drug Investig*. 2000;20:67–79.
100. Cenarro A, Artieda M, Castillo S, et al. A common variant in the ABCA1 gene is associated with a lower risk for premature coronary heart disease in familial hypercholesterolaemia. *J Med Genet*. 2003;40:163–168.
101. Harlan WR, Graham JB, Estes EH. Familial hypercholesterolemia: a genetic and metabolic study. *Medicine*. 1966;45:77–110.
102. Nilsson S, Mölstad S, Karlberg C, et al. No connection between the level of exposition to statins in the population and the incidence/mortality of acute myocardial infarction: an ecological study based on Sweden's municipalities. *J Negat Results Biomed*. 2011;10:6.
103. Kuklina EV, Yoon PW, Keenan NL. Trends in high levels of low-density lipoprotein cholesterol in the United States, 1999–2006. *JAMA*. 2009;302:2104–2110.
104. Vancheri F, Backlund L, Strender LE, et al. Time trends in statin utilisation and coronary mortality in Western European countries. *BMJ Open*. 2016;6:e010500.
105. Okuyama H, Hamazaki T, Hama R, et al. A critical review of the consensus statement from the European atherosclerosis society consensus panel 2017. *Pharmacology*. 2018;101:184–218.
106. Vallejo-Vaz AJ, Robertson M, Catapano AL, et al. LDL-cholesterol lowering for the primary prevention of cardiovascular disease among men with primary elevations of LDL-cholesterol levels of 190 mg/dL or above: analyses from the WOSCOPS 5-year randomised trial and 20-year observational follow-up. *Circulation*. 2017;136:1878–1891.
107. Ravnskov U, Okuyama H, Sultan S. Serious bias in 20 year follow-up study of statin trial. *BMJ*. 2017;359:j4906.