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Perspective

LDL-C Does Not Cause Cardiovascular Disease: a comprehensive review of current literature

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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 paper 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.

Key words. 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, if 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 CVD.

2. Does high TC cause atherosclerosis?

2.1 No association between TC and degree of atherosclerosis.

If high 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; e.g. the arteries of those whose lipid values are lowered the most should benefit the most. However, in a review of sixteen 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 US 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 twelve papers with such findings were searched for in the three reviews [11]. Only two of the papers were quoted correctly, and only in one of the reviews. About half of the contradictory papers were ignored. In the rest, statistically non-significant findings in favor of the cholesterol hypothesis were inflated, and unsupportive results were quoted as if they were supportive. Only one of 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 twelve such studies [12]. A 2004 Austrian study [13] published 2004 including 67,413 men and 82,237 women who had been followed for many years found that TC was weakly associated with coronary heart disease (CHD) mortality for men, except for those between age 50-64. For women, it was weakly associated among those below the age of 50 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.

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 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, 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 three 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; e.g. 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 upon 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; e.g., 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 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 (MVE) 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 two of 100 participants in the control group die but only one of 100 in the treatment group die, the absolute risk reduction (ARR) is only a one percent 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 eleven trials that they excluded [60-69]. As seen from figure 1 and 2 there was a weak, positive association in the included trials; whereas the association was inverse in the ignored trials.

Table 1, figure 1 and figure 2

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 5A, that illustrates the association, the authors have only included data from12 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.

Figure 3

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% per 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 paper, 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% per year per mmol/l reduction of LDL-C, respectively. However, as mentioned, they excluded at least eleven 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 as regards 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 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 US 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.

Figure 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 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 ten 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 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 PCSK-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 (PCSK9), 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 percent 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. 4,688 individuals aged 0-92 with FH were followed 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 who survived (88.2% versus 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 of 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 acute myocardial infarction (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, by exclusion of unsuccessful trials, by minimizing the side effects of cholesterol lowering, and by 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], 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 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.

12. 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.

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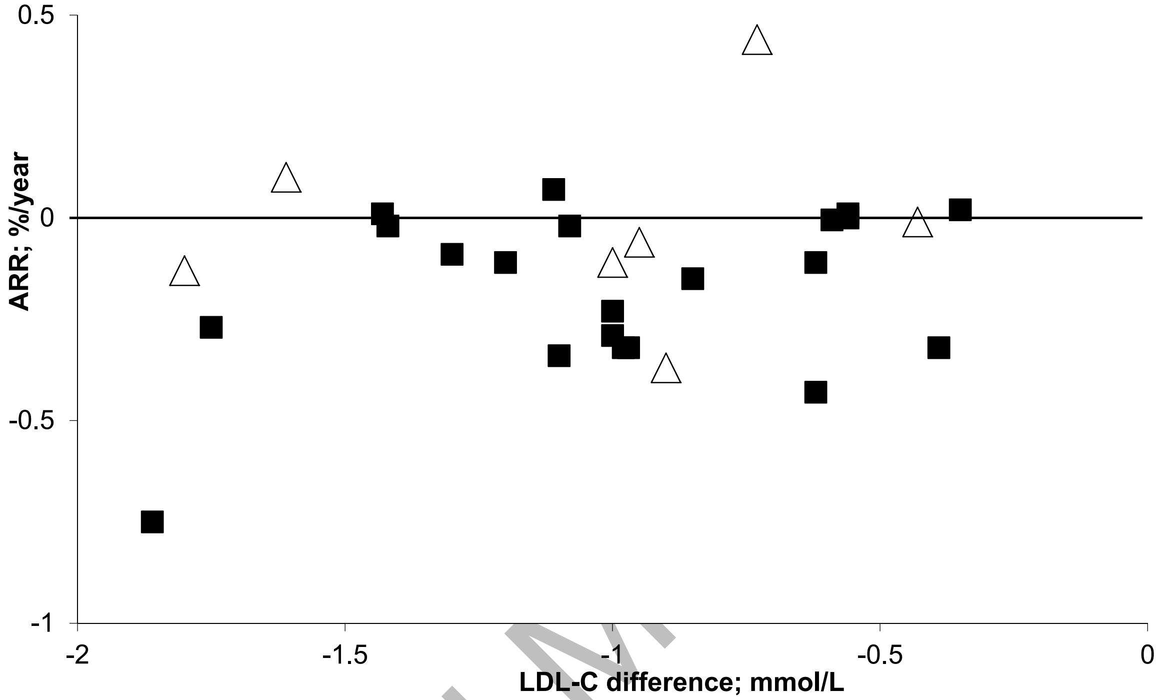
Declaration of Interest

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.

Figure 1. The association between degree of LDL-C lowering and the absolute risk reduction of CHD mortality (per cent per 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. ARR is associated with degree of LDL-C lowering in the included 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 (per cent per 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.

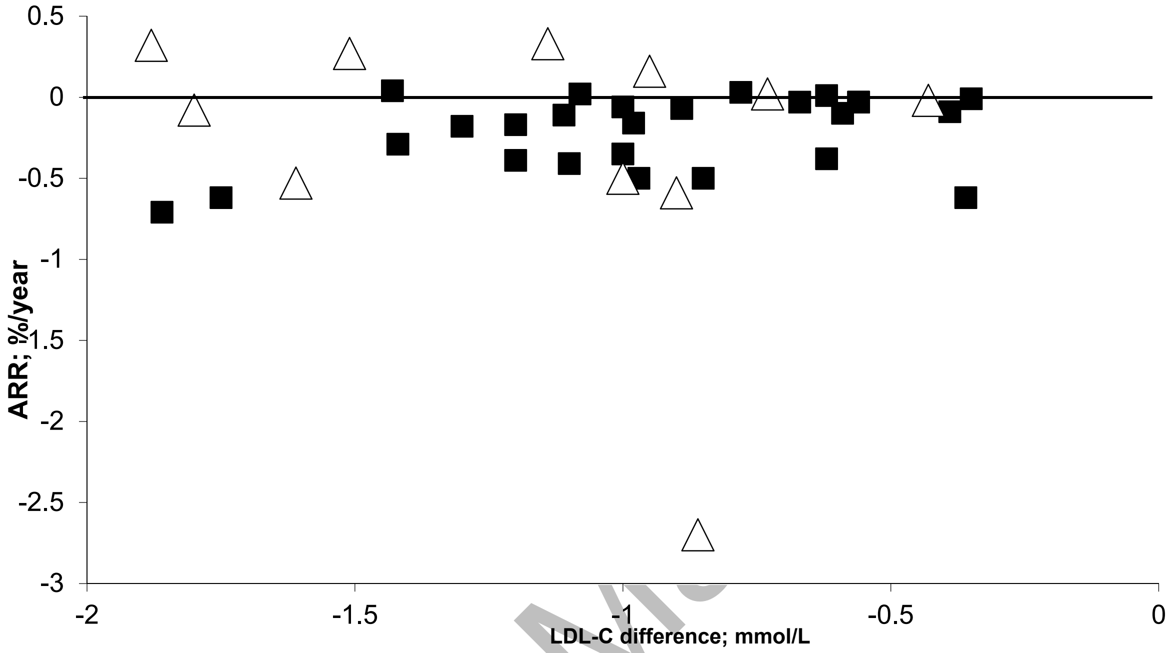
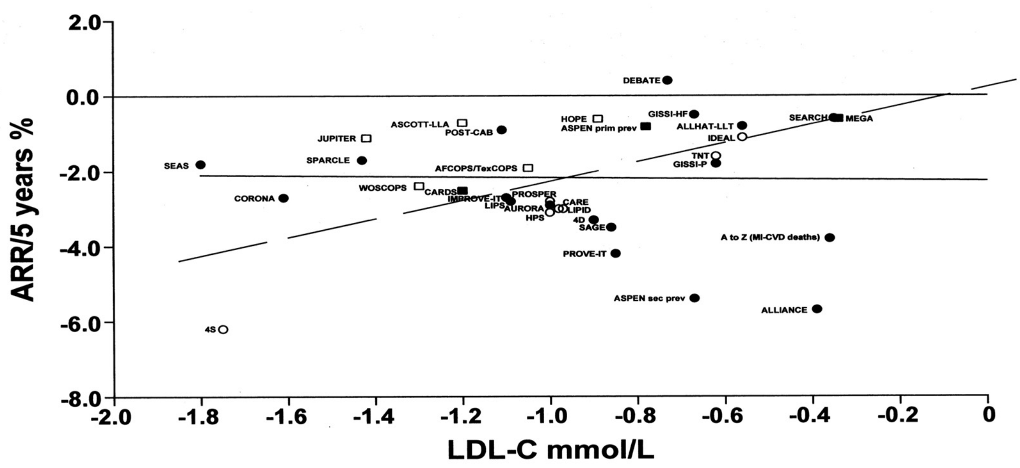


Figure 3. The association between the absolute five-year risk reduction (ARR) and the degree of LDL-C lowering in 12 trials included in table 4A in the paper by Ference et al. (r = 2.59) and from 21 trials they have ignored or excluded (r = -0.1).



White symbols: Trials included in the analysis by Ference et al. Black symbols: Excluded or ignored trials. Squares: Primary-preventive trials. Round symbols: Secundary-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 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

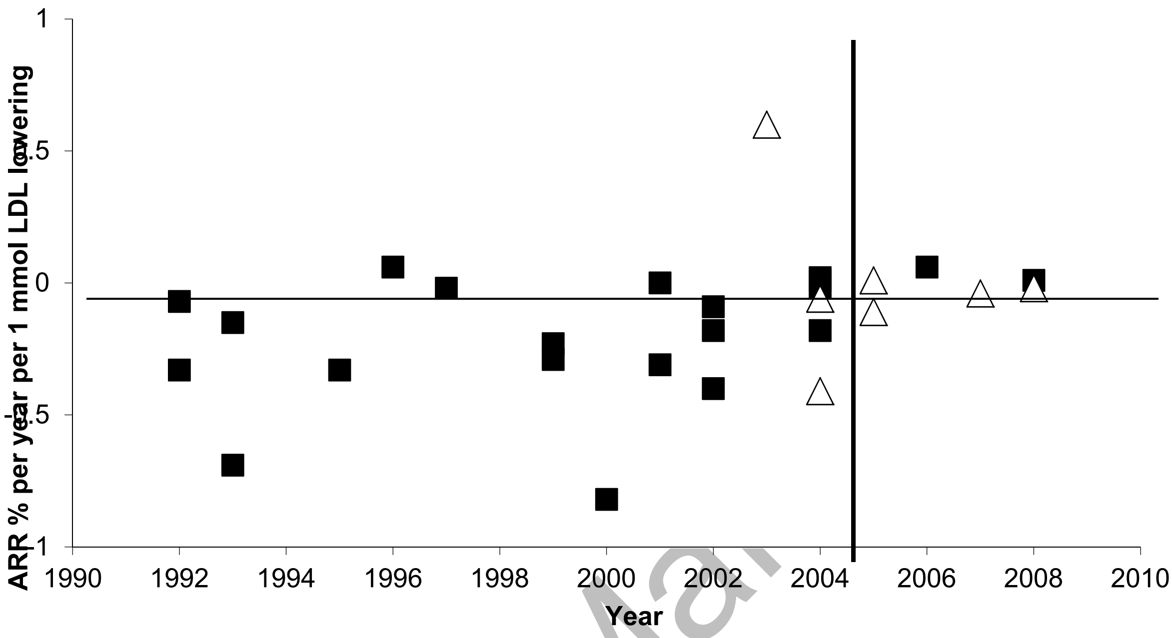


Figure 5. The association between the absolute risk reduction of total mortality in 26 statin trials included in the study by Silverman et al. and in 11 ignored trials; and the year where the trial protocols were published. The vertical line indicates the year where the new trial regulations were introduced.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

Statin trials	Length	Number of participants	Mortality (%)	ARR %	ARR per year (%)	ΔLDL-C

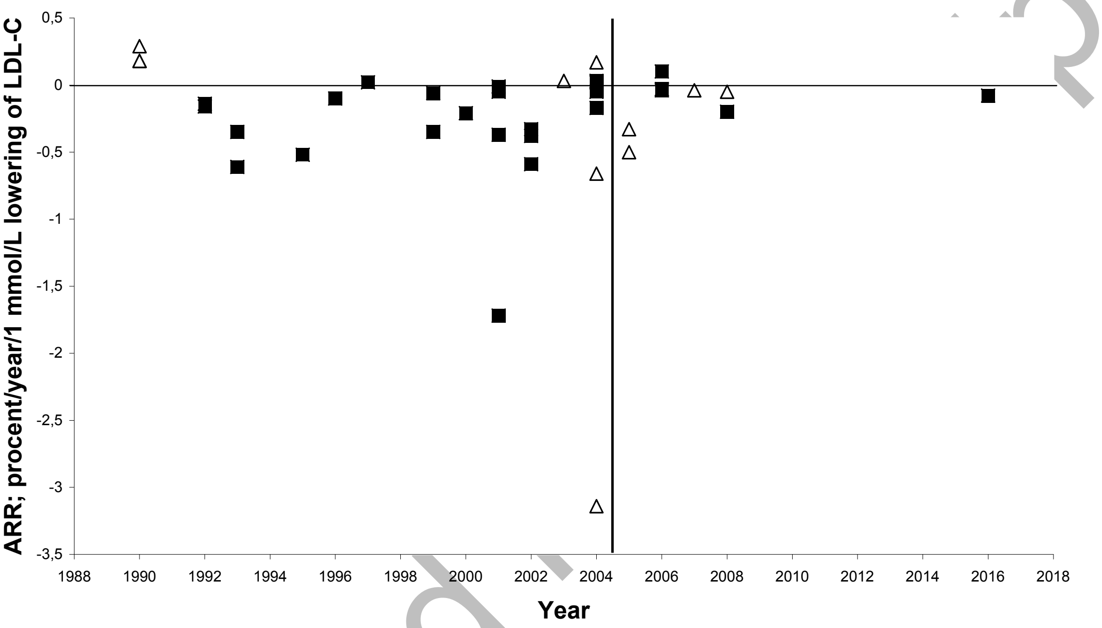


Table 1. Mortality in the statin trials included in the meta-analysis by Silverman et al. [2] and in 11 statin trials they have ignored and where the authors have reported coronary and/or total mortality. The figures for LDL-C lowering are the approximate mean differences between the treatment group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

		(years)	T/C	T/C			mmol/l
Primary-preventive trials included in the meta-analysis by Silverman et al. [2]							
WOSCOPS [35]	CM	4.9	3,302/3,293	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	3,304/3,301	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	5,168/5,137	3.58/4.13	-0.55	-0.17	-1.20
CARDS [38]	CM	3.95	1,428/1,410	1.26/1.70	-0.44	-0.11	-1.20
	TM			4.27/5.82	-1.55	-0.39	
MEGA¶ [39]	CM	5.3	3,866/3,966	0.051/0.076	-0.032	-0.005	-0.59
	TM			1.11/1.66	-0.55*	-0.10	
ASPEN prim. prev. [40]	TM	4	959/946	4.6/4.3	+0.3	+0.08	-0.78
JUPITER [41]	CM	1.9	8,901/8,901	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	6,361/6,344	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	2,221/2,223	1.35/2.83	-1.48***	-0.27	-1.75
	TM			8.19/11.5	-3.33***	-0.62	
CARE [44]	CM	5	2,081/2,078	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	4,512/4,502	6.36/8.29	-1.92***	-0.32	-0.97
	TM			11.04/14.06	-3.02***	-0.50	
GISSI-P [47]	CM	2	2,138/2,133	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¶ [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	2,891/2,913	3.25/4.19	-0.94*	-0.29	-1.0
	TM			10.31/10.50	-0.20	-0.06	
ALLHAT-LLT¶ [52]	CM	4.8	5,170/5,185	3.09/3.12	-0.03	0	-0.56
	TM			12.21/12.36	-0.15	-0.03	
PROVE-IT [53]	CM	2	2,099/2,063	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	2,265/2,232	4.59/5.82	-1.23	-0.62	-0.36
ALLIANCE¶ [55]	CM	4.3	1,217/1,225	3.53/4.98	-1.45	-0.32	-0.39
	TM			9.94/10.37	-0.43	-0.09	
TNT [56]	CM	4.9	4,995/5,006	2.02/2.54	-0.52	-0.11	-0.62
	TM			5.69/5.63	+0.06	+0.01	
IDEAL [57]	CM	4.8	4,439/4,449	4.0/3.94	+0.06	+0.01	-0.56
	TM			8.25/8.41	-0.16	-0.03	

SPARCL [58] CM TM	4.9	2,365/2,366	1.69/1.64 9.13/8.92	+0.04 +0.21	+0.01 +0.04	-1.43
ASPEN sec. prev. [40] TM	4	252/253	10.32/10.67	-0.35	-0.03	-0.67
SEARCH [59] CM TM	6.7	6,031/6,033	7.41/7.28 15.98/16.08	+0.14 -0.1	+0.02 -0.01	-0.35
Trials ignored by Silverman et al.						
EXCEL 20 mg/day [60,61] TM	0.92	1,642/1,663	0.5/0.2	+0.3	+0.33	-1.14
EXCEL 40 mg/day [60,61] TM	0.92	3,291/1,663	0.45/0.2	+0.25	+0.27	-1.51
EXCEL 80 mg/day [60,61] TM	0.92	1,649/1,663	0.5/0.2	+0.3	+0.33	-1.88
4D [62] CM TM	3.93	619/636	3.72/5.19 47.98/50.31	-1.47 -2.33	-0.37 -0.59	-0.9
DEBATE¶ [63] CM TM	3.4	199/201	7.5/6.0 18.1/17.4	+1.5 +0.07	+0.44 +0.02	-0.73
CORONA [64] CM TM	2.7	2,514/2,497	0.36/0.32 28.96/30.40	+0.04 -1.44	+0.01 -0.53	-1.61
SAGE [65] CM TM	1	446/445	0.4/1.3 1.34/4.04	-0.9 -2.70*	-0.9 -2.70	-0.86
SEAS [66] CM TM	4.35	944/929	0.53/1.08 11.12/10.76	-0.55 +0.36	-0.13 -0.08	-1.80
GISSI-HF [67] CM TM	3.9	2,285/2,289	0.44/0.66 28.75/28.13	-0.22 +0.62	-0.06 +0.16	-0.95
AURORA [68] CM TM	3.8	1,389/1,384	14.69/15.10 45.79/47.69	-0.41 -1.90	-0.11 -0.50	-1
IMPROVE-IT [69] CM TM	7	9,067/9,077	0.45/0.54 13.4/13.56	-0.09 -0.16	-0.01 -0.02	-0.43
Total number		112,599/110,981				

CM: Coronary mortality; TM: Total mortality; ARR: Absolut risk reduction; T: Treatment group or high-dose group; C: Control group or low-dose group. *: p<0.05; **: p<0.01; ***: p<0.001; ¶: Probably unblinded because no placebo-group was included; i.e. the treatment group was compared with “Usual care”.

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