

Misleading Recent Papers on Statin Drugs in Peer-Reviewed Medical Journals

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ABSTRACT

Three papers on clinical trials with statin drugs, published in 2004–2006, imply that the observed improvement in selected trial endpoints result from gross reductions in serum total cholesterol (TC) and cholesterol carried by low-density lipoprotein (LDL-C), despite evidence to the contrary, which was not cited in these papers.

The ASTEROID trial that showed atherosclerotic plaque reduction by rosuvastatin neglected to discuss the decrease in lumen size. The A to Z trial that promoted the use of higher doses of simvastatin rather than much lower doses arbitrarily eliminated subjects with both “high or low” LDL-C levels, favoring the higher dose. A retrospective study of statin-using compared with non-statin-using U.S. veterans, which was said to show longer lifespan in statin users, had non-equivalent treatment and control groups, favoring statin use.

Newspaper or television interviews with principal trial investigators contained statements that were far more positive than warranted by the trial results reported.

Introduction

Wider recognition of the problems with peer-reviewed papers in medical journals, especially those on clinical trials of new drugs, has done little so far to improve their quality.¹ Reports on studies on the antihyperlipidemic drugs called statins continue to appear in which the main emphasis is on lowering serum levels of total cholesterol (TC) and of cholesterol carried by low-density lipoprotein (LDL-C), the latter often called “bad cholesterol.” Decisions about prescribing statin drugs are usually made on the basis of “elevated” TC or LDL-C. Official guidelines were set at 200 mg/dL for TC and 100 mg/dL for LDL-C in 2001.^{2,3} Minor reductions in nonfatal myocardial infarction rates seen in most statin trials are actually understood to result from mechanisms other than cholesterol lowering, such as limiting production of the eicosanoids thromboxane A2 and B2, which is also an effect of aspirin.²

In the elderly, for whom statins are most commonly prescribed, “high” TC and LDL-C are not risk factors. Quite the opposite is true. In a study of residents of northern Manhattan, N.Y., 2,277 subjects were followed for 10 years. Two-thirds were women. About 30% were non-Hispanic white, 30% black, and 38% Hispanic. Ages ranged from 65–98 years at baseline, with a mean of 76. The chance of dying was twice as great in subjects with the *lowest* quartile of TC or LDL-C levels, compared with those in the highest quartile. The rate ratio (RR) was 1.8 for TC, 95% confidence level (CI) 1.3–2.4. High-density lipoprotein (HDL) and triglyceride levels were not related to all-cause mortality in this age group. See Table 1.

Women had higher baseline TC and LDL-C levels (206 mg/dL and 124 mg/dL, respectively) than men (191 mg/dL and 117 mg/dL), yet the women lived longer. Men with the same TC and LDL-C levels as women lived as long. One-fifth of the subjects were taking statin drugs to lower TC and LDL-C, and this would have pushed them into the lowest quartile.⁵

This study is an excellent confirmation that *high* TC and LDL-C levels are beneficial, certainly in the elderly who are most likely to be given a statin drug. The recent emphasis on the value of lowering

Table 1. Plasma Lipids v. Mortality in 2,277 Non-Demented Elderly

	No. subjects	Deaths (%)	Rate Ratio (RR)
Total cholesterol			
≤175 mg/dL	580	97 (16.7)	1.8
176–199	574	78 (13.6)	1.2
220–226	556	57 (10.3)	0.9
>226	567	59 (10.4)	1.0
LDL cholesterol			
≤ 97.8	572	90 (15.7)	2.0
97.9–144.0	568	83 (14.5)	1.6
120.7–144.0	571	65 (11.4)	1.2
>144.0	566	53 (9.4)	1.0

Adapted from Schupf N et al. 2005⁵ as in Kauffman 2006,⁶ with permission.

LDL-C, rather than lowering TC, promoted by health authorities and drug companies in the last few years, is invalidated by this study.⁶

In 351,000 men aged 35–57 in the MRFIT trial, all-cause mortality rose at TC levels *below* 170 mg/dL, and shot up *below* 140 mg/dL to the same level seen at 300 mg/dL.⁴ Serum TC level is not even predictive of cardiovascular disease (CVD) in men over the age of 47.^{7,8}

The Japan Lipid Intervention Trial (J-LIT), a primary-prevention trial utilizing simvastatin, involved 47,300 Japanese patients. Since Japanese are more sensitive to statin drugs than occidentals are, the dose was 5 mg/d for 90% of the subjects and 10 mg/d for 10%. All were followed for 6 years, including those who stopped the drug, which was open-labeled. There was no placebo group. Those whose TC was *most reduced* (to <160 mg/dL) had the *highest* all-cause death rate. Statin manufacturers often stress that the main “benefit” of statins is to reduce LDL-C rather than TC. Those with the *lowest* achieved levels of LDL-C (to <80 mg/dL) also had the *highest* all-cause death rate. Obviously, there is no reason to reduce TC below 200 mg/dL, or LDL-C below 130 mg/dL. The absolute differences in mortality are quite small, only 0.61% per year from best-to-worst levels of TC, and only 0.30% per year from best-to-worst levels of LDL-C. Here is the best evidence yet that the tiny gains in lifespan shown in some other trials on statin drugs with placebo groups are not explained by TC or LDL-C lowering.¹⁰

In a prospective cohort study in 403 elderly men with 4 years of follow-up, neither TC nor LDL-C had any predictive value for either cardiovascular or total mortality.¹¹

Therefore, in the three papers discussed below on lowering TC and LDL-C levels in elderly men, the emphasis on cholesterol is misplaced. Moreover, no trials have shown any statin drug to confer any survival benefit in men or women over 70 years of age.¹²

ASTEROID Trial

A press release headlined “A Drug is Found to Reduce Plaque in Arteries” claimed that “a statin drug [rosuvastatin] has been shown for the first time to reverse the buildup of plaque in coronary arteries...” and that “the changes in cholesterol levels seen...were the largest ever seen in a major trial of statin drugs....” “The results were shockingly positive,” said Dr. Steven E. Nissen, head author of the paper in *JAMA*.¹³

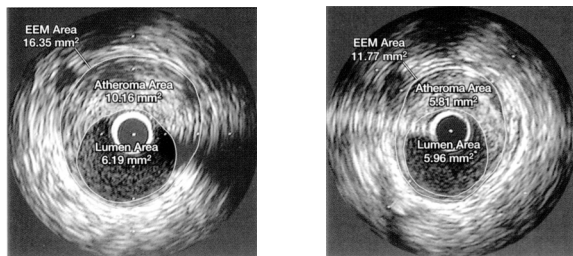


Figure 1. Ultrasound Image of Cross-Section of Coronary Artery Before (left) and After (right) Treatment with Rosuvastatin for 2 Years. (Adapted from Nissen et al., 2006¹⁴, with permission. Originally published in *JAMA*, vol 295, pp 1558-1565, Apr 5, 2006. Copyright 2006, American Medical Association. All rights reserved.)

Intravascular ultrasound examination of coronary arteries before and after high doses of rosuvastatin (at 40 mg/d for 2 years) in 349 patients produced images which showed that plaque “volume” was reduced by 40% in the most diseased arterial segment. Actually the cross-sectional areas of atheroma were compared, and assumed to be directly proportional to their volumes.¹⁴ Actual images of a coronary artery before and after statin treatment in what was said to be a representative case were shown in a figure in the paper, part of which is shown here as Figure 1. No spurious claims were made; we are simply supposed to infer that reduction of atheroma cross-section must be a great benefit, because we expect the area of the lumen to increase proportionally, an obvious benefit. In Figure 1, atheroma area was reduced by more than 40%. What was not discussed in the press release or the article, however, was that the lumen area *decreased* by 4%! The images also show that the arterial wall thickened; this is not necessarily a benefit, since a smaller lumen and a stiffer arterial wall would both tend to increase blood pressure, an effect that was also not addressed in the trial report.¹⁴

In the results section of the abstract, the authors state: “Adverse events were infrequent and similar to other statin trials.” Near the end of the comment section, they state that: “This very intensive statin regimen was well tolerated.”¹⁴ Actually, the total dropout rate was said to have been 12%. Subjects were 70% male, as is also typical of statin trials, in which the subjects are typically 80–100% male, since there is no benefit in women.^{6,7,12}

Funding and author affiliations were well described.

Phase Z of the A to Z Trial

This international, randomized, double-blind trial involved about 4,500 subjects (75–76% male, median age 61) with “acute coronary syndrome” (ACS) and some typical additional risk factors for CVD. The two regimens were: (1) placebo for 4 months followed by 20 mg/d of simvastatin and (2) 40 mg/d simvastatin for 1 month followed by 80 mg/d thereafter. Two years of follow-up were planned. Dropout rates for specific adverse events were said to be 2% for placebo and low-dose simvastatin, and 3% for high-dose simvastatin. Elsewhere it was noted that 32% of the placebo group and 34% of the high-dose group discontinued the trial “prematurely”; these subjects, however, were not considered to be dropouts.¹⁵

At 2 years there were no statistically significant differences in mortality, stroke, or readmission to hospital for ACS; there were barely significant improvements in the high-dose group for heart death and CVD.¹⁵ Dr. James A. de Lemos, lead author and cardiologist at University of Texas Southwestern Medical Center, said: “...even though the difference between the groups was small...it supports the emerging paradigm that lower cholesterol is better.”¹⁶

At first this seemed to be a well-run study with honest reporting of results. But a figure entitled “Patient Disposition” showed that subjects who were excluded had treated LDL-C higher than 130

mg/dL: 20 from the low-dose group and five from the high-dose group. This favored the high-dose group, since, in this age group, an LDL-C higher than 130 mg/dL is more healthful (Table 1). More importantly, patients were also dropped who had LDL-C ≤ 40 mg/L, 13 from the low-dose group, and 88 from the high-dose group. Since such levels are dangerous (as shown in Table 1, and at least three other studies^{6,7}), this also favored the high-dose group by removing from it the subjects at greatest risk. Why was this done if “...lower cholesterol is better”? All subjects with TC > 250 mg/dL at *baseline* were excluded as well.

Also shown in this patient-disposition figure is that 9% of the low-dose group dropped out because of an “...adverse experience or nonfatal end point,” as did 10% of the high-dose group. These numbers do not match the 2–3% adverse-effect claim made earlier in the paper.

We may justifiably suppose that the arbitrary dropping of subjects with the highest TC and LDL-C, as well as those with the lowest levels of LDL-C, biased the results of this trial, perhaps even reversing the results in the low-dose vs. the high-dose group.

Funding and author affiliations were well described.

Exclusion of subjects for “too high or too low” LDL-C levels is not unique to the A to Z Trial. In the SPARCL trial with 80 mg/d of atorvastatin, subjects were excluded who had pre-existing LDL-C levels higher than 190 mg/dL or less than 100 mg/dL. Treated subjects whose LDL-C dropped below 40 mg/dL were re-measured, but there was no explanation of what was done if such low levels were confirmed. Total mortality was slightly greater in the treatment group (9.1% vs. 8.9%) even though the primary outcome of all stroke events favored the drug (11.2% vs. 13.1%).¹⁷

Mortality in U.S. Veterans and Statin Use

A retrospective study was performed using data from 10 Veterans Affairs hospitals in the southern United States on elderly veterans of median age 70. Some 1,261,938 veterans (94% male) did not take statins, while 228,528 (98% male) did, most for 2–5 years. The former had baseline mean TC = 187 mg/dL and LDL-C = 112 mg/dL, while the latter had baseline mean TC = 203 mg/dL and LDL-C = 124 mg/dL. The levels in the latter group were actually more healthful, according to Table 1, although this group was considered much sicker by the authors.¹⁸ The period of observation was not clearly described. Statin use was associated with dying at a mean age of 2 years older, with $P < 0.0001$! See Figure 2.

The statins used were lovastatin (19%), long known to increase mortality rates in the only reported trials^{4,6,7,19,20} and simvastatin (77%), reported to have caused hundreds of premature deaths in both the United Kingdom and the United States.⁶

The greater risk of death before age 54 in non-statin users, with lower TC and LDL-C levels, is not unexpected in view of Table 1. The second point is that a few of the non-statin users lived to be as old as 104, while the statin users had died by age 94 (Figure 2). If statins really were beneficial, the lower bar chart should have a long-lived upper tail, and should not have the observed upward spike in deaths at age 78.

Furthermore, the authors believed that free drugs and physician consults from the VA ensured a high degree of compliance with drug regimens. However, the post-treatment mean of TC in users was 178 mg/dL, a drop of only 12% from 203 mg/dL, far less than the 20–30% drops observed in controlled trials. Similarly, mean LDL-C dropped only to 107 mg/dL, a decrease of only 14% from 124 mg/dL, far less than the 30–40% observed in controlled trials. This does not indicate a high degree of compliance with the drug regimens, but rather a compliance of about 35–50%, which is usual.⁶ The follow-up mean of TC in non-users was 190 mg/dL, and of LDL-C was 115 mg/dL, showing the expected increase with age.⁶

An attempt was made to show a correlation of the “benefits” of statins with conventional risk factors, which looked persuasive at first; however, two of the six risk factors were LDL-C ≥ 100 mg/dL and hypertension as conventionally defined, $\geq 140/90$ mmHg. Since these two risk factors have been shown to be invalid,⁶ the correlation might not have been so neat without them. In any event, the baseline non-equivalence of the two groups (users and non-users of statins) vitiates any claim of value of statin drugs, in my opinion.

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Results such as these are eagerly promoted, but the findings in the PROSPER Trial of pravastatin in the elderly, which was randomized, controlled, and prospective were not, because it showed no significant difference in mortality.²¹

Comment

The problems with these three articles were more subtle than those reviewed in my earlier paper in this journal,²² but they were misleading and bothersome nevertheless. Sophisticated medical science seemingly appeared in all of them, yet, on close examination, was not as rigorous as one would wish. Parts of the press releases based on the two *JAMA* papers were clearly overstated.

Henry Lorin, D.M.D., among others, would like to see the terms “good” and “bad” cholesterol buried.²³ Biochemists agree that LDL-C is the form of cholesterol that is carried to all the cells of the body, an essential function, so it must not be called or considered “bad cholesterol.”^{4,6,7}

Duane Graveline, M.D., M.P.H., wrote an entire book on statin drug side-effects and the misguided war on cholesterol.²⁴ Such side effects are not so much concealed by the statin manufacturers as simply not sought; thus, Bayer, for example, could not give bad news on cerivastatin to the FDA because Bayer claimed not to have any.²⁵

A systematic search of the Cochrane Database of Systematic Reviews, considered by many to be the most objective medical science reporting of all, showed that all of the industry-funded meta-analyses of drugs recommended the experimental drug without reservations, while none of the Cochrane reviews did so, even though the estimated treatment effects were the same in both cases.²⁶ Peter C. Gøtzsche at the Nordic Cochrane Center in Copenhagen, a coauthor of the meta-analyses report, said in an interview that he would now ignore any meta-analyses funded by drug companies.²⁷

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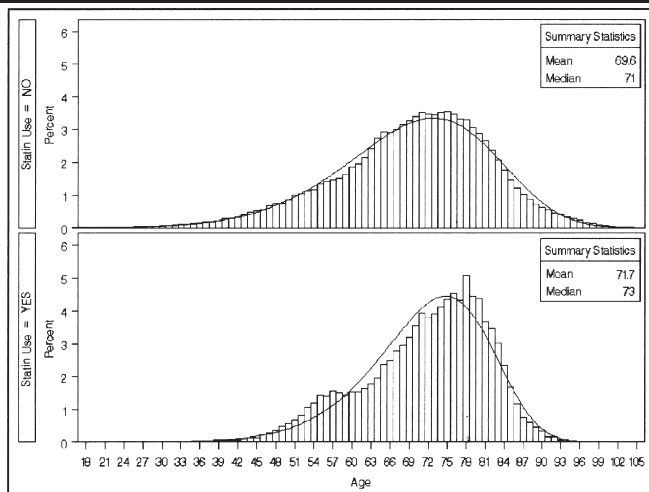


Figure 2. Age Distribution at Death in VA Study of Statin Nonusers and Users. (Reprinted from Mehta, et al.¹⁸, with permission from Elsevier.)