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Effect of the Magnitude of Lipid Lowering on Risk of Elevated Liver Enzymes, Rhabdomyolysis, and Cancer

Insights From Large Randomized Statin Trials

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Objectives We sought to assess the relationship between the magnitude of low-density lipoprotein cholesterol (LDL-C) lowering and rates of elevated liver enzymes, rhabdomyolysis, and cancer.

Background Although it is often assumed that statin-associated adverse events are proportional to LDL-C reduction, that assumption has not been validated.

Methods Adverse events reported in large prospective randomized statin trials were evaluated. The relationship between LDL-C reduction and rates of elevated liver enzymes, rhabdomyolysis, and cancer per 100,000 person-years was assessed using weighted univariate regression.

Results In 23 statin treatment arms with 309,506 person-years of follow-up, there was no significant relationship between percent LDL-C lowering and rates of elevated liver enzymes (R^2 <0.001, p = 0.91) or rhabdomyolysis (R^2 = 0.05, p = 0.16). Similar results were obtained when absolute LDL-C reduction or achieved LDL-C levels were considered. In contrast, for any 10% LDL-C reduction, rates of elevated liver enzymes increased significantly with higher statin doses. Additional analyses demonstrated a significant inverse association between cancer incidence and achieved LDL-C levels (R^2 = 0.43, p = 0.009), whereas no such association was demonstrated with percent LDL-C reduction (R^2 = 0.09, p = 0.92) or absolute LDL-C reduction (R^2 = 0.05, p = 0.23).

Conclusions Risk of statin-associated elevated liver enzymes or rhabdomyolysis is not related to the magnitude of LDL-C lowering. However, the risk of cancer is significantly associated with lower achieved LDL-C levels. These findings suggest that drug- and dose-specific effects are more important determinants of liver and muscle toxicity than magnitude of LDL-C lowering. Furthermore, the cardiovascular benefits of low achieved levels of LDL-C may in part be offset by an increased risk of cancer. (J Am Coll Cardiol 2007;50:409–18) © 2007 by the American College of Cardiology Foundation

Strategies aimed at lowering low-density lipoprotein cholesterol (LDL-C) remain a primary approach for cardiovascular risk reduction. Of the currently available lipid-altering drugs, hydroxyl methyl glutaryl coenzyme A (HMG-CoA) reductase inhibitors (statins) are the most effective in LDL-C lowering, and their efficacy in improving cardiovascular morbidity and mortality is supported by a large body of evidence. Recent data from large-scale statin trials have demonstrated that more intensive LDL-C lowering, beyond standard goals, offers significant incremental cardiovascular risk reduction (1–3). Relevant to this era of "lower is better" in lipid management are controversial concerns regarding the safety of intensive LDL-C lowering.

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Such concerns are compounded by observations linking the most potent statins to higher rates of reported adverse events, including elevated liver enzymes and rhabdomyolysis (4–6). However, whether the magnitude of LDL-C lowering per se is related to the risk of statin-associated adverse events is uncertain. The nature of such a relationship, if one indeed exists, is pertinent to recent national guidelines advocating more intensive LDL-C goals as a viable clinical strategy in very high-risk patients, and the use of higher statin doses required to achieve LDL-C reductions of 30% to 40% (3). Also relevant to the increasing emphasis on aggressively lowering LDL-C for cardiovascular protection

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Abbreviations and Acronyms

HMG-CoA = hydroxyl methyl glutaryl coenzyme A

LDL-C = low-density lipoprotein cholesterol

are earlier concerns associating lower cholesterol levels with an increased incidence of cancer. Hence, the present analysis examines the relationship between the degree of LDL-C lowering and the risk of abnormal liver enzymes and rhabdomyolysis in large randomized statin trials. In secondary analyses, potential associations between LDL-C lowering and the risk of cancer are also examined.

Methods

A MEDLINE search was conducted to identify prospective randomized controlled statin trials published up to November 2005. To ensure adequate exposure and optimize the yield of reported adverse events, only trials with exposures of at least 1,000 person-years of follow-up were evaluated. The following variables were extracted from the published manuscripts: statin used and dose, number of patients in the statin-treatment arm, duration of follow-up, baseline and achieved LDL-C levels, and number of patients experiencing elevated liver enzymes, rhabdomyolysis, or cancer. Cases of elevated liver enzymes or rhabdomyolysis were identified using the specific criteria for each trial. Rates of elevated liver enzymes, rhabdomyolysis, and cancer per 100,000 person-years were calculated.

LDL-C lowering and risk of elevated liver enzymes and rhabdomyolysis. The primary objective of the current analysis was to assess the relationship between percent LDL-C reduction and rates of elevated liver enzymes and rhabdomyolysis. Additional analyses were performed to assess the relationship between absolute LDL-C reduction or achieved LDL-C levels, and the observed rates of elevated liver enzymes and rhabdomyolysis. To assess the relationship between the statin dose and rates of adverse events after controlling for the magnitude of LDL-C lowering, we calculated the rates of elevated liver enzymes associated with each statin for every 10% reduction in LDL-C. Rates of elevated liver enzymes per 100,000 person-years for each 10% reduction in LDL-C were compared across the following categories of statin doses: low dose (lovastatin 20 mg, simvastatin 20 mg, and atorvastatin 10 mg), intermediate dose (lovastatin 40 mg, simvastatin 40 mg, and pravastatin 40 mg), and high dose (lovastatin 80 mg, simvastatin 80 mg, fluvastatin 80 mg, and atorvastatin 80 mg). A similar analysis also was performed for individual statins across the various doses used in the trials. Because such an analysis requires a range of doses to be examined, only statins for which different doses were used in several trials could be assessed individually (lovastatin, simvastatin, and atorvastatin). Furthermore, because of the small number of rhabdomyolysis cases across the various statin doses, the effect of varying statin dose on rates of rhabdomyolysis could not be reliably evaluated.

LDL-C lowering and cancer. Similarly, we assessed the relationship between percent LDL-C reduction and rates of newly diagnosed cancer in the statin treatment arms. Additional analyses were performed to assess the relationship between absolute LDL-C reduction or achieved LDL-C levels, and the observed rates of cancer. To assess the relationship between statin dose and rates of newly diagnosed cancer, a dose effect analysis similar to the one described previously for risk of elevated liver enzymes was performed across the following categories of statin doses: low dose, intermediate dose, and high dose.

Statistical methods. Relationships between the magnitude of LDL-C lowering and rates of elevated liver enzymes, rhabdomyolysis, and cancer were assessed using univariate regression models. To control for variability in trial size, all regression analyses were weighted by each trial's statin arm sample size. To assess for differences in elevated liver enzymes among the various statin dose categories, the chi-square test with appropriate degrees of freedom was used. A p value of <0.05 was considered statistically significant. SigmaStat version 3.1 (Systat Software, Inc., Point Richmond, California) was used for statistical analyses.

Results

A total of 23 statin treatment arms were identified with 75,317 statin-allocated patients and cumulative follow-up of 309,506 person-years. Several statins at varying doses were used across the trials with a wide range of baseline (106 to 192 mg/dl) and achieved (62 to 142 mg/dl) LDL-C levels (Table 1) (1,2,7–20).

Primary analysis: LDL-C lowering and risk of elevated liver enzymes and rhabdomyolysis. Of all the statin treatment arms examined (n = 23), the number of patients with elevated liver enzymes or rhabdomyolysis could be determined in 22 and 21 arms, respectively. There was no significant relationship between percent LDL-C lowering and rates of elevated liver enzymes ($R^2 < 0.001$, $p = 0.91$) (Fig. 1). Similar findings were obtained when absolute LDL-C reduction or achieved LDL-C values were examined ($R^2 = 0.07$, $p = 0.12$, and $R^2 < 0.001$, $p = 0.89$, respectively, data not shown). Likewise, there was no significant relationship between % LDL-C lowering and rates of rhabdomyolysis ($R^2 = 0.05$, $p = 0.16$) (Fig. 2). Similar findings were obtained when absolute LDL-C reduction or achieved LDL-C values were examined ($R^2 < 0.001$, $p = 0.62$, and $R^2 = 0.07$, $p = 0.14$, respectively, data not shown). To exclude the possibility that the analysis of LDL-C lowering versus risk of rhabdomyolysis was dominated by one trial with a high rate of rhabdomyolysis (simvastatin 80 mg arm of the A to Z trial), a repeat analysis was conducted without that arm, yielding similar findings of lack of a significant relationship between rates of rhabdomyolysis and percent LDL-C reduction ($R^2 = 0.01$, $p =$

Table 1 Characteristics of Large Prospective Randomized Controlled Statin Trials Included in the Present Analysis

Study Arm (Ref. No.)	Year	Statin	Dose*	n	Mean Follow-Up, yrs	Male, %	Mean Age, yrs
EXCEL (7)	1991	Lovastatin	20	1,642	0.9	59	56
EXCEL (7)	1991	Lovastatin	20 BID	1,646	0.9	59	56
EXCEL (7)	1991	Lovastatin	40	1,645	0.9	59	56
EXCEL (7)	1991	Lovastatin	80	1,649	0.9	59	56
4S (8)	1994	Simvastatin	20–40	2,221	5.4	82	58
WOSCOPS (9)	1995	Pravastatin	40	3,302	4.9	100	55
CARE (10)	1996	Pravastatin	40	2,081	5	86	59
AFCAPS/TexCAPS (11)	1998	Lovastatin	20–40	3,304	5.2	85	58
LIPID (12)	1998	Pravastatin	40	4,512	6.1	83	62
ALLHAT-LLT (13)	2002	Pravastatin	40	5,170	4.8	51	66
LIPS (14)	2002	Fluvastatin	80	844	3.9	84	60
HPS (15)	2002	Simvastatin	40	10,269	5	75	NR†
PROSPER (16)	2002	Pravastatin	40	2,888	3.2	48	75
ASCOT-LLA (17)	2003	Atorvastatin	10	5,168	3.3	81	63
A to Z (18)	2004	Simvastatin	20	2,232	2.0	75	61
A to Z (18)	2004	Simvastatin	80	2,265	2.0	76	61
CARDS (19)	2004	Atorvastatin	10	1,428	3.9	68	62
PROVE IT-TIMI 22 (1)	2004	Pravastatin	40	2,063	2	78	58
PROVE IT-TIMI 22 (1)	2004	Atorvastatin	80	2,099	2	78	58
TNT (2)	2005	Atorvastatin	10	5,006	4.9	81	61
TNT (2)	2005	Atorvastatin	80	4,995	4.9	81	61
IDEAL (20)	2005	Simvastatin	20	4,449	4.8	81	62
IDEAL (20)	2005	Atorvastatin	80	4,439	4.8	81	62

*Target dose in milligrams per day, unless otherwise specified. †Mean age not reported in original manuscript, but 48% of patients allocated to simvastatin were <65 years old.

AFCAPS/TexCAPS = Air Force/Texas Coronary Atherosclerosis Prevention Study; ALLHAT-LLT = The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial; ASCOT-LLA = Anglo-Scandinavian Cardiac Outcomes Trial-Lipid Lowering Arm; A to Z = Phase Z of the A to Z trial; BID = twice daily; CARDS = Collaborative Atorvastatin Diabetes Study; CARE = Cholesterol and Recurrent Events Trial; EXCEL = Expanded Clinical Evaluation of Lovastatin study; 4S = Scandinavian Simvastatin Survival Study; HPS = Heart Protection Study; IDEAL = Incremental Decrease in Endpoints through Aggressive Lipid Lowering study; LIPID = The Long-Term Intervention with Pravastatin in Ischemic Disease study; LIPS = Lescol Intervention Prevention Study; n = number of statin allocated patients; NR = not reported; PROSPER = Prospective Study of Pravastatin in the Elderly at Risk; PROVE IT-TIMI 22 = Pravastatin or Atorvastatin Evaluation and Infection Therapy–Thrombolysis in Myocardial Infarction 22 study; TNT = Treating to New Targets study; WOSCOP = West of Scotland Coronary Prevention Study.

0.36), absolute LDL-C reduction (R^2 <0.001, p = 0.53), or achieved LDL-C level (R^2 = 0.12, p = 0.26).

Effect of statin dose on risk of elevated liver enzymes. There was a positive and graded relationship between rates of elevated liver enzymes per 100,000 person-years and statin dose, with a significantly higher rate of elevated liver enzymes in the high-dose statin category compared with the intermediate-dose category, which in turn was significantly higher than the low-dose statin category (271 vs. 195 vs. 114 per 100,000 person-years for each 10% reduction in

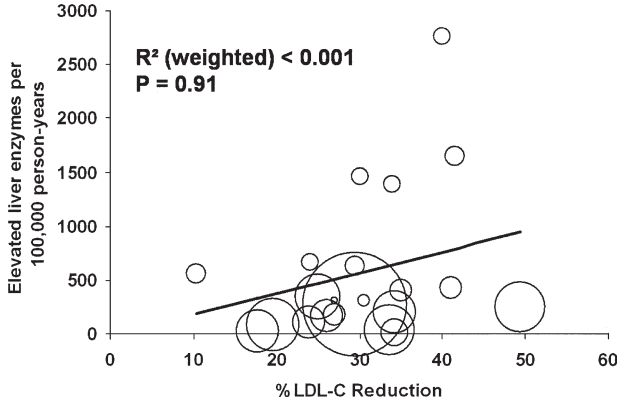

Figure 1 Relationship Between Rates of Elevated Liver Enzymes and % LDL-C Reduction

The sizes of the **open circles** represent the relative sizes of the statin treatment arms (i.e., number of patients in each arm). LDL-C = low-density lipoprotein cholesterol.

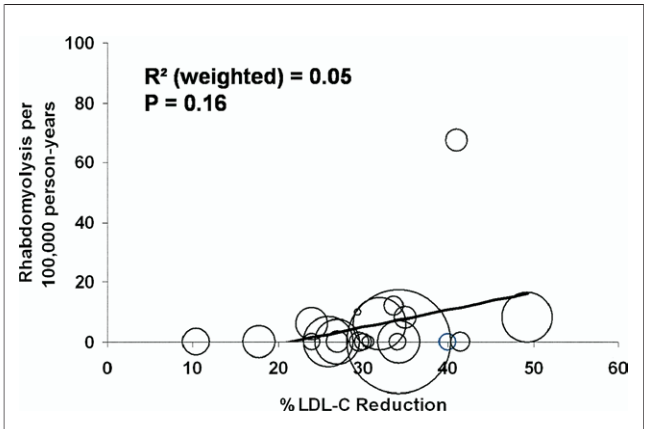

Figure 2 Relationship Between Rates of Rhabdomyolysis and % LDL-C Reduction

The sizes of the **open circles** represent the relative sizes of the statin treatment arms (i.e., number of patients in each arm). LDL-C = low-density lipoprotein cholesterol.

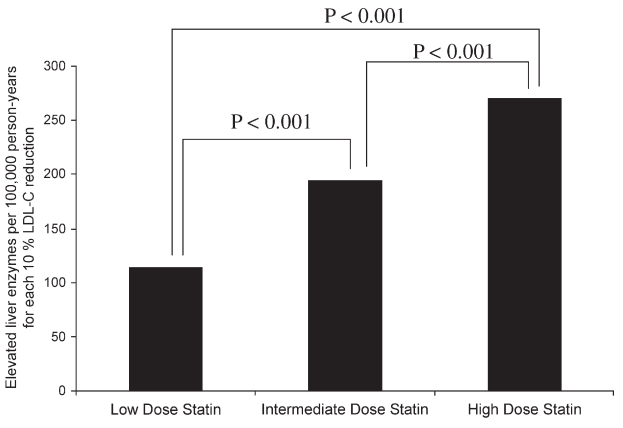

Figure 3 **Rate of Elevated Liver Enzymes by Statin Dose Category**

Rate of elevated liver enzymes per 100,000 person-years for each 10% reduction in low-density lipoprotein cholesterol (LDL-C) for the following statin dose categories: low dose (lovastatin 20 mg, simvastatin 20 mg, and atorvastatin 10 mg), intermediate dose (lovastatin 40 mg, simvastatin 40 mg, and pravastatin 40 mg), and high dose (lovastatin 80 mg, simvastatin 80 mg, fluvastatin 80 mg, and atorvastatin 80 mg).

LDL-C, $p < 0.001$ for all pair-wise comparisons) (Fig. 3). A similar pattern of higher rates of elevated liver enzymes with higher statin doses was also observed when individual statins were examined. For each 10% reduction in LDL-C, the rate of elevated liver enzymes per 100,000 person-years with high-dose lovastatin was 2.5 times higher compared with low-dose lovastatin ($p < 0.001$) (Fig. 4) and significantly higher than intermediate-dose lovastatin ($p < 0.001$) (Fig. 4). Likewise, the rate of elevated liver enzymes with higher doses of simvastatin (80 and 40 mg) was 1.6 times greater compared with low-dose simvastatin ($p = 0.006$) (Fig. 5). Similarly, the rate of elevated liver enzymes with high-dose atorvastatin was 4.0 times greater compared with low-dose atorvastatin ($p < 0.001$) (Fig. 6). There were insufficient data to examine intermediate doses of atorvastatin.

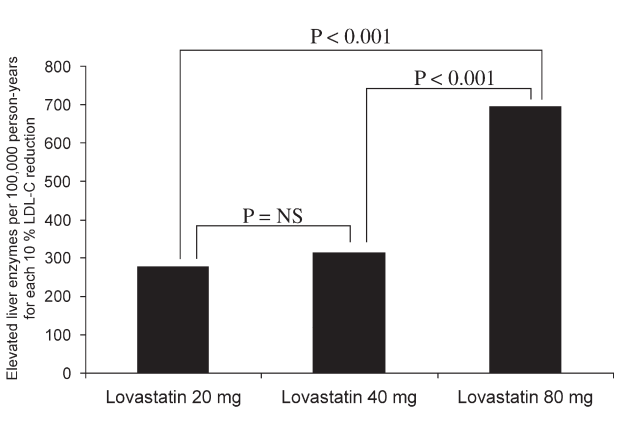

Figure 4 **Rate of Elevated Liver Enzymes by Lovastatin Dose Category**

Rate of elevated liver enzymes per 100,000 person-years for each 10% reduction in low-density lipoprotein cholesterol (LDL-C) for low-dose (20 mg), intermediate-dose (40 mg), and high-dose (80 mg) lovastatin.

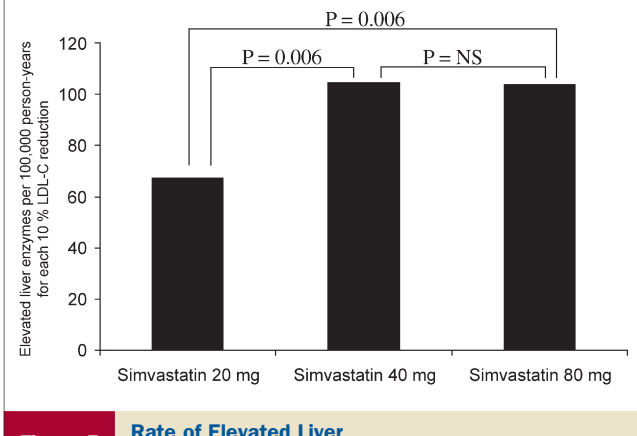

Figure 5 **Rate of Elevated Liver Enzymes by Simvastatin Dose Category**

Rate of elevated liver enzymes per 100,000 person-years for each 10% reduction in low-density lipoprotein cholesterol (LDL-C) for low-dose (20 mg), intermediate-dose (40 mg), and high-dose (80 mg) simvastatin.

Secondary analysis: LDL-C lowering and risk of cancer. Of all the statin treatment arms examined (n = 23), the number of patients with newly diagnosed cancer during follow-up could be determined in 13 arms. Detailed description of these statin arms is shown in Table 2. There was no significant relationship between percent LDL-C lowering and rates of cancer ($R^2 = 0.09$, $p = 0.92$) (Fig. 7). Similarly, there was no significant relationship between absolute LDL-C lowering and rates of cancer ($R^2 = 0.05$, $p = 0.23$) (Fig. 8). In contrast, there was a highly significant inverse relationship between achieved LDL-C levels and rates of newly diagnosed cancer ($R^2 = 0.43$, $p = 0.009$) (Fig. 9). The rates of incident cancer across the 3 statin dose categories (for each 10 % reduction in LDL-C) ranged from 408 to 498 per 100,000 person-years (Fig. 10). Although the difference between the high-dose and the low/intermediate-dose categories was statistically significant, the magnitude of this difference was relatively small (low dose 498 vs. intermediate dose 490 vs. high dose 408 per 100,000 person-years for each 10% reduction in LDL-C, $p = 0.823$ for low vs. intermediate, and $p = 0.003$ and 0.007 for high vs. low and intermediate, respectively) (Fig. 10).

Discussion

LDL-C lowering and risk of elevated liver enzymes and rhabdomyolysis. Recent reports suggesting an increased risk of adverse events with more potent statins have raised interest in the relationship between statin potency (as reflected by degree of LDL-C lowering) and statin toxicity. In the present analysis of large-scale randomized statin trials, we found no correlation between the magnitude of

LDL-C lowering and rates of statin-associated elevated liver enzymes or rhabdomyolysis. This was true whether the degree of LDL-C lowering was assessed as percent LDL-C reduction, absolute LDL-C reduction, or achieved LDL-C level. The present findings do not support the notion that LDL-C lowering per se is related to risk of liver or muscle adverse events. Instead, we observed that rates of elevated liver enzymes were significantly associated with the dose of statin used, even after controlling for the corresponding magnitude of LDL-C reduction, whether all statins are assessed as a group, or individually.

Furthermore, although a similar dose effect analysis could not be reliably preformed for rhabdomyolysis risk because of the small number of reported cases, it is worth noting that the one trial with high-dose simvastatin (80 mg in the A to Z trial) had a rate of rhabdomyolysis that was more than 7-fold higher than the reported rate in intermediate-dose simvastatin trials (67 vs. 9 cases of rhabdomyolysis per 100,000 person-years). However, the incremental percent LDL-C reduction with high- versus intermediate-dose simvastatin was only 9%, which is consistent with the hypothesis that the risk of rhabdomyolysis was driven by the increase in dose and not the incremental reduction in LDL-C. It is unclear whether this observation is unique to simvastatin only or whether it could be extrapolated to the risk of muscle toxicity with other statins, especially because an increased risk of rhabdomyolysis has not been observed in clinical trials of other high-dose statins such as atorvastatin, which has been extensively studied.

The present observations are relevant to the use of statins in clinical practice in light of recent evidence demonstrating that the use of high-dose statins to achieve more intensive LDL-C lowering results in greater reduction in cardiovascular risk (1–3). It is difficult from these trials to differentiate the influence of LDL-C lowering per se from that of drug and dose used. In other words, was the observed benefit conferred by the higher statin dose, or was the benefit instead derived from the greater magnitude of LDL-C lowering achieved by the higher dose of the statin?

Relevant to this question are recent studies examining the determinants of benefit with lipid-lowering therapy. A recent meta-analysis suggested that the absolute benefit seen in statin trials related primarily to the absolute reduction in LDL-C (21). Furthermore, in a recent analysis of randomized controlled trials using various methods for LDL-C reduction, the relationship between LDL-C lowering and cardiovascular risk in statin trials was similar to that found in non-statin trials, supporting the concept that reduction in risk is driven by reduction in LDL-C (22). Further insight is provided by subgroup analyses from the PROVE IT–TIMI-22 (Pravastatin or Atorvastatin Evaluation and Infection Therapy–Thrombolysis In Myocardial Infarction-22) trial, suggesting that once LDL-C target levels were achieved, the specific statin used did not appear to impact outcomes (23,24). Similar findings were reported in a recent study comparing the effects of aggressive versus conventional lipid lowering where positive changes in vessel wall parameters were primarily related to the magnitude of LDL-C reduction rather than the statin dose (25). Taken together, these reports suggest that the primary determinant of benefit with statin use is the magnitude of LDL-C reduction and not the particular statin or dose used.

The findings from the present study complement our understanding of the effects of statins by demonstrating that, unlike the case with statin benefit, the primary determinant of statin toxicity is not the magnitude of LDL-C reduction, but rather the statin dose used. Hence, based on the suggestion that a higher dose per se does not confer additional benefit after controlling for LDL-C reduction, and the present observation that a higher dose of statin is associated with increased risk of toxicity, it may be prudent not to use a statin dose beyond what is required to achieve the LDL-C target. It should be noted, however, that this approach is not supported by direct evidence from clinical trials. In the absence of such evidence, we are left with indirect ways of differentiating the effect of the statin and the dose from that of the resulting reduction in LDL-C on both benefit and toxicity.

The present analysis may also be relevant to our understanding of the mechanisms of statin toxicity, particularly statin-induced myopathy. Proposed theories for the mechanism of statin-induced myopathy invoke either structural instability of skeletal muscle cell membranes as a result of reduced cholesterol content, or inhibition of biosynthetic pathways such as ones that activate guanosine triphosphate-binding regulatory proteins (5). To the extent that serum LDL-C levels correlate with cell membrane cholesterol content, the lack of an association between LDL-C reduction and risk of rhabdomyolysis observed in this analysis suggests that reduced cell membrane cholesterol content is not the primary mechanism for statin-induced muscle

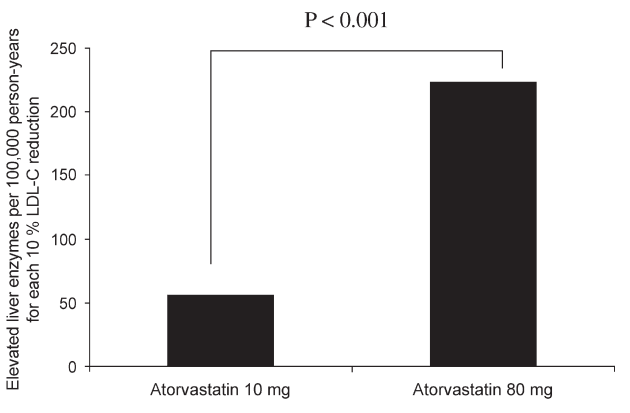

Figure 6 **Rate of Elevated Liver Enzymes by Atorvastatin Dose Category**

Rate of elevated liver enzymes per 100,000 person-years for each 10% reduction in low-density lipoprotein cholesterol (LDL-C) for low-dose (10 mg) and high-dose (80 mg) atorvastatin.

Table 2 Characteristics of Large Prospective Randomized Controlled Statin Trials in Which Incident Cancer Rates Were Reported, and Used for the Present Analysis

Study Arm (Ref. No.)	Year	Statin	Dose*	Dose Category	n	Follow-Up, yrs	Male, %	Age, yrs	Incident Cancer	% LDL Reduction	Absolute LDL Reduction	Achieved LDL	Cancer Site (Primary)
EXCEL (7)	1991	Lovastatin	20	Low	1,642	0.9	59	56	18	24	43	137	NR
EXCEL (7)	1991	Lovastatin	20 BID	Intermediate	1,646	0.9	59	56	8	34	61	119	NR
EXCEL (7)	1991	Lovastatin	40	Intermediate	1,645	0.9	59	56	20	30	54	126	NR
EXCEL (7)	1991	Lovastatin	80	High	1,649	0.9	59	56	18	40	72	108	NR
4S (8)	1994	Simvastatin	20–40	Intermediate	2,221	5.4	82	58	90	35	66	122	GI 12
WOSCOPS (9)	1995	Pravastatin	40	Intermediate	3,302	4.9	100	55	116	26	50	142	GU 32, GI 31, respiratory 27, other 26
CARE (10)	1996	Pravastatin	40	Intermediate	2,081	5	86	59	172	30	41	98	GI 26, breast 14, hematological 8, melanoma 4
AFCAPS/TexCAPS (11)	1998	Lovastatin	20–40	Intermediate	3,304	5.2	85	58	252	24	36	114	Prostate 109, colon 25, lung 22, melanoma 14, breast 13, lymphoma 12, bladder 12
LIPID (12)	1998	Pravastatin	40	Intermediate	4,512	6.1	83	62	379	25	38	113	Breast 10, no other sites reported
ALLHAT-LLT (13)	2002	Pravastatin	40	Intermediate	5,170	4.8	51	66	378	20	25	104	Lung 63, colon 46, breast 34
LIPS (14)	2002	Fluvastatin	80	High	844	3.9	84	60	46	27	35	96	NR
HPS (15)	2002	Simvastatin	40	Intermediate	10,269	5	75	NR†	814	29	39	93	GU 259, GI 228, respiratory 179, hematological 64, connective tissue 60, CNS 12
PROSPER (16)	2002	Pravastatin	40	Intermediate	2,888	3.2	48	75	245	34	50	97	GI 65, GU 58, respiratory 46, breast 18, other 58

*Target dose in milligrams per day, unless otherwise specified. Baseline and achieved LDL-C levels are in mg/dl. Mean follow-up in years is shown. Dose category is in reference to dose effect analysis shown in Figure 10. Primary cancer sites are as reported in the original publication of the trial. †Mean age not reported in original manuscript, but 48% of patients allocated to simvastatin were <65 years old.

CNS = central nervous system; GI = gastrointestinal; GU = genitourinary; LDL-C = low-density lipoprotein cholesterol; other abbreviations as in Table 1.

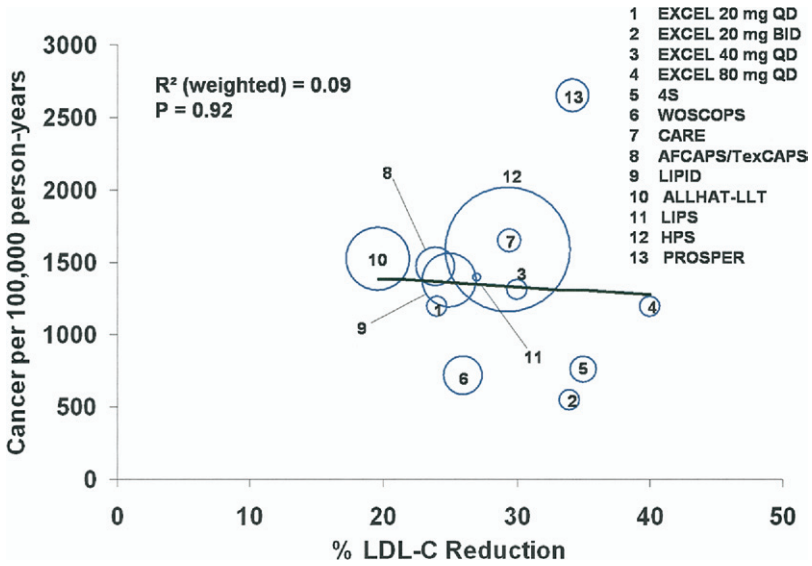

Figure 7 Relationship Between Rates of Newly Diagnosed Cancer per 100,000 Person-Years and % LDL-C Reduction

The sizes of the **open circles** represent the relative sizes of the statin treatment arms (i.e., number of patients in each arm). BID = twice daily; LDL-C = low-density lipoprotein-cholesterol; QD = once daily. See text for trial acronym definitions.

injury. Furthermore, based on the assumption that magnitude of LDL-C reduction with a statin is a marker for the degree of HMG-CoA reductase inhibition, the lack of an association between LDL-C reduction and risk of adverse events would suggest non–HMG-CoA reductase-dependent mechanisms for statin toxicity. Finally, the present observation that a higher statin dose is associated with increased risk of elevated liver enzymes for any given reduction in LDL-C is consistent with general clinical experience of increased risk of adverse events in settings that increase circulating statin concentrations (26).

LDL-C lowering and risk of cancer. Unlike the relationship between magnitude of LDL-C lowering and risk of abnormal liver enzymes or rhabdomyolysis, we observed a

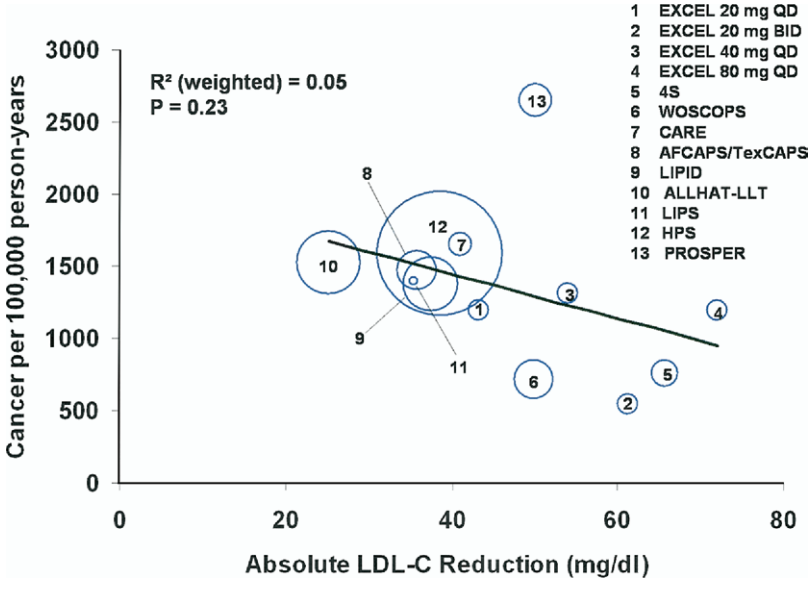

Figure 8 Relationship Between Rates of Newly Diagnosed Cancer per 100,000 Person-Years and Absolute LDL-C Reduction

The sizes of the **open circles** represent the relative sizes of the statin treatment arms (i.e., number of patients in each arm). Abbreviations as in Figure 7.

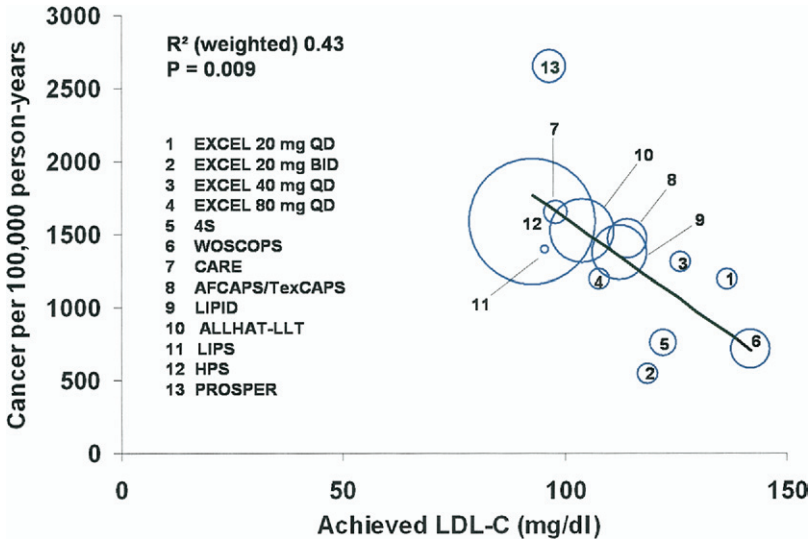

Figure 9 **Relationship Between Rates of Newly Diagnosed Cancer per 100,000 Person-Years and Achieved LDL-C Level**

The sizes of the **open circles** represent the relative sizes of the statin treatment arms (i.e., number of patients in each arm). Abbreviations as in Figure 7.

disturbing significant inverse relationship between achieved LDL-C levels and risk of newly diagnosed cancer. Several factors are critical to the proper interpretation of these findings, including the recognition that the present observation is exploratory and hypothesis-generating. In addition, the current findings do not demonstrate causality between low achieved LDL-C levels or statin use and cancer. However, it is also important to note that the primary end point utilized in the large-scale statin trials demonstrating benefit is typically a combined cardiovascular end point and not total mortality. The robust evidence demonstrating the efficacy of statins in cardiovascular protection is not undermined by the present analysis, and remains the basis for current guidelines and clinical practice.

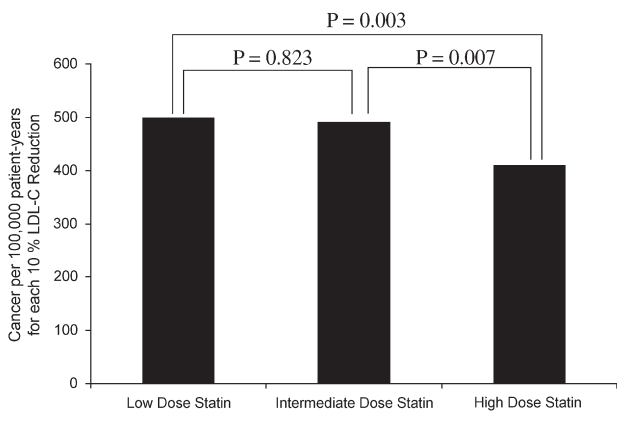

Figure 10 **Rate of Newly Diagnosed Cancer by Statin Dose Category**

Rate of newly diagnosed cancer per 100,000 person-years for each 10% reduction in low-density lipoprotein-cholesterol (LDL-C) for the following statin dose categories: low dose (lovastatin 20 mg), intermediate dose (lovastatin 40 mg, simvastatin 40 mg, and pravastatin 40 mg), and high dose (lovastatin 80 mg, fluvastatin 80 mg).

It is also important to differentiate the question posed by this analysis from the objectives of prior statin-cancer analyses. With the exception of the PROSPER (Prospective Study of Pravastatin in the Elderly at Risk), in which new cancer diagnoses were more frequent on pravastatin than on placebo (16), all large prospective randomized statin trials have shown no difference in the risk of incident cancer in statin-treated patients compared with placebo. In the Heart Protection Study, the largest randomized statin trial with more than 10,000 patients allocated to simvastatin, the incidence of new cancer diagnoses was similar in the statin arm compared with the placebo arm (event rate ratio 1.00, 95% confidence interval 0.91 to 1.11) (15).

In meta-analyses of randomized statin trials, The Cholesterol Treatment Trialists' Collaborators and other investigators have shown that statins have a neutral effect on incident cancer when compared with placebo in randomized controlled trials (21,27). This body of evidence is reassuring that statin use in itself is not associated with an increased risk of cancer compared with placebo. However, such meta-analyses do not answer the question addressed by the present study: What is the relationship between LDL-C lowering in statin-treated patients and incident cancer? This question is particularly relevant in the present-day era of "lower is better." The published meta-analyses are limited in addressing this question particularly because the 4 randomized trials of intensive LDL-C lowering (PROVE-IT–TIMI-22, A to Z, TNT [Treating to New Targets study],

and IDEAL [Incremental Decrease in Endpoints through Aggressive Lipid Lowering study]) were not placebo controlled and hence were not included in the meta-analyses.

The present observation is consistent with many epidemiologic studies associating low cholesterol levels with higher incidence of cancer (28). The increase in cancer deaths in epidemiologic studies appeared to counteract the lower cardiac mortality associated with lower cholesterol, resulting in a fairly neutral effect on overall mortality across cholesterol levels (29,30). In most of these studies, the incidence of cancer was greater in participants with baseline total cholesterol levels of <160 mg/dl compared with higher levels. A comprehensive overview of the epidemiologic data concluded that definitive interpretation of the association between low cholesterol levels and cancer was not possible but was likely explained by confounding (28). One potential explanation is the possibility that low cholesterol levels are simply the effect of the disease rather than the cause, and is present before the clinical manifestation of cancer (i.e., occult malignancy causes low cholesterol levels which are then associated with cancer when it becomes clinically manifest). This possibility is inconsistent with the persistence of statistical association between cancer and low cholesterol after excluding early deaths (within 5 years after study baseline) in some of the epidemiologic studies (28).

Study limitations. The present findings and their implications should be viewed within the context of several limitations. We used summary data as presented in the published manuscript of each trial. A more detailed analysis using individual patient data from all the trials may yield different results. The current analysis relies on rates of adverse events as reported in the controlled and relatively restricted environment of randomized clinical trials. Unlike common clinical practice, the controlled setting of a clinical trial often is characterized by stringent criteria to exclude subjects with certain conditions that may increase the risk of adverse events, along with close follow-up and awareness of early laboratory or clinical signs of toxicity. It is conceivable that the nature of the relationship between lipid lowering and adverse events is altered by these clinical trial characteristics, and that such a relationship may be different when examined in a "real-life" clinical environment.

Furthermore, we used adverse event rates as reported and defined in each study. Our findings are limited by this lack of standardization, to the extent that these trials vary in their population characteristics and protocols for monitoring and reporting adverse events. Moreover, given the small number of cases of rhabdomyolysis across the various statin doses, a reliable dose effect analysis of rhabdomyolysis rates could not be performed. Hence, it is unclear whether the observed impact of statin dose on rates of elevated liver enzymes could be extrapolated to the risk of rhabdomyolysis. Finally, it should be emphasized that the association of cancer with lower achieved LDL-C levels observed in the present analysis does not imply causality. Not withstanding the limitations of the approach, by using the cumulative size of patient exposure in these trials, the present analysis provides a unique and robust opportunity to examine the clinically relevant relationship between magnitude of LDL-C lowering and adverse events.

Conclusions

The present findings suggest that the risk of statin-associated liver enzyme elevations or muscle injury is not related to the magnitude of LDL-C lowering but is more likely determined by drug- and dose-specific effects. Furthermore, a concerning inverse relationship between achieved LDL-C levels in statin-treated patients and risk of cancer was observed, and requires further investigation.

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