

Effect of Different Antilipidemic Agents and Diets on Mortality

A Systematic Review

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Background: Guidelines for the prevention and treatment of hyperlipidemia are often based on trials using combined clinical end points. Mortality data are the most reliable data to assess efficacy of interventions. We aimed to assess efficacy and safety of different lipid-lowering interventions based on mortality data.

Methods: We conducted a systematic search of randomized controlled trials published up to June 2003, comparing any lipid-lowering intervention with placebo or usual diet with respect to mortality. Outcome measures were mortality from all, cardiac, and noncardiovascular causes.

Results: A total of 97 studies met eligibility criteria, with 137 140 individuals in intervention and 138 976 individuals in control groups. Compared with control groups, risk ratios for overall mortality were 0.87 for statins (95% confidence interval [CI], 0.81-0.94), 1.00 for fibrates (95%

CI, 0.91-1.11), 0.84 for resins (95% CI, 0.66-1.08), 0.96 for niacin (95% CI, 0.86-1.08), 0.77 for n-3 fatty acids (95% CI, 0.63-0.94), and 0.97 for diet (95% CI, 0.91-1.04). Compared with control groups, risk ratios for cardiac mortality indicated benefit from statins (0.78; 95% CI, 0.72-0.84), resins (0.70; 95% CI, 0.50-0.99) and n-3 fatty acids (0.68; 95% CI, 0.52-0.90). Risk ratios for noncardiovascular mortality of any intervention indicated no association when compared with control groups, with the exception of fibrates (risk ratio, 1.13; 95% CI, 1.01-1.27).

Conclusions: Statins and n-3 fatty acids are the most favorable lipid-lowering interventions with reduced risks of overall and cardiac mortality. Any potential reduction in cardiac mortality from fibrates is offset by an increased risk of death from noncardiovascular causes.

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LIPID-LOWERING AGENTS ARE basic drugs for primary and secondary prevention of cardiovascular diseases and have been now in use for more than 4 decades. The first lipid-lowering drugs with proven efficacy to lower both cardiovascular morbidity and overall mortality in a large-scale clinical trial were 3-hydroxymethyl-3-methylglutaryl coenzyme A reductase inhibitors (statins).¹ In previous meta-analyses, only statins showed statistically significant and clinically relevant reductions in coronary heart disease (CHD) and overall mortality.^{2,3} In addition to the potent lipid-lowering capacity of statins, more recent findings indicate that the positive effects of statins could also be the result of reductions in platelet aggregability and endothelial inflammation.⁴

Over the past 5 years, large trials of several statins and other lipid-lowering interventions provided important information on

the efficacy of these drugs in various risk groups and settings as well as in generally underinvestigated populations, such as women or the elderly. Large-scale meta-analyses of randomized controlled trials are important tools to document the overall benefit of interventions and to explore effect sizes of clinically relevant outcomes in important subgroups.⁵ The goal of the present meta-analysis is to investigate the efficacy and safety of different lipid-lowering interventions in the primary and secondary prevention of CHD based on mortality data.

METHODS

SEARCH FOR RELEVANT STUDIES

We included references from previous meta-analyses^{2,6} and 2 of us (M.S. and M.B.) searched MEDLINE, EMBASE, PASCAL, and the Cochrane Controlled Trials Register together

with a professional librarian to identify all randomized controlled trials published between 1965 and June 2003 that compared lipid-lowering agents or dietary interventions with placebo or usual care. No language restrictions were imposed.

STUDY SELECTION AND DATA ABSTRACTION

Trials were considered eligible for this meta-analysis if they compared any lipid-lowering intervention with placebo or usual care, used random allocation, had a follow-up of at least 6 months, and reported mortality data. We excluded trials that were restricted to heart transplant recipients; trials in coronary artery bypass grafts or acute coronary syndromes; trials using hormone therapy in men or those using postmenopausal hormone therapies (because these therapies were shown to be harmful for CHD prevention^{2,7}); trials using any combination of lipid-lowering intervention (not allowing us to classify the intervention to 1 drug); and trials with outdated interventions such as ileal bypass surgery. Details of included and excluded trials are provided at http://www.bice.ch/engl/publications_reports.htm.

Two of 3 investigators (M.S., M.B., and B.L.) assessed study eligibility and quality blinded to one another's rating and resolved any disagreement by consensus. Data of eligible trials were abstracted in duplicate, and authors of the original trials were contacted for additional data if needed. We assessed the quality of included trials with respect to concealment of treatment allocation; blinding of patients, caregivers, or assessors of clinical outcomes; and completeness of follow-up.⁸ When the article failed to provide explicit information about a quality component, we assumed it was not present.

Based on pharmacological characteristics, we classified trials according to the following groups⁹: statins (35 trials [A1-A35]), fibrates (17 trials [A36-A52]), resins (8 trials [A53-A60]), niacin (2 trials [A39 and A61]), n-3 fatty acids (14 trials [A67-A79]), and dietary interventions (17 trials [A53 and A80-A95]). We limited the analysis to interventions with at least 1000 individuals per group. Therefore data on policosanol (3 trials [A62-A64]), probucol (3 trials [A20, A65, and A66]), and garlic (2 trials [A96 and A97]) are only presented in an additional table at http://www.bice.ch/engl/publications_reports.htm. Trials in primary prevention of CHD were defined as trials with less than 10% of participants with CHD, whereas secondary prevention trials comprised 100% partici-

pants with CHD. The percentage of total cholesterol reduction for each trial was calculated as the difference in the mean change from baseline to end of follow-up in the intervention and control groups. End points of interest for overall benefit of lipid-lowering interventions were overall mortality and cardiac mortality (eg, death from myocardial infarction, sudden death, or heart failure) and deaths from noncardiovascular causes.

STATISTICAL ANALYSIS

We pooled treatment effects across studies for each of 6 predefined lipid-lowering interventions and calculated a weighted average risk ratio (RR) of all outcomes in the treatment and control groups by using a random effects model. We investigated the presence of publication bias by means of funnel plots.¹⁰ We tested for heterogeneity with the Cochran Q test and measured inconsistency (I^2 ; the percentage of total variation across studies that is due to heterogeneity rather than chance) of treatment effects across different lipid-lowering interventions.^{11,12}

We tested for the differences in the relative risk estimates of subgroups by calculating a z score, the difference in the subgroup logarithmic relative risk divided by the standard error of the difference.¹³ For sensitivity analysis we examined treatment effects according to quality components and in trials of primary and secondary prevention of CHD. We used inverse variance-weighted meta-regression analysis to investigate any association between overall mortality and the extent of cholesterol reduction, items about trial quality, percentage of patients with established CHD in trials, and the type and duration of lipid-lowering intervention.¹⁴ Numbers needed to treat per year to prevent 1 death in patients with and without pre-existing CHD were calculated by multiplying of the averaged-weighted mean annual baseline risk with the mean relative risk reduction in each intervention category.¹⁵ All statistical analyses were done using Stata 8.2 (StataCorp, College Station, Tex) and S-PLUS 2000 (MathSoft Inc, Cambridge/Mass) software.

RESULTS

We identified 10 977 trials that compared lipid-lowering interventions to placebo or usual care. Of these, 127 were randomized controlled trials reporting mortality data. We ex-

cluded 30 trials for reasons stated in the "Methods" section, thus leaving 97 trials for analysis (for details see http://www.bice.ch/engl/publications_reports.htm). Four of these trials (A20, A39, A53, and A72) had multiple treatment arms, so the control group was used for comparison against all treatment arms. In total, there were 137 140 individuals in the intervention and 138 976 individuals in the control groups. Analysis for publication bias indicated no evidence for such bias for any of the interventions.

The average relative reduction in levels of total cholesterol for statins was 20% (range, 7%-36%), for fibrates 8% (range, 0%-14%), for resins 15% (range, 8%-24%), for niacin 11% (range, 8%-14%), for n-3 fatty acids 2% (range, -2% to 9%), and for diet 10% (range, 1%-24%) (**Table 1**).

OVERALL MORTALITY

Risk ratios for overall mortality were statistically significantly reduced for statins (0.87; 95% CI, 0.81-0.94; test of heterogeneity, $P = .05$; $I^2 = 30%$ [95% uncertainty interval [UI], 0%-54%]), and n-3 fatty acids (0.77; 95% CI, 0.63-0.94; $P = .01$; $I^2 = 53%$ [95% UI, 14%-75%]) (**Figure**). For statins this effect was consistent in trials of primary and secondary prevention of CHD, but there was insufficient evidence to support a beneficial effect of n-3 fatty acids in primary prevention of CHD (Table 1). For trials with statins, n-3 fatty acids, and fibrates (RR, 1.00; 95% CI, 0.91-1.11; $P = .01$; $I^2 = 33%$ [95% UI, 0%-63%]) we found moderate heterogeneity ($P < .10$; $I^2 > 25%$). When exploring heterogeneity in sensitivity analyses, summary estimates of statin and fibrate trials with lower methodological quality had mostly higher risk reductions compared with summary estimates from trials that fulfilled respective quality components, but these differences were not statistically significant (**Table 2**). Heterogeneity for n-3 fatty acids was mainly due to 1 trial (Burr et al [A79; see http://www.bice.ch/engl/publications_reports.htm]) that contrasted the favorable risk reductions found in

Table 1. Effects of Different Lipid-Lowering Interventions on Overall Mortality

Type of Intervention*	Trials, No.	Individuals, T/C	Follow-up, Mean \pm SD, y	Cholesterol Reduction, Mean (Range), %	Overall Deaths, T/C	Overall Mortality, RR (95% CI)	Heterogeneity, P Value	Inconsistency, I ² (95% UI), %
Statins (all trials)	35	53 417/48 460	2.9 \pm 1.6	20 (7 to 36)	3793/4290	0.87 (0.81 to 0.94)	.05	30 (0 to 54)
Primary prevention of CHD	9	13 341/13 300	3.3 \pm 1.0	17 (13 to 22)	388/450	0.86 (0.76 to 0.99)	.50	0 (0 to 65)
Secondary prevention of CHD	20	13 584/13 548	2.6 \pm 1.7	21 (6 to 36)	972/1242	0.78 (0.71 to 0.86)	.42	3 (0 to 50)
Fibrates (all trials)	17	13 761/15 429	4.4 \pm 1.6	8 (0 to 14)	1257/1682	1.00 (0.91 to 1.11)	.01	33 (0 to 63)
Primary prevention of CHD	3	7463/7409	4.4 \pm 1.3	10 (9 to 12)	281/224	1.25 (1.05 to 1.48)	.50	0 (0 to 90)
Secondary prevention of CHD	9	5182/6892	5.2 (1.4)	8 (0 to 14)	779/1239	0.96 (0.86 to 1.08)	.21	26 (0 to 65)
Resins (all trials)	8	3280/3257	3.2 \pm 2.2	15 (8 to 24)	112/134	0.84 (0.66 to 1.08)	.86	0 (0 to 68)
Primary prevention of CHD	1	1906/1900	7.4	8 (NA)	68/71	0.95 (0.69 to 1.32)	NA	NA
Secondary prevention of CHD	2	101/102	4 \pm 1.4	20 (15 to 24)	5/10	0.56 (0.18 to 1.82)	.30	7 (NA)
Niacin (all trials)	2	1196/2932	4.7 \pm 2.1	11 (8 to 14)	288/736	0.96 (0.86 to 1.08)	.81	0 (NA)
Primary prevention of CHD	0	NA	NA	NA	NA	NA	NA	NA
Secondary prevention of CHD	2	1196/2932	4.7 \pm 2.1	11 (8 to 14)	288/736	0.96 (0.86 to 1.08)	.81	0 (NA)
n-3 Fatty acids (all trials)	14	10 122/10 138	1.9 \pm 1.2	2 (-2 to 9)	918/1038	0.77 (0.63 to 0.94)	.01	53 (14 to 75)
Primary prevention of CHD	1	51/105	2.0	-1 (NA)	1/0	6.1 (0.25 to 148)	NA	NA
Secondary prevention of CHD	9	9270/9236	2.1 \pm 1.5	1 (-2 to 4)	860/945	0.84 (0.66 to 1.06)†	.01†	59 (14 to 80)†
Diet (all trials)	17	54 411/60 899	4.2 \pm 2.5	10 (1 to 24)	3553/4775	0.97 (0.91 to 1.04)	.19	23 (0 to 56)
Primary prevention of CHD	5	48 137/54 675	6.7 \pm 2.0	8 (1 to 24)	2909/4111	0.99 (0.94 to 1.03)	.54	0 (0 to 79)
Secondary prevention of CHD	9	1253/1231	3.0 \pm 1.3	10 (3 to 18)	200/236	0.85 (0.66 to 1.09)	.10	41 (0 to 73)

Abbreviations: CHD, coronary heart disease; CI, confidence interval, NA, not applicable; RR, risk ratio; T/C, number of individuals in treatment/control groups; UI, uncertainty interval.

*Trials in primary prevention of CHD were defined as trials with less than 10% of participants with CHD, while secondary prevention trials comprised 100% participants with CHD. There are some trials with mixed study populations (eg, 55% of participants with CHD) that could not be confined to either category; these are therefore not included in this subgroup analysis.

†Sensitivity analysis without the trial of Burr et al (A79; see http://www.bice.ch/engl/publications_reports.htm): RR for overall mortality, 0.80 (95% CI, 0.69-0.92; P=.40; I²=6% [95% UI, 0%-69%]).

the remaining n-3 fatty acid trials. The quality of that trial in comparison with the other trials was low.¹⁶ With exclusion of that trial, the RR for overall mortality was 0.75 (95% CI, 0.65-0.87), and heterogeneity was substantially reduced (P=.36; I²=9% [95%UI, 0%-47%]).

CARDIAC MORTALITY

Risk ratios for cardiac deaths indicated a statistically significant benefit from statins (0.78; 95% CI, 0.72-0.84; P=.42; I²=3% [95% UI, 0%-30%]), resins (0.70; 95% CI, 0.50-0.99; P=.83; I²=0% [95% UI, 0%-68%]), and n-3 fatty acids (0.68; 95% CI, 0.52-0.90; P=.001; I²=66% [95% UI, 37%-81%]). Again, when excluding Burr et al (A79) in sensitivity analysis from the group of n-3

fatty acids, heterogeneity decreased immensely (RR, 0.70; 95% CI, 0.61-0.80; P=.47; I²=0% [95% UI, 0%-60%]).

MORTALITY FROM CAUSES OTHER THAN CARDIOVASCULAR DISEASE

Risk ratios for death from causes other than cardiovascular disease were all nonsignificant except for fibrates, for which we found an increased risk of death (RR, 1.13; 95% CI, 1.01-1.27; P=.80, I²=0% [95% UI, 0%-54%]). In a post hoc subgroup analysis, we did not find an increased risk of death from neoplasia in fibrate trials; however, the limited number of trials providing detailed noncardiovascular, cause-specific mortality data precluded a

more detailed analysis of noncardiovascular mortality.

META-REGRESSION ANALYSIS

In univariate meta-regression analysis, only the percentage of patients with established CHD (coefficient, -0.001; 95% CI, -0.003 to -0.0003) and trial duration (coefficient, 0.043; 95% CI, 0.014 to 0.072) were associated with and explained a statistically significant degree of variability in the log odds ratio for overall mortality. This indicates that the magnitude of the effect of a lipid-lowering intervention tends to increase in trials with a higher percentage of participants with established CHD and to decrease in trials of longer duration. Cholesterol level reduction was only statistically significant in the model

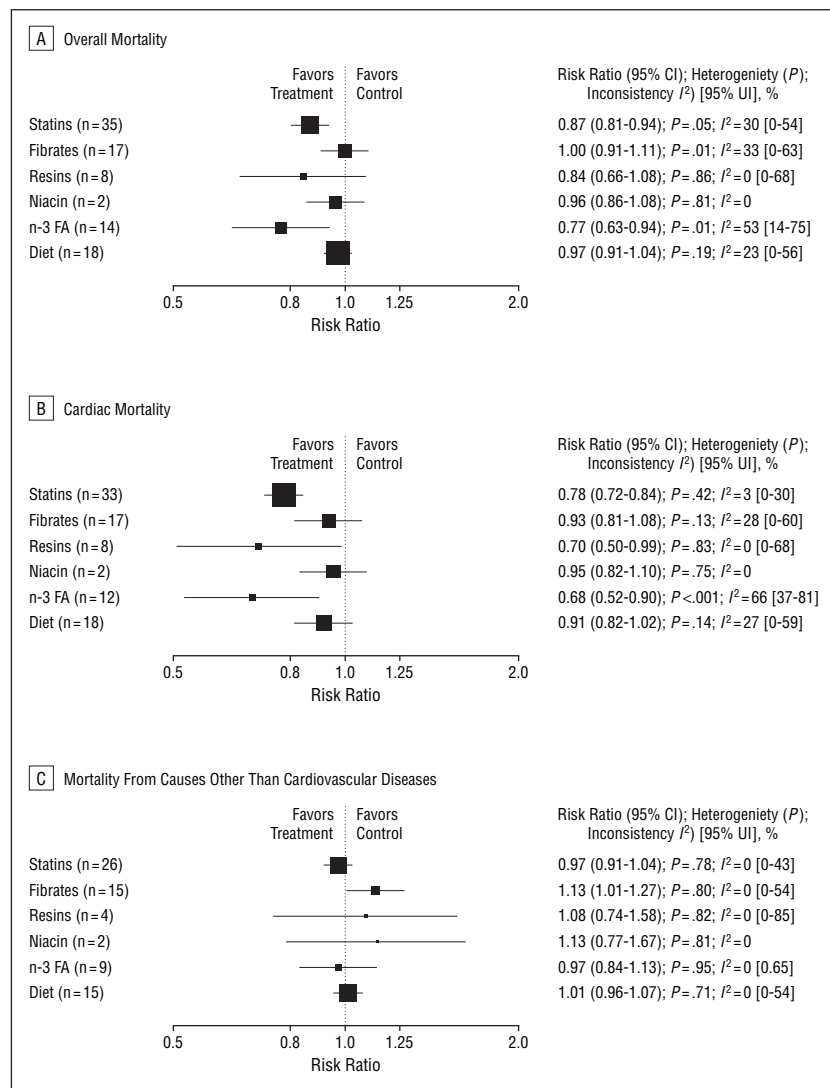


Figure. Summary estimates for overall mortality (A), cardiac mortality (B), and mortality from causes other than cardiovascular diseases (C) for different types of lipid-lowering interventions. The Cochran *Q* test for heterogeneity. *I*² as measure of inconsistency (in percent). CI indicates confidence interval; UI, uncertainty interval; n, number of trials available for analysis; n-3 FA, n-3 fatty acid.

when n-3 fatty acid trials were excluded (coefficient, -0.92 ; 95% CI, -1.52 to -0.32). When each lipid-lowering intervention was examined separately (eg, trials of fibrates vs trials of interventions other than fibrates), use of fibrates was the only intervention that explained a statistically significant degree of variability in the log odds ratio for overall mortality (coefficient, 0.14 ; 95% CI, 0.004 to 0.27), indicating a positive association of fibrates with overall mortality.

In meta-regression analysis within subgroups of different lipid-lowering interventions, the percentage of patients with established CHD explained all between-trial vari-

ance in the subgroup of trials with statins ($\tau^2=0.011$) and trials with fibrates ($\tau^2=0.017$). These findings are consistent with the observed decrease in heterogeneity in subgroups of primary and secondary prevention trials for these interventions (Table 1).

COMMENT

This systematic review of randomized controlled trials examines the association between different lipid-lowering interventions and mortality from various causes. Our study confirms the benefit of statins in reducing the risk of overall and cardiac mor-

tality² in patients with or without CHD and additionally shows that n-3 fatty acids reduce overall and cardiac mortality in patients with CHD. We estimated that 248 (95% CI, 170-538) patients in a secondary prevention situation with a mortality rate higher than 3% per year and 855 (95% CI, 585-1852) patients in a primary prevention situation with a mortality rate lower than 1% per year have to be treated with a statin for 1 year to prevent 1 death. For n-3 fatty acids, 140 (95% CI, 87-538) patients in a secondary prevention situation have to be treated for 1 year to prevent 1 death.

In contrast, we found no reduction in overall mortality and an increased risk of death from noncardiovascular causes in individuals taking fibrates compared with individuals in placebo or control groups. We found little evidence of heterogeneity in the summary estimates for noncardiovascular mortality in fibrate trials (test of heterogeneity $P=.80$; $I^2=0\%$), suggesting a consistent effect in trials using various fibrates. Niacin and fibrates have excellent properties to increase high-density lipoprotein cholesterol levels and reduce triglyceride levels. Current guidelines recommend the use of either drug in patients with hypertriglyceridemia, high levels of low-density lipoproteins, and metabolic syndrome.^{17,18} If used in appropriate doses, n-3 fatty acids are as effective as fibrates to reduce triglyceride levels¹⁹ but are associated with a reduction in overall mortality. However, n-3 fatty acids lower total cholesterol level to a very small extent, which indicates that beneficial effects must be mediated by other means. Studies suggest that n-3 fatty acids may have antiarrhythmic properties with membrane-stabilizing effects in addition to antithrombotic and anti-inflammatory properties on the endothelial level.¹⁶ Summary estimates for resins and dietary interventions indicated possible benefit in cardiac mortality, though confidence intervals were large or included an RR of 1. However, for both interventions we found little evidence that these interventions may affect overall mortality in primary or secondary prevention of CHD.

Table 2. Sensitivity Analysis of Quality Components for Statins, Fibrates, and n-3 Fatty Acids

Quality Component	Statins			Fibrates			n-3 Fatty Acids		
	Trials, No.	Overall Mortality, RR (95% CI)	Difference P Value	Trials, No.	Overall Mortality, RR (95% CI)	Difference P Value	Trials, No.	Overall Mortality, RR (95% CI)	Difference P Value
Concealed allocation									
Yes	11	0.90 (0.83-0.98)	.18	6	1.00 (0.92-1.08)	.88	5	0.76 (0.55-1.06)	.95
No	24	0.82 (0.71-0.93)		11	0.97 (0.77-1.23)		9	0.75 (0.55-1.03)	
Blinded patients and caregivers									
Yes	29	0.87 (0.80-0.94)	.46	14	1.01 (0.91-1.12)	.56	9	0.59 (0.41-0.86)	.07*
No	6	0.77 (0.54-1.09)		3	0.81 (0.43-1.54)		5	0.82 (0.65-1.04)*	
Blinded outcome assessors									
Yes	20	0.85 (0.80-0.92)	.59	9	1.01 (0.90-1.15)	.69	11	0.72 (0.61-0.86)	<.001†
No	15	0.96 (0.67-1.36)		8	0.95 (0.75-1.21)		3	1.15 (0.98-1.34)†	
Follow-up >90%									
Yes	24	0.87 (0.81-0.93)	.90	13	1.01 (0.89-1.14)	.76	8	0.78 (0.60-1.01)	.56
No	11	0.91 (0.51-1.63)		4	0.96 (0.74-1.24)		6	0.71 (0.56-0.91)	

Abbreviations: CI, confidence interval; RR, risk ratio.

*Sensitivity analysis without the trial of Burr et al (A79; see http://www.bice.ch/engl/publications_reports.htm): RR for overall mortality, 0.75 (95% CI, 0.60-0.92); difference P value, .15.

†Sensitivity analysis without the trial of Burr et al (A79): RR for overall mortality, 1.25 (95% CI, 0.31-5.07); difference P value, .78.

Our study has several strengths and limitations. We have conducted an extensive literature search to retrieve all relevant eligible trials. Although formal testing for publication bias indicated little evidence for such bias, it cannot be ruled out. For clinical end points we exclusively used mortality data that may be less prone to ascertainment bias. Given the heterogeneity in all included trials ($P < .001$; $I^2 = 37\%$ [95% UI, 19%-51%]), a subgroup analysis was justifiable. We have limited our subgroup analyses to the clinically relevant question of whether different lipid-lowering interventions provide similar benefit in trials for primary and secondary prevention of CHD. Nevertheless, such analyses may be prone to bias and should be carefully interpreted.²⁰ In particular, our evaluation of different lipid-lowering interventions relies on between-trial rather than within-trial comparisons. Thus, apparent differences in efficacy between interventions inferred from between-trial comparisons may actually be due to factors other than the intervention, including differences in study design and populations. Finally, it may be argued that our classification of lipid-lowering interventions combines antilipidemic agents or diets with important pharmacological differences or mechanisms of action.⁹ For example, trials of n-3 fatty

acids used different dietary and non-dietary sources with food supplements of n-3 fatty acids or n-3 fatty acid precursors.

In conclusion, this systematic review suggests that statins and n-3 fatty acids offer the most favorable benefits by reducing the risk of cardiac and overall mortality. Use of fibrates may be associated with an increased risk of noncardiovascular mortality. Future trials should explore whether n-3 fatty acids in combination with statins lead to additional reduction in CHD mortality, especially in patients with metabolic syndrome.

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Correction

Omissions in Byline. In the Original Investigation by Cohen et al titled “Emerging Credentialing Practices, Malpractice Liability Policies, and Guidelines Governing Complementary and Alternative Medical Practices and Dietary Supplement Recommendations: A Descriptive Study of 19 Integrative Health Care Centers in the United States,” published in the February 14 issue of the ARCHIVES (2005;165:289-295), 2 authors were inadvertently omitted from the byline on page 289. The byline should have appeared as follows: “Michael H. Cohen, JD; Andrea Hrbek; Roger B. Davis ScD; Steven C. Schachter, MD; Kathi J. Kemper, MD, MPH; Edward W. Boyer, MD, PhD; David M. Eisenberg, MD.”