Systematic Review on the Risk and Benefit of Different Cholesterol-Lowering Interventions

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Abstract—Meta-analyses have investigated the efficacy of cholesterol-lowering interventions in relation to the underlying risk of coronary heart disease and the extent and duration of cholesterol reduction. We systematically reviewed the efficacy of antilipidemic interventions on major mortality outcomes in relation to drug classes. We searched MEDLINE and EMBASE from 1966 through October 1996 for randomized, controlled trials of any cholesterol-lowering interventions reporting mortality data. We included 59 trials involving 85 431 participants in the intervention and 87 729 participants in the control groups. We pooled these trials into 7 pharmacological categories of cholesterol-lowering interventions: statins (13 trials), fibrates (12 trials), resins (8 trials), hormones (8 trials), niacin acid (2 trials), n-3 fatty acids (3 trials), and dietary interventions (16 trials). Of the cholesterol-lowering interventions, only statins showed a large and statistically significant reduction in mortality from coronary heart disease (risk ratio, 0.66; 95% confidence interval [CI], 0.54 to 0.79) and from all causes (risk ratio, 0.75; 95% CI, 0.65 to 0.86). For both all-cause and cardiovascular mortality, the difference between statins and the combined estimate of the other classes of agents was unlikely to be due to chance ($P<0.02$ for both comparisons). Meta-regression analysis demonstrated that variability in results across trials could be largely explained on the basis of differences in the magnitude of cholesterol reduction. Statins have the largest effect on the reduction of cardiovascular and all-cause mortality, and this result recommends their use in preference to other antilipidemic agents. The greater effect of statins is likely due to the larger reduction in cholesterol. **(*Arterioscler Thromb Vasc Biol.* 1999;19:187-195.)**

Key Words: coronary disease ■ hypercholesterolemia ■ meta-analysis ■ myocardial infarction ■ mortality

Recently, 2 large clinical trials in the primary and secondary prevention of coronary heart disease have shown that cholesterol-lowering interventions with 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors reduce coronary heart disease and overall mortality.[1,2] In contrast to previous trials, both of these studies showed no increase in risk of death from noncardiovascular causes.[3–6] These findings suggest that the net benefit and adverse effects of cholesterol-lowering interventions may depend on drug class. Recent guidelines, including those of the American College of Physicians,[7,8] have therefore emphasized the need to base treatment decisions on the separate evaluation of each type of cholesterol-lowering intervention.

However, information from systematic reviews of the efficacy of cholesterol-lowering interventions according to drug classes is limited.[9] The focus of previous systematic reviews was primarily on the underlying risk of coronary heart disease[5] or the extent and duration of cholesterol reduction in relation to the expected benefit,[5,10] and all were based on data before publication of the large HMG-CoA reductase inhibitor trials. We present a comprehensive, systematic review that specifically examines the effects of different types of cholesterol-lowering interventions on mortality outcomes.

Methods

Selection Criteria

We systematically searched the literature by using MEDLINE, EMBASE, and previously published meta-analyses to identify randomized, controlled trials of any cholesterol-lowering intervention published from 1966 through October 1996. We included all trials that reported mortality outcomes irrespective of the duration, the type of cholesterol-lowering intervention (multifactorial or unifactorial cholesterol-lowering intervention), or setting (primary or secondary prevention trials of coronary heart disease). Angiographic studies that fulfilled the selection criteria were also included. For trials with missing mortality data, we contacted the authors of the original publications or the authors of previously published meta-analyses and requested the missing information. We evaluated the impact of treatment on total mortality, mortality from coronary heart disease, and mortality from causes other than coronary heart disease.

We identified 66 randomized, controlled trials reporting mortality data. We classified trials based on similar pharmacological characteristics to lower cholesterol into the following categories: HMG-CoA reductase inhibitors, 13 trials (lovastatin, 5 trials[11–15]; prava-

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TABLE 1. Baseline Characteristics and Mortality Data From Various Causes in Randomized, Controlled Trials of Cholesterol-Lowering Interventions

Study (Year of Publication) Reference No.	Type of Intervention	Type of Study	Duration, y	Baseline Cholesterol, mmol/L (Percent Reduction)	No. of Individuals Intervention/ Control	Fatal Coronary Heart Disease: No. Intervention/ Control	Fatal Coronary Heart Disease: Risk Ratio (95% CI)
Statins							
Sahni (1991)[11]	Lovastastin/placebo	S,U	2.0	5.4 (12.8)	79/78	2/4	0.55 (0.12–2.50)
EXCEL (1991)[12]	Lovastatin/placebo	P,U	0.9	6.7 (24.0)	6582/1663	28/3	2.06 (0.68–6.24)
MARS (1993)[13]	Lovastatin/placebo	S,U	2.0	6.0 (32.0)	123/124	0/1	0.34 (0.01–8.17)
PMSG (1993)[16]	Pravastatin/placebo	S,U	0.5	6.8 (18.4)	530/532	0/1	0.33 (0.01–8.20)
Weintraub (1994)[14]	Lovastatin/placebo	S,U	0.5	5.3 (34.0)	203/201	3/1	2.31 (0.34–15.50)
SSSS (1994)[1]	Simvastatin/placebo	S,U	5.4	6.75 (26.0)	2221/2223	111/189	0.59 (0.47–0.74)
MAAS (1994)[21]	Simvastatin/placebo	S,U	4.0	6.4 (22.7)	193/188	4/5	0.80 (0.23–2.73)
Waters (1994)[15]	Lovastatin/placebo	S,U	2.0	6.5 (19.6)	165/166	2/1	1.68 (0.22–12.55)
Furberg (1994)[17]	Pravastatin/placebo	S,U	3.0	4.3 (29.0)	75/76	2/2	1.01 (0.18–5.68)
REGRESS (1995)[18]	Pravastatin/placebo	S,U	2.0	6.0 (18.7)	450/434	1/1	0.96 (0.10–9.24)
WOSCOPS (1995)[2]	Pravastatin/placebo	S,U	4.9	7.1 (20.0)	3302/3293	38/52	0.73 (0.48–1.11)
KAPS (1995)[19]	Pravastatin/placebo	S,U	3.0	6.7 (20.1)	224/223	0/2	0.20 (0.01–4.12)
CARE (1996)[20]	Pravastatin/placebo	S,U	5.0	5.4 (20.0)	2081/2078	96/116	0.81 (0.62–1.05)
n-3 Long-chain fatty acids and precursors							
DART (1989)[50]	Fish/low fat	S,U	2.0	6.5 (4.0)	1015/1018	78/116	0.67 (0.51–0.89)
de Lorgeril (1994)[51]	α-Linoleic acid/usual diet	S,U	2.3	6.5 (5.1)	302/303	3/16	0.21 (0.07–0.67)
Sacks (1995)[52]	Fish oil/olive oil	S,U	2.4	4.9 (0.12)	31/28	0/1	0.30 (0.01–7.13)
Fibrates							
Harrold (1969)[22]	Clofibrate/placebo	S,U	1.0	NA	30/33	0/2	0.22 (0.01–4.39)
Newcastle (1971)[23]	Clofibrate/placebo	S,U	5.0	6.5 (9.8)	244/253	25/44	0.59 (0.38–0.94)
Scottish (1971)[24]	Clofibrate/placebo	S,U	6.0	7.0 (16.0)	350/367	34/35	1.02 (0.65–1.50)
Begg (1971)[25]	Clofibrate/placebo	S,U	3.5	6.5 (10.8)	76/79	4/9	0.49 (0.17–1.45)
Acheson (1972)[26]	Clofibrate/placebo	S,U	6.0	7.5 (8.5)	47/48	13/5	2.51 (1.01–6.21)
VA Neurology Section (1974)[27]	Clofibrate/placebo	S,U	1.8	6.3 (3.0)	268/264	11/12	0.91 (0.41–1.98)
Cullen (1974)[28]	Clofibrate/placebo	P,U	2.0	NA	20/20	0/1	
CDP (1975)[29]	Clofibrate/placebo	S,U	6.2	6.5 (6.8)	1103/2789	195/583	0.85 (0.73–0.98)
WHO (1978)[30]	Clofibrate/olive oil	P,U	5.3	6.8 (9.0)	5331/5296	91/77	1.17 (0.87–1.58)
Frick (1987)[32]	Gemfibrozil/placebo	P,U	5.0	6.9 (10.1)	2051/2030	14/19	0.74 (0.37–1.45)
Frick (1993)[31]	Gemfibrozil/placebo	S,U	5.0	6.9 (8.5)	311/317	17/8	2.10 (0.94–4.69)
Ericsson (1996)[33]	Bezafibrate/placebo	S,U	5.0	6.9 (8.4)	42/39	2/0	
Resins							
Gross (1973)[38]	Colestipol/placebo	S,U	1.0	8.0 (19.5)	23/29	1/0	3.75 (0.16–87.98)
Ryan (1974)[39]	Colestipol/placebo	P,U	3.0	7.6 (16.0)	44/48	1/1	1.09 (0.12–10.09)
Gundersen (1976)[41]	Colestipol/placebo	P,U	0.8	6.0 (15.1)	36/30	36/29	0.28 (0.01–6.62)
Dorr (1978)[37]	Colestipol/placebo	P,U	1.9	7.9 (9.4)	1149/1129	19/31	0.61 (0.35–1.06)
Ruoff (1978)[40]	Colestipol/placebo	P,U	3.2	7.8 (22.4)	21/19	21/18	0.30 (0.01–7.02)
NHLBI (1984)[36]	Cholestyramine/ placebo	S,U	5.0	8.4 (11.5)	71/72	5/6	0.86 (0.29–2.55)
LCCPPT (1984)[36]	Cholestyramine/ placebo	P,U	7.4	7.2 (8.5)	1906/1900	30/38	0.79 (0.49–1.26)
STARS (1992)[34]	Cholestyramine/ usual diet	S,U	3.0	7.2 (23.8)	30/30	0/3	0.14 (0.01–2.65)
Niacin							
VA drug (1968)[44]	Niacin/placebo	S,U	3.2	6.2 (13.2)	77/143	71/23	1.02 (0.67–1.57)
CDP (1975)[29]	Niacin/placebo	S,U	6.2	6.5 (8.2)	1119/2789	203/583	
Hormones							
Oliver (1961)[46]	Estrogen/lactose	S,U	5.0	6.1 (12.4)	50/50	13/10	1.29 (0.63–2.61)
Marmorstein (1962)[42]	Estrogen/placebo	S,U	5.0	NA	285/147	63/29	1.11 (0.75–1.64)
Stamler (1963)[43]	Estrogen/placebo	S,U	5.0	6.4 (3.0)	156/119	34/39	0.67 (0.45–0.99)
VA Neurology Section (1966)[48]	Estrogen/placebo	S,U	1.4	NA	295/287	11/11	0.97 (0.44–2.17)

S indicates secondary prevention; U, unifactorial design; P, primary prevention; M, multifactorial design; and NA, not applicable.

TABLE 1. Continued

All Deaths		Non–Coronary Heart Disease Deaths	
No. Intervention/ Control	Risk Ratio (95% CI)	No. Intervention/ Control	Risk Ratio (95% CI)
4/5	0.81 (0.24–2.70)	2/1	1.65 (0.22–12.16)
33/3	2.42 (0.81–7.27)	5/0	2.78 (0.15–50.26)
1/0	1.01 (0.11–9.56)	1/0	3.02 (0.12–73.53)
0/1	0.33 (0.01–8.20)	0/0	
3/1	2.31 (0.34–15.50)	0/0	
182/256	0.71 (0.60–0.85)	71/67	1.06 (0.76–1.47)
4/11	0.38 (0.13–1.11)	0/6	0.07 (0.0–1.32)
2/2	1.01 (0.18–5.73)	0/1	0.34 (0.01–8.17)
3/5	0.64 (0.18–2.37)	1/3	0.43 (0.07–2.86)
3/3	0.96 (0.22–4.22)	2/2	0.96 (0.17–5.54)
106/136	0.78 (0.61–1.01)	68/83	0.82 (0.60–1.12)
3/4	0.77 (0.19–3.09)	1/2	0.60 (0.08–4.48)
180/196	0.92 (0.75–1.11)	84/77	1.08 (0.80–1.47)
94/130	0.72 (0.56–0.93)	16/14	1.14 (0.56–2.30)
8/20	0.42 (0.19–0.91)	5/4	1.23 (0.36–4.22)
0/1	0.30 (0.01–7.13)	0/0	
0/3	0.16 (0.01–2.91)	0/1	0.37 (0.02–8.65)
31/51	0.63 (0.42–0.95)	6/7	0.90 (0.32–2.53)
42/45	0.98 (0.66–1.45)	8/10	0.85 (0.35–2.07)
4/10	0.45 (0.15–1.28)	0/1	0.35 (0.01–8.37)
23/20	1.17 (0.75–1.81)	10/15	0.69 (0.35–1.36)
22/30	0.73 (0.43–1.22)	11/18	0.61 (0.30–1.25)
1/2	0.60 (0.09–4.14)	1/1	
281/723	0.98 (0.87–1.11)	86/140	1.56 (1.20–2.01)
236/91	2.57 (2.02–3.26)	145/14	9.97 (5.82–17.08)
44/43	1.01 (0.67–1.53)	30/24	1.23 (0.73–2.09)
19/12	1.59 (0.80–3.18)	2/4	0.57 (0.12–2.64)
2/0		0/0	
1/2	0.75 (0.11–5.28)	0/2	0.25 (0.01–4.96)
1/1	1.09 (0.12–10.09)	0/0	
0/1	0.28 (0.01–6.62)	0/0	
37/48	0.76 (0.50–1.15)	18/17	1.04 (0.54–1.99)
0/1	0.30 (0.01–7.02)	0/0	0.91 (0.02–43.71)
5/7	0.74 (0.26–2.13)	0/1	0.34 (0.01–8.16)
68/71	0.96 (0.69–1.32)	38/33	1.15 (0.72–1.81)
0/3	0.14 (0.01–2.65)	0/0	
81/27	1.0 (0.68–1.47)	10/4	0.79 (0.26–2.33)
273/723		70/140	
17/12	1.40 (0.76–2.59)	4/2	1.80 (0.40–8.04)
71/32	1.14 (0.79–1.64)	8/3	1.26 (0.37–4.29)
37/40	0.71 (0.49–1.03)	3/1	1.78 (0.27–11.90)
34/29	1.14 (0.72–1.81)	23/18	1.24 (0.69–2.22)

statin, 6 trials[2,16–20]; and simvastatin, 2 trials[1,21]); fibrates, 12 trials (clofibrate, 9 trials[22–30]; gemfibrozil, 2 trials[31,32]; and bezafibrate, 1 trial[33]); resins, 8 trials (cholestyramine, 3 trials[34–36]; colestipol, 5 trials[37–41]); hormones, 8 trials (estrogen, 7 trials[42–48]; thyroxine, 1 trial[49]); n-3 fatty acids and their precursors, 3 trials[50–52]; and niacin, 2 trials.[29,44] Sixteen trials were dietary interventions and were grouped into 1 category.[34,53–67] Two trials were single interventions with probucol[68] and partial ileal bypass grafting[69] and were therefore not grouped.

We excluded 6 trials with multiple drug interventions[70–75] because these studies did not allow us to assign them to a specific type of cholesterol-lowering intervention. We additionally excluded 1 study because no cause-specific mortality data were reported[76] and 1 trial that was conducted in patients with cardiac transplantation.[77] Thus, we included 59 trials involving 85 431 subjects in the intervention and 87 729 subjects in the control groups. Table 1 provides detailed information about relevant data from the included trials.

Statistical Analysis

We computed summary estimates with 95% confidence intervals (CIs) for each cholesterol-lowering category and calculated a weighted-average risk ratio of all outcomes by using a random-effect model.[78] We report 2-tailed *P* values for all analyses. We tested for heterogeneity by using the Breslow-Day test.[79] When we found a relevant treatment effect for a specific drug category, we tested whether this difference was statistically significant when compared with the total of all other cholesterol-lowering interventions. We used the *z* score from such drug categories and from the remaining studies and divided the difference of the summary log relative risk from both groups by the standard error of the difference.

For the control group of each trial, we calculated the death rate from coronary heart disease per 1000 person-years. This rate reflects the degree of risk of death from coronary heart disease for participants enrolled in a trial and randomly allocated to the no-treatment group. The rate was calculated by dividing the number of deaths from coronary heart disease occurring in the control group by an approximation of the person-years at risk in the study by using the following formula[5]: {coronary heart disease deaths/year of follow-up×[number alive at the end of the trial+0.5 (number dying during the study)]}×1000. Coronary heart disease death rates were then combined for each intervention category. Each trial was weighted by the inverse of the variance. Data on average cholesterol reduction by intervention category represent the unweighted mean percent reduction.

To further explore the relationship of the type of cholesterol-lowering intervention with coronary heart disease and overall mortality, we conducted a meta-regression by using a weighted least-squares linear regression model. The dependent variable in the model was the natural logarithm of the relative risk (ln RR) for each study, and the weights were the reciprocals of the variances for the ln RR.[80] The independent variables we considered for analysis were the type of intervention (HMG-CoA reductase inhibitors versus all other interventions), trial setting (primary versus secondary prevention), trial design (unifactorial versus multifactorial intervention), baseline risk for coronary heart disease, and absolute and relative reductions of cholesterol. All analyses were conducted using the Statistical Analysis System.[81]

Results

Coronary Heart Disease Mortality

Trials with HMG-CoA reductase inhibitors achieved the highest mean cholesterol reduction (22.9%; range, 12.8% to 32.0%) compared with the other intervention categories. The baseline risk of death from coronary heart disease in trials with HMG-CoA reductase inhibitors was 2% and lower when compared with other drug or dietary interventions. Of all cholesterol-lowering interventions, only HMG-CoA reductase inhibitors showed a statistically significant reduction of

TABLE 1. Continued

Study (Year of Publication) Reference No.	Type of Intervention	Type of Study	Duration, y	Baseline Cholesterol, mmol/L (Percent Reduction)	No. of Individuals Intervention/ Control	Fatal Coronary Heart Disease	
						No. Intervention/ Control	Risk Ratio (95% CI)
VA drug (1968)[44]	Estrogen/thyroxine/ placebo	S,U	3.2	6.2 (6.3)	427/143	11/11	1.06 (0.58–1.95)
CDP (1975)[49]	Thyroxine/placebo	S,U	3.0	6.5 (11.0)	1083/2715	119/274	1.09 (0.89–1.34)
CDP (1975)[47]	Estrogen 5.0 mg/placebo	S,U	1.5	6.5 (n.a.)	1119/2788	67/133	1.26 (0.95–1.67)
CDP (1975)[46]	Estrogen 2.5 mg/placebo	S,U	4.7	6.5 (NA)	1101/2789	162/410	1.00 (0.85–1.19)
Dietary interventions							
Low fat (1965)[53]	Low fat/usual diet	S,U	3.0	6.8 (6.6)	123/129	17/20	0.89 (0.50–1.61)
Rose (1965)[54]	Olive oil/usual diet	S,U	2.0	6.7 (3.6)	54/26	8/1	2.78 (0.52–14.83)
Dayton (1969)[55]	Diet/usual diet	P,U	8.0	6.1 (12.7)	424/422	41/50	0.82 (0.55–1.21)
Soya bean (1968)[56]	Soya bean oil/usual diet	S,U	3.2	7.0 (14.3)	199/194	25/25	0.98 (0.58–1.63)
Oslo diet (1970)[57]	Diet/usual diet	S,U	5.0	7.7 (14.4)	206/206	37/50	0.74 (0.51–1.08)
Woodhill (1978)[58]	Diet/usual diet	S,U	5.0	7.3 (4.0)	221/237	35/26	1.44 (0.90–2.30)
Kallio (1979)[59]	Diet/usual diet	S,M	3.0	6.0 (12.0)	188/187	35/55	0.64 (0.44–0.92)
Hjermann (1981)[60]	Diet/usual diet	P,M	6.5	8.4 (10.0)	604/628	6/14	0.47 (0.19–1.17)
MRFIT (1982)[61]	Diet/usual diet	P,M	6.5	6.5 (2.0)	6428/6438	115/124	0.93 (0.72–1.19)
Miettinen (1985)[62]	Diet, drugs/usual diet	P,M	5.0	7.1 (6.0)	612/610	4/1	2.99 (0.47–18.91)
WHO collaborative (1986)[63]	Diet/usual diet	P,M	5.5	5.5 (1.0)	24 615/25 169	428/398	0.95 (0.83–1.09)
Gothenburg (1986)[64]	Diet drugs/no intervention	P,M	10.0	6.5 (0)	10 004/20 028	462/923	1.00 (0.90–1.12)
Minnesota (1989)[65]	Diet/usual diet	P,U	1.0	5.4 (13.8)	4541/4516	61/54	1.12 (0.78–1.61)
Ornish (1990)[66]	Diet/usual diet	S,M	1.0	6.1 (25.8)	28/20	1/0	2.17 (0.09–50.75)
STARS (1992)[34]	Diet/usual diet	S,U	3.0	7.2 (11.1)	30/30	1/3	0.43 (0.07–2.72)
Singh (1992)[67]	Strict diet/usual diet	S,U	2.0	5.9 (9.0)	204/202	25/45	0.55 (0.36–0.87)
Nongrouped interventions							
McCaughan (1981)[68]	Probucol/placebo	S,U	1.0	7.9 (8.0)	88/30	2/2	0.35 (0.06–1.92)
POSCH (1990)[69]	Partial ileum bypass surgery/control	S,U	6.5	6.5 (22.5)	421/417	32/44	0.72 (0.47–1.11)
Trials using different combination therapies that reported mortality data were excluded from the analysis.							
CLAS (1987)[70]	Colestipol, niacin/placebo	S,U	2.0	6.3 (22.0)	94/94	0/1	0.33 (0.01–8.08)
Stockholm (1988)[71]	Clofibrate, niacin/placebo	S,U	5.0	6.4 (13.0)	279/276	47/73	0.64 (0.46–0.88)
SCOR (1990)[72]	Various drugs/diet	P,U	2.0	9.6 (24.5)	48/49	0/0	
FATS (1990)[73]	Various drugs/diet	S,U	2.5	7.0 (24.9)	94/52	1/0	1.67 (0.07–40.37)
SCRIP (1994)[74]	Various drugs/usual care	S,M	4.0	5.9 (15.1)	145/155	2/3	0.76 (0.15–3.81)
HARP (1994)[75]	Various drugs/placebo	S,U	2.5	5.4 (28.0)	40/39	1/1	0.98 (0.11–8.99)

S indicates secondary prevention; U, unifactorial design; P, primary prevention; M, multifactorial design; and NA, not applicable.

coronary heart disease mortality (Table 2 and Figure 1). The risk ratio of death from coronary heart disease was 0.69 (95% CI, 0.59 to 0.80). This estimate was statistically significantly different from the combined estimates of all other interventions (risk ratio of coronary heart disease mortality from all trials with the exception of HMG-CoA reductase inhibitors, 1.03; 95% CI, 0.86 to 1.24; *P* value for difference of summary estimates=0.02). For resins, we found a risk ratio of borderline significance (0.71; 95% CI, 0.51 to 0.99), but there was also significant heterogeneity. For all other interventions, summary estimates did not reach conventional levels of significance.

Overall Mortality

HMG-CoA reductase inhibitors and n-3 fatty acids and their precursors were the intervention categories that showed a statistically significant reduction in overall mortality (Table 2 and Figure 2). For HMG-CoA reductase inhibitors, the risk ratio of death from all causes was 0.79 (95% CI, 0.71 to 0.89). The summary risk ratio for

TABLE 1. Continued

All Deaths		Non–Coronary Heart Disease Deaths	
No. Intervention/ Control	Risk Ratio (95% CI)	No. Intervention/ Control	Risk Ratio (95% CI)
34/29	1.04 (0.60–1.82)	23/18	1.03 (0.22–4.70)
160/339	1.18 (1.00–1.41)	41/65	1.59 (1.08–2.33)
91/193	1.18 (0.93–1.50)	24/60	1.01 (0.63–1.60)
219/525	1.06 (0.92–1.22)	57/115	1.26 (0.93–1.72)
20/24	0.88 (0.52–1.49)	3/4	0.82 (0.21–3.23)
8/1	2.78 (0.52–14.83)	0/0	
174/178	0.97 (0.83–1.14)	133/128	1.03 (0.85–1.26)
28/31	0.88 (0.55–1.41)	3/6	0.53 (0.15–1.90)
41/55	0.75 (0.53–1.06)	4/5	0.82 (0.24–2.80)
39/28	1.49 (0.95–2.32)	4/2	1.93 (0.42–8.96)
41/56	0.73 (0.52–1.03)	6/1	4.31 (0.74–25.15)
16/24	0.70 (0.38–1.29)	10/10	1.04 (0.45–2.43)
265/260	1.02 (0.86–1.21)	150/136	1.10 (0.88–1.39)
10/5	1.90 (0.68–5.31)	6/4	1.44 (0.44–4.76)
1325/1186	0.99 (0.92–1.07)	897/788	1.01 (0.92–1.11)
1293/1636	1.58 (1.48–1.70)	831/1713	0.97 (0.90–1.05)
269/248	1.08 (0.91–1.28)	208/194	1.07 (0.88–1.29)
1/0	2.17 (0.09–50.75)	0/0	
1/3	0.43 (0.07–2.72)	0/0	
28/51	0.55 (0.36–0.83)	3/6	0.53 (0.15–1.93)
2/3	0.25 (0.05–1.20)	0/1	0.12 (0–2.78)
49/62	0.78 (0.55–1.11)	17/18	0.94 (0.49–1.77)
0/1	0.33 (0.01–8.08)	0/0	
61/82	0.74 (0.55–0.98)	14/9	1.51 (0.68–3.36)
0/1	0.34 (0.01–8.15)	0/1	0.34 (0.01–8.15)
1/0	1.67 (0.07–40.37)	0/0	
3/3	1.07 (0.25–4.62)	1/0	3.21 (0.13–78.07)
1/1	0.98 (0.11–8.99)	0/0	

HMG-CoA reductase inhibitors was statistically significantly different when compared with the combined estimates of all other interventions (risk ratio of overall mortality from all trials with the exception of HMG-CoA reductase inhibitors, 1.03; 95% CI, 0.86 to 1.25; *P* value for difference=0.02). For n-3 fatty acids, the risk ratio of death from all causes was 0.68 (95% CI, 0.53 to 0.88), which was statistically significantly different when compared with all other cholesterol-lowering interventions (risk ratio, 1.00; 95% CI, 0.88 to 1.13; *P* value for difference=0.007).

Mortality From Causes Other Than Coronary Heart Disease

For HMG-CoA reductase inhibitors, the risk ratio of death from causes other than coronary heart disease was 0.97 (95% CI, 0.81 to 1.16; Table 2 and Figure 3). This estimate was also statistically significantly different when compared with all other cholesterol-lowering interventions (risk ratio, 1.51; 95% CI, 1.07 to 2.13). The summary estimate for hormones indicated harm, with increased mortality from non–coronary heart disease causes (risk ratio, 1.29; 95% CI, 1.06 to 1.57) and mortality from all causes (risk ratio, 1.09; 95% CI, 1.00 to 1.20).

Exploring Additional Reasons for Variability in Results

In a meta-regression analysis, we further explored the relationship of the type of cholesterol-lowering intervention and coronary heart disease and overall mortality. In univariate analysis, the type of intervention (HMG-CoA reductase inhibitors compared with other interventions) was highly significantly related to both coronary heart disease and overall mortality ($P=0.006$ for each end point). Additional factors that were statistically significantly related to overall mortality were trial setting (lower mortality reduction in primary versus secondary prevention trials; $P=0.0001$), trial design (higher mortality reduction in unifactorial versus multifactorial intervention trials; $P=0.0001$), baseline risk for coronary heart disease (higher mortality reduction in trials in which patients were at higher risk; $P=0.0006$), and the absolute and relative reductions of cholesterol (higher mortality reduction when cholesterol reduction was greater; $P=0.0001$ in both cases). The factors that were additionally related to coronary heart disease mortality were the absolute and relative reductions of cholesterol (higher mortality reduction when cholesterol reduction was greater; $P=0.001$ and $P=0.002$, respectively).

Multivariable analysis showed that after entering the trial setting (primary versus secondary prevention), trial design (unifactorial versus multifactorial intervention), and baseline risk for coronary heart disease into the model, the type of intervention still explained a statistically significant degree of variability for both cardiovascular and all-cause mortality ($P=0.004$ for overall mortality and $P=0.0001$ for coronary heart disease mortality). However, when we entered the degree of cholesterol reduction into the model, no other variable explained a statistically significant degree of the remaining variability in analysis of either end point.

Discussion

Recent guidelines on cholesterol screening in asymptomatic adults have stressed 3 important concepts.[7,8,82] First, patients with a higher risk of coronary heart disease receive greater benefit from lowering their cholesterol. Second, clinicians should make treatment recommendations based on the patient's overall risk for coronary heart disease and not simply on the their cholesterol level. Finally, the benefits of cholesterol-lowering agents should be assessed separately for each drug treatment category.

TABLE 2. Risk Ratio for Mortality From Coronary Heart Disease, All Causes, and Non–Coronary Heart Disease According to Type of Cholesterol-Lowering Intervention in 59 Randomized, Controlled Trials

Type of Cholesterol-Lowering Intervention (Reference No.)	Number of Trials	Intervention, n	Control, n	Cholesterol Reduction, Mean % (Range)	Follow-up Mean y (Range)	Mortality From Coronary Heart Disease in Control Groups,* %
Statins[1,2,11–21]	13	16 228	11 279	22.86 (12.8–32.0)	2.67 (0.9–5.0)	2
n-3 Long-chain fatty acids and precursors[50–52]	3	1348	1349	3.07 (0.1–5.1)	2.23 (2.0–2.4)	9
Fibrates[22–27,29–33,68]	12†	9873	11 496	9.09 (3.0–16.0)‡	4.06 (1.00–6.20)	5
Resins[22,34,36–42]	8§	3280	3257	15.78 (8.5–23.8)	2.81 (0.8–7.4)	2
Hormones[42–46,48,49,53]	8†	4516	9039	8.18 (3.0–12.4)‡	3.6 (1.4–5.0)	8
Niacin acids[29,44]	2†	1196	2932	10.70 (8.2–13.2)	4.70 (3.2–6.2)	21
Probucol[68]	1	88	30	8.00	1.0	8
Partial ileum bypass surgery[69]	1	421	417	22.50	6.5	1.2
Diet[34,53–67]	16§	48 481	59 042	9.14 (0–25.8)	4.48 (1.0–10.0)	2

*Adjusted for individual trial size.
†The Coronary Drug Project[29] had 4 intervention arms.
‡Missing data from 2 trials.
§The STARS study[34] had 2 intervention arms.

Available guidelines[7,8] rely on meta-analyses that were published before publication of the large HMG-CoA reductase inhibitor trials. These meta-analyses[3–6] have led to much controversy because they suggested that antilipidemic treatment increased mortality from causes other than coronary heart disease. Some authors therefore excluded trials with negative results from their analysis and concluded that cholesterol lowering may reduce mortality in primary prevention.[83] The post hoc exclusion of trials with negative results, however, may be biased toward finding a favorable effect, even if there is none.

The present systematic review differs from previous reviews because it examines to what extent the type of cholesterol-lowering regimen has on coronary heart disease and overall mortality. We considered only mortality data as end points because mortality data are more reliably and consistently reported. There are a number of reasons that our finding that HMG-CoA reductase inhibitors preferentially lower cardiac and overall mortality is robust.[84] First, the cardiovascular and total mortality difference between HMG-CoA reductase inhibitors and other agents was both clinically important and statistically significant. Second, participants in the HMG-CoA reductase inhibitor trials had a similar or lower risk of death than in other trials. Third, trials with statins achieved the highest reduction of cholesterol, providing a biological rationale for higher efficacy. Indeed, our

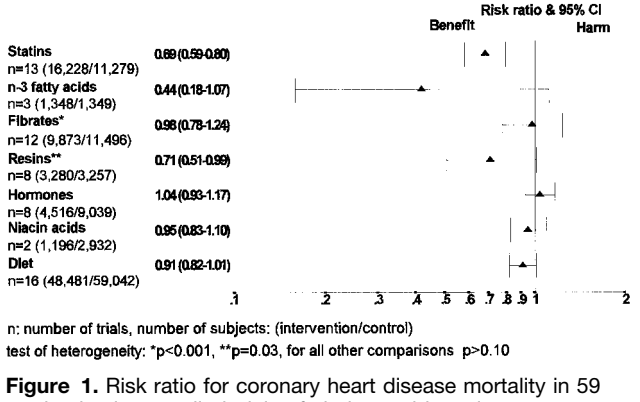

Figure 1. Risk ratio for coronary heart disease mortality in 59 randomized, controlled trials of cholesterol-lowering interventions.

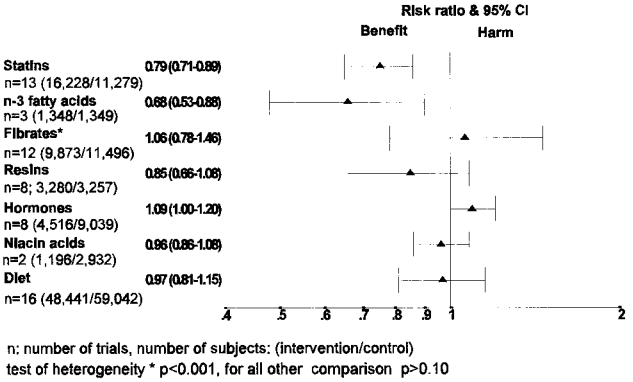

Figure 2. Risk ratio for overall mortality in 59 randomized, controlled trials of cholesterol-lowering interventions.

TABLE 2. Continued

Risk Ratio (95% CI) [*P* Value for Test of Heterogeneity]		
Coronary Heart Disease Mortality	Total Mortality	Non–Coronary Heart Disease Mortality
0.69 (0.59–0.80)	0.79 (0.71–0.89)	0.97 (0.81–1.16)
[*P*>0.10]	[*P*>0.10]	[*P*>0.10]
0.44 (0.18–1.07)	0.68 (0.53–0.88)	1.15 (0.63–2.11)
[*P*>0.10]	[*P*>0.10]	[*P*>0.10]
0.98 (0.78–1.24)	1.06 (0.78–1.46)	1.16 (0.63–2.12)
[*P*<0.001]	[*P*<0.001]	[*P*<0.001]
0.71 (0.51–0.99)	0.85 (0.66–1.08)	1.07 (0.74–1.56)
[*P*=0.03]	[*P*>0.10]	[*P*>0.10]
1.04 (0.93–1.17)	1.09 (1.00–1.20)	1.29 (1.06–1.57)
[*P*>0.10]	[*P*>0.10]	[*P*>0.10]
0.95 (0.83–1.10)	0.96 (0.86–1.08)	0.99 (0.76–1.29)
[*P*>0.10]	[*P*>0.10]	[*P*>0.10]
0.34 (0.06–1.91)	0.24 (0.05–1.20)	0.12 (0.0–2.78)
0.72 (0.46–1.13)	0.78 (0.55–1.11)	0.93 (0.49–1.77)
0.91 (0.82–1.01)	0.97 (0.81–1.15)	1.00 (0.95–1.05)
[*P*<0.001]	[*P*=0.10]	[*P*>0.10]

multivariable meta-regression analyses showed that the extent of cholesterol reduction was the most powerful factor in explaining the difference in mortality reduction across trials. This finding provides support for the suggestion that the greater benefit of HMG-CoA reductase inhibitors is related to their increased ability to lower serum cholesterol. Finally, we restricted our analysis to 1 subgroup comparison, the type of intervention, which reduces the possibility of a false-positive finding from multiple-hypothesis testing.

Not only are HMG-CoA reductase inhibitors the most effective cholesterol-lowering drugs, but they also show a favorable risk profile. We found no suggestion of an increase in non–coronary heart disease mortality with HMG-CoA reductase inhibitors. Mortality from non–coronary heart disease was statistically significantly lower in HMG-CoA reductase inhibitor trials when compared with all other interventions.

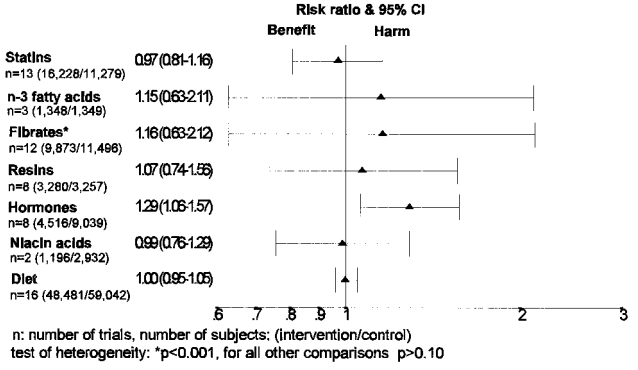

Figure 3. Risk ratio for mortality other than from coronary heart disease in 59 randomized, controlled trials of cholesterol-lowering interventions.

We also found a statistically significant reduction in overall but not in cardiovascular mortality with n-3 fatty acids and their precursors. Given the small number of trials and the large CIs, a lack of statistical power is the most likely explanation for our failure to show a reduction in coronary heart disease mortality with this intervention. n-3 Fatty acids and their precursors reduce triglycerides and have antithrombotic effects on platelets and thus may have additional mechanisms of cardioprotective effects. Our results suggest that n-3 fatty acids and precursors may warrant investigation in a larger trial.

Fibrates, resins, and hormones all showed a trend toward an increased mortality from causes other than coronary heart disease and smaller effects on coronary artery disease mortality than did HMG-CoA reductase inhibitors. There seems little reason to use these drugs, with the possible exception of patients at high risk of coronary heart disease who have large elevations in serum triglycerides. Whether newer fibrates like bezafibrate or fenofibrate have a more favorable risk profile must be investigated in clinical trials examining mortality end points. Estrogens may be beneficial for the primary prevention of coronary heart disease in females, and a large-scale, randomized, controlled trial to address this issue is underway.

In conclusion, HMG-CoA reductase inhibitors are currently the only cholesterol-lowering drugs that should be used in primary and secondary prevention of coronary heart disease. Because of limited data on the long-term safety of HMG-CoA reductase inhibitors, their use in hypercholesterolemic patients at very low risk of coronary events remains questionable.[82,85] In addition, treatment of patients with hyperlipidemia and a low risk of coronary heart disease would compete with other uses for societal resources, potentially both within and outside the healthcare system.[86] In higher-risk patients, however, the arguments for HMG-CoA reductase inhibitor administration are strong.

Note Added in Proof

At completion of this meta-analysis, the full results of 2 large randomized trials with HMG-CoA reductase inhibitors, the AFCAPS/TexCAPS trial and the LIPID trial, were not yet available but have since been published.

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