Cholesterol Reduction Yields Clinical Benefit
Impact of Statin Trials

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Background—We determined the effect of incorporating the results of eight recently published trials of Hmg CoA reductase inhibitors ("statins") on the conclusions from our previously published meta-analysis regarding the clinical benefit of cholesterol lowering.

Methods and Results—We used the same analytic approach as in our previous investigation, separating the specific effects of cholesterol lowering from the effects attributable to the different types of intervention studied. The reductions in coronary heart disease (CHD) and total mortality risk observed for the statins fell near the predictions from our earlier meta-analysis. Including the statin trial findings into the calculations led to a prediction that for every 10 percentage points of cholesterol lowering, CHD mortality risk would be reduced by 15% ($P<.001$), and total mortality risk would be reduced by 11% ($P<.001$), as opposed to the values of 13% and 10%, respectively, reported previously. Cholesterol lowering in general and by the statins in particular does not increase non-CHD mortality risk.

Conclusions—Adding the results from the statin trials confirmed our original conclusion that lowering cholesterol is clinically beneficial. The relationships (slope) between cholesterol lowering and reduction in CHD and total mortality risk became stronger, and the standard error of the estimated slopes decreased by about half. Use of statins does not increase non-CHD mortality risk. The effect of the statins on CHD and total mortality risk can be explained by their lipid-lowering ability and appears to be directly proportional to the degree to which they lower lipids. **(*Circulation*. 1998;97:946-952.)**

Key Words: cholesterol ■ meta-analysis ■ mortality

Reports on the outcome of a number of trials of Hmg CoA reductase inhibitors ("statins") have appeared[1–8] since the publication of our meta-analysis demonstrating that net decreases in total serum cholesterol attributable to an intervention translate linearly to net decreases in total mortality risk and coronary heart disease (CHD) mortality risk.[9] The statins represent an especially effective class of lipid-lowering drugs that were not included in the meta-analysis. We report here (1) the consistency of findings from the statin trials with the predictions based on nonstatin interventions from our earlier meta-analysis and (2) updated estimates (and standard errors) of the effects of cholesterol reduction and therapy class incorporating this new information.

Methods

We used the same methods as in our original meta-analysis,[9] adding the results from eight trials of statins that were published since the meta-analysis appeared and considering additional models exploring the effect of the statin findings. Table 1 lists the findings from the studies included in the analyses, with the findings from the eight additional trials italicized. Tables 3 and 4 of the published meta-analysis inadvertently excluded the Scottish study[10]; the "original" findings presented here include that study and do not differ materially from the original results.

The findings for the various causes of mortality were analyzed by use of a series of models (Table 2) involving separate intercepts for each of the intervention classes and either a common slope for all the interventions or separate slopes for the statins and nonstatins. The same approach was used in our earlier meta-analysis, although many fewer models were needed because fewer intervention classes were studied. These models provide a way to address such questions as, (1) Does the risk of CHD or total mortality decrease steadily as net cholesterol reduction improves, or is there even more (or less) risk reduction with large reductions in total cholesterol? (2) Is the reduction in CHD and total mortality risk realized with 2 or more years of statin therapy consistent with what might be expected from their ability to lower cholesterol, or is there some specific attribute of statins as a class that confers extra benefit? (3) Do the statins have any specific effects on non-CHD mortality?

Models in Table 2 that set the intercept to zero for a particular class of interventions as, for example, model 3 does for "other/diet" say that the intervention has no specific effect on the degree of risk reduction. This means that if the intervention has the same effect on cholesterol reduction as a concurrent control, then it has the same effect on risk reduction. This would not be true, and the intercept would not be zero, if the intervention were inherently toxic, when there would be an excess of adverse events on the intervention, including mortality, even if the intervention and control reduced cholesterol equally. The "Appendix" describes the process for identifying appropriate models. The significance levels (probability values) reported in the "Results" section were determined by use of the

Received August 15, 1997; revision received November 14, 1997; accepted November 18, 1997.

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The opinions expressed in this manuscript are those of the authors and do not necessarily reflect the views of the National Institutes of Health.

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TABLE 1. Study Set

	Study Reference	Net Cholesterol Reduction, %	Duration, y	Intervention/ Control No. at Risk	All Deaths	CHD Deaths	Non-CHD Deaths*
Unifactorial Primary Prevention—Drug							
Lipid Research Clinics, cholestyramine	11	9	7.4	1906/1900	68/71	32/44	36/27
Helsinki Heart Study, gemfibrozil	12	9.9	5	2051/2030	45/42	14/19	30/24
WHO, clofibrate.	13–15	8.5	5.3	5331/5296	236/181	91/77	139/102
Dorr et al, colestipol	16	9.8	2	1149/1129	37/48	19/31	15/14
West of Scotland, pravastatin	*1*	*20*	*4.9*	*3302/3293*	*106/135*	*41/61*	*65/74*
Unifactorial Primary Prevention—Diet							
Dayton et al	17	12.7	7	424/422	174/177	41/50	101/102
Multifactorial Primary Prevention							
Göteborg, diet	18	0	10	10 004/10 011	1293/1304	462/453	831/851
MRFIT, diet	19	2.9	7	6428/6438	265/260	115/124	150/136
Miettinen, diet and clofibrate	20	6.3	5	612/610	10/5	4/1	6/4
Oslo Study Group, diet	21	9.1	5	604/628	15/24	6/14	9/10
Unifactorial Secondary Prevention—Surgery							
POSCH	22	23.3†	9.7	421/417	49/62	33/47	16/15
Unifactorial Secondary Prevention—Drug							
Stockholm Study, clofibrate and nicotinic acid	23	13	5	279/276	61/82	47/73	14/9
Coronary Drug Project, dextrothyroxine	24	12	3	1083/2789	160/339	119/274	41/65
Schoch, nicotinic acid	25	14	4	77/143	15/27	13/23	2/4
Schoch, estrogen	25	2	4	141/143	27/27	25/23	2/4
Schoch, dextrothyroxine/estrogen	25	7	4	141/143	23/27	18/23	5/4
Frick et al, gemfibrozil	26	8.5	5	311/317	19/12	17/8	2/4
Scottish Society, clofibrate	10	16	5	350/367	43/47	34/35	8/10
Coronary Drug Project, nicotinic acid	27, 28	9.9	6.2	1119/2789	277/723	238/632	39/86
Coronary Drug Project, clofibrate	27, 28	6.5	6.2	1103/2789	288/723	240/632	42/86
Acheson and Hutchinson, clofibrate	29	9	7	47/48	23/20	NA	NA
Newcastle, clofibrate	30	11	12	244/253	NA	25/44	2/4
Oliver and Boyd, estrogen	31	9.5	5	50/50	17/12	13/10	4/2
4S, simvastatin	*2*	*26*	*5.4*	*2221/2223*	*182/256*	*111/189*	*71/67*
CARE, pravastatin	*3*	*20*	*5*	*2081/2078*	*180/196*	*96/119*	*84/77*
Unifactorial Secondary Prevention—Diet							
Burr et al (DART)	32	4	2	1018/1015	111/113	97/97	14/16
Woodhill et al	33	4.3	5	221/237	39/28	37/24	2/4
MRC, low fat	34	8.3	3	123/129	20/24	17/20	3/4
Rose et al	35	8.8	7	54/26	NA	8/1	NA
MRC, soybean	36	13.5	4	199/194	28/31	25/25	4/6
Leren	37	13.9	5	206/206	41/56	37/50	3/5
Unifactorial Angiography							
FATS, lovastatin/colestipol	38	30.3	2.5	38/52	1/0‡	1/0‡	0/0‡
FATS, niacin/colestipol	38	19.1	2.5	36/52	0/0‡	0/0‡	0/0‡
STARS, diet alone	39	12.2	3	26/28	1/3	1/3	0/0‡
STARS, diet and cholestyramine	39	23.3	3	24/28	0/3	0/3	0/0‡
NHLBI Type 2, cholestyramine	40	16	5	71/72	5/7	NA	NA
CLAS, colestipol	41	22	2	94/94	NA	0/1‡	NA
Sahni et al, lovastatin	42,43	12.1	2	76/75	NA	2/4	NA
ACAPS, lovastatin	*4*	*20§*	*2*	*460/459*	*1/8*	*0/6*	*1/2*
MARS, lovastatin	*5*	*31*	*2*	*123/124*	*2/1*	*NA*	*NA*
CCAIT, lovastatin	*6*	*20*	*3*	*168/166*	*2/2*	*2/1*	*0/1*
MAAS, simvastatin	*7*	*22*	*4*	*193/188*	*4/11*	*4/4*	*0/7*
Pooled atheroma trials, pravastatin	*8*	*20§*	*3*	*955/936*	*15/23*	*10/12*	*5/11*

CHD indicates coronary heart disease. New trials are italicized. NA indicates not available.

*Supplemented with data from Law et al.[44] †Percent difference at 5 years as reported in POSCH manuscript. ‡Omitted from calculations to preserve numerical stability. §Net percent reduction in total cholesterol not reported; estimated at 5/7 of net percent reduction in LDL cholesterol using information from studies that provided both values.

TABLE 2. Models Used to Analyze Mortality Findings

Model	No. of Parameters in Model	Separate Intercept for				Slope	
		Fibrate	Hormone	Other/Diet	Statin	All Interventions Combined	Statins and Nonstatins Separately
1	6	X	X	X	X		X
2	5	X	X	X	X	X	
3	5	X	X		X		X
4	4	X	X		X	X	
5	4	X	X				X
6	3	X	X			X	
7	3		X				X
8	2		X			X	
9	2	X				X	
10	2	X	X				
11	1	X					
12	1		X				
13	1					X	

Intercept indicates 0 for term without X.

hierarchical testing scheme. The "Appendix" also illustrates how these significance levels are calculated.

We report here the findings for CHD, non-CHD, and total mortality. As in the original analysis, statistical significance refers to two-sided tests with $\alpha=0.05$. The figures illustrate the analytic findings by plotting the observed log odds ratios for event occurrence in each trial on the y axis against the net reduction in cholesterol caused by the intervention on the x axis, with the predicted lines relating risk reduction to net cholesterol reduction for each type of intervention when appropriate. Larger studies, with many patients and many events, are represented with larger symbols on the figures because they estimate the log odds ratio more precisely than smaller studies and thus have a larger influence on the estimates of slope and intercepts; the symbol area is proportional to the variance of the log odds ratio.

Results

CHD Mortality

The only significant factors affecting CHD mortality risk reduction are net cholesterol reduction, with the same slope for all interventions, and an intercept term for hormone interventions (model 8, $P=.011$ to .013) in all but the primary prevention trials, which did not include hormone interventions. Our previous meta-analysis gave the same result. The facts that the intercept for statins is zero in this model and that a common slope applies for all interventions implies that (1) there is no evidence to conclude that CHD mortality risk reduction is anything other than proportional to net reduction in total cholesterol even when the cholesterol reduction is large and (2) that statins as a class or individually do not appear to have any specific effects on CHD mortality risk.

Table 3 summarizes the computational results and gives the results from our original meta-analysis[9] for comparison. Fig 1 displays the relationship between cholesterol reduction and CHD mortality risk reduction. The slope becomes slightly more pronounced when the statin trial results are included (slope=−0.0166 versus −0.0138, a nonsignificant difference). However, the results from the statin trials fall about where the

TABLE 3. CHD Mortality: Estimates of Effect of Cholesterol Reduction and Influential Interventions Using the Original Study Set and After Adding Published Statin Trial Findings

Study Set	All Trials	Unifactorial Trials		
		All	Primary Prevention	Secondary Prevention
Augmented				
No. of trials	38	33	6	27
Slope	−0.0166 (0.0027)	−0.0164 (0.0027)	−0.0175 (0.0072)	−0.0163 (0.0029)
Hormone	0.271 (0.106)	0.269 (0.106)	. . .	0.267 (0.106)
P	.012	.011	.014	.013
Original				
No. of trials	30	26	5	21
Slope	−0.0138 (0.0041)	−0.0134 (0.0041)	−0.0078 (0.0088)	−0.0131 (0.0045)
Hormone	0.242 (0.111)	0.237 (0.111)	. . .	0.235 (0.112)

CHD indicates coronary heart disease. Values in parentheses are standard errors.

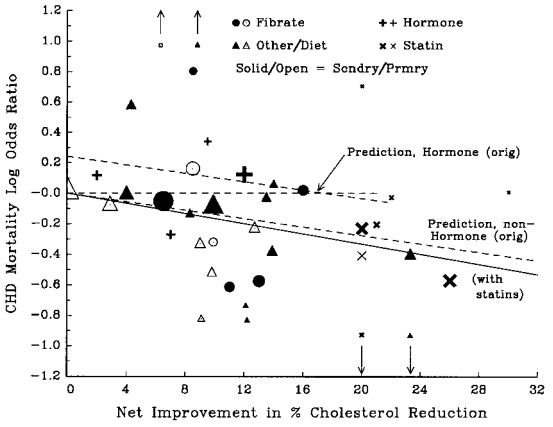

Figure 1. Observed log odds ratios and predicted lines relating log odds ratios for coronary heart disease (CHD) mortality to net improvement in percent total serum cholesterol reduction. Dashed lines present the relationships predicted from the data in our earlier meta-analysis[9]; solid line presents the relationship based on all the data included in the analysis reported here.

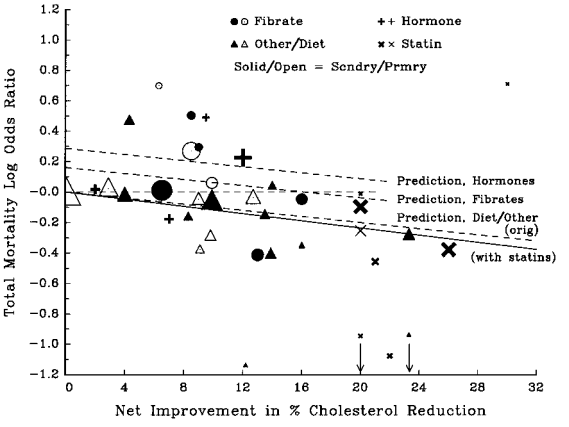

Figure 2. Observed log odds ratios and predicted lines relating log odds ratios for total mortality to net improvement in percent total serum cholesterol reduction. Dashed lines present the relationships predicted from the data in our earlier meta-analysis[9]; solid line presents the relationship based on all the data included in the analysis reported here. CHD indicates coronary heart disease.

original meta-analysis would have predicted. The trials whose findings deviate most from the prediction lines (ACAPS, MARS, and MAAS) are small atheroma trials with few deaths.

Total Mortality

The only significant factors affecting total mortality risk reduction are net cholesterol reduction, same slope for all interventions, and whether the intervention was a fibrate or a hormone (model 6, $P<.01$) when all trials and all unifactorial trials are considered, net cholesterol reduction and whether the intervention was a hormone (model 8, $P<.01$) when the unifactorial secondary prevention trials are considered, and net cholesterol reduction and whether the intervention was a fibrate for the primary prevention trials (model 9, $P=.038$) The fibrate effect loses significance ($P<.05$) when the WHO trial results are excluded. These findings are the same as for our previous meta-analysis, except for the primary prevention trials in which the original analysis did not reveal a significant effect of net cholesterol reduction. As with CHD mortality, there is no evidence for anything other than proportionality of total mortality risk reduction to net total cholesterol reduction, and statins as a class do not appear to have any specific effects on total mortality risk.

Table 4 summarizes the computational results and, for comparison, the results from the original meta-analysis. Fig 2 displays the relationship between cholesterol reduction and total mortality risk reduction. The statin trial results increase the slope slightly from what was reported in the original meta-analysis. As with CHD mortality, the results from the statin trials fall about where the original meta-analysis would have predicted.

Non-CHD Mortality

There is no relationship between degree of cholesterol reduction and non-CHD mortality risk. As our earlier meta-analysis

TABLE 4. Total Mortality: Estimates of Effect of Cholesterol Reduction and Influential Interventions Using the Original Study Set and After Adding Published Statin Trial Findings

		Unifactorial Trials		
Study Set	**All Trials**	**All**	**Primary Prevention**	**Secondary Prevention**
Augmented				
No. of trials	37	33	6	27
Slope	−0.0118 (0.0023)	−0.0117 (0.0023)	−0.0109 (0.0053)	−0.0112 (0.0025)
Fibrate	0.175 (0.058)	0.169 (0.058)	0.0328 (0.102)	. . .
Hormone	0.305 (0.095)	0.304 (0.095)	. . .	0.300 (0.095)
P	.004	.002	.038	.002
Original (corrected; see text)				
No. of trials	29	25	5	20
Slope	−0.010 (0.0042)	−0.010 (0.0043)	−0.0078 (0.0088)	−0.0088 (0.0042)
Fibrate	0.162 (0.065)	0.154 (0.066)	0.301 (0.119)	. . .
Hormone	0.286 (0.102)	0.288 (0.102)	. . .	0.275 (0.102)

Values in parentheses are standard errors.

TABLE 5. Non-CHD Mortality: Estimates of Effect of Cholesterol Reduction and Influential Interventions Using the Original Study Set and After Adding Published Statin Trial Findings

		Unifactorial Trials		
Study Set	**All Trials**	**All**	**Primary Prevention**	**Secondary Prevention**
Augmented				
No. of trials	34	30	6	24
Slope*	−0.0009 (0.0034)	−0.0011 (0.0034)	−0.0027 (0.0068)	−0.0002 (0.0039)
Fibrate	0.241 (0.094)	0.238 (0.095)	0.292 (0.119)	0.140 (0.159)
Hormone	0.437 (0.186)	0.437 (0.186)	Not applicable	0.436 (0.186)
P	.022	.022	.013	.022
Original (corrected; see text)				
No. of trials	26	22	5	17
Slope*	0.0031 (0.0076)	0.0023 (0.0078)	0.0040 (0.011)	0.0016 (0.011)
Fibrate	0.241 (0.094)	0.238 (0.095)	0.292 (0.119)	0.140 (0.159)
Hormone	0.437 (0.186)	0.437 (0.186)	NA	0.436 (0.186)

CHD indicates coronary heart disease. Values in parentheses are standard errors.
*From model including slope, fibrates, and (except primary prevention trials) hormones.

found, higher risk of non-CHD mortality is associated with the use of a fibrate or a hormone (model 10; all trials, all unifactorial trials, $P=.022$) or just the use of a hormone (model 12; unifactorial secondary prevention trials, $P=.022$) or a fibrate (model 11; primary prevention trials, $P=.013$). The fibrate effect loses significance ($P>.05$) when the WHO trial results are omitted. Table 5 summarizes the computational results and, for comparison, the results from our original meta-analysis. Fig 3 displays the results, including the findings from the statin trials.

Statin Slopes

The slope of the relationship between cholesterol reduction and mortality risk reduction is the same for statins and nonstatins. The computations for the models fitting separate slopes for statins and nonstatins that included all of the trials gave the same estimates and standard errors for the statin slopes as the computations including only the statin trials. The slopes for statins and nonstatins and their standard errors obtained by fitting models 7 (hormone intercept and separate slopes) and 8 (hormone intercept and common slope) to the unifactorial trials (without WHO) are given in Table 6. A simple test for a difference between the statin and nonstatin slopes—eg, $(0.0125-0.0081)/\sqrt{14(0.00278^2+0.00375^2)} = 0.0044/0.0046 < 1$—confirms the conclusion of the maximum likelihood analyses that the relationship of mortality risk reduction to cholesterol reduction can be explained adequately by a common slope for statins and nonstatins.

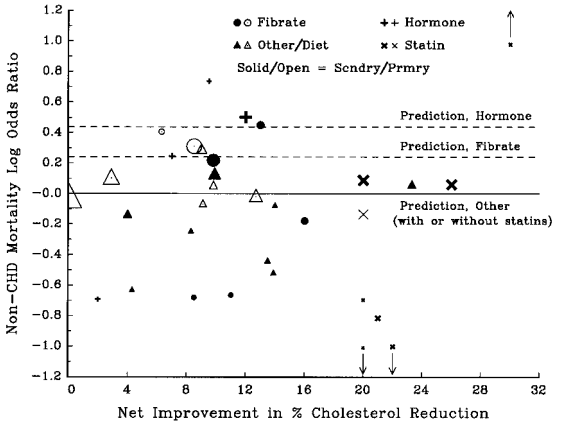

Figure 3. Observed log odds ratios and predicted lines relating log odds ratios for non–coronary heart disease (CHD) mortality to net improvement in percent total serum cholesterol reduction. Dashed lines present the relationships predicted from the data in our earlier meta-analysis[9]; solid line presents the relationship based on all the data included in the analysis reported here.

Discussion

The cholesterol reductions produced by the statins studied in the trials listed in Table 1 lead to reductions in CHD and total mortality risk that are close to the predictions from our original meta-analysis for nonfibrate, nonhormone interventions.

Including the data from the statin trials in the analyses provides a clinically modest improvement in the slopes relating CHD and total mortality to net cholesterol reduction. A net reduction in total serum cholesterol of 10 percentage points translates to an expected 15% reduction in CHD mortality risk and an expected 11% reduction in total mortality risk when the statin trial data are included, as opposed to the 13% and 10% reductions, respectively, predicted by the original meta-analysis.

The estimated effects of fibrates and hormones remain essentially unchanged: Hormones and fibrates (at least clofibrate and gemfibrozil) remain significantly associated with increased total mortality risk when the analysis includes all the trials or all the

TABLE 6. Slope Relating Cholesterol Reduction and Mortality Risk Reduction

Mortality Cause	Statin	Nonstatin	Common
Total	−0.0125 (0.00278)	−0.0081 (0.00375)	−0.011 (0.00223)
CHD	−0.019 (0.00356)	−0.015 (0.00426)	−0.017 (0.00273)

CHD indicates coronary heart disease. Values in parentheses are standard errors.

TABLE 7. Times Log Likelihoods for the Models Fitted to the Data

Model	1	...	6	7	8	9	10	11	12	13
Parameters in Model	**6**	...	**3**	**3**	**2**	**2**	**2**	**1**	**1**	**1**
CHD mortality										
Unifactorial trials	176.45	...	179.15	179.12	**180.07**	191.92	216.14	217.07	217.81	186.42
All trials	200.01	...	201.48	201.86	**202.67**	208.40	239.98	240.90	241.40	209.10
Secondary prevention	...	...	145.41	144.63	**145.44**	151.64	174.18	175.10	177.22	151.64
Total mortality										
Unifactorial trials	179.31	...	**180.73**	185.97	189.14	190.91	206.26	210.17	207.85	197.86
All trials	204.34	...	**205.11**	211.09	214.30	215.32	231.08	234.99	233.02	223.00
Secondary prevention	138.68	...	140.27	140.90	**141.40**	150.47	161.72	165.64	161.84	151.10
Non-CHD Mortality										
Unifactorial trials	141.65	...	142.44	145.29	148.65	147.68	**144.35**	149.59	150.98	...
All trials	120.68	...	121.32	124.26	127.32	126.61	**123.25**	128.50	129.55	...
Secondary prevention	88.79	...	89.22	89.55	89.95	94.20	91.08	96.32	**91.85**	...

CHD indicates coronary heart disease.
Values in bold correspond to the model adopted for each set of studies.

unifactorial trials. Only hormones are associated with increased risk when the analysis includes just the secondary prevention trials (all unifactorial) or, as in our earlier analysis, when the WHO trial data are omitted from the calculations.

Statin Effects

The analyses summarized in Tables 3 through 5 establish clearly that the mortality risk reduction realized over periods of 2 years and longer in the statin trials is a consequence of the reduction in cholesterol. These analyses exclude trials of less than 2 years' duration and so cannot address possible shorter-term effects of statins on events such as plaque stabilization. The statins used in these trials do not increase non-CHD mortality risk. The rate of reduction in total or CHD mortality risk with increasing net decrease in serum cholesterol is the same for statins and nonstatins. Statins reduce CHD and total mortality risk more than other currently available therapies because they reduce cholesterol levels more effectively without increasing non-CHD mortality.

Appendix

The models in Table 2 are naturally ordered in the sense that some models are special cases of others. For example, a model that includes a single slope for all interventions is a special case of a model that allows for separate slopes for statins and nonstatins because the separate slopes could be equal. Consequently, model 2 is a special case of model 1, model 4 is a special case of model 3, etc. Likewise, a model that includes some but not all of the intercept terms that another model includes is a special case of the model with more terms (the extra terms could be zero), so for example, models 3, 5, and 7 are special cases of model 1. This natural ordering of the models provides a way to identify appropriate models via conventional likelihood ratio tests. Table 7 contains values of -2 times the logarithm of the likelihood for various models. The tests reported in this article all concern whether a simpler model describes the observed outcomes as well as a more complex model of which the simpler model is a special case. The additional factors of the more complex model are unlikely to be important if a simpler model describes the observed outcomes as well. Tests proceed by taking the difference between the values in Table 7 corresponding to pairs of models differing only in the effects of interest and comparing the difference to a central χ^2 table with degrees of freedom equal to the difference between the numbers of parameters in the models.

Table 8 illustrates the calculation of the significance levels reported in Tables 3 and 4 for the unifactorial trials. The resulting significance levels apply to the model as a whole relative to any simpler model. Separate evaluations of individual parameters can be carried out in the usual way in terms of the ratio estimate/standard error.

TABLE 8. Computation of Significance Levels for Models Presented in Tables 3 and 4 Applied to Unifactorial Trials

			CHD Mortality		Total Mortality	
Starting Model	**Simpler Model**	***df***	χ^2	***P***	χ^2	***P***
1, Intercepts for each intervention, separate statin and nonstatin slopes	Fibrate & hormone intercepts, common slope	3	3.62	NS	0.42	NS
2a, Fibrate and hormone intercepts, common slope	Fibrate intercept, common slope	1	12.8	*	10.2	*
2b, Fibrate and hormone intercepts, common slope	Hormone intercept, common slope	1	0.92	NS	8.41	*
2c, Fibrate and hormone intercepts, common slope	Fibrate and hormone intercepts, zero slope	1	37.0	*	25.5	*
3a, Hormone intercept, common slope	Hormone intercept, zero slope	1	37.7	*	...	...
3b, Hormone intercept, common slope	Common slope	1	6.35	0.012	...	...

χ^2 is the difference between the values in Table 6 for the two models.
*$P<.01$.

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Circulation. 1998;97:946-952
doi: 10.1161/01.CIR.97.10.946
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231

Print ISSN: 0009-7322. Online ISSN: 1524-4539