

About 10% of the patients in each group did not complete their first year on study (Figure 1). The primary reasons for discontinuation during the first year were protocol violations, relocation or unknown reasons (i.e. the status of the patient was unknown at the time of withdrawal).

The most common reason for discontinuation was an adverse event (Table 5, 9.9% LOVA vs. 8.6% PLA). There was a higher percentage of participants in the placebo group who discontinued due to lack of efficacy⁶ (0.3% LOVA vs. 4.1% PLA) and use of other lipid-lowering drugs⁷ (0.8% LOVA vs. 4.0% PLA). Approximately 2% of the placebo patients withdrew each year of the study due to lack of efficacy. Since discontinued patients are followed and counted in the ITT analysis, placebo patients switching to active treatment could potentially lead to a diminished treatment difference.

Table 5. Patient Disposition and Reasons for Discontinuation

	Lovastatin	Placebo
Randomized	3304	3301
Reasons for Discontinuation		
Adverse event	328 (9.9%)	285 (8.6%)
Trial endpoint	121 (3.7%)	170 (5.1%)
Protocol violator	263 (8.0%)	295 (8.9%)
Patient decision	72 (2.2%)	54 (1.6%)
Moved or status unknown	122 (3.7%)	141 (4.3%)
Used investigational drug	17 (0.5%)	4 (0.1%)
Used other lipid-lowering drug	26 (0.8%)	131 (4.0%)
Lack of efficacy	10 (0.3%)	134 (4.1%)
Other	10 (0.3%)	6 (0.2%)
Completed Study	2335 (70.7%)	2081 (63.0%)
Endpoint and Vital Status Ascertained at End of Trial	3245 (98.2%)	3231 (97.9%)

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⁶ Patients were withdrawn for lack of efficacy if LDL > 190 mg/dL or TG > 400 mg/dL.

⁷ Patients were withdrawn if their personal physician prescribed lipid lowering drugs; almost 90% of these withdrawals occurred during the last 3 years of the study.

Baseline Demographics and Patient Characteristics

The treatment groups were well-balanced for baseline demographics and patient characteristics (Table 6). The majority of the patients were men (85%) and white (89%). The average age was 58 years (63 for women and 57 for men); about 20% of the patients were 65 years or older at baseline (35% of women and 19% of men).

Table 6. Summary of Baseline Demographics and Patient Characteristics

	Lovastatin n=3304	Placebo n=3301	Total Cohort N=6605
Gender			
Men	2805 (85%)	2803 (85%)	5608 (85%)
Women	499 (15%)	498 (15%)	997 (15%)
Age (Years)			
<50	481 (15%)	504 (15%)	985 (15%)
50 to <55	579 (18%)	592 (18%)	1171 (18%)
55 to <60	800 (24%)	776 (24%)	1576 (24%)
60 to <65	729 (22%)	728 (22%)	1457 (22%)
65 to <70	470 (14%)	482 (15%)	952 (14%)
70+	245 (7%)	219 (7%)	464 (7%)
Race			
White	2925 (89%)	2935 (89%)	5860 (89%)
Black	105 (3%)	101 (3%)	206 (3%)
Hispanic	247 (7%)	240 (7%)	487 (7%)
Asian	20 (1%)	17 (1%)	37 (1%)
Other	7 (0%)	8 (0%)	15 (0%)
Member of military	1372 (42%)	1389 (42%)	2761 (42%)
No regular strenuous exercise	2160 (65%)	2131 (65%)	4291 (65%)
Current smoker	429 (13%)	389 (12%)	818 (12%)
History of NIDDM	84 (3%)	71 (2%)	155 (2%)
History of hypertension	719 (22%)	729 (22%)	1448 (22%)
Obesity	30 (1%)	29 (1%)	59 (1%)
Family history of MI/angina before age 55			
Yes	497 (15%)	538 (16%)	1035 (16%)
No	2688 (81%)	2637 (80%)	5325 (81%)
Unknown	119 (4%)	126 (4%)	245 (4%)
LDL-C (mg/dL) (mean±SD)	150 ± 17	151 ± 17	150 ± 17
Range	93, 213	90, 235	90, 235
TC (mg/dL) (mean±SD)	220 ± 21	221 ± 21	221 ± 21
Range	151, 295	163, 343	151, 343
HDL-C (mg/dL) (mean±SD)	37 ± 6	37 ± 6	37 ± 6
Range	20, 61	18, 56	18, 61
TC/HDL-C (mean±SD)	6 ± 1	6 ± 1	6 ± 1
Range	4, 11	4, 13	4, 13
TG (mg/dL) (mean±SD)	169 ± 65	167 ± 63	168 ± 64
Range	35, 620	42, 497	35, 620

NCEP determined risk factors for CAD were assessed at baseline and included: hypertension (22% of the patients), non-insulin treated DM (2%), current smoking (12%), family history of premature CHD (16%), and HDL-C < 35 mg/dL (35%). All participants had at least one risk factor due to the age restrictions. Approximately two-thirds of the cohort had ≥ 2 risk factors. This characteristic of the study cohort is particularly important when determining whether the presence of risk factors affected the endpoints. Based on current NCEP guidelines only 16.6% of these patients would have been recommended for lipid-lowering drug therapy based on LDL-C ≥ 160 mg/dL and ≥ 2 risk factors.

Use of concomitant medications

The baseline and concomitant use of other medications were determined and there were no significant differences between the lovastatin and placebo groups (Table 7). The use of many of these agents, including aspirin, increased from baseline reports and may have been the result of an aging cohort of patients with subsequent requirement for these medications or an increased awareness and detection of certain medical conditions because of enrollment in a clinical trial.

Table 7. Concomitant medications used in AFCAPS/TexCAPS

	Lovastatin (N=3304) n (%)	Placebo (N=3301) n (%)
ACE inhibitors	529 (16.0)	527 (16.0)
Alpha blockers	417 (12.6)	416 (12.6)
Antihypertensives ¹	1281 (38.8)	1273 (38.6)
Aspirin	1516 (45.9)	1456 (44.1)
Beta blockers	328 (9.9)	339 (10.3)
Calcium channel blockers	436 (13.2)	449 (13.6)
Diuretics	397 (12.0)	360 (10.9)
Estrogen +/- progestins ^{2,3}	289 (57.9)	281 (56.4)
Estrogen ²	281 (56.3)	261 (52.4)
Estrogen + progestins ²	33 (6.6)	40 (8.0)
NSAIDs	1751 (53.0)	1681 (50.9)
Oral hypoglycemics	120 (3.6)	112 (3.4)
Thyroid replacement hormone	192 (5.8)	164 (5.0)

¹ Includes ACE inhibitors, alpha and beta blockers, calcium channel blockers and diuretics.
² Women only (n=499 lovastatin, n=498 placebo).
³ Includes women taking estrogens and those taking estrogens + progestins.

Patient Compliance

Compliance for study drug adherence was assessed by pharmacists by tablet counts at all protocol visits. A compliance rate of >75% was reported by 99.3% of the lovastatin group and 99.4 % of the placebo group.

Changes in Lipid Profile

Of the 3,304 patients randomized to lovastatin 20 mg qd, 1,657 (50.2%) were titrated to 40 mg qd after 18 weeks and none of these were subsequently back-titrated. After 1 year of treatment the lovastatin group (note from Table 8 below that the results by dose are similar) had a mean reduction in LDL-C of 25%, TC 18%, TG 15%, and increase of HDL-C by 6%. The ratios of TC/HDL-C and LDL-C/HDL-C were reduced by 22% and 28%, respectively. By comparison, the placebo group demonstrated small changes in lipid levels that were not clinically significant. The results for LDL and HDL overall and by baseline quartiles are shown in Table 8 below.

Table 8. LDL and HDL change from baseline and % change from baseline at the end of the first year on therapy

	Placebo (n=2807)	Lovastatin 20 (n=1369)	Lovastatin 40 (n=1505)
LDL	+1 mg/dl (+2%)	-36 mg/dl (-24%)	-44 mg/dl (-26%)
LDL by baseline quartiles			
<141	+12 (+11%)	-22 (-16%)	-19 (-14%)
141-153	+3 (+2%)	-38 (-25%)	-35 (-24%)
154-170	-1 (-1%)	-46 (-29%)	-45 (-28%)
>170	-11% (-6%)	-57 (-32%)	-58 (-31%)
HDL	+0.1 (+1%)	+2 (+6%)	+2 (+6%)
HDL by baseline quartiles			
<33	+2 (+7%)	+3 (+12%)	+3 (+12%)
34-37	+1 (+2%)	+2 (+7%)	+2 (+7%)
38-42	-0.3 (-0.7%)	+2 (+4%)	+2 (+4%)
>42	-2 (-4%)	-0.1 (+0.02%)	-0.4 (-0.5%)

Statistical Methods

All randomized patients were included in the analyses regardless of treatment compliance; for about 98% of the patients, vital status and endpoint were ascertained at the end of the trial.

The main analyses performed by the FDA were time-to-event analyses where the treatment groups were compared using the Cox proportional hazards model with treatment and study site in the model. The sponsor included a term for gender in their model as proposed in the protocol; inclusion of the gender term does not modify the results in any appreciable way.

Subgroup analyses were performed by the FDA to examine the consistency of effect across important subgroups. Subgroups defined by gender, age and study site were proposed in the protocol; other subgroups were chosen to examine consistency of results with other databases (such as CARE) and to examine the impact of risk factors on the results.

Event rates were computed in two ways by the sponsor (neither was prespecified in the protocol): 1) as the number of participants with endpoints per 1000 person-years at risk and 2) as the cumulative probability of failure which is a life table estimate (this is the estimate the sponsor proposed for the labeling).

The life table estimates presented by the sponsor are 4.0% for lovastatin and 6.8% for placebo. Upon review by FDA, it was discovered that these estimates were incorrectly computed. The study report explicitly states that these estimates represent the incidence "at the end of the follow-up"; however, a total of 4 (3 lovastatin and 1 placebo) events were excluded. The effect on the estimate is shown in the first 2 lines of the table below. Note that Merck's estimates produce a treatment difference of 2.8% compared to a difference of 2.2% when computed correctly and also that the corrected estimate is close to the Kaplan-Meier estimate (which includes all the events). It should be pointed out, also, that the sponsor presents their estimates in the NDA as coming from intent-to-treat analyses. Clearly this is not the case.

	LOVASTATIN	PLACEBO
Merck's estimate	4.0%	6.8%
Correct estimate	4.9%	7.1%
Kaplan-Meier estimate	5.1%	7.2%

The sponsor's life table estimates are based on interval estimation (an actuarial approach) meaning that interval sizes must be pre-specified. According to the sponsor's statistical analysis plan⁸, 3-month intervals were chosen. This decision was unrelated to the design of the trial in that event dates were recorded as observed (i.e. on a continuum not in intervals). The problem with the sponsor's approach is that the cumulative estimates are dependent on the interval sizes; the table below illustrates this. Therefore, one may maximize the treatment difference by one's choice of interval size. It is worth

⁸ The sponsor's statistical analysis plan was not presented as part of the protocol and is dated 5/97; the second interim analysis for this study (upon which a decision to stop the trial was made) was performed in 4/97.

noting that none of the treatment differences in the table below (where all events are counted) are as large as the difference presented by the sponsor.

	LOVASTATIN	PLACEBO
3 month interval	4.9%	7.1%
5 month interval	4.8%	7.4%
10 month interval	4.9%	7.4%
12 month interval	4.9%	7.1%

The sponsor's estimates are unacceptable for 2 reasons: 1) they were computed excluding data and 2) cumulative estimates based on grouping the data into intervals is inappropriate for data collected continuously over time where exact times are known.

The event rates reported in the tables in this review are simply crude event rates (number of events observed divided by the total number of patients at risk); these rates were chosen to be consistent with rates presented in related reviews (4S, WOSCOPS and CARE) and in labeling for other statins. Also, these rates are representative of the results of this 5-year trial; for example, for the primary endpoint, the placebo annual incidence rate is about 1% (5.5% overall crude rate) and the lovastatin annual incidence rate is about 0.6% (3.5% overall crude rate).

To illustrate the relationship between the crude rate and the sponsor's person-year rate, the results for the primary endpoint are presented in the table below. The ratio of the rates using both the crude rate and the person year rate is approximately 0.63 (the estimate of the relative risk based on the Cox model).

Table 9. Two ways of computing the event rate for the primary endpoint

	Lovastatin	Placebo
Crude Rate		
# of events	116	183
# at risk	3304	3301
rate (%)	3.5%	5.5%
Person Year Rate		
# of events	116	183
# of person years	17041	16865
rate (events/1000 PYR)	6.8	10.9

Interim analyses

Two interim analyses were planned and both were performed; the first yielded a p-value of .025 (boundary of .004) and the second, a p-value < .001 (boundary of .023). Since the results of the second analysis exceeded the stopping rule, the DSMB voted to terminate the study early for efficacy reasons. An additional 32 primary events were observed after the second interim analysis and these events were included in the final analysis.

Primary Endpoint Results

The primary endpoint in AFCAPS/TexCAPS was time to first occurrence of sudden cardiac death, fatal or nonfatal MI, or unstable angina.

Figure 2 Survival Curves for the Primary Endpoint

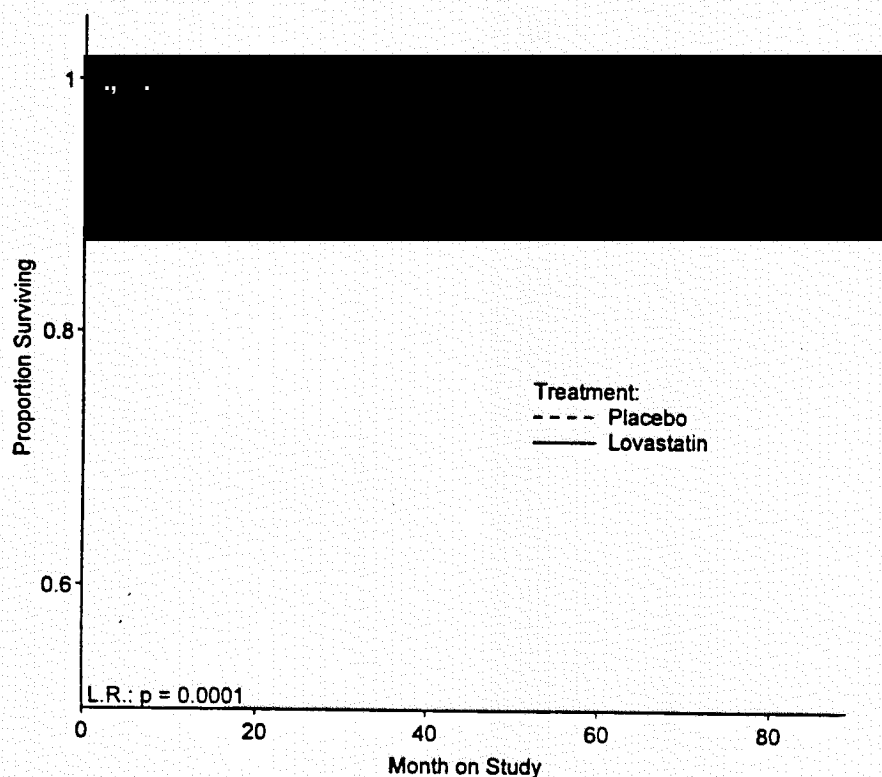


**Table 10. AFCAPS
Primary Endpoint Results**

	Lovastatin	Placebo	Relative Risk	95% CI	P-value
All patients	116/3304 (3.5%)	183/3301 (5.5%)	0.63	0.49, 0.79	.0001

Lovastatin reduced the risk of experiencing a primary endpoint by 37% ($p < .0001$). There were 116 primary endpoint events in the lovastatin group and 183 in the placebo group with nonfatal events comprising > 90% of events in either group. Table 11 summarizes the number of events for each component of the primary endpoint in the lovastatin and placebo group.

Table 11. Summary of Participants with Primary Endpoint Event (First Event Only)

Primary Endpoint	Number of Participants	
	Lovastatin	Placebo
Fatal MI	2	5
Sudden cardiac death	8	9
Witnessed sudden cardiac death	6	5
Unwitnessed sudden cardiac death	2	3
Sudden death occurring >1hr and ≤24hr after collapse	0	1
Non-fatal MI	52	89
Definite acute Q-wave MI	28	56
Non-Q-wave MI	21	28
Silent subclinical (remote) MI	3	5
Unstable angina pectoris	54	80
Total number of participants with primary endpoint events	116	183

To assess the impact of including unstable angina as a component of the endpoint, the primary endpoint was re-analyzed by FDA without unstable angina. The results were similar to the overall results with a relative risk of .62 ($p=.002$).

Since about 50% of the lovastatin patients were titrated to the higher dose of 40 mg, the primary endpoint results by dose were examined by FDA. Figure 3 illustrates small differences between the two dose levels. Each dose demonstrated benefit over placebo ($p<.02$).

Figure 3 Survival curves by dose for the primary endpoint

