

Fatal and Nonfatal Cardiovascular Events

This secondary endpoint is the most comprehensive and includes the primary endpoint events, coronary revascularization procedures, CVAs (excluding hemorrhagic), TIAs, cerebrovascular surgeries (excluding bleeding) peripheral bypass procedures, CHF, sudden death (other than those classified as a primary endpoint), and stable angina. There were 194 events reported in the lovastatin group and 255 in the placebo group. The majority of these events were the primary endpoint events (nonfatal MIs and unstable angina). Approximately 25% of all events in the lovastatin group were MIs and 26% were unstable angina. Within the placebo group, approximately 30% of all events were MIs and 30% were unstable angina. The incidence of fatal and nonfatal cardiovascular events in the lovastatin group was 5.9% and 7.7% in the placebo group with a relative risk of 0.76.

It is interesting to note that for this secondary endpoint, where 50% more events were included than for the primary endpoint, the subgroup analysis results remain consistent. No significant treatment effects are seen for women, patients 65 or older, patients with LDL<130 and for patients with only 1 risk factor.

Table 17. Results for Fatal and Nonfatal Cardiovascular Events

	Lovastatin	Placebo	Relative Risk	95% CI	P-value
All patients	194/3304 (5.9%)	255/3301 (7.7%)	0.75	0.63, 0.91	.003
Gender					
Male	180/2805 (6.4%)	234/2805 (8.4%)	0.76	0.63, 0.92	.006
Female	14/499 (2.8%)	21/498 (4.2%)	0.67	0.34, 1.31	.24
Age					
<65	115/2589 (4.4%)	172/2600 (6.6%)	0.67	0.35, 0.84	.0007
≥65	67/612 (11.0%)	73/594 (12.3%)	0.89	0.64, 1.24	.49
Baseline LDL					
<130	22/348 (6.3%)	27/343 (7.9%)	0.80	0.46, 1.41	.45
≥130	172/2956 (5.8%)	228/2958 (7.7%)	0.75	0.61, 0.91	.004
Baseline LDL					
<160	171/2381 (7.2%)	139/2402 (5.8%)	0.80	0.64, 1.0	.05
≥160	55/902 (6.1%)	84/920 (9.1%)	0.66	0.47, 0.93	.02
Risk factors					
1	48/1241 (3.9%)	57/1229 (4.6%)	0.83	0.57, 1.23	.35
≥2	146/2063 (7.1%)	198/2072 (9.6%)	0.73	0.59, 0.90	.004

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Fatal and Nonfatal Coronary Events

These events included all the primary endpoint events, fatal and nonfatal coronary revascularization procedures, new onset CHF, and stable angina. There were 163 coronary events reported as first occurrence in the lovastatin group and 215 in the placebo group. Again, the majority of these cases were nonfatal MIs and unstable angina. The incidence rate was 4.9% in the lovastatin group and 6.5% in the placebo group with a relative risk of 0.75.

The subgroup results are consistent with those of all the previously mentioned secondary endpoints.

Table 18. Results for Fatal and Nonfatal Coronary Events

	Lovastatin	Placebo	Relative Risk	95% CI	P-value
All patients	163/3304 (4.9%)	215/3301 (6.5%)	0.75	0.61, 0.92	.006
Gender					
Male	154/2805 (5.5%)	199/2803 (7.1%)	0.77	0.62, 0.95	.01
Female	9/499 (1.8%)	16/498 (3.2%)	0.57	0.25, 1.28	.17
Age					
<65	100/2589 (3.9%)	140/2600 (5.6%)	0.68	0.53, 0.88	.003
≥65	53/612 (8.7%)	63/594 (10.6%)	0.81	0.56, 1.17	.27
Baseline LDL					
<130	20/348 (5.8%)	24/343 (7.0%)	0.82	0.45, 1.48	.51
≥130	143/2956 (4.8%)	191/2958 (6.5%)	0.74	0.60, 0.92	.007
Baseline LDL					
<160	115/2402 (4.8%)	140/2381 (5.9%)	0.81	0.63, 1.04	.09
≥160	48/902 (5.3%)	75/920 (8.2%)	0.65	0.45, 0.93	.02
Risk factors					
1	42/1241 (3.4%)	44/1229 (3.6%)	0.95	0.62, 1.45	.81
≥2	121/2063 (5.9%)	171/2072 (8.3%)	0.70	0.56, 0.88	.003

Cardiovascular and CHD Mortality

The number of fatal cardiovascular and CHD events were few and did not differ significantly between the two treatment groups. This finding is not surprising when the patient population being studied is a relatively healthy population with low risks for developing a fatal cardiovascular event as the initial presentation for CVD.

Table 19. Results for Cardiovascular and CHD Mortality

	Lovastatin	Placebo	Relative Risk	95% CI	P-value
Cardiovascular Mortality	17/3304 (0.5%)	25/3301 (0.8%)	0.68	0.37, 1.36	.22
CHD Mortality	11/3304 (0.3%)	15/3301 (0.5%)	0.73	0.34, 1.6	.43

Conclusions from the Secondary Endpoints Results

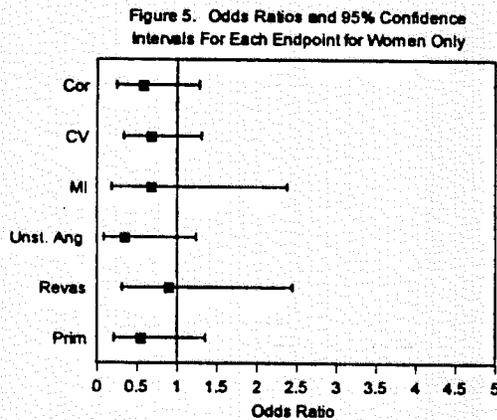
The treatment effect of lovastatin was consistently statistically significant across all the secondary endpoints examined except cardiovascular and CHD mortality. Those

secondary endpoints which incorporated components of the primary endpoint (unstable angina and fatal/nonfatal Mis) confirmed the robustness for the primary endpoint results by showing results consistent with the primary endpoint results.

Subgroup analyses confirmed the consistent and significant risk reductions found in those patients with ≥ 2 risk factors treated with lovastatin. Again, the placebo event rate in those patients with ≥ 2 risk factors exceeded the placebo event rate in the entire cohort for all the secondary endpoints wherein a subgroup analysis was performed.

Significant effects were also consistently observed for patients with LDL of 130 or greater, for patients under 65 and for men.

The effects for women are tenuous given the small number of events observed as illustrated by the size of the confidence intervals (CI) and given that the upper limit of the CI exceeds 1.0 for all endpoints (Figure 5).



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Tertiary Endpoint Results:

Tertiary endpoints examined included total mortality, noncardiovascular mortality, fatal and nonfatal cancer incidence, and discontinuations for adverse drug effects. Discontinuations for adverse drug effects are discussed under the Safety Results section.

Total and Noncardiovascular Mortality

There were a total of 157 deaths in the entire AFCAPS/TexCAPS cohort occurring either during or after discontinuation of treatment. Eighty deaths occurred in the lovastatin group (2.4%) and 77 in the placebo group (2.3%) (Table 20). Of note, the number of cardiovascular deaths was low and may be a reflection of both the patient population studied (i.e. primary prevention) and the national trend wherein a majority of initial cardiovascular events present as nonfatal events. There were no excess deaths from violence in the lovastatin treatment group, however, there were more cancer deaths in the lovastatin group (n=48) versus placebo group (n=34) accounting for the excess noncardiovascular mortality in the lovastatin group. Unlike other lipid-lowering trials this study did not exclude any participant with a prior history of malignancy provided that there were no contraindications to study treatment. Five participants in the lovastatin group and 3 in the placebo group died of a preexisting malignancy. This difference in cancer deaths between treatment and placebo groups deaths was not statistically significant.

Table 20. Number of participants by cause of death

Cause of Death	Number of Participants	
	Lovastatin	Placebo
Death from MI	2	5
Witnessed sudden cardiac death	6	5
Unwitnessed (presumed cardiac) sudden death	2	4
Sudden death occurring < 1 hr and ≤ 24 hrs after collapse	0	1
Fatal CVA	0	1
CHF mortality	1	0
Violent death	1	3
Cancer	48	34
Other cardiovascular fatality not meeting ECC event criteria	6	9
Other noncardiovascular fatality	14	15
Total number of mortality events	80	77

Examination of cancer incidence by body systems revealed no statistically significant differences between treatment and placebo groups.

Table 21. Cancer incidence by body systems

Body System	Lovastatin (N=3304)	Placebo (N=3301)	Between Group p-value
	n (%)	n (%)	
Digestive	39 (1.2)	28 (0.2)	0.22
Endocrine	1 (0.0)	6 (0.2)	0.07
Hematologic/Lymphatic	24 (0.7)	23 (0.7)	>0.99
Musculoskeletal	2 (0.1)	1 (0.0)	>0.99
Nervous	3 (0.1)	3 (0.1)	>0.99
Skin/Appendage	8 (0.2)	10 (0.3)	0.65
Urogenital	141 (4.3)	139 (4.2)	0.95

Further examination of body systems for cancer types revealed an imbalance for the hepatocellular carcinomas. There were 3 deaths from newly diagnosed hepatocellular carcinoma in the lovastatin group and 0 in the placebo group. Careful evaluation of these 3 patients' records were performed and revealed the following:

- a 69 year-old male who had a history of prostate cancer prior to randomization. He was randomized to lovastatin treatment in December 1990 and was diagnosed with hepatocellular carcinoma in November 1993. Study drug was discontinued in September 1994 and the patient died 1 year later.
- a 55 year-old male who was hepatitis B positive (unknown until September 1994) and had an ongoing history of alcohol abuse. He was on lovastatin treatment from June 1991 through January 1995 and was diagnosed with hepatocellular carcinoma in February 1997.
- a 73 year-old female treated with lovastatin from August 1992 through May 1995. She had a history of squamous cell carcinoma of the vulva diagnosed in 1980. Lovastatin therapy was discontinued after complaints of right upper quadrant pain, elevated liver enzymes, and an ultrasound revealed a 10 cm mass consistent with hepatocellular carcinoma. The patient died of liver cancer in January 1996.

Of these events, only 2 occurred while on lovastatin therapy and the third occurred 2 years after drug discontinuation in the presence of a known risk factor, hepatitis B seropositivity. Hepatoma is reported in the current labeling and the development of hepatocellular carcinoma was seen in rodent studies at drug exposures between 2-7 times that of the maximum human daily dose (80 mg). Previous clinical trials involving lovastatin have not reported a greater incidence of liver cancer in treatment groups and the number of events in the AFCAPS/TexCAPS trial are too small to establish causality.

Of significance is that overall mortality in the AFCAPS/TexCAPS trial did not demonstrate a benefit in subjects randomized to lovastatin therapy. The finding that treatment with lovastatin did not improve all-cause mortality may be a consequence of conducting a primary prevention trial in a patient population with a lower cardiovascular mortality risk than patients with established CAD.

Fatal and Nonfatal Cancer Incidence

The incidence of fatal and nonfatal cancer between the lovastatin group (9.0%) and placebo (9.0%) was not different. The most common malignancy occurring during treatment and follow-up was prostate with 109 cases reported in the lovastatin group and 108 in the placebo group.

Safety Results

Only adverse events (AEs) which occurred from randomization through discontinuation that were serious, drug-related, or causing discontinuation were presented in the clinical safety report for the AFCAPS/TexCAPS trial. Common AEs were defined as having an incidence of $\geq 0.2\%$ in either treatment group and were also reported by body system. Participants were only counted once per category. All deaths are considered serious AEs, however, deaths are summarized in the tertiary endpoints section of efficacy results.

Serious Adverse Events (SAEs)

SAEs occurred in 1131 (34.2%) participants in the lovastatin group and 1126 (34.1%) in the placebo group ($p=0.938$). There were expectedly fewer cardiovascular SAEs

reported in the lovastatin versus placebo group (260 vs. 310, $p=0.028$). There were more SAEs reported in the lovastatin group by body system than on placebo. The significant differences were seen in Nervous System/Psychiatric Disorders system (62 vs. 38, $p=0.020$), hemorrhoids (7 vs. 0, $p=0.016$), and cataracts (122 vs. 90, $p=0.030$). Examining the individual categories listed under Nervous System/Psychiatric Disorders revealed that the predominant events reported were falling (9 lovastatin, 7 placebo) and radiculopathies (10 lovastatin, 9 placebo); the incidence for all other categories was $< 0.1\%$ for the lovastatin group.

SAEs for cataracts were defined as a cataract extraction scheduled after randomization at either study site and was not based on the presence or absence of cataracts at baseline. Formal slit lamp examinations for cataracts were performed only at the San Antonio Clinic and revealed no difference between the two treatment groups.

The 7 cases of hemorrhoids classified as SAEs in the lovastatin group were related to hemorrhoidectomy requiring hospitalization. The number of pre-existing hemorrhoid cases were not significantly different between the lovastatin (12.4%) and placebo (12.0%) group.

Drug-related Adverse Events

Drug-related adverse events occurred in 577 (17.5%) participants in the lovastatin group and 525 (15.9%) in the placebo group ($p=0.092$). One patient treated with lovastatin developed Stevens-Johnson's syndrome which resolved after drug discontinuation and was classified as a serious drug-related AE. There were more participants in the lovastatin than placebo group with drug-related increases in ALT (110 vs. 70, $p=0.003$).

Adverse Events Causing Study Drug Discontinuation

There were significantly fewer study drug discontinuations in the lovastatin group compared to placebo for cardiovascular AEs (189 vs. 230, $p=0.039$) and significantly more musculoskeletal AEs in the lovastatin group requiring discontinuation of study drug compared to placebo (56 vs. 35, $p=0.034$). The most frequently reported complaints within the lovastatin group for musculoskeletal categories were arthritis, traumatic arthropathy, disc displacement, osteoarthritis, and spinal stenosis. There were no discontinuations secondary to drug-induced myopathy.

CPK Elevations and Associated Myopathy

CPK elevations > 10 times upper limit of normal (ULN) were rare and the incidence was similar between lovastatin 20 and 40 mg versus placebo (0.7% in both groups). There were no cases of drug-induced myopathy (defined as muscle symptoms accompanied with CPK elevations $> 10 \times$ the ULN). There were 3 cases of rhabdomyolysis: 2 occurred in the placebo group and 1 patient randomized to lovastatin. In this latter case the patient developed rhabdomyolysis associated with transient renal failure 1 day after surgery for prostate cancer. His preadmission CPK, BUN, and creatinine were normal and lovastatin was discontinued at time of admission.

Abnormalities of Liver Function Tests

Clinically important elevations of LFTs were classified as consecutive elevations of hepatic transaminases (AST or ALT) > 3 times ULN (AST 111 IU/L and ALT 120 IU/L). The incidence of consecutive elevations of AST and/or ALT > 3 times ULN was not significantly different between the 2 treatment groups (18 (0.6%) lovastatin vs. 11 (0.3%) placebo). When evaluated for time to event, of the 18 lovastatin-treated subjects