Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TexCAPS): Additional Perspectives on Tolerability of Long-Term Treatment With *Lovastatin*

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This study presents the long-term safety data from AFCAPS/TexCAPS, the first primary prevention trial to demonstrate that men and women with average levels of low-density lipoprotein cholesterol (LDL-C) and below average levels of high-density lipoprotein cholesterol (HDL-C) can significantly benefit from long-term treatment to lower LDL-C; lovastatin 20 to 40 mg/day reduced the risk of a first acute major coronary event (fatal or nonfatal myocardial infarction, unstable angina, or sudden death) by 37% (p = 0.00008). This double-blind randomized, placebo-controlled trial, in 6,605 generally healthy middle-aged and older men and women, had prespecified end point and cancer analyses. All analyses were intention-to-treat. Safety monitoring included history, physical examination, and laboratory studies (including hepatic transaminases and creatine phosphokinase [CPK]). All participants, even those who discontinued treatment, were contacted annually for vital status, cardiovascular events, and cancer history. After an average of 5.2 years of follow-up, there were 157 deaths (80 receiving lovastatin and 77 receiving placebo; relative risk [RR] 1.04; 95% confidence interval [CI] 0.76 to 1.42; p = 0.82); of which 115 were noncardiovascular (RR 1.21; CI 0.84 to 1.74; p = 0.31), and of these, 82 were due to cancer (RR 1.41; CI 0.91 to 2.19; p = 0.13). There were no significant differences between treatment groups in overall cancer rates, discontinuations for noncardiovascular adverse experiences, or clinically important elevations of hepatic transaminases or CPK. Among those who used cytochrome P450 isoform (CYP3A4) inhibitors, there were no treatment group differences in the frequency of clinically important muscle-related adverse events. Treatment with lovastatin 20 to 40 mg daily for primary prevention of coronary heart disease was well tolerated and reduced the risk of first acute coronary events without increasing the risk of either noncardiovascular mortality or cancer.

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The Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TexCAPS) demonstrated that the benefits of lipid modification in primary prevention can be extended to those with average total and low-density lipoprotein cholesterol (LDL-C) and below average high-density lipoprotein cholesterol (HDL-C). In this double-blind, placebo-controlled study, treatment with lovastatin 20 to 40 mg resulted in a 37% reduction in first acute major coronary events: fatal or nonfatal myocardial infarction, unstable angina, or sudden death (p = 0.00008). However, 83% of AFCAPS/TexCAPS participants would not have been recommended for pharmacologic intervention by National Cholesterol Education Panel II Guidelines because they had average to mildly elevated total cholesterol (4.65 to 6.82 mmol/L [180 to 264 mg/dl]) and no clinical evidence of atherosclerotic cardiovascular disease. For a primary prevention cohort with a relatively low risk of coronary heart disease (CHD) (11 per 1,000 patient–years), such as that studied in AFCAPS/TexCAPS,[1] it is especially important to consider the safety and tolerability of long-term treatment with lovastatin. This study summarizes, in more detail than was possible in the initial results publication, safety and tolerability data for lovastatin as gathered over a range of 4 to 7 years (average 5.2 years) of follow-up in a cohort that included women, the elderly, and those with preexisting cancer.

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METHODS

The design and methods have been previously described.[2] Following 12 weeks of American Heart As-

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sociation Step 1 diet, 5,608 men (45 to 73 years old) and 997 women (55 to 73 years old) were randomized to long-term treatment with either placebo or lovastatin 20 mg daily. Half of those receiving lovastatin (n = 1,657) had an average on-treatment (weeks 6 and 12) LDL-C of >2.84 mmol/L (110 mg/dl) and were titrated from 20 to 40 mg daily of lovastatin at week 18. An equal number of randomly selected placebo-treated participants were titrated to 2 tablets daily to maintain the double-blind protocol of the study. To allow generalization of the data to primary prevention cohorts, the exclusion criteria were limited; a history of cancer was not an exclusion criterion.

At every clinic visit, participants were questioned about adverse experiences. Routine laboratory safety measurements including creatine kinase (CK), alanine aminotransferase (ALT), and aspartate aminotransferase (AST) were performed at every clinic visit, which took place at baseline, day 1, every 6 weeks during the first year, and semiannually thereafter.

The study was powered to detect a difference in first acute major coronary events. Prespecified tertiary hypotheses stated that in both treatment groups there would be similar rates of the following end points: (1) total mortality, (2) noncardiovascular mortality (with subset analyses for accidental and/or violent death and for death from cancer), and (3) fatal and nonfatal cancer (excluding nonmelanoma skin cancers; i.e., basal cell and squamous cell skin cancers).

Analyses were intention-to-treat. For all end points, all statistical tests were 2-tailed. The log-rank statistic stratified by study site and gender was used to test between treatment differences. Relative risk estimates and 95% confidence intervals (CIs) stratified by study site and gender were obtained from the Cox proportional hazards model.

Treatment groups were compared with regard to incidence of categorical outcomes using Fisher's exact test. When a treatment group imbalance was observed, post hoc survival analyses were performed to assess the effect of time to event. Prespecified assessment of treatment effects on liver and muscle enzymes using Fisher's exact test compared ALT and/or AST elevations at various cut-points above the upper limit of normal (ULN) and CK elevations >10 × ULN. The ability to predict subsequent elevations was assessed using Cox's proportional hazard model to evaluate the effect of baseline values and/or early elevations (within the first 100 days) on subsequent elevations. For ALT, AST, and CK, comparisons between treatment groups were made using an analysis of variance model on median-aligned ranks of change from baseline with treatment, study center, and gender as model effects. Fisher's exact test was also used to compare treatment group frequencies of clinically important CK elevations and musculoskeletal adverse experiences in the subgroup of participants taking CYP3A4 inhibitors.

RESULTS

Overall, treatment with lovastatin was well tolerated and compliance to treatment regimens was high. More participants treated with lovastatin than placebo completed the trial (2,335 [71%] and 2,081 [63%], respectively). This small difference is likely due to the number who discontinued to use other lipid-lowering agents (1.1% receiving lovastatin and 8.0% receiving placebo). Although participants receiving placebo experienced more cardiovascular end point events,[1] there were no treatment group differences in the number of non–end-point adverse experiences (Table 1).

TABLE 1 Adverse Experience Summary Excluding Cardiovascular End-point Events

No. (%) of Participants With Adverse Experiences	Lovastatin (n = 3,304)	Placebo (n = 3,304)
Serious*	1,045 (32)	1,025 (31)
Drug related†	577 (17)	525 (16)
Serious and drug related*†	1 (<1)	0 (0)
Reason discontinued	328 (10)	285 (9)
Reason discontinued and drug related†	80 (2)	68 (2)

*Life-threatening, causing death or permanent disability, resulting in or prolonging hospitalization, or diagnosis of any type of cancer.
†Determined by the investigator to be possibly, probably, or definitely drug related.

Hepatic transaminases (ALT and AST): Lovastatin treatment was associated with small but statistically significant increases in ALT and AST levels (median increases from baseline at years 1 to 5 for each were <3 IU/L; p <0.001 for between treatment group change). Despite extensive liver function testing (>100,000 tests were performed over the course of the trial), clinically meaningful elevations (>3 × ULN) were infrequent (Table 2). Of the 18 subjects with confirmed ALT and/or AST elevations >3 × ULN who received lovastatin, most either recovered while on treatment or had a negative rechallenge. The 1 positive rechallenge was associated with cholelithiasis. Increased dose was not associated with increased frequency of confirmed ALT and/or AST elevations >3 × ULN (11 of 1,585 [0.7%] and 7 of 1,675 [0.4%] participants receiving lovastatin 20 and 40 mg, respectively).

In both treatment groups, 50% of participants with confirmed elevations > 3 x ULN experienced the elevation during the first year of treatment (9 of 18 and 5 of 11 of those receiving lovastatin and placebo, respectively). However, 50% of the AST and ALT tests performed in the study were performed in the first year (among those receiving lovastatin, 26,481 of 50,904 ALT and 26,487 of 50,900 AST tests were performed in the first year). When the database was analyzed to determine if elevations > 3 × ULN in ALT or AST either in baseline or in the first 100 days of the study were predictive of subsequent elevations, the analysis showed that elevations at baseline and post-treatment elevations (within the first 100 days) similarly predicted subsequent elevations. Furthermore, the relation was independent of treatment group; elevations occurring within 100 days of initiating lovastatin treatment were not significantly more predictive of subsequent elevations than elevations

TABLE 2 Elevations in Alanine Aminotransferase (ALT) and Aspartate Aminotransferase (AST)

No. (%) with ALT and/or AST	Lovastatin	Placebo	p Value
≥1 elevations >1 × ULN*	1,180/3,242 (36%)	970/3,248 (30%)	<0.001
Consecutive elevations >1 × ULN*	476/3,242 (15%)	348/3,248 (11%)	<0.001
Consecutive elevations >2 × ULN*	54/3,242 (1.7%)	39/3,248 (1.2%)	0.118
Consecutive elevations >3 × ULN*	18/3,242 (0.6%)	11/3,248 (0.3%)	0.199
Outcome in those with consecutive elevation >3 × ULN*	(n = 18)	(n = 11)	
Negative rechallenge or resolved on treatment	14	6	
Discontinued treatment and had alternative diagnosis†	3	3	
Positive rechallenge	1	2	

*ULN = upper limit of normal range; for ALT ULN = 40 IU/L; for AST ULN = 37 IU/L.
†Chronic active hepatitis, hepatitis A, fatty liver, cholelithiasis, or other lipid-lowering medication.

occurring within 100 days of initiating placebo treatment.

Creatine kinase and muscle symptoms: Small increases in CK (median <5 IU/L) from baseline were observed at years 1 to 5 in those treated with lovastatin ($p < 0.001$ for between treatment change). There was no treatment group difference in the frequency of CK elevations >10 × ULN (21 of participants [0.6%] in each of the treatment groups). Of those with elevations who received lovastatin, nearly all (20 of 21) recovered while on treatment; the other participant, after a brief interruption, resumed treatment without subsequent elevations. Rhabdomyolysis, a severe form of myopathy, was rare. There were 2 cases reported among those receiving placebo and 1 case unrelated to lovastatin treatment. In the latter case, the participant had been off study treatment when he experienced postoperative rhabdomyolysis; after discharge, he resumed lovastatin treatment without experiencing an increase in CK. No participants experienced uncomplicated myopathy (defined as CK elevation >10 × ULN with muscle symptoms).

The total number of participants reporting any musculoskeletal symptoms during the study was similar between treatment groups (2,053 of 3,304 [62.1%] and 1,971 of 3,301 [59.7%] receiving lovastatin and placebo, respectively; $p = 0.563$). Discontinuations due to myalgia were similar in both groups (11 and 9 with lovastatin and placebo, respectively; $p = 0.824$), and there was no apparent association with dose (6 of 1,647 and 5 of 1,657, receiving 20 and 40 mg of lovastatin, respectively).

Clinical experiences associated with concomitant use of drugs that inhibit CYP3A4: Approximately equal numbers of participants in each treatment group took 1 of the following CYP3A4 inhibitors after randomization to study drug: diltiazem, verapamil, nifedipine, amlodipine, felodipine, nicardipine hydrochloride, erythromycin, erythromycin/ethylsuccinate, clarithromycin, ketoconazole, or itraconazole. These concomitant medications were classified as either modest CYP3A4 inhibitors (calcium channel blockers) or potent inhibitors (erythromycin, erythromycin/ethylsuccinate, clarithromycin, ketoconazole, or itraconazole). There were no significant treatment group differences in musculoskeletal adverse experiences reported for those taking modest inhibitors (290 of 422 [68.7%] receiving lovastatin and 295 of 443 [66.6%] receiving placebo; $p = 0.51$) or for those taking potent inhibitors (406 of 535 [75.9%] receiving lovastatin and 386 of 511 [75.5%] receiving placebo; $p = 0.94$). There were no significant treatment group differences in the frequency of myalgia reported for those taking modest CYP3A4 inhibitors (18 of 422 [4.3%] receiving lovastatin and 32 of 443 [7.2%] receiving placebo; $p = 0.08$) or potent CYP3A4 inhibitors (35 of 535 [6.5%] receiving lovastatin and 44 of 511 [8.6%] receiving placebo; $p = 0.24$). When data for modest and potent CYP3A4 inhibitors were pooled, no treatment group differences were observed for musculoskeletal adverse experiences (628 of 877 [71.6%] and 619 of 872 [71.0%] treated with lovastatin and placebo, respectively; $p = 0.79$) or CK >10 × ULN (8 of 877 [0.9%] and 9 of 872 [1.0%], respectively; $p = 0.81$). Among those taking any CYP3A4 inhibitor, fewer participants receiving lovastatin than placebo experienced myalgia (45 of 877 [5.1%] and 68 of 872 [7.8%], respectively; $p = 0.02$). There were no reported cases of uncomplicated myopathy or rhabdomyolysis in those receiving lovastatin concomitantly with CPY3A4 inhibitors. Within the lovastatin treatment group the dose did not affect the frequency of adverse experiences.

Mortality: Rates for overall mortality, cardiovascular mortality, noncardiovascular mortality, and fatal cancer were low, and there were no treatment group differences (Table 3). Although rare, there were fewer traumatic deaths among those treated with lovastatin (1 subject on lovastatin and 3 on placebo).

The most frequent cause of death was cancer, and the number of cancer fatalities in each treatment group was similar (48 occurred in the lovastatin group and 34 in the placebo group [0.9 vs 0.6 deaths per 1,000 person–years at risk; $p = 0.125$ for treatment group difference]). Preexisting cancer was associated with 5 deaths in the lovastatin group (2 from lymphoma, and 1 each from melanoma, lung cancer, and prostate cancer) and 3 in the placebo group (1 each from lymphoma, ovarian, and lung cancer). Annual rates of fatal cancer were similar between treatment groups (lovastatin/placebo fatal cancer rate ratios were 1.50, 1.75, 1.80, 1.43, and 1.18 during years 1 through 5). A higher dose of lovastatin did not appear to be associated with a higher frequency of fatal cancer (23 of 1,647 [1.4%] treated with 20 mg and 25 of 1,657 [1.5%] treated with 40 mg daily of lovastatin). Furthermore, among those treated with lovastatin, the frequency of fatal cancer by LDL-C tertiles at baseline, year 1, and the percent change from baseline to year 1 was similar across each set of tertiles.

TABLE 3 Summary of Mortality Survival Analyses

Tertiary End Point	Lovastatin n (%)*	Placebo n (%)*	Between Treatment p Value†	Proportional Assumption p Value‡	Relative Risk (95% CI)
Total mortality	80 (3.1)	77 (2.9)	0.823	0.793	1.04 (0.76–1.42)
Noncardiovascular mortality	63 (2.4)	52 (2.1)	0.311	0.648	1.21 (0.84–1.74)
Cancer mortality	48 (1.9)	34 (1.4)	0.125	0.837	1.41 (0.91–2.19)

*Cumulative incidence from unstratified lifetable model.
†Log-rank statistic, stratified by study center and gender.
‡Cox proportional hazard model, stratified by study center and gender.

Nonfatal cancer: The combined incidence of cancer (excluding nonmelanoma skin cancer) was similar (15.1 and 15.6 per 1,000 person–years [252 and 259 cases] in the lovastatin and placebo groups, respectively; relative risk 0.97 with a 95% CI of 0.81 to 1.15; $p = 0.706$ by log-rank statistic, stratified by study site and gender) (Figure 1). Being a smoker at the beginning of the study appeared to be associated with an increased risk of cancer in both treatment groups (8.4% for lovastatin and 7.5% for smokers and nonsmokers; 9.0% and 7.7% for placebo, respectively).

Numerically, more lovastatin participants (165 [5.0%]) than placebo participants (140 [4.2%]) had preexisting nonskin cancer or melanoma. The most frequent of these preexisting cancers were melanoma (1.0% and 0.8% treated with lovastatin and placebo, respectively) and prostate cancer (1.2% of men in both treatment groups). During the study, prostate cancer remained the most frequently reported of these cancers (3.9% of men; 109 of 2,805 and 108 of 2,803 treated with lovastatin and placebo, respectively). Melanoma was the only type of cancer that was reported at a significantly different frequency between groups (0.4% [14 of 3,304] and 0.8% [27 of 3,301] for lovastatin and placebo, respectively; $p = 0.043$). The frequency of specific types of other cancer (lymphoma and colon, lung, breast, and bladder cancer) were similar in both treatment groups.

History of nonmelanoma skin cancer (basal cell and squamous cell skin cancer) was a frequently reported prestudy condition (7.6% of cohort; 257 and 248 treated with lovastatin and placebo, respectively). During the study, the frequency remained similar between groups (7.6% [250 of 3,304] receiving lovastatin and 7.4% [243 of 3,301] receiving placebo; $p = 0.779$). Regardless of treatment group, participants who reported prestudy basal or squamous cell cancer were almost twice as likely to subsequently develop nonskin cancer or melanoma than those who reported no prestudy basal or squamous cell cancer (13% [33 of 252] and 12% [32 of 259] with a history of receiving lovastatin and placebo, respectively, compared with 7.2% [219 of 3,047] and 7.4% [227 of 3,053] without a history of receiving lovastatin and placebo, respectively).

Adverse experiences frequently cited in trials: headache, dizziness, and sleep disturbance: Treatment groups were balanced with regard to adverse experiences of headache, dizziness, and sleep disturbances. For those receiving lovastatin and placebo, respectively, the frequencies were 293 of 3,304 (9%) and 259 of 3,301 (8%) ($p = 0.142$) for headache; 317 of 3,304 (10%) and 344 of 3,301 (10%) ($p = 0.268$) for dizziness); and 163 of 3,304 (5%) and 148 of 3,301 (4%) ($p = 0.416$) for sleep disturbance.

DISCUSSION

With 6,605 men and women followed for an average of 5.2 years, AFCAPS/TexCAPS has provided an opportunity to study the safety of long-term treatment with lovastatin in a CHD primary-prevention cohort at lower risk due to average cholesterol levels and the absence of symptomatic CHD.

The large number of participants studied in AFCAPS/TexCAPS provided an opportunity to detect rare adverse events, such as myopathy. No new (as yet not described in the package circular on lovastatin) drug-related adverse experiences were identified in AFCAPS/TexCAPS. No clinically important or statistically significant treatment group differences were seen in prespecified safety end points: total and noncardiovascular mortality, cancer (melanoma and nonskin cancer, and fatal cancer), and discontinuations for adverse experiences. The frequency of cerebrovascular events was low and similar in both treatment groups (0.069% and 0.168% per year in the lovastatin and placebo groups, respectively). Furthermore, long-term use of lovastatin 20 to 40 mg daily was not associated with an increased frequency of clinically important liver and muscle side effects despite intensive laboratory screening for these disease markers.

Screening for transaminase elevations was not clinically useful in detecting hepatotoxicity. Small increases in mean liver transaminase levels have been observed with all statins,[3–9] and increases were also observed in AFCAPS/TexCAPS participants treated with lovastatin; however, treatment with lovastatin 20 to 40 mg daily was not associated with hepatotoxicity. Data from nearly 7,000 participants receiving either placebo or lovastatin 20 mg daily in Expanded Clinical Evaluation of Lovastatin (EXCEL)[8] and AFCAPS/TexCAPS demonstrated no significant differences in the frequency of confirmed AST or ALT elevations $>3 \times$ ULN. Over 100,000 liver transaminase tests were performed in AFCAPS/TexCAPS, but only 18 participants receiving lovastatin had clinically important elevations (confirmed elevations $>3 \times$ ULN) and no cases of lovastatin-induced hepatitis were identified. The frequency of elevations appeared to be associated with the number of tests performed; half of the elevations occurred in the first year as did half of the tests performed. Although prior elevations did predict subsequent elevations, the risk was independent of treatment, suggesting that lovastatin does not increase the risk for any clinically important transaminase elevations. The large (approximately

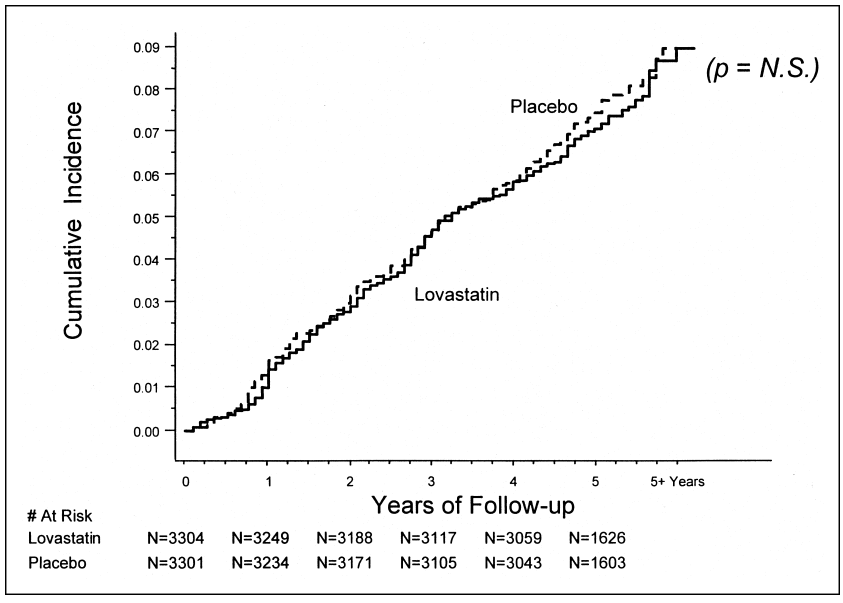

FIGURE 1. Cumulative incidence rate of fatal and nonfatal cancer events (excluding nonmelanoma skin cancer)

30%) frequency of sporadic elevations >1 × ULN in both treatment groups suggest that transaminase elevations should be expected with routine monitoring.

In the last few years it has been recognized that lovastatin, like many medications, is metabolized by CYP3A4. Concomitant use of CYP3A4 inhibitors increase circulating levels of drugs metabolized by CYP3A4, such as lovastatin.[10] Because AFCAPS/TexCAPS was conducted before an association with CYP3A4 inhibitors was well recognized, both the clinical impact and frequency of use of potent CYP3A4 inhibitors can be assessed. Erythromycin was the most commonly used potent CYP3A4 inhibitor and some antifungal agents were also used. Although >500 participants received a potent CYP3A4 inhibitors for short periods of time while taking lovastatin 20 to 40 mg daily, these participants did not experience increased frequencies of myopathy, myalgia, or increased levels of CK. AFCAPS/TexCAPS data regarding concomitant use of calcium channel blockers, modest CYP3A4 inhibitors, are consistent with data from EXCEL[11] and indicate that long-term concomitant use of lovastatin 20 to 40 mg daily and calcium channel blockers is generally well tolerated.

The lower frequency of melanoma in those treated with lovastatin (14 [0.4%] and 27 [0.8%] with lovastatin and placebo, respectively; $p = 0.04$) was unexpected and must be interpreted with caution. The number of participants with melanoma is small, the p value is not particularly robust, and one might expect to find a random statistically significant difference given the number of statistical tests performed without adjustment for multiplicity. Furthermore, risk reduction of melanoma has not been reported in either long-term trials with other statins[3–7] or the shorter duration lovastatin trial, EXCEL.[8] However, these findings are interesting given the recently published data concerning the antiatherothrombotic properties of statins[12] and the observed association between cancer,[13] including malignant melanoma,[14] and activation of systemic coagulation. One could hypothesize that by indirectly decreasing thrombin, a growth factor for melanoma,[14] lovastatin decreases the incidence and/or severity of melanoma. Large controlled studies of those at elevated risk of developing melanoma are required to test the validity of AFCAPS/TexCAPS findings among the relatively small number of participants who experienced melanoma.

Worldwide, the incidence of skin cancer appears to be rising, and exposure to sunlight is considered a risk factor.[15] As expected in a cohort living in the American Southwest, nonmelanoma skin cancer was frequently reported in both treatment groups. Epidemiologic studies have suggested that basal cell carcinoma may be predictive of risk for subsequent nonskin cancer.[16,17] Our data indicate that there was a higher percentage of those with a history of basal or squamous cell cancer among the group with a subsequent diagnosis of nonskin cancer or melanoma than those without these cancers. More research is required to confirm this association.

AFCAPS/TexCAPS, like the Long-term Intervention with Pravastatin in Ischaemic Disease (LIPID)[6] and Scandinavian Simvastatin Survival Study (4S),[4,5] did not demonstrate the treatment group imbalance in the frequency of fatal and nonfatal breast cancer observed in the Cholesterol and Recurrent Events (CARE) trial[3] (West of Scotland Coronary Prevention Study [WOSCOPS][7] excluded women). Prostate cancer was the most common type of nonskin cancer as one would expect in a cohort comprised of middle age to elderly men who underwent annual physical examination and, if indicated, subsequent prostate-specific antigen testing. As with breast cancer, there was no imbalance between treatment groups in the frequency of prostate cancer or any other type of cancer in AFCAPS/TexCAPS, except melanoma.

Not surprisingly, the most common cause of death in AFCAPS/TexCAPS was cancer; participants with clinical symptoms of cardiovascular disease were excluded from the trial, whereas those with preexisting cancer were not (5% of lovastatin- and 4% of placebo-treated participants had preexisting melanoma or nonskin cancer). AFCAPS/TexCAPS data support those from other long-term CHD prevention trials of statins,[3–7] demonstrating no treatment group differences in the frequency of noncardiovascular mortality, in-

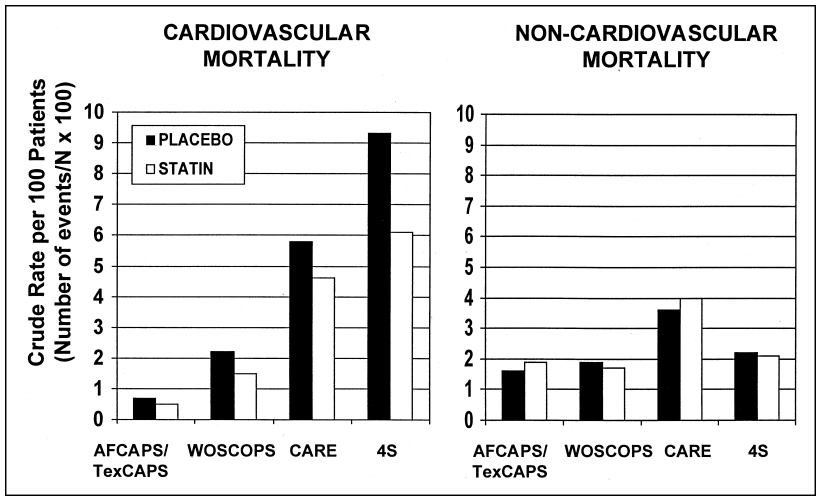

FIGURE 2. Cardiovascular and noncardiovascular mortality rates.

cluding deaths due to cancer, suicides, or accidents. A recent meta-analysis of trials lasting >2 years concluded that cholesterol lowering with statins reduced CHD without increasing non-CHD mortality.[18]

Differences between the statin trials in the frequency of total mortality and the number of noncardiovascular deaths compared with cardiovascular deaths are a function of differing levels of risk for fatal CHD events (Figure 2). As intended by design, AFCAPS/TexCAPS was not powered to detect a significant difference in total mortality. Assuming a 30% to 35% reduction in cardiovascular deaths (32% reduction actually observed) and no effect on noncardiovascular deaths, AFCAPS/TexCAPS had only 7.6% to 9.3% power to observe a significant treatment difference in total mortality.[2] Because there was no between-group difference in the total number of deaths (157 total; 80 and 77 with lovastatin and placebo, respectively), some have questioned the benefit of using lipid modification in primary prevention, particularly in those with average LDL-C levels. However, for Americans, who are 60 years old, with a residual life expectancy of 20 years,[19] the value of primary prevention may depend as much upon extending healthy longevity by delaying or preventing the first nonfatal coronary event, as upon preventing cardiovascular death.

AFCAPS/TexCAPS has demonstrated that treatment with lovastatin can significantly reduce the first occurrence of cardiovascular morbidity (including unstable angina and myocardial infarction) in those with average LDL-C and below average HDL-C. Long-term safety data from AFCAPS/TexCAPS provides a profile that is reassuring for the prescribing physician who must weigh the benefits of CHD primary prevention against long-term commitment to pharmacologic intervention.

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