

CENTER FOR DRUG EVALUATION AND RESEARCH

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MEDICAL REVIEW(S)

NDA# 19-643/S-055

Mevacor (lovastatin sodium) tablets

Merck Research Labs

Date of submission: April 28, 1998

Efficacy supplement based on data from AFCAPS/TexCAPS

Team leader note on NDA supplement

Summary of AFCAPS/TexCAPS

AFCAPS/TexCAPS was a large-scale coronary morbidity and mortality study designed to assess whether treatment with lovastatin 20-40 mg daily would reduce the risk of CHD events compared to placebo in a cohort of middle-aged and elderly men and women without CHD symptoms and with average to moderately elevated total-C and LDL-C but with below average HDL-C. This was a double-blind, randomized, multicenter trial with an average duration of follow up of 5.2 years that enrolled men aged 45-73 years, women aged 55-73 years with average TC= 221 mg/dL, mean LDL-C= 150 mg/dL, and mean HDL-C=37 mg/dL. Average TG was 168 mg/dL, and average ratio of TC to HDL-C was 6.0. With regard to overall atherosclerosis risk, in addition to elevation in TC/HDL-C (88% of the cohort had a ratio of 5.0 or greater), 33% of the cohort had HDL-C < 35 mg/dL, 22% had hypertension, 12% were current smokers, and 16% had a positive family history of premature CHD. There were very few diabetics in this study. All patients had age as a risk factor for CHD. All told approximately two thirds of the cohort had 2 or more CHD risk factors.

The treatment goal in this trial was LDL-C <110 mg/dL, with escalation in dose in the lova group (from 20 mg to 40 mg) at 18 weeks for those patients not yet achieving target LDL levels. To maintain the blind, for each lova patient so escalated, a randomly chosen placebo patient had a similar adjustment in dosage. Patients with LDL-C > 195 mg/dL were withdrawn in order to permit effective lipid lowering therapy outside of the constraints of the trial. Approximately 50% of the lova patients were titrated to the 40 mg dose. For similar ethical reasons, patients experiencing events were discontinued from the trial (but still followed to trial closure) in order to permit effective lipid altering therapy.

The primary outcome variable of the study was time to first event for the composite of fatal and nonfatal MI, unstable angina, or sudden cardiac death with rigorous requirements per protocol for the adjudication of events. Secondary and tertiary endpoints included the individual components of the primary endpoint (where a single patient could contribute to more than one endpoint calculation) as well as total mortality, cardiovascular mortality, and total fatal and nonfatal cardiovascular events. Finally, the incidences of fatal and nonfatal cancer were analyzed.

The average change in LDL-C for the lovastatin group (placebo subtracted) was -25% and the change in HDL-C was +5% (also placebo subtracted). Approximately 71% of the lovastatin-treated patients and 63% of the placebo-treated patients completed the trial with reasons for discontinuation generally balanced across the treatment groups except

for the reasons of lack of efficacy and use of other lipid altering medication (placebo rate > lova rate).

Analysis of trial outcomes showed a highly significant 37% risk reduction for the primary endpoint with crude incidence rates of 5.5% in the placebo group and 3.5% in the lova group. The majority of events were non-fatal and approximately half were unstable angina as the first presentation of CHD.

Subgroup analyses were revealing for the fact that approximately 75% of the total primary endpoint events occurred in the two-thirds of the cohort with two or more risk factors. While the trends suggesting a beneficial effect of lovastatin as compared to placebo held for most of the minority subgroups in the trial, there were two few events among women and those at low risk because of low baseline LDL-C (< 130 mg/dL) or with fewer than two risk factors to adequately assess the treatment effect in those groups.

The non-primary cardiovascular endpoint results paralleled those for the primary endpoint and the results of the subgroup analyses were likewise similar and pointed up the same limitations of the study with regard to permitting conclusions about the treatment effect in women and in low risk patients.

For total mortality, there was no difference between the treatment groups. There were relative few deaths (77 placebo, 80 lovastatin) and few cardiovascular deaths (28 placebo, 18 lovastatin). There was a non-significant excess of cancer deaths in the lovastatin group (34 placebo, 48 lovastatin). The only notable imbalance in site-specific cancer death was for hepatocellular carcinoma (3 lova, 0 placebo). One of the cases occurred two years after discontinuation of therapy in the context of a history of hepatitis B infection. There was a non-significant excess of incident cancers in the lovastatin group, the imbalance due in part to excess digestive system cancers (non-significant). Finally, there was a small, non-specific imbalance in breast cancer across treatment groups (13 lova, 9 placebo).

Conclusions from the trial

In sum, this trial demonstrated the clinical benefits of cholesterol lowering in a high risk subset of middle-aged-to-elderly patients with average to moderately elevated total-C and LDL-C and below average HDL-C, thus with increased ratio of total-C to HDL-C. This identifies a new group of individuals, heretofore not targeted for therapy, in whom cholesterol lowering intervention should be considered. Certain of these patients, whose only obvious lipid/lipoprotein abnormality is a below-average HDL-C, particularly in the context of multiple non-lipid risk factors (age, cigarette smoking, diabetes, hypertension, family history of premature CHD), may well benefit from interventions to lower LDL-C (thus lowering the ratio of total-C to HDL-C).

There were no new safety issues that emerged from this trial.

Labeling

Labeling based on AFCAPS has been negotiated and includes changes to Clinical Pharmacology/Clinical Studies, regarding the design features and salient results of the trial. The population is described in terms of baseline LDL-C, HDL-C, ratio of TC to HDL-C, and risk factor profiles. The Division felt strongly that the ratio of total-C to HDL-C should be included even though not a criterion for intervention according to treatment guidelines. This was because the great majority of enrollees had ratios elevated above "normal" by commercial labs (88% had ratios greater than 5.0). Of note, the indications based on the AFCAPS results do not mention TC/HDL-C.

With regard to the trial results, crude event rates are cited for primary and secondary endpoints and Kaplan-Meier event-free survival curves are included as Figure 1. The indications for use of Mevacor in the primary prevention of CHD list expected reductions in the components of the primary endpoint and secondary endpoints for which the treatment effect was statistically significant. The use of the term "acute major coronary events," which refers to the composite primary endpoint of the trial, was rejected as poorly descriptive of the results of the study and based upon precedent in labeling conveying the results of other similar trials.

The only other significant changes to labeling were in Warnings/Liver Dysfunction in which the LFT data from AFCAPS are cited and in Adverse Reactions where the tolerability of lovastatin in AFCAPS is discussed in brief. No changes are being made at this time pertaining to recommendations for LFT monitoring of patients treated with lovastatin.

Recommendation

Pending final agreement on labeling, this supplement should be approved.

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Joint Clinical and Statistical Review

NDA #: 19-643/Labeling supplement 055

Drug: MEVACOR (lovastatin sodium) tablets

Sponsor: Merck Research Laboratories

Indication: Primary prevention of coronary heart disease based on the AFCAPS/TEXCAPS study

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Documents Reviewed: Volumes 1-10

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INTRODUCTION

Historical Perspectives of Lipid-lowering Trials

The role of elevated total cholesterol (TC) and low-density lipoprotein cholesterol (LDL-C) in cardiovascular disease (CVD) is well-established in epidemiologic, animal, and clinical trials. Furthermore, the benefits of lipid-altering drugs in conjunction with a low cholesterol diet with respect to reducing risks for fatal and nonfatal cardiovascular events have been demonstrated in large clinical trials such as the Lipid Research Clinics Coronary Primary Prevention Trial (LRC-CPPT) and the Helsinki Heart Study.

Despite this information, concerns regarding the clinical benefit of lipid-lowering were still raised with critics referencing the findings of increased noncardiovascular deaths and the inability to demonstrate a benefit in overall survival in the above-mentioned trials. Recognizing these issues, the National Cholesterol Education Program (NCEP) published the first guidelines for cholesterol reduction in 1988 and the most recent recommendations in 1993. These guidelines focused on the following: identifying risk factors for coronary heart disease (CHD), establishing target LDL-C levels based on these risk factors, and distinguishing between those patients without clinical evidence of CHD (primary prevention) and those with established disease (secondary prevention). Therapeutic emphasis was placed on dietary and lifestyle intervention as the first line of treatment followed by pharmacotherapy if initial intervention was unsuccessful. This latter point was stressed primarily because of the lack of long-term safety data on use of lipid-lowering drugs. Table 1 summarizes the current NCEP treatment guidelines.¹

Table 1. Treatment recommendations based on LDL-C levels

Patient Category	Initiation Level	LDL Goal
Dietary Therapy		
w/o CAD, < 2 risk factors	≥160 mg/dL (4.1 mmol/L)	<160 mg/dL (4.1 mmol/L)
w/o CAD, ≥ 2 risk factors	≥130 mg/dL (3.4 mmol/L)	<130 mg/dL (3.4 mmol/L)
w/ CAD	>100 mg/dL (2.6 mmol/L)	≤100 mg/dL (2.6 mmol/L)
Drug Treatment		
w/o CAD, < 2 risk factors	≥190 mg/dL (4.9 mmol/L)	<160 mg/dL (4.1 mmol/L)
w/o CAD, ≥ 2 risk factors	≥160 mg/dL (4.1 mmol/L)	<130 mg/dL (3.4 mmol/L)
w/ CAD	≥130 mg/dL (3.4 mmol/L)	≤100 mg/dL (2.6 mmol/L)

Since the publication of these guidelines, several large long-term clinical trials (Scandinavian Simvastatin Survival Study (4S), Cholesterol and Recurrent Events Trial (CARE) and West of Scotland Coronary Prevention Study (WOSCOPS)) involving the class of lipid-lowering drugs known as, HMG-coA reductase inhibitors or statins, have confirmed the clinical benefits of the NCEP treatment recommendations. Furthermore, these trials demonstrated that patients with high risks for initial or recurrent cardiovascular events had significantly fewer cardiovascular events when treated with a

¹ Summary of the Second Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel II). *JAMA* 1993;269:3015-3023.

statin compared to placebo and this benefit was not offset by an increased number of deaths from noncardiovascular causes.

Both the 4S and CARE studies were conducted in patients with established CHD (secondary prevention trials). In 4S, 4,444 patients with a history of myocardial infarction (MI) were randomized to simvastatin or placebo; those patients randomized to simvastatin had a 30% risk reduction in all cause mortality compared to the placebo-treated patients (Table 2). In CARE, 4,159 patients with a recent MI and TC < 240 mg/dL were randomized to pravastatin or placebo; pravastatin-treated patients showed a 24% risk reduction in fatal coronary events or nonfatal MI's. WOSCOPS was a primary prevention study of 6,595 men without clinical evidence of CHD but at high risk for the disease based on their baseline cholesterol levels (TC > 252 mg/dL, LDL-C < 155 mg/dL) and lifestyle. In this study, those patients randomized to pravastatin had a 31% risk reduction in nonfatal MI's and CHD mortality compared to placebo.

Table 2. Primary (bolded) and secondary endpoint results for three large statin trials

	Statin	Placebo	Relative Risk
4S			
Total Mortality	182/2221 (8.2%)	256/2223 (11.5%)	.70
Coronary Mortality	111/2221 (5.0%)	189/2223 (8.5%)	.58
Non-fatal MI	286/2221 (12.9%)	436/2223 (19.6%)	.63
Revas. Proc.	252/2221 (11.4%)	382/2223 (17.2%)	.64
CARE			
Total Mortality	180/2081 (8.6%)	196/2078 (9.4%)	.91
NF-MI/fatal CHD	212/2081 (10.2%)	274/2078 (13.2%)	.76
Non-fatal MI	135/2081 (6.5%)	173/2078 (8.3%)	.77
Revas. Proc.	284/2081 (13.6%)	391/2078 (18.8%)	.73
WOSCOPS			
Total Mortality	106/3302 (3.2%)	135/3293 (4.1%)	.78
NF-MI/fatal CHD	174/3302 (5.3%)	248/3293 (7.5%)	.69
Non-fatal MI	143/3302 (4.3%)	204/3293 (6.2%)	.68
Revas. Proc.	51/3302 (1.5%)	80/3293 (2.4%)	.63

Rationale for AFCAPS/TexCAPS

The Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TexCAPS) is a primary prevention trial using lovastatin (Mevacor). AFCAPS/TexCAPS is unique from other previously conducted primary prevention studies in several aspects: 1) the target population had a mild to moderately elevated TC and LDL-C, 2) unstable angina was included as a primary endpoint 3) women, Hispanics, and an older patient population were studied 4) a lower LDL-C treatment goal was used, and 5) a lower than average HDL-C was used as an entry criterion. Table 3 compares and distinguishes AFCAPS/TexCAPS from other primary prevention trials.

Table 3. Patient population in AFCAPS/TexCAPS and other primary prevention trials

Baseline characteristics	AFCAPS/TexCAPS	WOSCOPS	Helsinki Heart Study	LRC-CPPT
Total Enrolled (M/F)	6605 (5608/997)	6596 (6595/0)	4081 (4081/0)	3806 (3806/0)
Age (mean)	58 ± 7	55.2 ± 5.5	47.3 ± 4.7	47.8 ± NA
TC (mean)	221 ± 21	272 ± 23	244.7 ± 45.1	291.8 ± NA
LDL-C (mean)	150 ± 17	192 ± 17	195.4 ± 45.9	216.2 ± NA
HDL-C (mean)	37 ± 6	44 ± 9	49.4 ± 11.9	45.1 ± NA
TG (mean)	158 ± 76	162 ± 70	NA	158.4 ± NA

NA = not available

The impetus for the design of AFCAPS/TexCAPS was the observation that the risk for developing CHD over a range of cholesterol levels was continuous and graded and that cardiovascular events occurred in patients with cholesterol levels in the lower range.² In addition, studies have shown that low HDL-C represents a significant risk factor for CHD with increased cardiovascular events for HDL-C < 35 mg/dL. For example, the Framingham Study showed that the incidence rate for initial CHD events in men and women with TC < 200 mg/dL was about 4% for patients with HDL of 40 mg/dL or greater and 12% in those patients with the HDL < 40 mg/dL.³ Also, a study of patients with premature CHD revealed that approximately 20% of those patients had a low HDL-C (mean \pm SD 36 \pm 11) in the setting of average LDL-C (156 \pm 51).⁴ Conversely, the protective role of high-density lipoprotein cholesterol (HDL-C) in the development of atherosclerosis has been established with elevated HDL-C (> 60 mg/dL) considered a negative risk factor under recent NCEP guidelines. Hence, while the risk for developing CHD rises with increasing TC and LDL-C, the atherogenic potential of a low HDL-C may be a significant contributor to CAD in patients with normal to mildly elevated TC and LDL-C. Hence, AFCAPS/TexCAPS was designed to extend observations from previous lipid-lowering trials to an at-risk population characterized by lipid profiles with a higher than average ratio of total-C/HDL-C (88% of the cohort had TC/HDL-C > 5.0 at baseline).

AFCAPS/TexCAPS (conducted 5/90 to 9/97)

Study Design and Objectives

AFCAPS/TexCAPS was a double-blinded, randomized, placebo-controlled study which enrolled civilian and military personnel from Lackland Air Force Base in San Antonio, Texas and the University of North Texas Health Science Center in Fort Worth, Texas. The objectives of the trial were:

1. **Primary:** to demonstrate that treatment with lovastatin 20 to 40 mg qd in patients without clinical evidence of CHD and moderately elevated TC and LDL-C and low HDL-C would decrease the time to first event over a period of at least 5 years of the combined endpoints: fatal CHD, nonfatal MI, and unstable angina.
2. **Secondary:** to investigate whether treatment with lovastatin compared to placebo would decrease the time to first occurrence of: (1) fatal and nonfatal coronary revascularization procedures, (2) new onset unstable angina, (3) fatal and nonfatal MI, (4) fatal and nonfatal cardiovascular events, (5) fatal and nonfatal coronary events, (6) cardiovascular mortality, and (7) CHD mortality.
3. **Tertiary:** to further investigate the long-term safety of lovastatin therapy with respect to: (1) total mortality, (2) noncardiovascular mortality (with subset analyses for accidental/violent death and for death from cancer), (3) fatal and nonfatal cancer incidence (excluding nonmelanoma skin cancer), and (4) discontinuations for adverse drug effects.

² Stamler J et al: Is Relationship Between Serum Cholesterol and Risk of Premature Death From Coronary Heart Disease Continuous and Graded. The MRFIT Study. *JAMA* 1986; 256:2823-2828.

³ Castelli WP et al: Incidence of Coronary Heart Disease and Lipoprotein Cholesterol Levels. The Framingham Study. *JAMA* 1986;256:2835-2838.

⁴ Genest J et al: Lipoprotein Cholesterol, Apolipoprotein A-1 and B and Lp (a) Abnormalities in Men with Premature Coronary Artery Disease. *J Am Coll Cardiol* 1992;19:792-802.

Inclusion Criteria

- men ages 45-73 years and postmenopausal women ages 55-73 years
- TC 180-264 mg/dL, LDL-C 130-190 mg/dL, HDL-C \leq 45 mg/dL for men and \leq 47 mg/dL for women, TG \leq 400 mg/dL. Subjects with LDL-C 125-129 mg/dL were included when the ratio of TC/HDL-C was $>$ 6.0. Lipid values from weeks -4 and -2 were averaged to evaluate study eligibility.
- no prior history of CVD (including definite MI, angina, claudication, cerebrovascular accident [CVA], or transient ischemic attack [TIA])

Exclusion Criteria

- clinical evidence of CVD demonstrated as prior definite history of MI by ECG or enzyme elevation, definite angina, or intermittent claudication
- presence of secondary causes of dyslipidemia such as hypothyroidism (unless corrected by L-thyroxine), nephrotic syndrome, uncontrolled or insulin-dependent diabetes mellitus (IDDM) (HbA1c $>$ 20% above the upper limit of normal [ULN])
- uncontrolled hypertension (DBP $>$ 95 mmHg or SBP \geq 180 mmHg at baseline)
- ventricular ectopy requiring medication
- clinically important valvular heart disease
- impaired hepatic function by history or liver function tests (LFTs) with values more than 20% above the normal range, recent history of hepatitis or other liver function abnormalities
- recent history of drug or alcohol abuse
- reduced life expectancy
- current treatment with an investigational drug
- concomitant use of prescription lipid-altering drug, probucol, immunosuppressive agents, or anticoagulants
- body weight $>$ 50% over ideal for height
- history of partial ileal bypass surgery
- hypersensitivity to lovastatin
- pregnancy and lactation
- any subject who is deemed incapable of or inappropriate by the clinical investigator(s) for participation in a clinical trial

Pre-randomization and Randomization

All participants were instructed on the use of the American Heart Association (AHA) Step 1 diet at week -12 of the pre-randomization period. Diet was reinforced at weeks -4 and -2 and continued throughout the treatment period. Physical exams, ophthalmologic exams (San Antonio clinic only), chest x-ray, ECG monitoring, lipid analysis, hematology, serum chemistries, and urinalysis were also performed at selected times during the prerandomization period. Participants then entered a 2 week placebo baseline run-in period followed by randomization of eligible compliant subjects to treatment with either lovastatin 20 mg qd or placebo. The randomization was stratified by study site and gender.

Study Drug Dosing and Titration

Patients randomized to lovastatin were all initiated on 20 mg qd. The LDL-C target goal in AFCAPS/TexCAPS was 110 mg/dL. If a lovastatin patient's LDL-C remained $>$ 110 mg/dL at Weeks 6 and 12, the dose was titrated to 40 mg qd by taking two 20 mg tablets daily starting at Week 18. To maintain blinding, an equal number of randomly selected

Endpoints Classification

All endpoint events (fatal and nonfatal MI, unstable angina, sudden cardiac death, coronary revascularization procedures, cardiovascular events, coronary events, cardiovascular mortality, CHD mortality, total mortality and noncardiovascular mortality) were predefined. The primary endpoint was a composite one that included fatal and nonfatal MI, unstable angina, or sudden cardiac death. This was the first primary prevention trial which included unstable angina as a primary endpoint and reflected the current clinical practice of treating CAD prior to development of an MI. The prespecified criteria for the primary endpoints were:

Fatal MI or Sudden Cardiac Death required that there was no noncardiac cause of death and one of the following:

- fatal MI within 28 days from the onset of symptoms of a definite acute MI
- witnessed unexpected sudden cardiac death within 1 hour of onset of symptoms; death occurring > 1 hour but ≤ 24 hours after collapse
- unwitnessed unexpected death must have confirmatory autopsy or preceding history of CHD events or symptoms

Nonfatal MI was defined as:

- acute Q-wave MI with definitive ECG
- acute non-Q-wave MI required definitive ECG or, if the ECG was equivocal, then presence of diagnostic enzymes
- silent subclinical MI required definitive ECG or if equivocal, focal wall motion abnormality consistent with MI on echo or stress thallium and on catheterization, a ≥ 50% stenosis in the major corresponding epicardial vessel

Unstable angina was defined as new onset exertional and/or accelerated or rest angina that was demonstrated by at least one of the following:

- stress perfusion study: ≥ 1 mm ST-segment changes and reversible defect
- epicardial vessel stenosis or ≥ 50% stenosis in the left main
- ≥ 1 mm ST-segment changes with pain on stress testing and/or resting ECG and evidence of ≥ 50% stenosis in a major epicardial vessel

The protocol was initially written to allow participants who developed a nonfatal primary endpoint to continue in the study, provided that the participant agreed to continue and there were no contraindications as deemed by the clinical investigator. After the NCEP guidelines were published recommending LDL-C goal of <100 mg/dL for patients with established CAD, participants who developed nonfatal primary endpoints were withdrawn from the study to assure adequate lipid-lowering therapy.

Protocol Amendments

A total of 4 amendments were made to the original protocol dated March 1, 1990. Most of these changes were minor including broadening the age range and lipid entry criteria, removing slit lamp examinations requirements at one study site, and changes in study visits. A significant amendment was introduced in July 1993 wherein unstable angina was included as a component of the primary endpoint in addition to fatal cardiovascular events and nonfatal MI. The decision to include unstable angina as a primary endpoint was made by the DSMB at the time of initiation of the study (November, 1990) and was based on the recognized trend of initial cardiovascular events presenting as unstable

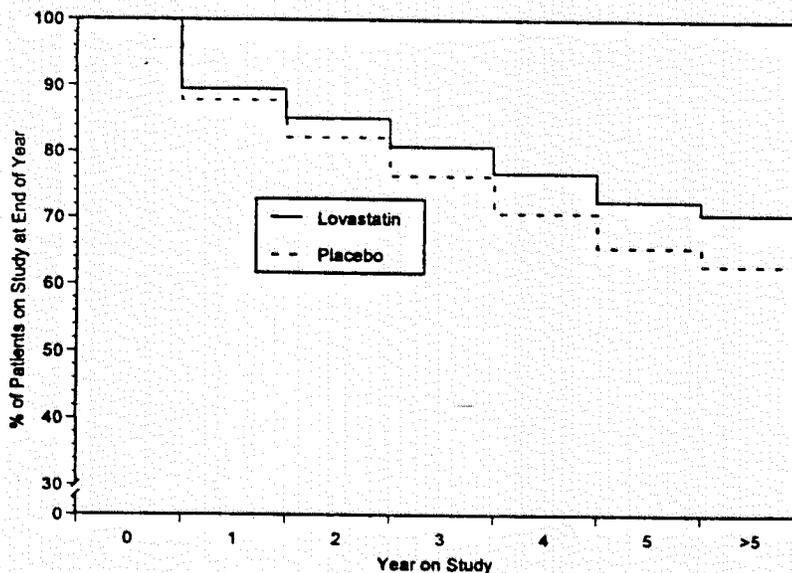
angina. This amendment decreased the required sample size from 8,000 to 6,605 and increased the primary endpoints required from 270 to 320.

RESULTS OF AFCAPS/TexCAPS

Patient Disposition

A total of 6,605 subjects were randomized to treatment with lovastatin (n=3,304) or placebo (n=3,301) from 2 sites in Texas (Wilford Hall Medical Center at Lackland Air Force Base in San Antonio [57% of patients] and the University of North Texas Health Sciences Center in Fort Worth [43% of patients]) from May 30, 1990 through February 12, 1993. Approximately 71% of patients in the lovastatin group and 63% in the placebo group completed the study (Figure 1). The mean duration of follow-up for the entire cohort was 5.2 years (median of 5.1)⁵ and was similar in the two treatment groups. For about 98% of the patients in each group, vital status and endpoint status were ascertained at the end of the trial.

Figure 1 Percent of patients on study by year and treatment group



⁵ The protocol was amended in 1992 to add the Fort Worth site so recruitment at that site began two years after recruitment at the San Antonio site. The mean duration of follow-up was 4.6 years (maximum of 5.1 years) at the Fort Worth site and 5.7 years (maximum of 7.3 years) at the San Antonio site.