AD-A227 977

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REPORT DOCUMENTATION PAGE

Form Approved
OMB No. 0704-0188

1. AGENCY USE ONLY (Leave blank)	2. REPORT DATE	3. REPORT TYPE AND DATES COVERED
	Aug 1990	XXXXXX/DISSERTATION

4. TITLE AND SUBTITLE
The Comparison of Gemfibrozil and Lovastatin Therapy in Patients with High LDL and Low HDL Cholesterol Levels

5. FUNDING NUMBERS

6. AUTHOR(S)
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7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)
AFIT Student Attending: Medical College of Virginia

8. PERFORMING ORGANIZATION REPORT NUMBER
AFIT/CI/CIA-90-023D

9. SPONSORING/MONITORING AGENCY NAME(S) AND ADDRESS(ES)
AFIT/CI
Wright-Patterson AFB OH 45433-6583

10. SPONSORING/MONITORING AGENCY REPORT NUMBER

11. SUPPLEMENTARY NOTES

12a. DISTRIBUTION/AVAILABILITY STATEMENT
Approved for Public Release IAW 190-1
Distributed Unlimited
ERNEST A. HAYGOOD, 1st Lt, USAF
Executive Officer

12b. DISTRIBUTION CODE

13. ABSTRACT (Maximum 200 words)

14. SUBJECT TERMS

15. NUMBER OF PAGES
36

16. PRICE CODE

17. SECURITY CLASSIFICATION OF REPORT	SECURITY CLASSIFICATION OF THIS PAGE	19. SECURITY CLASSIFICATION OF ABSTRACT	20. LIMITATION OF ABSTRACT

The comparison of gemfibrozil and lovastatin therapy in patients with high LDL and low HDL cholesterol levels.

by

Michael Dean Barnett

B.S. in Pharmacy, State University of New York at Buffalo, 1983

RESEARCH REPORT

submitted in partial fulfillment of the requirement for the

Doctor of Pharmacy Degree

School of Pharmacy

Medical College of Virginia

Richmond, Virginia

August 1990

This research report by Michael Dean Barnett is accepted in its present form as satisfying the research requirement for the Doctor of Pharmacy Degree.

Date: Approved:

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Advisor, Chairman of Research Committee

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for
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Oct 1985 to Apr 1988	Chief, Pharmacy Services 43rd Strategic Clinic (SAC) Andersen AFB, Guam
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CLINICAL EXPERIENCE:

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Sep 1989 to Oct 1989 (4 weeks)	Drug Information Consultation I Preceptors: Craig F. Kirkwood, Pharm. D. and Patricia Mullins, Pharm. D.
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Jan 1990 to Apr 1990 (12 weeks)	Pharmacy Services Administration Preceptor: Thomas Reinders, Pharm. D.

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Oct 1985 to Apr 1988	**Chief, Pharmacy Services**, 43rd Strategic Clinic Was responsible for the management, supervision, and operations of the 43rd Strategic Clinic Pharmacy Services.
Nov 1983 to Oct 1985	**Staff Pharmacist**, USAF Hospital Davis Monthan Responsible for overseeing the inpatient operations and implementation of a pharmacy intravenous admixture program and chemotherapy program.

Graduate Management Courses:

Jun 1990 to Jul 1990	BUS 641 Organizational Behavior (3 credit hours)
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Sep 1988 to Dec 1988	BUS 640 Management Theory and Practice (3 credit hours)

HONORS/AWARDS:

Academic:

1990	Member of the Rho Chi Honor Society
1988 to 1990	Full Academic Scholarship (Air Force Institute of Technology)
1983	Pharmacy Academic Merit Scholarship (SUNYAB School of Pharmacy)
1977	Freshman Scholarship (Houghton College)

Military:

1988	Received the highest rating (Outstanding) and citation for pharmacy administration, the only one given in over six years, by the Air Force Health Services Management Inspection Team (Inspector General's inspection).
1988	Meritorious Service Medal (for outstanding meritorious service from Oct 1985 through Apr 1988)
1985	Air Force Commendation Medal (for meritorious service from Nov 1983 to Oct 1985).

Governmental:

1988	Received a commendation from the Government of Guam for helping establish a urinalysis drug testing program for their law enforcement agencies.

ACTIVE MEMBERSHIP:

American Society of Hospital Pharmacists: active member since 1986

Air Force Institute of Technology Association of Graduates

Air Force Association

APPOINTMENTS:

Governmental (non-hospital appointments):

May 1987 to Apr 1988	Consultant and military liaison to the Government of Guam in establishing a urinalysis drug testing program for their law enforcement agencies.
Oct 1985 to Apr 1988	Urinalysis Drug Testing Program Coordinator for the 43rd Bombardment Wing, Andersen AFB Guam.
Dec 1989 to Apr 1988	Member, Andersen Air Force Base Officers' Club Advisory Board
Oct 1984 to Dec 1984	Summary Court Officer, handling the estates of deceased service members.

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Oct 1985 to Apr 1988	Coordinator and Member, 43rd Strategic Clinic's Pharmacy and Therapeutics Committee.
Oct 1985 to Apr 1988	Member, 43rd Strategic Clinic's Medical Staff Committee.
Nov 1987 to Apr 1988	Member, 43rd Strategic Clinic's Medical Staff Quality Assurance Committee.
Aug 1987 to Apr 1988	Continuing Medical Training Instructor, 43rd Strategic Clinic.
Feb 1984 to Oct 1985	Medical Technician Training Instructor, USAF Hospital Davis-Monthan.

PRESENTATIONS/SEMINARS:

Jun 1990	***The comparison of gemfibrozil and lovastatin in a subpopulation of patients with high LDL and low HDL cholesterol levels.*** Doctoral research presentation to faculty of the Department of Pharmacy and Pharmaceutics.
Dec 1989	***Implementing a Radiology Pharmacy Satellite*** Presented to faculty and students in Pharmacy Management PHA 631.
Oct 1989	***Drug Dosage Calculations: A Dimensional Analysis Approach*** Combined lecture and tutoring session given to J. Sergeant Reynolds nursing students.
Sep 1989	***Primary Hyperaldosteronism*** Presented to faculty and students during internal medicine rotation II.
Sep 1989	***Recombinant Erythropoietin (rEPO)*** Presented in to attending, residents, interns and medical students during internal medicine rotation II.
July 1989	***Withdrawal of chronic antihypertensive and anticonvulsive therapy*** Presented to faculty/staff and students, during ambulatory care rotation.
Jun 1989	***Pharmacokinetics in Obesity*** Presented to faculty/staff and students during pharmacokinetics rotation. Requested to present again to ICU pharmacists on staff who were unable to attend first presentation.
Feb 1989	***Pharmacy Quality Assurance: an Overview*** Pharmacy and Pharmaceutics Seminar given to faculty/staff and students.
Dec 1987	***Effectively Managing Pain*** CME Lecture given to the Oral Surgeons and Dental staff of the 43rd Strategic Clinic.
Feb 1985	***Non-Steroidal Anti-Inflammatory Agents*** Presented to Phase II Physician Assistant Residents, USAF Hospital Davis-Monthan.
Oct 1984	***Treatment of Urinary Tract Infections*** Seminar given Phase II Physician Assistant Residents, USAF Hospital Davis-Monthan.

PUBLICATIONS:

Refereed Journals:

Barnett MB, Kirkwood CF. Ticlopidine: a new stroke preventative. ***Hosp Therapy.*** 1990; 15:458-64.

Barnett MB, Kirkwood CF. Ticlopidine: a new stroke preventative. ***Drug Therapy.*** 1990; 20(4);70-72.

Barnett MB, Fary D, Carroll NV, et al. Management of pharmacotherapy: the role of pharmacy as quality assurance. ***Top Hosp Pharm Manage.*** 1990; 10(3):(In press)

McGee BA, Barnett MB, and Small RE. The pathophysiology and treatment of systemic scleroderma. ***Clin Pharm.*** (In press, to be published by Feb 1991)

Non-refereed:

Ticlopidine. Monograph developed for the Medical College of Virginia, Drug Information Service (Oct 1989).

The risk of hypomagnesemia with peritoneal cis-platin therapy, developed for the Medical College of Virginia, Drug Information Service (Oct 1989).

The safety and efficacy of intravenous verapamil as a continuous infusion, developed for the Medical College of Virginia, Drug Information Service (Oct 1989).

Served as editor and primary author of the monthly ***Pharmacy and Therapeutics Newsletter*** published for the 43rd Strategic Clinic (from Oct 1985 to Apr 1988).

Served as primary author of the bi-monthly ***Pharmacy and Therapeutics Information Briefing*** published for the USAF Hospital Davis Monthan (from Jan 1984 to Oct 1985).

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Introduction

Pharmacologic interventions in primary hypercholesteremia are usually considered after saturated fat restricted diet has failed to achieve an adequate control. The specific drug selected may be based, among other things, on its cholesterol lowering efficacy, ability to decrease the incidence of coronary heart disease (CHD), long term safety record, and cost.[1] In addition, the individual patient lipoprotein profile and the established effects of agents on specific profile components may be considered.

Framingham, MRFIT, and other epidemiological studies demonstrated that patients with increased low-density lipoprotein (LDL) cholesterol have an increased risk of developing CHD.[2-7] The Lipid Research Clinics Trial showed that lowering elevated levels of LDL cholesterol significantly lowered the risk of CHD development.[8,9] Framingham and other epidemiological studies,[3-7] have also demonstrated that CHD mortality is inversely related to HDL cholesterol. The Helsinki Heart Study[10,11] suggests that increasing HDL cholesterol and lowering the LDL cholesterol with diet and pharmacologic intervention, reduces CHD risk. These data imply that patients with high LDL and low HDL have a high risk for CHD and should receive aggressive medical treatment.

Gemfibrozil is known to increase HDL cholesterol, decrease VLDL cholesterol and triglycerides, as well as lower LDL cholesterol.[11,12] An advantage of gemfibrozil over other established agents, such as bile acid binding-resins and nicotinic acid, is that it is easily administered and well tolerated.[12,13] Lovastatin, the first 3-hydroxy-3-methylglutaryl coenzyme A (HMG CoA) reductase inhibitor introduced, substantially more effective in decreasing LDL cholesterol compared to gemfibrozil but, has little effect on HDL cholesterol and VLDL cholesterol.[12,14,15] Like gemfibrozil, lovastatin is easily administered and well tolerated by most patients.[15]

Gemfibrozil and lovastatin have been compared in the Finnish Multicenter Study in patients with total cholesterol levels $\geq$ 240 mg/dl[12] and by Vega and Grundy in normolipidemic patients with low HDL cholesterol.[16] These studies left unaddressed the comparative efficacy of these two drugs in patients with high LDL cholesterol and low HDL cholesterol.

This study, using a randomized, double-blind, cross-over design compared the effects of gemfibrozil versus lovastatin in patients which have both a clinically high LDL cholesterol and concurrent low HDL cholesterol.

Methods

Patients

Adult males and postmenopausal women with LDL cholesterol levels greater than 160 mg/dl and HDL cholesterol levels less than 40 mg/dl following one month of a step 1 diet[1] were eligible to participate in the study. Patients were excluded if they had major concomitant diseases including severe cardiovascular compromise, diabetes mellitus, abnormal liver function, renal disease, thyroid disease, psychiatric illness, or poor mental function which might affect compliance with the protocol, and drug abuse or excessive alcohol use. Also excluded were patients with triglyceride levels greater than 350 mg/dl, obesity (> 40% of ideal body weight), and concomitant treatment with drugs that may alter cholesterol levels including anti-hyperlipidemics, anticonvulsants, corticosteroids, and barbiturates. Patients stabilized on a fixed dose of antihypertensive maintenance therapy or conjugated estrogens for greater than six months were allowed to participate at their same dosage regime throughout the entire study. Patients who had received lipid lowering therapy prior to the study had this therapy discontinued a minimum of four weeks prior to the diet lead-in phase. Patients who were non-compliant with the protocol or had medically unacceptable adverse effects were discontinued. A total of nine patients (eight men and one woman who met the criteria) participated in the study. All patients gave informed consent for the protocol which had been approved by the institutional review board.

Study design

The study utilized a randomized, double-blind, cross-over comparison of gemfibrozil and lovastatin (see Figure 1). Patients were initially screened by laboratory assessment and physical examination. Patients with LDL levels > 160 mg/dl and HDL levels < 40 mg/dl were placed on a saturated fat/cholesterol restricted step 1 diet[1] for a minimum of four weeks. Compliance with the diet was established through a three-day diet diary which was scored by a registered dietician using a food factor rating scale (FRR).[17] Patients had to maintain an average FRR score of ≤ 15. This diet was continued throughout the study and monitored during each treatment phase. Patients who met the inclusion criteria were then placed on a single-blind placebo twice daily for two weeks. At week 0, the patients were randomized to receive phase I treatment, either gemfibrozil 600 mg twice daily or lovastatin 20 mg twice daily. After six weeks of phase I treatment, the patients were crossed-over to phase II treatment where they received the other treatment, lovastatin 20 mg twice daily or gemfibrozil 600 mg twice daily for six more weeks. Both phase I and phase II treatments were double-blinded. All placebos and active treatments appeared identical.

Fourteen-hour fasting lipid and lipoprotein measurements were obtained at the end of the diet lead-in and placebo phases (at weeks -2 and 0 on Figure 1). Fourteen-hour fasting lipid and lipoprotein measurements were also obtained at weeks 4 and 6 (phase I treatment) and at weeks 10 and 12 (phase II treatment).

Compliance throughout the study was assessed by capsule counts at each visit. Baseline cholesterol was taken to be the average of the last two lipoprotein measurements obtained prior to randomization. The treatment cholesterol levels were the average of the two measurements obtained during the fourth and sixth weeks of each treatment phase. It was determined prior to the study that if one of the two measurements was not available during a treatment phase, the one measurement obtained would serve as the patient's value for the treatment phase.

Laboratory Methods

Lipid profiles were measured at the Medical College of Virginia Hospital Laboratory using methods standardized by the Centers for Disease Control Lipid Standardization Program. Total serum cholesterol (TC) was measured enzymatically with Boehringer Mannhiem Diagnostics (Indianapolis, IN) reagents (no. 692905) and calibrators (no. 125512) using a Cobas-Bio analyzer (Roche Diagnostics, Nutley, N.J.). The test for TC had a precision level of (±SD) ±5.0 mg/dl. HDL cholesterol levels were determined by fractionating the plasma with 0.092 M manganese and 182,000 U/l heparin solution followed by centrifugation.[18] The HDL containing supernatant fraction was assayed for cholesterol with same method as for TC; however, precision of the HDL measurements were (±SD) ±1.5 mg/dl. Triglycerides (TG) were measured enzymatically with Behring Diagnostics (Somerville, N.J.) reagents (no. 869263) using a Cobas-Bio analyzer with correction for free glycerol, with the extinction coefficient of NADH used for

quantitation. The TG assay was precise to (±SD) ±2.5 mg/dl. The LDL cholesterol was calculated using the Friedewald formula applied to the measured values.[19] Very low-density lipoprotein (VLDL) cholesterol levels were estimated by dividing the triglyceride level by six as described by Delong et al.[20]

A full physical exam, including an ophthalmological slit-lamp, was performed during the initial screening period and following the study. Routine hematology and blood chemistries were obtained during the initial screening and during each treatment phase.

Statistical Analysis

Efficacy analysis were performed using the all-patients treated approach including those patients with efficacy data from all three study periods, the baseline and both treatment periods. All statistics were performed using SAS programming on the Medical College of Virginia's VAX computer system. An analysis of variance (ANOVA) General Linear Model (GLM) Procedure, was performed to assess the differences from the baseline/placebo lipid levels (TC and TG levels), lipoprotein cholesterol levels (LDL, VLDL, and HDL cholesterol levels), and the cholesterol ratios between the two treatments (at α=0.05 and β=0.2). Since there was no washout period between treatments, the ANOVA GLM Procedure was also applied in testing the data for possible sequence and period affect differences. A Tukey's Studentized Range test was performed on the treatment differences from

baseline/placebo, to assess and determine the minimal critical difference between their means (at α=0.05). Assumptions of normality were tested prior to the ANOVA GLM Procedure. The minimum sample size estimation at a power (1-β) of 90%, α=0.05, and β=0.1 for a two-period cross-over study, was determined to be 15.[21]

Results

Study patient baseline characteristics:

Ten patients were selected to start the study, one patient was withdrawn during phase I treatment due to non-compliance with the study protocol and was not included in the analysis. The baseline characteristics of the nine patients who completed the study are summarized on Table 1. All three patients who were receiving cholesterol-lowering drugs prior to the study discontinued their therapy for a minimum of four weeks prior to the diet lead-in phase. One study patient was maintained on a metoprolol regime for hypertension management throughout the study.

Effects on lipid and lipoprotein cholesterol levels:

The mean lipid and lipoprotein cholesterol levels observed in each study phase are given in Table 2. Mean cholesterol ratios attained from each study phase are presented in Table 3. The mean differences in lipids, lipoprotein cholesterol levels, and the cholesterol ratios observed from baseline/placebo with gemfibrozil and lovastatin treatments are given on Tables 4 and 5. The statistical p values from the ANOVA GLM Procedure and the Tukey's Minimum Critical Difference for each of the mean treatment differences from baseline/placebo, in lipid and lipoprotein cholesterol levels, are given in Table 4 and displayed in Figure 2. Significant differences ($p < 0.05$) were noted between treatments in all lipid and

lipoprotein cholesterol differences tested. Lovastatin therapy produced significantly greater reductions in the mean TC and LDL cholesterol levels than gemfibrozil. Conversely, gemfibrozil produced significantly greater reductions in the mean TG and VLDL cholesterol levels than lovastatin. The mean HDL cholesterol levels were increased significantly more by the gemfibrozil than by the lovastatin.

The statistical p values from the ANOVA GLM Procedure and the Tukey's Minimum Critical Difference for each of the mean treatment differences from baseline/placebo, in cholesterol ratios, are given in Table 5. Lovastatin produced statistically greater reductions in the LDL/HDL and increases in the HDL/TC ratios than did gemfibrozil. Conversely, gemfibrozil produced a significantly greater reduction in the VLDL/HDL ratio than did lovastatin. The differences between the treatments in the difference from the baseline/placebo TC/HDL ratio was not significant (P=0.1).

No significant sequence effects were noted for any of the values tested; however, statistically significant period effects were noted in the TG, VLDL cholesterol, and VLDL/HDL cholesterol ratio data.

The individual patient mean LDL cholesterol levels attained during each study phase are displayed in Figure 3. In general, lovastatin produced more pronounced

decreases in the individual LDL cholesterol levels from the baseline/placebo levels than did gemfibrozil. However, in one patient gemfibrozil produced greater decreases in LDL cholesterol than did lovastatin. The individual patient mean HDL cholesterol levels attained during each study phase are displayed in Figure 4. In general, gemfibrozil produced greater increases in HDL cholesterol than lovastatin. However, two patients exhibited greater increases in HDL cholesterol while receiving lovastatin than with gemfibrozil. Additionally, one patient's HDL cholesterol decreased from the baseline/placebo mean while receiving gemfibrozil and decreased even further while receiving lovastatin.

Adverse reactions:

Five of the nine patients who completed the study reported adverse reactions. These are summarized on Table 6. None of the reactions were considered severe and none interfered in the execution of the research protocol. In addition to the reactions presented in Table 6, the patient who was withdrawn from the study due to noncompliance, reported lower-back and lower-leg pain during the single-blind placebo.

Discussion

Our study demonstrated that in patients with clinically high LDL cholesterol and low HDL cholesterol, lovastatin was superior to gemfibrozil in producing current recommended reductions in the cholesterol profile.[1] Lovastatin reduced TC, LDL cholesterol, and the LDL/HDL cholesterol ratio significantly greater than gemfibrozil ($p < 0.05$). Though the study demonstrated that gemfibrozil produced significantly greater elevations in HDL cholesterol, it was not enough to offset the magnitude of LDL cholesterol lowering by the lovastatin in lowering the LDL/HDL cholesterol ratio. In contrast, gemfibrozil produced greater reductions in both TG and VLDL cholesterol than lovastatin. Since there is little evidence to demonstrate a strong association between CHD risk and TG or VLDL cholesterol levels, the main emphasis of treatment should be on the specific cholesterol levels which have been associated with CHD risk.[1-11]

Our study employed a lead-in phase with two consecutive treatment phases of six weeks in length. The decision to place active treatment phases consecutively without a washout phase was based on observations that following cessation of lovastatin or gemfibrozil therapy, a return to original baseline was noted within two weeks.[13,15] Additionally, we statistically tested for possible sequence and period effects to add validity to this assumption. In all parameters tested, no sequence effect was noted. Furthermore, in all parameters which were considered

vital in the efficacy comparison, no period effects were noted. However, we noted the inter-subject variability in the TG levels was much greater than for LDL cholesterol or TC (see Table 2 and 4). This large variability is believed to be the major contributor to the significant period effect detected in the TG, VLDL cholesterol (calculated directly from the TG levels) and VLDL/HDL cholesterol ratio differences from baseline. As previously stated, the study's main concern was in the drugs' efficacy of lowering LDL and raising HDL cholesterol; thereby, the parameters in which a period effect was detected is of less concern.

Though there are a number of risk factors for the development of CHD, elevated LDL levels is well established.[1] Furthermore, reducing elevated levels of LDL cholesterol has been demonstrated to decrease the risk of developing CHD.[8,9] Low HDL cholesterol levels have also been associated with an increased risk of developing CHD.[3-7] However, studies designed to examine the effects on CHD in raising low HDL levels with diet, drugs or other interventions have not been completed.[22] Furthermore, there are reports that fail to demonstrate a consistent increased CHD risk with a genetic deficiency of HDL cholesterol.[23,24] There is consistency though, in noting a high risk of developing CHD in those patients which have high LDL and concurrent low HDL cholesterol levels.[4,25] The epidemiological studies[3-7] and more convincingly, the Helsinki Heart study[10,11] give evidence that decreasing the LDL/HDL cholesterol ratio by pharmacologically increasing HDL levels with only modest lowering of LDL levels can decrease the

risk of developing CHD. To promote LDL/HDL ratio lowering, nicotinic acid or a bile acid binding-resin and nicotinic acid combination, would be a logical choice; however, nicotinic acid is not well tolerated at the doses necessary to achieve this effect and bile acid binding-resins pose additional palatability problems.[26] Gemfibrozil and the recently introduced HMG CoA reductase inhibitor, lovastatin, have beneficial effects on the LDL/HDL cholesterol ratio. Furthermore, both of these drugs have a limited side effect profile and are relatively easy to administer.[10-14]

Two other studies have directly compared the efficacy of gemfibrozil to lovastatin.[12,16] The Finnish Multicenter Study[12] compared gemfibrozil to lovastatin using a parallel study design in patients who had TC levels of $\geq$ 240 mg/dl. The patients were stratified as to TC level. During the first six weeks of active treatment, patients with a baseline TC $\geq$ 300 mg/dl received the same daily doses of the two study drugs as in our study for the first six weeks of active treatment. The baseline mean LDL and HDL values reported in the Finnish Multicenter Study were much greater than those in our study; however, the mean LDL/HDL ratio of patients in Stratum II (TC $\geq$ 300 mg/dl) was similar to our baseline/placebo mean (5.4 and 6.2 versus 5.4 for our study). Furthermore, on examining the percent change from baseline at six weeks for the Finnish Multicenter Study (see Figure 5), the results were similar to our study's resultant percent changes (Figure 6). As in the Stratum II group of the Finnish Multicenter

Study, our study demonstrated that lovastatin produced significantly greater reductions in TC levels, LDL levels, and in the LDL/HDL cholesterol ratio than did gemfibrozil. Conversely, in both studies, gemfibrozil produced significantly greater increases in HDL and reductions in TG.

Vega and Grundy[16] compared gemfibrozil to lovastatin in 22 male patients with LDL cholesterol < 160 mg/dl and HDL cholesterol < 35 mg/dl also had similar results. The exception was that a statistically significant greater elevation in HDL cholesterol was observed in the lovastatin treatment compared to the gemfibrozil treatment.

Based on the Finnish Multicenter Study,[12] Vega et al.,[16] and this study, we can conclude that lovastatin is consistently more effective in lowering TC, LDL, and the LDL/HDL cholesterol ratio than gemfibrozil. Even though our study and the Finnish Multicenter trial noted that gemfibrozil was more effective in raising HDL cholesterol levels, all three studies noted that lovastatin also exhibited a elevating property on HDL cholesterol. Therefore, lovastatin appears to have an overall greater efficacious effect on the cholesterol profile than gemfibrozil and may be more beneficial in the pharmacological treatment of patients with high LDL and low HDL cholesterol. In the decision to institute pharmacotherapy, other considerations, such as the individual's cholesterol response, should be made. The inter-patient cholesterol levels in our study, (Figures 3 and 4) demonstrated that

not all patients responded as favorably to lovastatin. Thereby, tailoring pharmacotherapy to the changes in the individual patient cholesterol profiles should be considered.

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Table 1. Baseline study patient characteristics.
(n=9)

Demographics		
Male	8	89%
Female	1	11%
Mean Age in Years (±SD)	48.9	(±8.7)
Mean Baseline Weight (±SD)	177.8	(±33.6)
Risk Factors		
Hypertension	1	11%
Family History of CHD	3	33%
HDL < 35 mg/dl	8	89%
Male Sex	8	89%
History of CVD and/or PVD	1	11%
No. with 3 Risk Factors	3	33%
No. with only 2 Risk Factors	5	56%
No. with only 1 Risk Factor	1	11%
Concurrent Medication History		
Prior hyperlipidemia treatment	3	33%
ß-blocker therapy	1	11%

Table 2. Mean concentrations (±SD) of plasma lipids and lipoproteins during each study phase.

Plasma Lipids and Lipoproteins	Baseline Placebo mg/dl	Gemfibrozil mg/dl	Lovastatin mg/dl
Total Cholesterol	250.7 (±18.4)	220.9 (±25.5)	179.7 (±25.3)
Triglycerides	156.1 (±64.1)	80.6 (±39.9)	109.8 (±69.7)
LDL Cholesterol	181.9 (±17.0)	166.3 (±23.5)	117.5 (±27.7)
HDL Cholesterol	33.8 (±3.3)	39.2 (±3.7)	35.9 (±4.0)
VLDL Cholesterol	26.0 (±10.7)	13.4 (±6.6)	18.3 (±11.6)

Table 3. Mean cholesterol ratios (±SD) during each study phase.

Cholesterol Ratio	Baseline Placebo	Gemfibrozil	Lovastatin
TC/HDL	7.49 (±0.91)	5.73 (±0.96)	5.19 (±1.21)
LDL/HDL	5.42 (±0.61)	4.19 (±0.99)	3.41 (±1.11)
VLDL/HDL	0.79 (±0.37)	0.35 (±0.21)	0.59 (±0.40)
HDL/TC	0.25 (±0.12)	0.59 (±0.26)	0.42 (±0.19)

Table 4. Mean difference in plasma lipids and cholesterol levels (±SD) from mean baseline placebo levels.

Lipid and lipoprotein cholesterols	Treatment Phase Differences		Tukey's Minimum Critical Difference	p Value ANOVA
	Gemfibrozil mg/dl	Lovastatin mg/dl		
TC	-29.8 (±18.1)	-71.0 (±15.6)	15.318	0.0003
TG	-75.5 (±46.3)	-46.2 (±40.4)	24.267	0.0164[a]
LDL	-15.6 (±17.7)	-64.4 (±17.9)	18.949	0.0004
HDL	5.3 (±4.1)	2.1 (±4.4)	2.306	0.0106
VLDL	-12.6 (±7.7)	-7.7 (±6.7)	4.029	0.0166[a]

Table 5. Mean difference in cholesterol ratios from baseline placebo during each study phase.

Cholesterol Ratio	Difference by Treatment Phase		Tukey's Minimum Critical Difference	p Value (ANOVA)
	Gemfibrozil mg/dl	Lovastatin mg/dl		
TC/HDL	-1.76 (±0.62)	-2.28 (±1.09)	0.702	0.1
LDL/HDL	-1.22 (±0.57)	-2.01 (±1.09)	0.743	0.03
VLDL/HDL	-0.44 (±0.27)	-0.26 (±0.21)	0.150	0.01[a]
HDL/TC	0.04 (±0.02)	0.07 (±0.04)	0.024	0.03

Table 6. Adverse reactions reported.[a]

Placebo Phase (n=2)		
Flatulence	2	(22%)
Epigastric Pain	1	(11%)
Headache	1	(11%)
Rash	1	(11%)
Gemfibrozil Phase (n=2)		
Headache	1	(11%)
GI distress	1	(11%)
Lovastatin Phase (n=1)		
Arthralgias	1	(11%)

[a] Total of 5 patients reported ADRs

Figure 1
Study Design

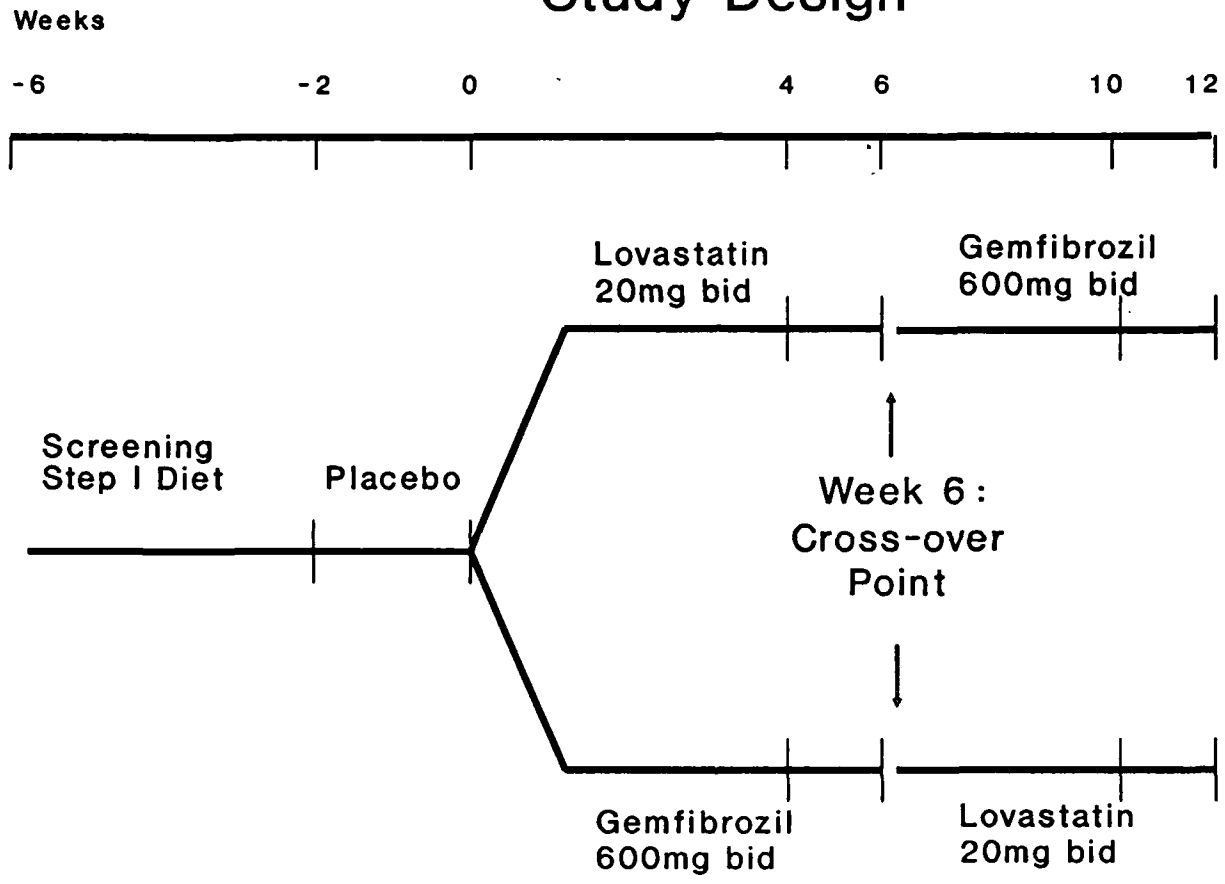
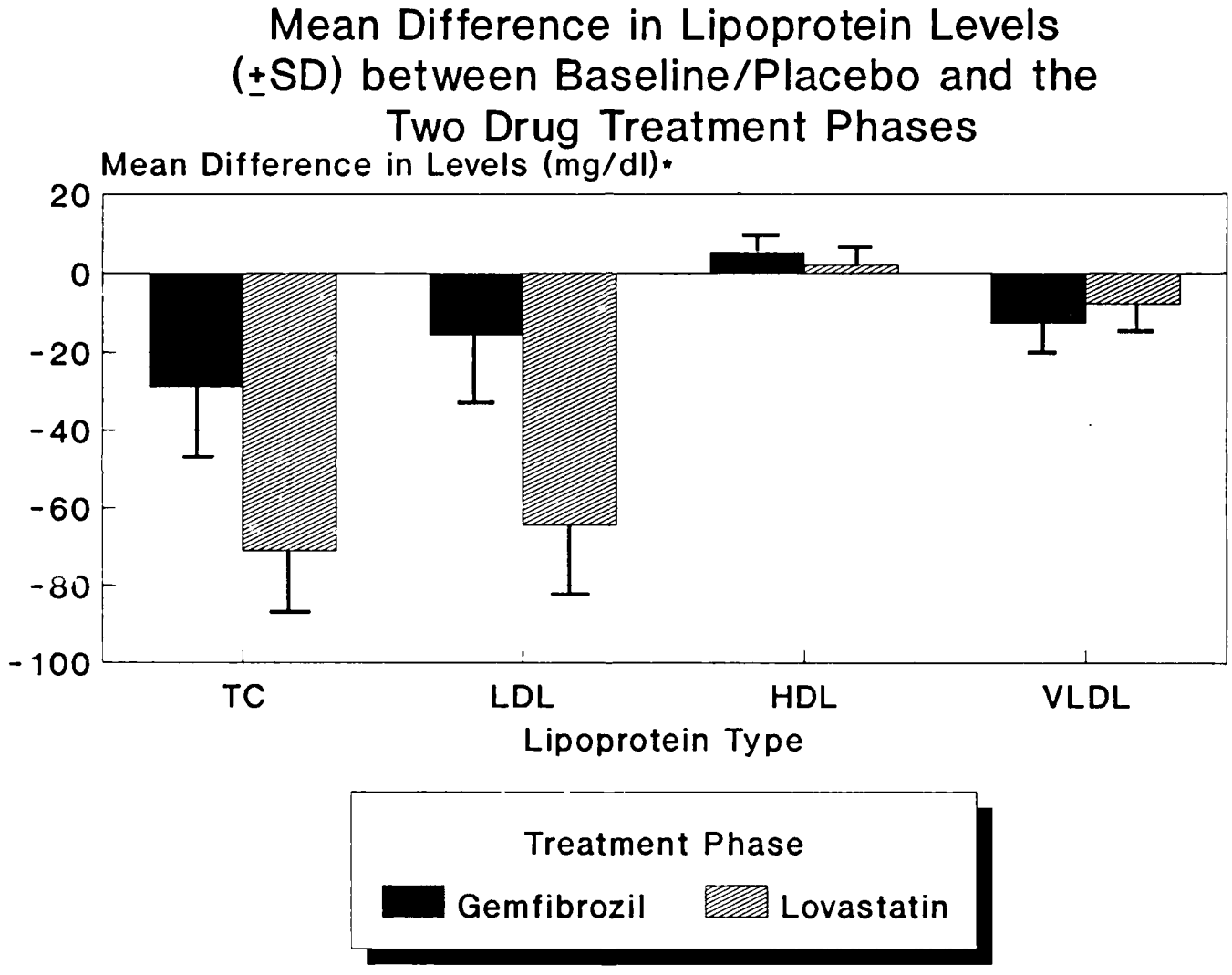


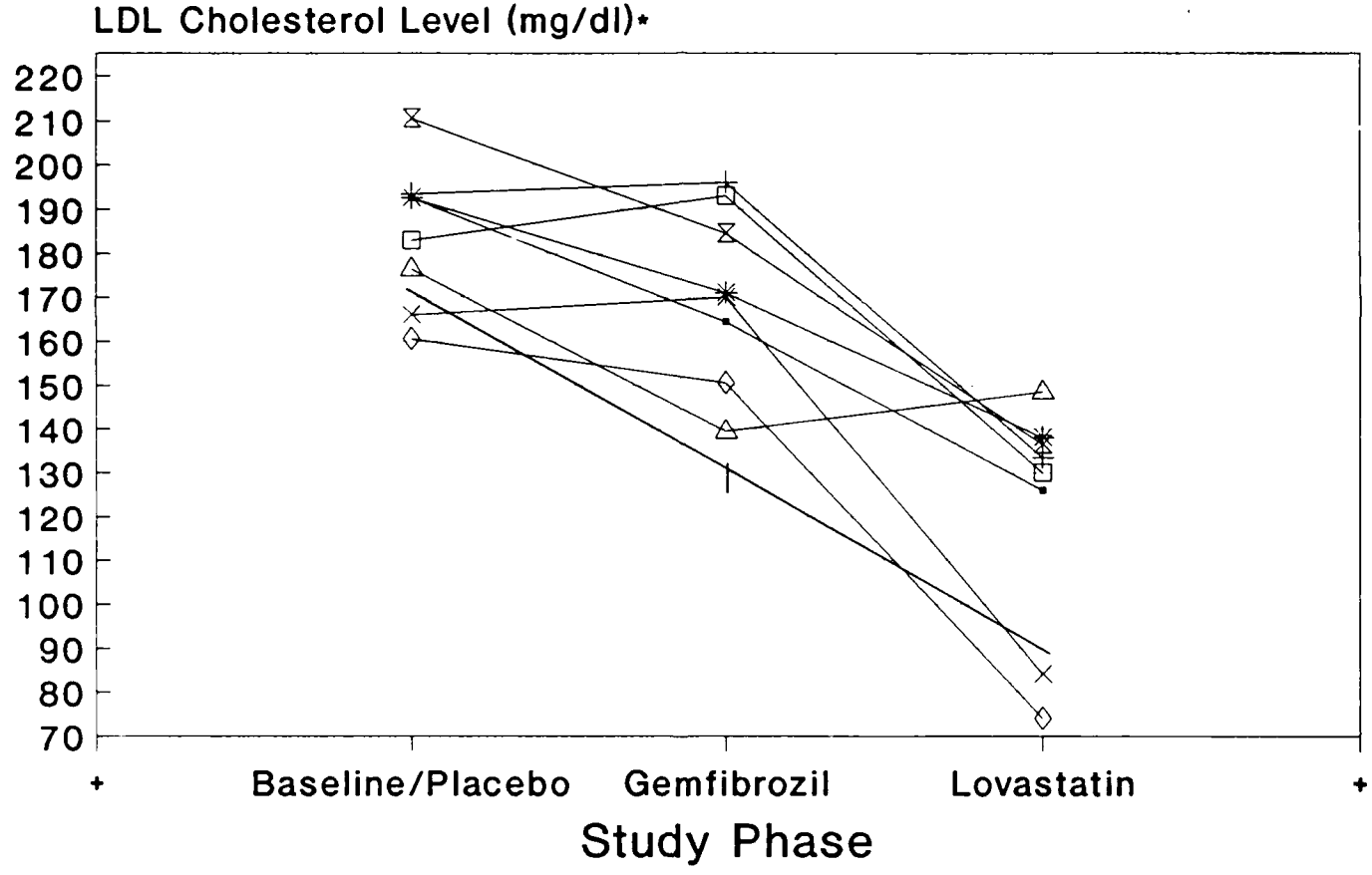
Figure 2.



* Mean of: Treatment Levels - Baseline/Placebo Levels

Figure 3.

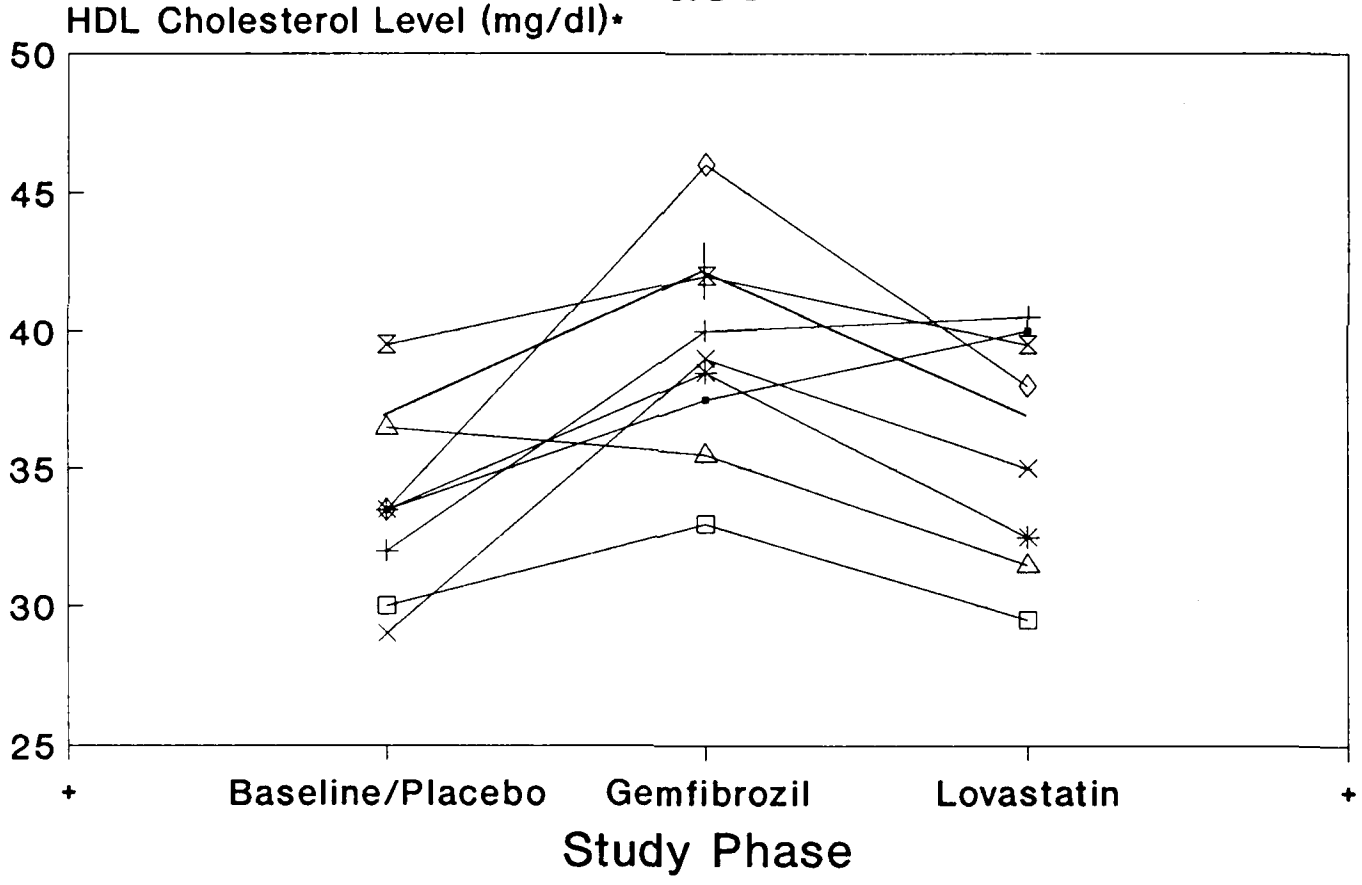
LDL Cholesterol Level Changes in Individual Patients During Each Study Phase



* Mean LDL level during each study phase
(The mean of the 4th and 6th week of each treatment phase)

Figure 4.

HDL Cholesterol Level Changes in Individual Patients During Each Study Phase



* Mean HDL level during each study phase
(The mean of the 4th and 6th week of each treatment phase)

Figure 5.

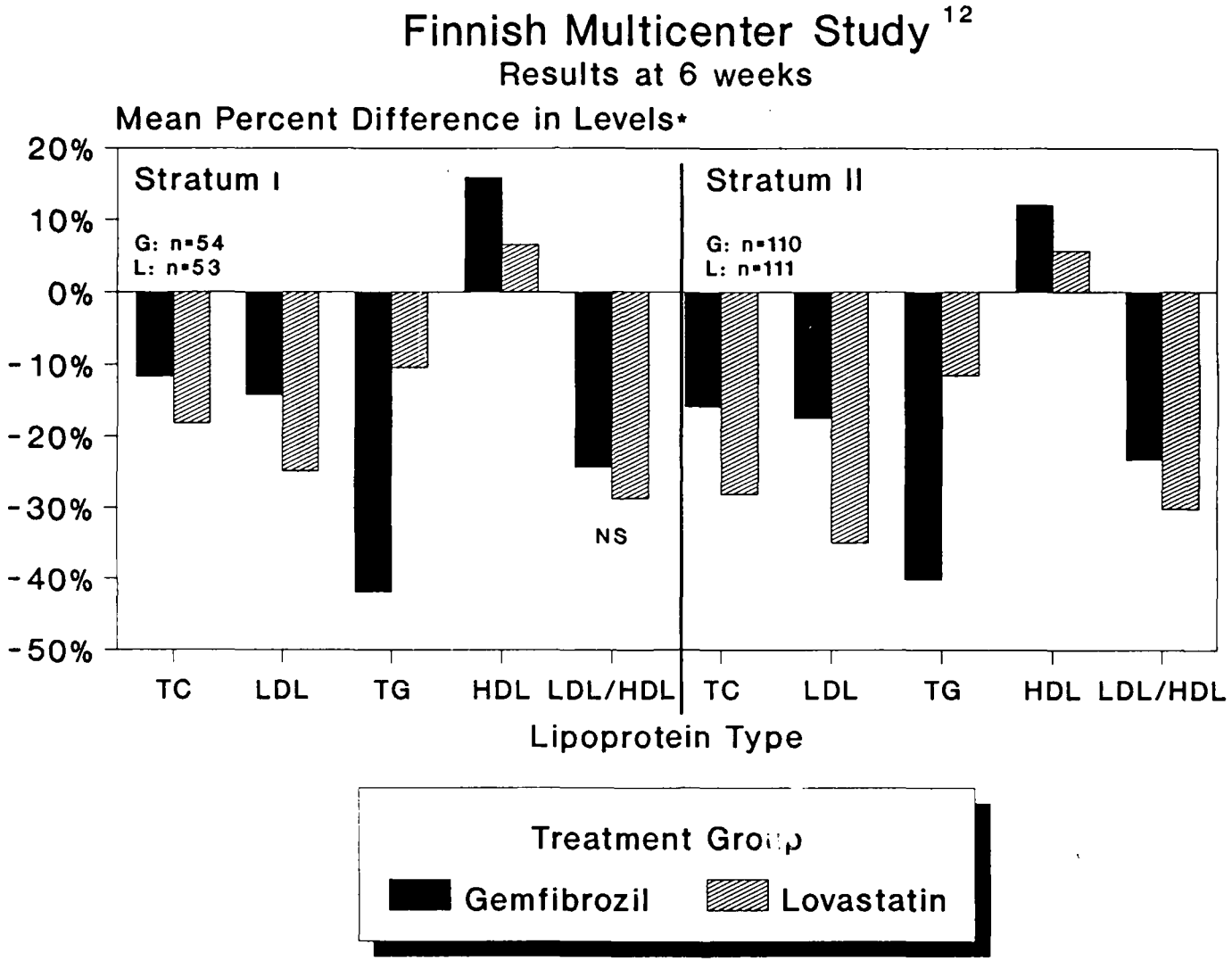
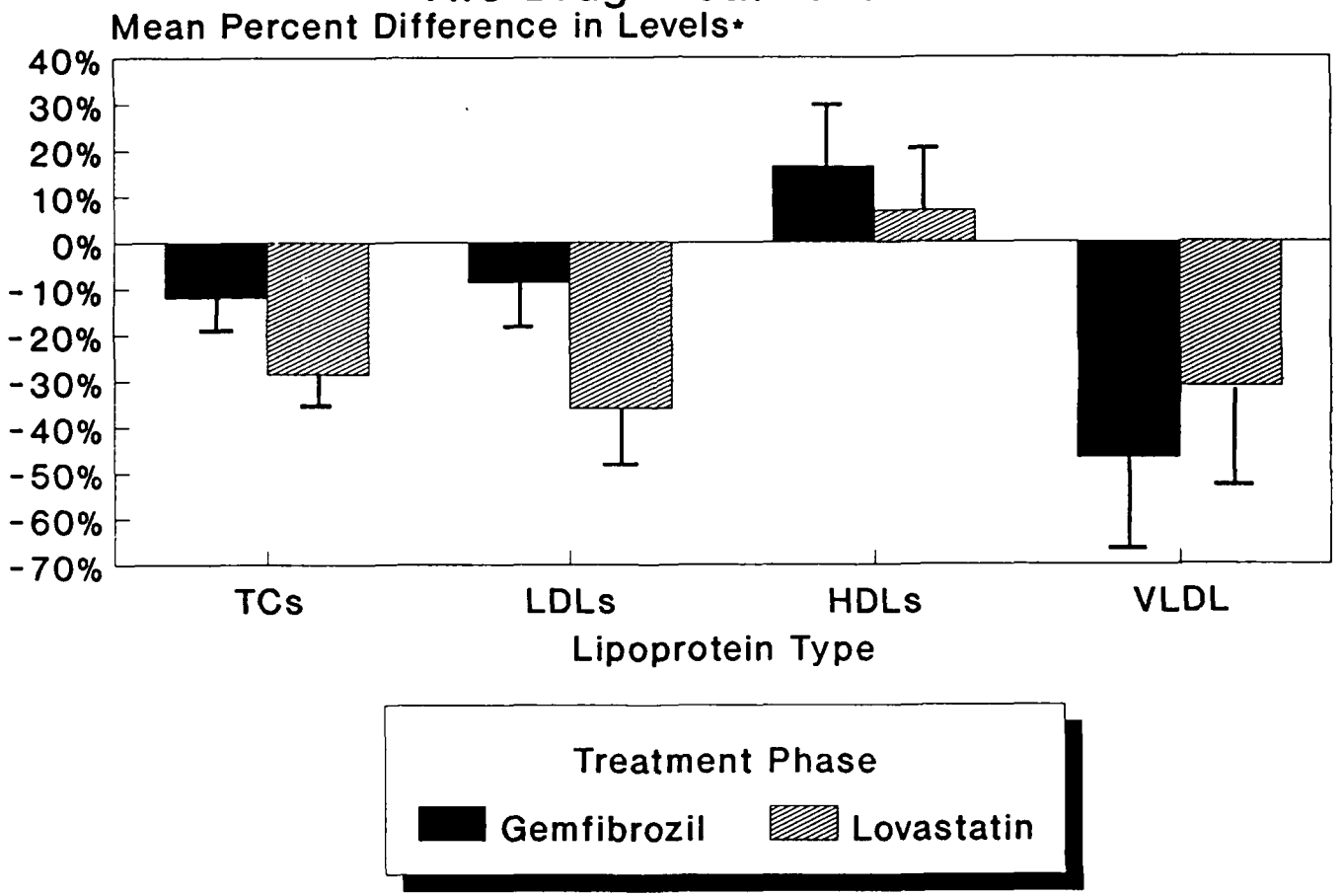

Finnish Multicenter Study [12]
Results at 6 weeks
Mean Percent Difference in Levels*
20%
10%
0%
-10%
-20%
-30%
-40%
-50%
Stratum I
G: n=54
L: n=53
Stratum II
G: n=110
L: n=111
NS
TC
LDL
TG
HDL
LDL/HDL
TC
LDL
TG
HDL
LDL/HDL
Lipoprotein Type
Treatment Group
Gemfibrozil
Lovastatin

Figure 6.

Mean Percent Difference in Lipoprotein Levels Between Baseline/Placebo and the Two Drug Treatment Phases



* ((Mean Treatment Phase Level - Baseline/Placebo Level)/ Baseline/Placebo Level) X 100%

APPENDIX I. Actual Study Data.

Tx 0 = Pretreatment (diet alone and placebo)
Tx 1 = Gemfibrozil
Tx 2 = Lovastatin

Pt	Tx	Per	Seq	TC 1	TC 2	LDL 1	LDL 2	HDL 1	HDL 2	TG 1	TG 2	VLDL1	VLDL2	TC/HDL1	TC/HDL2	LDL/HDL1
1	0	0	0	242	254	187	198	33	34	108	110	18.0	18.3	7.33	7.47	5.67
1	1	1	1	208	214	161	168	36	39	53	34	8.8	5.7	5.78	5.49	4.47
1	2	2	1	170	188	118	134	39	41	66	65	11.0	10.8	4.36	4.59	3.03
2	0	0	0	271	235	216	171	34	30	107	168	17.8	28.0	7.97	7.83	6.35
2	1	1	1	237	260	182	210	40	40	76	52	12.7	8.7	5.93	6.50	4.55
2	2	2	1	195	197	133	134	37	44	66	65	11.0	10.8	5.27	4.48	3.59
3	0	0	0	260	288	177	208	33	34	249	228	41.5	38.0	7.88	8.47	5.36
3	1	1	1	208	234	161	181	37	40	86	65	14.3	10.8	5.62	5.85	4.35
3	2	2	1	189	195	124	152	41	24	121	95	20.2	15.8	4.61	8.13	3.02
4	0	0	0	250	286	164	202	31	29	275	277	45.8	46.2	8.06	9.86	5.29
4	1	2	2	259		193		33		164		27.3		7.85		5.85
4	2	1	2	202	227	121	139	28	31	263	283	43.8	47.2	7.21	7.32	4.32
5	0	0	0	236	222	180	152	27	31	143	196	23.8	32.7	8.74	7.16	6.67
5	1	2	2	218	225	166	174	37	41	73	52	12.2	8.7	5.89	5.49	4.49
5	2	1	2	140	143	84	84	31	39	127	98	21.2	16.3	4.52	3.67	2.71
6	0	0	0	288	224	166	155	32	35	152	170	25.3	28.3	9.00	6.40	5.19
6	1	2	2	214	203	160	141	41	51	65	55	10.8	9.2	5.22	3.98	3.90
6	2	1	2	169	164	105	107	38	38	129	94	21.5	15.7	4.45	4.32	2.76

APPENDIX I. Actual Study Data.

Tx 0 = Pretreatment (diet alone and placebo)
Tx 1 = Gemfibrozil
Tx 2 = Lovastatin

Pt	Tx	Per	Seq	TC 1	TC 2	LDL 1	LDL 2	HDL 1	HDL 2	TG 1	TG 2	VLDL1	VLDL2	TC/HDL1	TC/HDL2	LDL/HDL1
7	0	0	0	221	254	162	191	35	38	120	124	20.0	20.7	6.31	6.68	4.63
7	1	1	1	209	184	151	128	39	32	95	118	15.8	19.7	5.36	5.75	3.87
7	2	2	1	204	182	165	132	25	38	71	61	11.8	10.2	8.16	4.79	6.60
8	0	0	0	265	274	210	211	40	39	77	84	12.8	14.0	6.63	7.03	5.25
8	1	1	1	236	240	183	186	42	42	56	58	9.3	9.7	5.62	5.71	4.36
8	2	2	1	193	185	142	131	40	39	54	75	9.0	12.5	4.83	4.74	3.55
9	0	0	0	231	212	169	155	38	36	118	104	19.7	17.3	6.08	5.89	4.45
9	1	2	2	181	172	130	125	41	41	49	32	8.2	5.3	4.41	4.20	3.17
9	2	1	2	142	134	92	82	38	36	61	80	10.2	13.3	3.74	3.72	2.42

APPENDIX I. Actual Study Data.

Tx 0 = Pretreatment (diet alone and placebo)

Tx 1 = Gemfibrozil

Tx 2 = Lovastatin

							Other Parameters							
Pt	Tx	LDL/HDL2	VLDL/HDL	VLDL/HDL	HDL/TC1	HDL/TC2	Wt 1	Wt 2	Ave Wt	FRR	Bili	ALP	AST	ALT
1	0	5.82	0.55	0.54	0.14	0.13	188.0	187.5	187.8	9.0	0.4	78	41	34
1	1	4.31	0.25	0.15	0.17	0.18	185.8	186.0	185.9					
1	2	3.27	0.28	0.26	0.23	0.22	189.5		189.5	11.0				
2	0	5.70	0.52	0.93	0.13	0.13	153.5	152.0	152.8	7.0	0.5	104	28	35
2	1	5.25	0.32	0.22	0.17	0.15	150.5	151.0	150.8	5.0				
2	2	3.05	0.30	0.25	0.19	0.22	151.5	150.5	151.0	5.0				
3	0	6.12	1.26	1.12	0.13	0.12	212.0	213.0	212.5	11.0	0.5	49	19	29
3	1	4.53	0.39	0.27	0.18	0.17	212.0	210.0	211.0	7.0	0.5	52	19	37
3	2	6.33	0.49	0.66	0.22	0.12	211.8	211.0	211.4	12.0	0.4	65	23	32
4	0	6.97	1.48	1.59	0.12	0.10	220.0	219.0	219.5	8.8	0.5	63	31	36
4	1		0.83		0.13		224.5		224.5	15.0	0.5	51	33	53
4	2	4.48	1.57	1.52	0.14	0.14	223.0	220.0	221.5	12.0	0.6	59	35	56
5	0	4.90	0.88	1.05	0.11	0.14	183.0	183.0	183.0	15.3	0.4	97	16	14
5	1	4.24	0.33	0.21	0.17	0.18	182.0		182.0	14.0	0.3	102	46	46
5	2	2.15	0.68	0.42	0.22	0.27	186.0	184.8	185.4	9.0	0.4	98	24	24
6	0	4.43	0.79	0.81	0.11	0.16	175.8	174.5	175.1	9.0	0.2	93	19	22
6	1	2.76	0.26	0.18	0.19	0.25	178.0	182.5	180.3	10.0	0.7	46	28	33
6	2	2.82	0.57	0.41	0.22	0.23	178.5	178.3	178.4	3.0	0.5	47	31	46

APPENDIX I. Actual Study Data.

Tx 0 = Pretreatment (diet alone and placebo)

Tx 1 = Gemfibrozil

Tx 2 = Lovastatin

Pt	Tx	LDL/HDL2	VLDL/HDL	VLDL/HDL	HDL/TC1	HDL/TC2	Wt 1	Wt 2	Ave Wt	FRR	Bili	ALP	AST	ALT
7	0	5.03	0.57	0.54	0.16	0.15	175.0	172.0	173.5	14.5	0.7	45	23	24
7	1	4.00	0.41	0.61	0.19	0.17	175.0	172.5	173.8	13.3				
7	2	3.47	0.47	0.27	0.12	0.21	175.0	175.0	175.0	15.0				
8	0	5.41	0.32	0.36	0.15	0.14	104	107	105.5	15	0.5	54	33	14
8	1	4.43	0.22	0.23	0.18	0.18	106	106	106	11	0.5	63	25	16
8	2	3.36	0.23	0.32	0.21	0.21	108	107	107.5	8	0.8	55	18	9
9	0	4.31	0.52	0.48	0.16	0.17	190.5	190.5	190.5	15	0.5	126	24	20
9	1	3.05	0.20	0.13	0.23	0.24	188.5	185.3	186.9	10	0.8	145	24	18
9	2	2.28	0.27	0.37	0.27	0.27	190.5	188.7	189.6	9	0.9	146	21	11

Appendix II. Individual study patient data
Mean differences from baseline/placebo.

Pt	Trt	Seq	Per	TCs	LDLs	HDLs	TGs	VLDL	TC/HDL	VLDL/HD	LDL/HDL	HDL/TC
1	1	1	1	-37.0	-28.0	4.0	-65.5	-10.9	-1.77	-0.35	-1.36	0.04
2	1	1	1	-4.5	2.5	8.0	-73.5	-12.3	-1.69	-0.45	-1.13	0.03
3	1	1	1	-53.0	-21.5	5.0	-163.0	-27.2	-2.44	-0.86	-1.30	0.05
4	1	2	2	-9.0	10.0	3.0	-112.0	-18.7	-1.08	-0.71	-0.28	0.02
5	1	2	2	-7.5	4.0	10.0	-107.0	-17.8	-2.21	-0.71	-1.42	0.05
6	1	2	2	-39.5	-10.0	12.5	-49.0	-8.2	-2.74	-0.40	-2.41	0.08
7	1	1	1	-41.0	-37.0	-1.0	-15.5	-2.6	-0.95	-0.06	-0.89	0.03
8	1	1	1	-31.5	-26.0	2.5	-23.5	-3.9	-1.16	-0.11	-0.94	0.03
9	1	2	2	-45.0	-34.5	4.0	-70.5	-11.8	-1.68	-0.34	-1.27	0.07
1	2	1	2	-69.0	-66.5	6.5	-43.5	-7.3	-2.93	-0.27	-2.60	0.09
2	2	1	2	-57.0	-60.0	8.5	-72.0	-12.0	-3.03	-0.45	-2.71	0.08
3	2	1	2	-82.0	-54.5	-1.0	-130.5	-21.8	-1.81	-0.63	-1.06	0.05
4	2	2	1	-53.5	-53.0	-0.5	-3.0	-0.5	-1.66	0.01	-1.73	0.03
5	2	2	1	-87.5	-82.0	6.0	-57.0	-9.5	-3.81	-0.44	-3.35	0.12
6	2	2	1	-81.5	-86.5	4.5	2.5	0.4	-2.96	-0.08	-2.96	0.09
7	2	1	2	-44.5	-28.0	-5.0	-56.0	-9.3	-0.03	-0.21	0.21	0.01
8	2	1	2	-80.5	-74.0	0.0	-16.0	-2.7	-2.04	-0.07	-1.88	0.06
9	2	2	1	-83.5	-75.0	0.0	-40.5	-6.8	-2.26	-0.18	-2.03	0.10

APPENDIX III. Minimum sample size estimations.

	Est n*	n*	$2\delta e^2$	$(2(\hat{u}1-\hat{u}2))^2$	δe^2	$\hat{u}1-\hat{u}2$
TC	2	0.00	377.650	6797.013	188.825	41.222
LDL	2	0.00	577.886	9517.173	288.943	48.778
HDL	5	0.00	8.555	41.525	4.278	3.222
TG	6	0.00	947.784	3429.274	473.892	29.280
VLDL	6	0.00	26.106	95.180	13.053	4.878
TC/HDL	15	0.00	0.793	1.143	0.396	0.534
VLDL/HDL	6	0.00	0.036	0.138	0.018	0.186
LDL/HDL	8	0.00	0.889	2.496	0.445	0.790
HDL/TC	13	0.00	0.001	0.003	0.000	0.026

Pre-established Constants:

alpha=0.05

ß=0.1

$(Z\text{alpha}/2+Z\beta)^2 = 10.50408$

Assumption: $\hat{u}1-\hat{u}2 = T1-T2$

Equation for estimating minimum sample size for a two-period, cross-over study (from reference 21).

$$n^* = \frac{2(2\delta e^2\ (Z\text{alpha}/2+Z\beta)^2}{(2(T1-T2))^2}$$