Effects of Fenofibrate on Atherogenic Dyslipidemia in Hypertriglyceridemic Subjects

MICHAEL H. DAVIDSON, M.D.,*† HAROLD E. BAYS, M.D.,‡ EVAN STEIN, M.D., PH.D.,§ KEVIN C. MAKI, PH.D.,†//
ROBERT A. SHALWITZ, M.D.,# RALPH DOYLE, B.A.,# FOR THE TRIMS INVESTIGATORS

*Department of Cardiology, Rush University Medical College, and †Radiant Research, Chicago, Illinois; ‡L-MARC Research Center, Louisville, Kentucky; §Metabolic and Atherosclerosis Research Center, Cincinnati, Ohio; //Provident Clinical Research, Bloomington, Indiana; #Reliant Pharmaceutical, Inc., Liberty Corner, New Jersey, USA

Summary

Background: The metabolic syndrome (MS) is often accompanied by atherogenic dyslipidemia, which is characterized by elevated triglycerides (TG), reduced high-density lipoprotein cholesterol (HDL-C), and elevated numbers of small, dense low-density lipoprotein (LDL) particles.

Hypothesis: It was hypothesized that a threshold exists for the circulating TG level needed to produce changes in LDL subclass distribution.

Methods: Hypertriglyceridemic (TG ≥ 300 and < 1000 mg/dl) subjects with the MS were randomly assigned to placebo (n = 50) or 130 mg/day of micronized fenofibrate-coated microgranules (n = 96) for 8 weeks.

Results: In the overall analysis, fenofibrate treatment resulted in significant ($p < 0.05$) changes versus placebo in TG (-36.6%), non-HDL-C (-7.5%), very low-density lipoprotein-C (-32.7%), LDL-C (15.0%), HDL-C (14.0%), remnant lipoprotein-C (-35.1%), apolipoprotein B (-6.0%), apolipoprotein A-I (5.3%), and apolipoprotein C-III (-29.7%). Changes in LDL particle diameter in the fenofibrate group

were significantly inversely associated with the TG level achieved on treatment ($p = 0.019$). When individually matched for percent change in TG, subjects with on-treatment TG < 200 mg/dl, in contrast to those with on-treatment values ≥ 200 mg/dl, had significantly different median responses ($p < 0.05$) in LDL size (0.79 vs. -0.06 nm) and cholesterol carried by small (-35 vs. 21 mg/dl) and large (31 vs. 11 mg/dl) particles.

Conclusion: These data support the view that a threshold exists below which the TG level must be lowered to produce shifts in LDL particle size.

Key words: triglycerides, hypertriglyceridemia, low-density lipoprotein, particle size, fenofibrate

Introduction

Patients with the metabolic syndrome (MS) often have atherogenic dyslipidemia, characterized by elevated triglycerides (TG) and TG-rich lipoprotein remnants, reduced high-density lipoprotein cholesterol (HDL-C), and elevated numbers of small, dense, low-density lipoprotein (LDL) particles.^{1–3} This lipid profile is associated with substantial elevation in coronary heart disease (CHD) event risk.^{2,3} The present trial, the Triglyceride Reduction in Metabolic Syndrome (TRIMS) study, was designed to assess effects of fenofibrate therapy on atherogenic dyslipidemia and other cardiovascular risk markers in patients with hypertriglyceridemia (≥ 300 and < 1000 mg/dl) and the MS. The results of the study are reported herein, with particular emphasis on an exploration of on-treatment TG concentration and degree of TG reduction as determinants of shifts in LDL particle size.

Patients and Methods

Study Design

This was a multicenter, randomized, double-blind, placebo-controlled study with 8 weeks of treatment. After institutional

Reliant Pharmaceuticals, Inc., funded the trial reported in this paper and is the manufacturer of the drug studied (AntaraTM). Drs. Maki and Stein have been consultants to Reliant and Drs. Maki and Bays have received research grants from Reliant; Dr. Bays has also received research grants from Abbott Laboratories. Drs. Shalwitz and Doyle are full-time employees of Reliant.

Address for reprints:

Michael H. Davidson, M.D.
Radiant Research
515 North State St., Suite 2700
Chicago, IL 60610, USA
e-mail: michael davidson@radiantresearch.com.

Received: February 1, 2006

Accepted with revision: March 24, 2006

review board approval, 146 men and women (21–79 years) provided informed consent and were enrolled in the study. Subjects were instructed to discontinue any lipid-lowering drugs and supplements, and to follow the National Cholesterol Education Program (NCEP) Therapeutics Lifestyles Changes diet.³ To be randomized, subjects needed fasting TG levels ≥ 300 and < 1000 mg/dl, and at least two of four additional components of the MS as defined by the NCEP Adult Treatment Panel III, which includes the presence of ≥ 3 of the following risk factors: (1) abdominal obesity (waist circumference > 102 cm [> 40 in] or > 88 cm [> 35 in] in men and women, respectively); (2) TG level ≥ 150 mg/dl; (3) high-density lipoprotein cholesterol (HDL-C) concentration < 40 or < 50 mg/dl in men and women, respectively; (4) systolic and/or diastolic blood pressure $\geq 130/85$ mmHg (or use of antihypertensive medication); and (5) fasting glucose ≥ 110 mg/dl (or diagnosed diabetes mellitus).³

Subjects were assigned 1:1:1 to receive fenofibrate therapy (130 mg⁴) with food, fenofibrate without food, or placebo daily for 8 weeks. Because no material differences in response were found between subjects who consumed fenofibrate with and without food,¹ this factor was ignored for the present analyses.

Efficacy Endpoints

The efficacy endpoints were changes or percent changes from baseline to the end-of-treatment. The fasting TG response was the primary efficacy endpoint. Other endpoints included total cholesterol (total-C); LDL-C; HDL-C; the total-C/HDL-C ratio; very low-density lipoprotein (VLDL)-C; non-HDL-C; apolipoproteins (Apo) A-I, B, and C-III; and remnant lipoprotein (RLP)-C.

The concentration and size (diameter) of LDL particles as well as the concentrations of cholesterol carried by small and large LDL particles were measured by nuclear magnetic resonance spectroscopy (LipoScience, Inc., Raleigh, N.C., USA).^{5, 6} Low-density lipoprotein particle sizes of 23.0 to 20.6 nm were defined as “large LDL,” while LDL particles 20.5 to 18.0 nm were defined as “small LDL.”

All other clinical laboratory tests were performed centrally by the Mayo Central Laboratory for Clinical Trials, Rochester, Minnesota, which participates in the lipid measurement standardization program of the Centers for Disease Control and Prevention and the National Heart, Lung and Blood Institute.⁷

Statistical Procedures

Analyses were completed on all subjects who were randomized, took at least one dose of study drug, and returned for at least one post-randomization efficacy evaluation. In all analyses, statistical significance was set at a two-tailed alpha level ≤ 0.05 . Rank transformations were employed when data were not normally distributed. P values for continuous variables were generated by analysis of variance (ANOVA). Multivariate linear regression was used to evaluate the relationship between change in TG concentration and LDL particle size.

Results

Subject Characteristics

In all, 146 subjects were randomized to placebo ($n = 50$) or fenofibrate ($n = 96$) treatment. The study groups were well matched with regard to baseline characteristics (Table I), including cardiovascular risk markers (Table II). Among the subjects with type 2 diabetes mellitus, 10 in the fenofibrate group and 5 in the placebo group were on stable treatment with a thiazolidinedione compound. There were no differences in response among thiazolidinedione users versus nonusers (data not shown).

Efficacy

Lipids: The TG-lowering effect of fenofibrate was evident and near maximal within the first 2 weeks of treatment (Fig. 1) and continued throughout the 8-week study period. Table II shows baseline values and responses to treatment for cardiovascular risk markers by group. At end-of-treatment, the mean percent decrease from baseline for TG was 36.6% in the fenofibrate group compared with essentially no change in the placebo group ($p < 0.001$).

Low-density lipoprotein cholesterol increased by a mean of 15.0% in the fenofibrate group compared with 3.2% ($p = 0.006$) in the placebo group. However, non-HDL cholesterol (LDL-C + VLDL-C) decreased significantly more in the fenofibrate group (-7.5% vs. -1.1% ; $p = 0.009$) because VLDL-C declined by nearly 33% with fenofibrate compared with a 1.6% decline with placebo treatment ($p < 0.001$). High-

TABLE I Demographic and baseline characteristics of randomized patients

Variable	Fenofibrate (n = 96)	Placebo (n = 50)	p Value
Gender, n (%)			0.864
Male	59 (61.5)	30 (60.0)	
Female	37 (38.5)	20 (40.0)	
Race, n (%)			0.808
White	89 (92.7)	48 (96.0)	
Black	4 (4.2)	2 (4.0)	
Asian	1 (1.0)	0 (0.0)	
Other	2 (2.1)	0 (0.0)	
Diabetes, n (%)	25 (26.0)	19 (38.0)	0.135
	Mean $\pm$ SEM		
Age (years)	56.5 $\pm$ 1.0	55.3 $\pm$ 1.5	0.478
Weight (kg)	91.8 $\pm$ 1.5	92.3 $\pm$ 2.6	0.859
Height (cm)	172.5 $\pm$ 1.1	170.8 $\pm$ 1.4	0.338
Body mass index (kg/m ²)	30.8 $\pm$ 0.4	31.5 $\pm$ 0.7	0.372
Waist (cm)	105.1 $\pm$ 1.1	105.6 $\pm$ 2.0	0.805
Blood pressure			
Systolic (mmHg)	126.1 $\pm$ 1.1	127.5 $\pm$ 1.7	0.490
Diastolic (mmHg)	77.9 $\pm$ 0.7	77.8 $\pm$ 1.1	0.938

TABLE II Effects of fenofibrate on lipids and other cardiovascular risk markers

Variable	Fenofibrate (n = 96)		Placebo (n = 50)		p Value
	Baseline	Change	Baseline	Change	
	Mean ± SEM				
Triglycerides (mg/dl)	480 ± 19	−36.6 ± 2.4%	479 ± 21	0.7 ± 5.3%	<0.001
LDL cholesterol (mg/dl)	121 ± 4	15.0 ± 2.6%	116 ± 6	3.2 ± 3.2%	0.006
Non-HDL cholesterol (mg/dl)	209 ± 5	−7.5 ± 1.5%	202 ± 6	−1.1 ± 1.6%	0.009
VLDL cholesterol (mg/dl)	88 ± 3	−32.7 ± 2.5%	87 ± 3	−1.6 ± 4.2%	<0.001
HDL cholesterol (mg/dl)	36 ± 1	14.0 ± 1.6%	35 ± 1	0.8 ± 2.2%	<0.001
Total cholesterol (mg/dl)	245 ± 5	−4.3 ± 1.3%	237 ± 6	−0.8 ± 1.4%	0.085
Total/HDL cholesterol ratio	7.1 ± 0.2	−14.2 ± 1.8%	7.0 ± 0.2	0.8 ± 2.9%	<0.001
RLP cholesterol (mg/dl)	48 ± 5	−35.1 ± 5.4%	42 ± 4	12.3 ± 10.6%	<0.001
Apolipoprotein AI (mg/dl)	117 ± 2	5.3 ± 1.7%	115 ± 3	2.0 ± 1.7%	0.212
Apolipoprotein B (mg/dl)	108 ± 2	−6.0 ± 1.8%	105 ± 3	1.6 ± 2.3%	0.013
Apolipoprotein B/AI ratio	0.95 ± 0.02	−8.4 ± 2.7%	0.93 ± 0.03	0.7 ± 2.6%	<0.001
Apolipoprotein CIII (mg/dl)	32 ± 1	−29.7 ± 2.4%	30 ± 1	3.6 ± 5.3%	<0.001
	Median (minimum, maximum)				
LDL particle concentration (nmol/l)	1780 (678, 3696)	59 (−1812, 1603)	1689 (780, 2759)	60 (−1495, 732)	0.464
LDL particle size (nm)	19.70 (18.9, 20.7)	0.27 (−0.8, 1.8)	19.68 (19.1, 21.7)	0.06 (−1.7, 1.6)	0.058
Small LDL cholesterol ^a (mg/dl)	92.8 (34, 206)	−1.3 (−117, 85)	89.8 (20, 147)	4.7 (−87, 59)	0.814
Large LDL cholesterol ^a (mg/dl)	16.0 (0, 92)	10.3 (−43, 112)	13.3 (0, 61)	1.2 (−33, 81)	0.002

^a Large LDL = 23.0 to 20.6 nm; small LDL = 20.5 to 18.0 nm.

Abbreviations: LDL = low-density lipoprotein, HDL = high-density lipoprotein, VLDL = very low-density lipoprotein, RLP = remnant lipoprotein, SEM = standard error of the mean.

density lipoprotein cholesterol increased by a mean of 14.0% in the fenofibrate group compared with 0.8% for placebo ($p < 0.001$). Total cholesterol was not significantly affected by fenofibrate treatment; however, the ratio of total to HDL-C decreased with fenofibrate compared with placebo (-14.2 vs. 0.8%; $p < 0.001$). Consistent with the declines in VLDL-C and triglycerides, a significant reduction in RLP-C was observed with fenofibrate treatment (-35.1 vs. 12.3%, $p < 0.001$).

Apolipoproteins: The rise in Apo AI in the fenofibrate group was not significantly different from the placebo response (5.3 vs. 2.0%). Apolipoprotein B and the Apo B/AI ra-

tio declined significantly with fenofibrate compared with placebo ($p = 0.013$ and $p < 0.001$, respectively). In addition, Apo C-III was reduced markedly in the fenofibrate group ($p < 0.001$).

Low-density lipoprotein particle measurements: The change from baseline in LDL particle concentration did not differ significantly between the placebo and fenofibrate groups. Nearly all subjects in both groups (98.6%) showed a predominance of small, dense LDL particles (LDL subclass pattern B) at baseline. A trend was present toward increased LDL particle diameter in the fenofibrate group ($p = 0.058$). No significant difference was noted between groups in the changes from baseline in cholesterol carried by small LDL particles, but the amount carried by large LDL particles increased to a significantly greater extent ($p = 0.002$) among subjects in the fenofibrate group.

Influence of end-of-treatment triglyceride concentration on response: It has been hypothesized that formation of small, dense LDL particles results when the TG concentration rises above a threshold level that varies from person to person, but is typically in the range of 100 to 200 mg/dl.^{3,8,9} To investigate this issue in the present trial, we categorized subjects in the fenofibrate group based on end-of-treatment TG value and found a significant inverse relationship with the change in LDL particle diameter (p value for trend = 0.019). Those with end-of-treatment values < 200 mg/dl ($n = 22$) showed a medi-

Fig. 1 Mean triglyceride concentration by treatment group and week of study. —■— = Fenofibrate, - - -○- - = placebo.

an increase of 0.56 nm, while those with end-of-treatment values between 200 and 299 mg/dl ($n = 33$) had a median increase of 0.31 nm, and those with end-of-treatment values ≥ 300 mg/dl ($n = 29$) showed essentially no change in LDL particle diameter (median increase = 0.02 nm).

However, there was also a significant relationship between end-of-treatment TG concentration and the degree of TG reduction (p for trend < 0.001), with median changes from baseline of -56.4% (-223 mg/dl), -36.8% (-149 mg/dl), and -22.8% (-115 mg/dl) in the end-of-treatment TG < 200 , 200 to 299, and ≥ 300 mg/dl subgroups, respectively. In a multivariate model, the end-of-treatment TG concentration remained a significant predictor ($p = 0.008$) of the change in LDL particle diameter after adjustment for the change in TG concentration.

To control for responsiveness to fenofibrate further, subjects with end-of-treatment TG < 200 mg/dl were individually matched for percent change from baseline TG concentration to subjects who had end-of-treatment TG concentrations ≥ 200 mg/dl. An acceptable match ($\pm 2.5\%$) was found for 13 pairs. Among those with end-of-treatment TG < 200 mg/dl, there was clear evidence of a shift in LDL particle size toward larger, more buoyant particles that was absent among subjects with end-of-treatment triglycerides ≥ 200 mg/dl (Table III). This is reflected by an increase in LDL particle diameter (0.79 vs. -0.06 nm, $p = 0.003$), a reduction in cholesterol carried by small, dense LDL particles (-35 vs. 21 mg/dl, $p = 0.005$) and

a greater increase in cholesterol carried by large, buoyant particles (31 vs. 11 mg/dl, $p = 0.012$) in the subset with end-of-treatment TG < 200 mg/dl compared with the matched group with end-of-treatment TG ≥ 200 mg/dl. Finally, LDL particle concentrations were significantly different between the matched subsets, the subset with end-of-treatment TG < 200 mg/dl showed a median decline (-381 nmol/l), while the subset with final TG ≥ 200 mg/dl had a median increase (472 nmol/l; $p = 0.029$ for comparison).

Slightly more than half (7 of 13, or 53.8%) of the subjects with end-of-treatment TG < 200 mg/dl converted from LDL subclass pattern B to A, whereas 15.4% (2 of 13) did so among those with end-of-treatment TG ≥ 200 mg/dl ($p = 0.097$). Among subjects who did ($n = 9$) and did not ($n = 17$) convert to pattern A, the median changes in LDL particle size were 1.31 and -0.14 nm, respectively ($p < 0.001$).

Discussion

The results of this double-blind, placebo-controlled trial confirm that fenofibrate lowers TG and produces improvements in several lipid markers for cardiovascular disease risk in subjects with hypertriglyceridemia and the MS. Favorable changes were observed in levels of non-HDL-C, HDL-C, RLP-C, Apo B, and Apo CIII in the fenofibrate group. In addi-

TABLE III Low-density-lipoprotein particle measurements in fenofibrate-treated subjects individually matched for percent change in triglyceride concentration with end-of-treatment triglyceride levels < 200 or ≥ 200 mg/dl

Variable	End-of-treatment triglyceride concentration < 200 mg/dl ($n = 13$)		End-of-treatment triglyceride concentration ≥ 200 mg/dl ($n = 13$)		p Value
	Baseline	Change	Baseline	Change	
	Median (minimum, maximum)				
Triglycerides, mg/dl ^a	364 (283, 536)	-52% (-63% , -41%)	559 (352, 907)	-52% (-64% , -42%)	0.927
LDL particle size, nm	19.73 (19.2, 20.7)	0.79 (-0.7 , 1.8)	19.73 (19.3, 20.3)	-0.06 (-0.8 , 1.6)	0.003
Small LDL cholesterol, mg/dl ^b	90 (57, 153)	-35 (-83 , 38)	81 (34, 144)	21 (-81 , 45)	0.005
Large LDL cholesterol, mg/dl ^b	23 (3, 92)	31 (-43 , 75)	11 (4, 34)	11 (-14 , 67)	0.012
LDL particle concentration, nmol/l	1826 (1078, 3002)	-381 (-841 , 507)	1456 (678, 2635)	472 (-969 , 782)	0.029
LDL cholesterol, mg/dl	131 (49, 211)	4% (-22% , 53%)	114 (45, 171)	24% (-17% , 69%)	0.229
Non-HDL cholesterol, mg/dl	201 (133, 268)	-18% (-29% , 6%)	214 (108, 288)	-15% (-31% , 6%)	0.164
HDL cholesterol, mg/dl	39 (27, 52)	15% (-1% , 62%)	32 (27, 40)	19% (-16% , 50%)	0.983

^a Values are means; each subject in the subset with an end-of-treatment triglyceride value < 200 mg/dl was individually matched, based on percent change from baseline in triglyceride concentration (within $\pm 2.5\%$), to a subject with an end-of-treatment triglyceride value ≥ 200 mg/dl.

^b Large LDL = 23.0 to 20.6 nm; small LDL = 20.5 to 18.0 nm.

Abbreviations as in Table II.

tion, fenofibrate produced a shift toward larger, more buoyant LDL particles that was marginally significant ($p = 0.058$) in the overall study sample, but strongly associated with the end-of-treatment TG value ($p = 0.019$).

Several previous studies have shown that fibrate therapy increases LDL particle size.^{10–12} In the Diabetes Atherosclerosis Intervention Study (DAIS), fenofibrate reduced the rate of coronary artery disease progression in subjects with type 2 diabetes mellitus.¹³ Multivariate regression demonstrated that LDL particle size was an independent predictor of the degree of disease progression in models containing LDL-C or Apo B.¹³ The change in LDL particle size also correlated inversely with the plasma TG level achieved.¹³ Subjects in the lowest tertile of on-treatment TG concentration (< 113 mg/dl) had a mean increase of 1.19 nm in LDL particle diameter, whereas those in the highest tertile (> 160 mg/dl) had a mean increase of 0.69 nm.

It has been hypothesized that changes in LDL particle size do not occur uniformly, but rather follow a pattern wherein larger, more buoyant LDL particles predominate (LDL subclass pattern A) when the circulating TG concentration is low, but that a shift occurs to a predominance of small, dense LDL particles (LDL subclass pattern B) when the TG level increases above a threshold value.⁸ The threshold at which this shift in LDL subclass pattern occurs may be largely hereditary and, in a majority of individuals, appears to occur in the range of 100 to 200 mg/dl. Population data indicate that at a TG value of 200 mg/dl, the prevalence of pattern B is ~75% and when the TG is 100 mg/dl, the prevalence of pattern B is ~18%.¹⁴ Because a TG concentration > 300 mg/dl was required for participation in the present trial, nearly all subjects (98.6%) had LDL subclass pattern B at baseline.

This threshold model would suggest that TG lowering will not substantially alter LDL subclass distribution if the TG level remains above the individual's threshold for conversion from pattern B to pattern A. In the present study, by pairing fenofibrate-treated subjects with on-treatment TG values < 200 or ≥ 200 mg/dl for percent change in TG, we were able to isolate the influences of the TG value achieved from the degree of TG lowering. It is notable that the subset with end-of-treatment TG ≥ 200 mg/dl showed no increase in LDL particle diameter despite a median decline of $> 50\%$ from baseline in TG concentration. In addition, very little increase in LDL particle diameter was observed in subjects with end-of-treatment TG values < 200 mg/dl in the absence of a conversion to LDL subclass pattern A. These results are concordant with the proposed model.

The recently published findings of the Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study indicated that fenofibrate did not significantly reduce the risk of the primary outcome of coronary events.¹⁵ Notably, the median baseline TG concentration in the FIELD study was approximately 153 mg/dl, suggesting that a substantial fraction of the study sample may have had TG levels below the threshold for conversion to LDL subclass pattern B. No data on LDL subclass distribution have been published to date from the FIELD study. However, results from previous outcomes studies have

suggested that the greatest risk reduction with fibrate therapy occurs in subjects with TG > 200 mg/dl or 2.3 mmol/l.^{16–19} One potential explanation for the greater risk reduction in those with hypertriglyceridemia, and for the failure of the FIELD study to demonstrate a reduction in risk for the primary outcome, is that the greatest benefit of fibrate therapy accrues to subjects in whom treatment induces a shift from LDL subclass pattern B to pattern A. It will be of interest to examine this hypothesis in the FIELD study dataset.

For many patients with high or very high TG concentrations, a single agent will not reduce the TG level to a degree sufficient to induce a shift in LDL subclass distribution pattern. In a recent national survey of lipid management in clinical practice, 25% of patients receiving treatment for dyslipidemia had an on-treatment TG concentration ≥ 200 mg/dl.²⁰ Additional research is needed to confirm the findings of the present investigation with other TG-lowering agents or combinations of agents. Moreover, it should be emphasized that data from clinical outcomes trials will be needed to demonstrate that treatment-induced changes in LDL particle size will translate into reductions in event risk above and beyond those attributable to modification of the standard lipoprotein profile (LDL-C, non-HDL-C, and HDL-C).

Conclusion

The results of the present trial indicate that fenofibrate effectively lowers TG concentration and produces other favorable changes in several lipid markers for cardiovascular disease risk in hypertriglyceridemic subjects with the MS. Improvements in LDL particle size were absent or modest unless the on-treatment TG concentration was low enough to produce a shift in LDL subclass distribution pattern. The threshold TG value was < 200 mg/dl for most patients. Additional research is needed to determine whether lowering the TG value to the level required to produce a shift toward larger, more buoyant LDL species will translate into additional lowering of cardiovascular event risk.

Acknowledgments

The authors gratefully acknowledge the TRIMS investigators (a list of participants is provided in Reference 1); Michael Rooney, Ron Galant, MarySue Witchger, and Marjorie Bell at Radiant Research, Inc.; and Doug Kling and John Marshall at Reliant Pharmaceuticals, Inc., for their help with the study and manuscript preparation.

References

1. Davidson MH, Bays H, Rhyne J, Stein E, Rotenberg K, Doyle R: Efficacy and safety profile of fenofibrate 130 mg (fenofibrate-coated microgranules), with and without food, in patients with hypertriglyceridemia and the metabolic syndrome: An 8-week, randomized, double-blind, placebo-controlled study. *Clin Ther* 2005;27:715–727

2. Davidson MH: Emerging therapeutic strategies for the management of dyslipidemia in patients with the metabolic syndrome. *Am J Cardiol* 2004;93(suppl):3C–11C
3. Executive Summary of the Third Report of the National Cholesterol Education Program Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). *J Am Med Assoc* 2001;285:2486–2497. Accessed on June 10, 2005 at: http://www.nhlbi.nih.gov/guidelines/cholesterol/atp3_rpt.htm.
4. Antara™ capsules [package insert]. Liberty Corner, N.J.: Reliant Pharmaceuticals, Inc; 2005. Accessed on January 25, 2006 at: <http://www.antarax.com/PI.pdf>.
5. Otvos JD, Jeyarajah EJ, Bennett DW: Quantification of plasma lipoproteins by proton nuclear magnetic resonance spectroscopy. *Clin Chem* 1991;37:377–386
6. Otvos JD, Jeyarajah EJ, Cromwell WC: Measurement issues related to lipoprotein heterogeneity. *Am J Cardiol* 2002;90(suppl):22i–29i
7. Myers GL, Cooper GR, Winn CL, Smith SJ: The Centers for Disease Control–National Heart, Lung, and Blood Institute Lipid Standardization Program. An approach to accurate and precise lipid measurements. *Clin Lab Med* 1989;9:105–135
8. Packard CJ: Triacylglycerol-rich lipoproteins and the generation of small, dense low-density lipoprotein. *Biochem Soc Trans* 2003;31(Pt 5):1066–1069
9. Austin MA, King MC, Vranizan KM, Krauss RM: Atherogenic lipoprotein phenotype. A proposed genetic marker for coronary heart disease risk. *Circulation* 1990;82(2):495–506
10. Lemieux I, Laperrière L, Dzavik V, Tremblay G, Bourgeois J, Despres JP: A 16-week fenofibrate treatment increases LDL particle size in type IIA dyslipidemic patients. *Atherosclerosis* 2002;162(2):363–371
11. Frost RJ, Otto C, Geiss HC, Schwandt P, Parhofer KG: Effects of atorvastatin versus fenofibrate on lipoprotein profiles, low-density lipoprotein subfraction distribution, and hemorheologic parameters in type 2 diabetes mellitus with mixed hyperlipoproteinemia. *Am J Cardiol* 2001;87(1):44–48
12. Ikewaki K, Tohyama J, Nakata Y, Wakikawa T, Kido T, Mochizuki S: Fenofibrate effectively reduces remnants, and small dense LDL, and increases HDL particle number in hypertriglyceridemic men—a nuclear magnetic resonance study. *J Atheroscler Thromb* 2004;11:278–285
13. Vakkilainen J, Steiner G, Ansquer JC, Aubin F, Rattier S, Foucher C, Hamsten A, Taskinen MR, DAIS Group: Relationships between low-density lipoprotein particle size, plasma lipoproteins, and progression of coronary artery disease: The Diabetes Atherosclerosis Intervention Study (DAIS). *Circulation* 2003;107(13):1733–1737
14. Superko HR: Small dense LDL: The new coronary artery disease risk factor and how it is changing the treatment of CAD. *Prev Cardiol* 1998;1:16–24
15. Keech A, Simes RJ, Barter P, Best J, Scott R, Taskinen MR, Forder P, Pillai A, Davis T, Glasziou P, Drury P, Kesaniemi YA, Sullivan D, Hunt D, Colman P, d'Emden M, Whiting M, Ehnholm C, Laakso M, and the FIELD study investigators: Effects of long-term fenofibrate therapy on cardiovascular events in 9,795 people with type 2 diabetes mellitus (the FIELD study): Randomised controlled trial. *Lancet* 2005;366(9500):1849–1861
16. Secondary prevention by raising HDL cholesterol and reducing triglycerides in patients with coronary artery disease: The Bezafibrate Infarction Prevention (BIP) Study. *Circulation* 2000;102:21–27
17. Frick MH, Elo O, Haapa K, Heinonen OP, Heinsalmi P, Helo P, Huttunen JK, Kaitaniemi P, Koskinen P, Manninen V, Maenpaa H, Malkonen M, Manttari M, Norola S, Pasternack A, Pikkarainen J, Romo M, Sjöblom T, Niskilä EA: Helsinki Heart Study: Primary-prevention trial with gemfibrozil in middle-aged men with dyslipidemia. Safety of treatment, changes in risk factors, and incidence of coronary heart disease. *N Engl J Med* 1987;317:1237–1245
18. Manninen V, Tenkanen L, Koskinen P, Huttunen JK, Manttari M, Heinonen OP, Frick MH: Joint effects of serum triglyceride and LDL cholesterol and HDL cholesterol concentrations on coronary heart disease risk in the Helsinki Heart Study. Implications for treatment. *Circulation* 1992;85:37–45
19. Robins SJ, Collins D, Wittes JT, Papademetriou V, Deedwania PC, Schaefer EJ, McNamara JR, Kashyap ML, Hershman JM, Wexler LF, Rubins HB, for the VA-HIT Study Group: Relation of gemfibrozil treatment and lipid levels with major coronary events: VA-HIT: A randomized controlled trial. *J Am Med Assoc* 2001;285:1585–1591
20. Davidson MH, Maki KC, Pearson TA, Pasternak RC, Deedwania PC, McKenney JM, Fonarow GC, Maron DJ, Ansell BJ, Clark LT, Ballantyne CM: Results of the National Cholesterol Education (NCEP) Program Evaluation Project Utilizing Novel E-Technology (NEPTUNE) II survey and implications for treatment under the recent NCEP Writing Group recommendations. *Am J Cardiol* 2005;96(4):556–563