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EXPEDITED REVIEWS

The Reduction of Inflammatory Biomarkers by Statin, Fibrate, and Combination Therapy Among Diabetic Patients With Mixed Dyslipidemia

The DIACOR (Diabetes and Combined Lipid Therapy Regimen) Study

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OBJECTIVES The primary objective was to determine the effect of statin-fibrate combination therapy on inflammatory biomarkers in patients with diabetes.

BACKGROUND Atherosclerosis is a long-term, chronic inflammatory disease that is exacerbated in patients with diabetes.

METHODS Patients (n = 300) with type II diabetes, mixed dyslipidemia (2 or more of low-density lipoprotein ≥100 mg/dl, triglycerides ≥200 mg/dl, or high-density lipoprotein <40 mg/dl), and no history of coronary heart disease were randomly assigned to receive simvastatin 20 mg, fenofibrate 160 mg, or a combination of simvastatin 20 mg and fenofibrate 160 mg daily. At 12 weeks after randomization, we measured levels of high-sensitivity C-reactive protein (hsCRP) and lipoprotein-associated phospholipase A_2 (Lp-PLA_2).

RESULTS At 12 weeks, median hsCRP was significantly reduced (−14.6%, $p = 0.004$) from baseline, but the effect did not differ between treatments. The effect was greatest among patients with baseline hsCRP levels >2.0 mg/l (fenofibrate = −18.9%, $p = 0.002$ vs. baseline; simvastatin = −24.8%, $p < 0.0001$; combination = −27.3%, $p = 0.002$). Likewise, median Lp-PLA_2 levels in the overall study population were significantly reduced (−16.8%, $p < 0.0001$), and the effect did not differ among treatments. This effect also was greatest among patients with increased baseline levels of Lp-PLA_2 greater than the median of 320.9 ng/ml (fenofibrate = −41.3%, $p < 0.0001$; simvastatin = −47.5%, $p < 0.0001$; combination = −46.8%, $p < 0.0001$).

CONCLUSIONS Simvastatin, fenofibrate, and combination therapy each lowered hsCRP and Lp-PLA_2. These anti-inflammatory effects were most pronounced among patients with increased baseline levels. Combination therapy was no more effective than either form of monotherapy. (The DIACOR Study; http://www.clinicaltrials.gov/ct/show/NCT00309712?order=1) (J Am Coll Cardiol 2006;48:396–401) © 2006 by the American College of Cardiology Foundation

Diabetes mellitus confers a 2- to 4-fold increase in cardiovascular risk compared with the general population (1). Although microvascular complications of diabetes result in increased rates of morbidity, macrovascular complications, including coronary artery disease, often cause death (2). Cardiovascular disease and diabetes are both associated with elevated levels of inflammatory biomarkers, including C-reactive protein (CRP) (3). C-reactive protein is the most well-studied inflammatory marker of atherothrombotic risk (4) and is incremental to the Framingham Risk Score (5). Lipoprotein-associated phospholipase A_2 (Lp-PLA_2) is a newer inflammatory biomarker that has been proposed to be more specific to vascular inflammation.

Statin and fibrate therapy have been shown to variably lower levels of CRP (6,7), as well as levels of Lp-PLA_2 (8). However, the influence of a statin and fibrate combination on levels of inflammatory markers requires further investigation (9,10). Therefore, among patients with type II diabetes, we assessed the effect of statin, fibrate, and combination therapy on inflammatory biomarkers in the DIACOR (Diabetes and Combined Lipid Therapy Regimen) study.

METHODS

Patients. Patients with a clinical diagnosis of type II diabetes mellitus and biochemical evidence of mixed dyslipidemia were considered for enrollment in the study. The study protocol was approved by the institutional review board, and all patients provided written informed consent. Patients meeting prescreening criteria were required to undergo wash-

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Abbreviations and Acronyms

CRP = C-reactive protein
HDL-C = high-density lipoprotein cholesterol
hsCRP = high-sensitivity C-reactive protein
LDL-C = low-density lipoprotein cholesterol
Lp-PLA_2 = lipoprotein-associated phospholipase A_2

out if currently receiving lipid therapy. A complete list of inclusion/exclusion criteria is found in Table 1.

Protocol. We undertook a single-center, randomized, double-blind, and placebo-controlled 12-week study. Those participants satisfying all inclusion/exclusion criteria were assigned randomly to receive 1 of 3 daily oral treatments: simvastatin 20 mg taken in the evening/fenofibrate placebo taken in the morning with food, fenofibrate 160 mg taking in the morning with food/simvastatin placebo taken in the evening, or simvastatin 20 mg taken in the evening and fenofibrate 160 mg taken in the morning with food. Coordinators, investigators, statistical personnel, and patients remained blinded to patient treatment assignment.

Follow-up visits were scheduled 6 and 12 weeks after randomization, where assessment of adverse events and 12-h fasting laboratory measurements were made. A creatine kinase was drawn if the patient complained of any muscle aches at those visits or at any time throughout the study period.

Laboratory measurements. Laboratory samples were analyzed in an Intermountain Healthcare laboratory (LDS Hospital, Salt Lake City, Utah, or McKay Dee Hospital, Ogden, Utah). Total cholesterol and triglycerides were quantified using dry-slide measurement on the VITROS 950 Analyzer (Ortho Clinical Diagnostics, Raritan, New Jersey). High-density lipoprotein cholesterol (HDL-C) was

Table 1. Inclusion and Exclusion Criteria

Inclusion Criteria	Exclusion Criteria
Controlled type II diabetes mellitus (hemoglobin A1C ≤9%)	Plasma creatine kinase levels >50% above the upper limit of normal (ULN)
If taking chronic hypoglycemic therapy including pioglitazone, rosiglitazone, metformin, sulfonlylureas, or insulin, alone or in combination, must be on a stable dosing regimen for the previous 3 months	Known history of coronary heart disease; myopathy, or rhabdomyolysis; active liver disease (positive antibodies to hepatitis B or C) or serum alanine aminotransferase or aspartate aminotransferase levels >30% above the ULN
If taking warfarin or warfarin-like anticoagulants, agree to have their anticoagulation levels drawn per standard of care for adjustment of anticoagulant dose	History of alcohol consumption: ≥2 drinks/day or ≥10 drinks/week
Documented post-washout dyslipidemia, defined as having at least two of the following: LDL ≥100 mg/dl, triglycerides ≥200 mg/dl, HDL <40 mg/dl	The use of lipid-lowering agents taken within 6 (bile acid sequestrants, statins, fish oil, nicotinic acid [doses >200 mg/day], or niacin) or 8 (fibrates) weeks prior to randomization assessment
Able to give voluntary informed consent	Serum creatinine >1.5 mg/dl (if between 1.2 and 1.49 mg/dl, the calculated creatinine clearance using the Crockcroft/Gault formula has to be >50 ml/min)
	Uncontrolled hypertension (systolic blood pressure >160 mm Hg or diastolic blood pressure >100 mm Hg)
	Proteinuria (dipstick >+1 or nephrotic syndrome)
	Hypothyroidism (thyroid-stimulating hormone >6 μU/ml)
	Concomitant use of cyclosporine, systemic itraconazole or ketoconazole, erythromycin or clarithromycin, nefazadone, HIV protease inhibitors, glucocorticoids, verapamil, or consumption of >1 quart of grapefruit juice per day
	Known hypersensitivity to statins or fibrates (elevated muscle or liver test, jaundice, hepatotoxicity, or myopathy)
	Partial ileal bypass
	Treatment with any other investigational drug within the previous 30 days
	Currently using illicit drugs or history of drug or alcohol abuse within the last 5 years
	Type I diabetes mellitus or diagnosis of homozygous familial hypercholesterolemia or types I or V hyperlipidemia
	Hyperlipidemic pancreatitis, or known presence of cholelithiasis
	Any therapy or condition that would pose a risk to the patient or make it difficult to comply with study requirements
	Pregnant and/or lactating women and women of child bearing potential not using acceptable means of contraception

Table 2. Characteristics Overall and Among Treatments at Study Baseline (*$p < 0.05$)

Variable	Overall (n = 300)	Fenofibrate (n = 100)	Simvastatin (n = 100)	Combined (n = 100)
Gender (male)	55.0%	48.0%	59.0%	58.0%
Age (yrs)	60.6	61.5	61.4	58.8
History of CVA	4.0%	3.0%	4.0%	5.0%
History of PVD	3.3%	3.0%	3.0%	4.0%
Family history of CAD	24.3%	24.0%	24.0%	25.0%
Taking warfarin	5.7%	3.0%	6.0%	8.0%
Hypertension	73.0%	73.0%	69.0%	77.0%
Control diabetes through				
Diet	15.7%	17.2%	14.0%	16.0%
Oral antidiabetic agents	87.0%	86.0%	87.0%	88.0%
Insulin	10.7%	12.0%	7.0%	13.0%
Wash off lipid medication	68.3%	76.0%	63.0%	66.0%
Wash off a statin	57.7%	63.0%	58.0%	52.0%
Wash off a fibrate*	11.0%	16.0%	2.0%	15.0%
Wash off a niacin	1.7%	3.0%	1.0%	1.0%
Taking a diuretic	21.6%	25.0%	13.3%	25.6%
Taking beta-blocker	13.8%	15.6%	9.6%	15.6%
Taking an ACE inhibitor	38.7%	37.5%	38.6%	40.0%
Taking thiazolidinediones	32.3%	27.1%	31.3%	38.9%
Taking sulfonylureas	19.7%	16.7%	24.1%	18.9%
Taking metformin at baseline	46.5%	45.8%	47.0%	46.7%

ACE = angiotensin-converting enzyme; CAD = coronary artery disease; CVA = cerebrovascular accident; PVD = peripheral vascular disease.

measured with the same instrument after treatment with VITROS HDL-Cholesterol Magnetic Reagent (Ortho Clinical Diagnostics); low-density lipoprotein cholesterol (LDL-C) was calculated from the total cholesterol and triglyceride measurements.

The concentration of high-sensitivity C-reactive protein (hsCRP) was determined using an immunoturbidimetric assay on the Hitachi 917 analyzer (Roche Diagnostics, Indianapolis, Indiana), using reagents and calibrators from Denka Seiken (Niigata, Japan). This assay has a sensitivity of 0.03 mg/l. The day-to-day variability of the assay at concentrations of 0.91 mg/l, 3.07 mg/l, and 13.38 mg/l are 2.81%, 1.61%, and 1.1%, respectively. Any patient with an hsCRP >10 mg/l was excluded from the analysis. We measured Lp-PLA_2 by using the PLAC test (diaDexus, Inc., San Francisco, California), and testing was performed at diaDexus, Inc., as described in the package insert, a modification of the originally published protocol (11).

Statistical analysis. This study was designed to provide an 80% power to detect a 20% difference in achievement of the primary study end point (percent of patients achieving triglyceride levels of <200 mg/dl after 12 weeks of treatment, which results are not described here) among study treatments with 100 patients in each group. Analysis was performed blinded by assigning each patient a letter (A, B, or C) that corresponded to their treatment group using the intention-to-treat model. Descriptive statistics were used to summarize characteristics of the study population and biomarker measurements. For evaluations of concentrations of triglycerides, hsCRP, and Lp-PLA_2, these variables were transformed using the natural logarithm to normalize the distributions before within-group analyses. Differences in baseline and 12-week levels were evaluated using the paired *t* test. The effect of study therapy on mean percent reduction from baseline levels of lipids, hsCRP, and Lp-PLA_2 was analyzed using analysis of variance and the Tukey's HSD

Table 3. High-Sensitivity C-Reactive Protein (hsCRP) (mg/l), Lipoprotein-Associated Phospholipase A_2 (Lp-PLA_2) (ng/ml), and Lipid (mg/dl) Levels at Baseline and 12 Weeks Post-Baseline, and Percent Change at 12 Weeks

	Fenofibrate				Simvastatin				Combined			
Parameter	Baseline	12 Weeks	% Change	p Value	Baseline	12 Weeks	% Change	p Value	Baseline	12 Weeks	% Change	p Value
hsCRP*	1.99	1.45	−14.1	0.17	2.10	1.80	−16.0	0.04	2.24	2.12	−15.9	0.10
Lp-PLA_2*	324.8	245.1	−26.9	<0.001	313.6	221.2	−34.5	<0.001	331.3	217.5	−36.2	<0.001
Total cholesterol	226.2	196.1	−1.2	<0.001	229.3	169.1	−26.2	<0.001	230.7	165.2	−27.1	<0.001
LDL-C	135.4	121.7	−5.6	<0.001	141.3	92.0	−34.1	<0.001	136.9	92.0	−29.1	<0.001
HDL-C	36.7	41.6	+13.7	<0.001	37.1	39.3	+7.4	0.001	36.1	40.0	+13.0	<0.001
Triglycerides*	270.5	154.5	−38.2	<0.001	230.0	182.5	−24.8	<0.001	284.0	138.0	−49.4	<0.001
Non–HDL-C	188.1	153.6	−16.1	<0.001	193.4	129.8	−32.5	<0.001	195.0	124.7	−34.3	<0.001

The p values represent a comparison between baseline and 12-week levels within each treatment. *Median levels reported due non-normal distribution of the data.
HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol.

test. Pearson's correlation coefficient was used to determine correlations among percent change at 12 weeks for hsCRP, Lp-PLA_2, and individual lipid parameters. Two-tailed p values are presented, with 0.05 designated as nominally significant.

RESULTS

Table 2 summarizes the baseline characteristics of the overall study population (n = 300) and also among each treatment group. Overall, significant changes between baseline and 12 weeks were found in median levels of hsCRP: 2.11 and 1.81 mg/l (−14.6%, p = 0.004); of Lp-PLA_2: 320.9 and 229.4 ng/ml (−33.2%, p < 0.0001); of triglycerides: 260.0 and 160.0 mg/dl (−36.2%, p < 0.0001); in mean levels of total cholesterol: 228.7 and 176.9 mg/dl (−21.6%, p < 0.0001); of LDL-C: 137.9 and 101.9 mg/dl (−23.2%, p < 0.0001); of HDL-C: 36.6 and 40.3 mg/dl (+11.3%, p < 0.0001); and of non–HDL-C: 192.1 and 136.2 (−27.6%, p < 0.0001), respectively. Table 3 shows levels of hsCRP, Lp-PLA_2, and lipids at baseline and 12 weeks with their percent change by treatment group. Table 4 displays comparisons of absolute changes among treatment groups for their ability to modify lipids, hsCRP, and Lp-PLA_2. No significant difference in effect on either inflammatory marker was noted between treatment groups. For those missing 12-week information (n = 10), analysis using 6-week information was performed and did not alter the results.

For those with increased levels of baseline hsCRP (>2.0 mg/l, n = 141), the median percent change within each treatment arm was greater and highly significant (Fig. 1). For these patients, median hsCRP levels within each treatment at baseline and 12 weeks were fenofibrate = 4.05 and 2.79 mg/l, simvastatin = 3.88 and 2.83 mg/l, and combination = 3.98 and 2.93 mg/l, respectively. Likewise, the percent reduction of Lp-PLA_2 was greatest among those with baseline levels greater than the median of 320.9 (n = 137) (Fig. 2). For patients with Lp-PLA_2 greater than the median, median levels at baseline and 12 weeks were fenofibrate = 459.3 and 237.9 ng/ml, simvastatin = 434.9 and 231.9 ng/ml, and combined = 439.1 and 228.2 ng/ml, respectively.

Table 4. Statistical Comparisons (p Values) Among Treatment Groups in the Medications' Ability to Modify Lipids, High-Sensitivity C-Reactive Protein (hsCRP) (mg/l), and Lipoprotein-Associated Phospholipase A_2 (Lp-PLA_2) (ng/ml)

Parameter	F vs. S	F vs. C	S vs. C
hsCRP	0.99	0.99	0.96
Lp-PLA_2	0.93	0.88	0.99
Total cholesterol	<0.0001	<0.0001	0.64
LDL-C	<0.0001	<0.0001	0.61
Non–HDL-C	<0.0001	<0.0001	0.46
HDL-C	0.15	0.84	0.41
Triglycerides	0.001	0.07	<0.0001

C = combined fenofibrate and simvastatin; F = fenofibrate; S = simvastatin; other abbreviations as in Table 3.

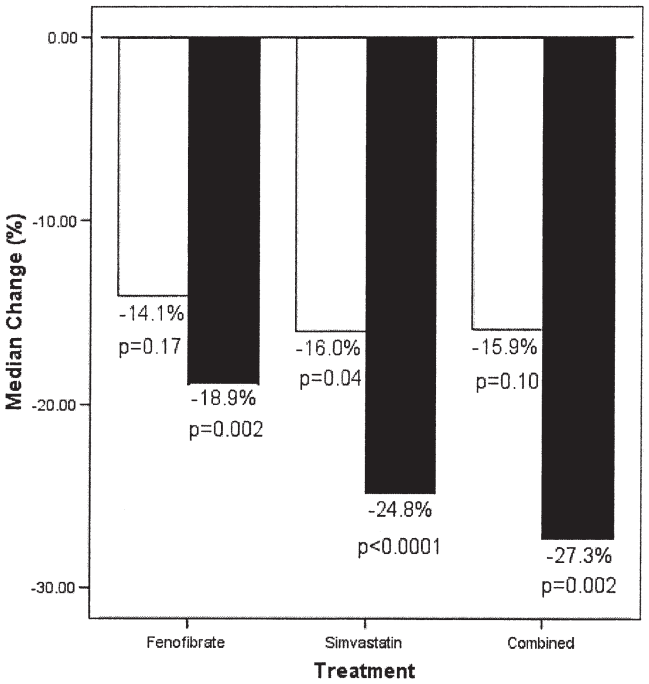

Figure 1. Comparison within each treatment for the median percent change from baseline to 12 weeks in high-sensitivity C-reactive protein (hsCRP) overall **(open bars)** and for those >2.0 mg/l **(solid bars)** (n = 141).

The percent change of hsCRP was not correlated with the percent change of Lp-PLA_2 or any lipids. A decrease in Lp-PLA_2 was significantly correlated with a decrease in total cholesterol (r = 0.46, p < 0.001), LDL-C (r = 0.35, p < 0.001), and non–HDL-C (r = 0.45, p < 0.001) with simvastatin but not with fenofibrate or combination therapy

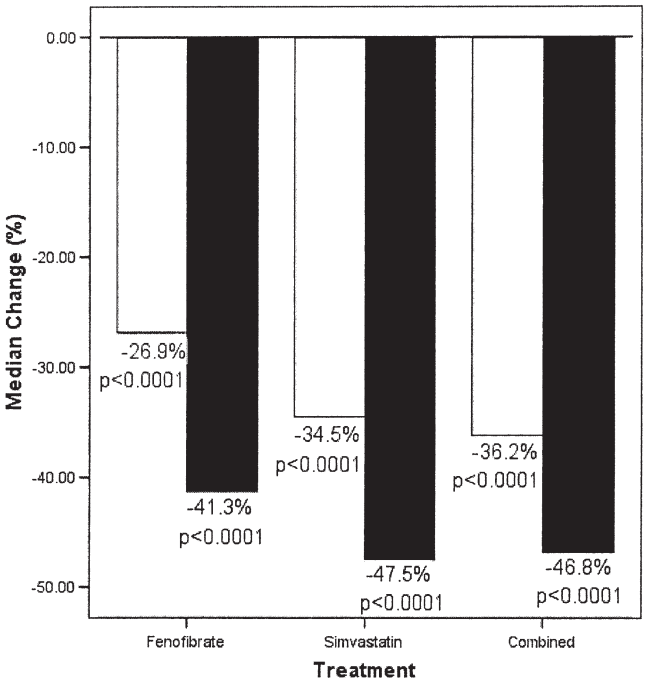

Figure 2. Comparison within each treatment for the median percent change from baseline to 12 weeks in lipoprotein-associated phospholipase A_2 overall **(open bars)** and for those >320.9 ng/ml **(solid bars)**.

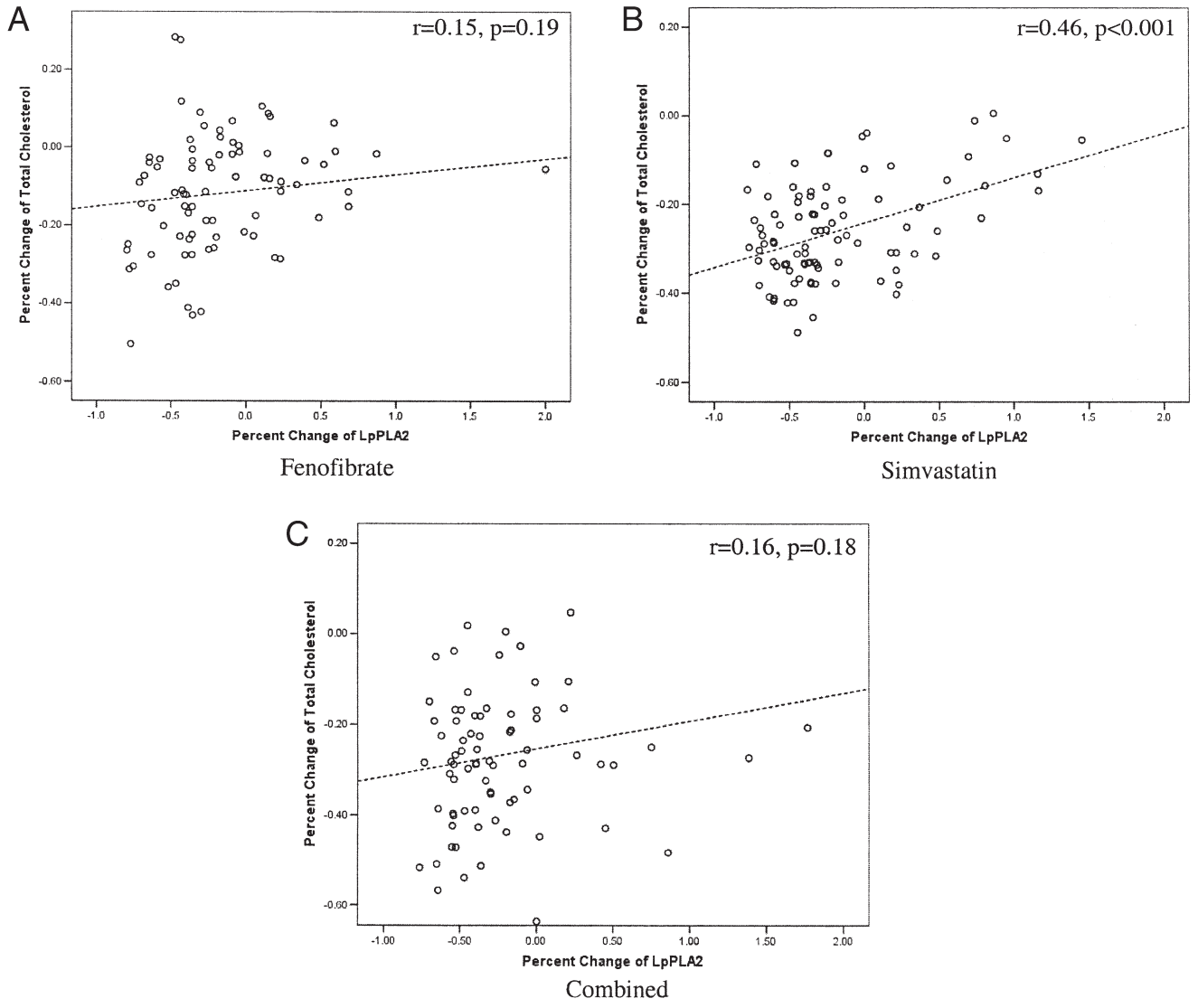

Figure 3. Scatter plots showing correlations between change in total cholesterol and change in lipoprotein-associated phospholipase A_2 ($LpPLA_2$) for each treatment group (**A** = fenofibrate; **B** = simvastatin; **C** = combined).

(Fig. 3). No other treatments correlated significantly with inflammatory markers and lipids.

Clinical adverse events were similar among all treatment groups. There were no cases of rhabdomyolysis, clinical myopathy (creatine kinase >10 upper limit of control), persistent myalgias, or adverse liver-related events, even among those subjects who dropped out of the study (n = 19). No serious drug-related clinical adverse events were noted throughout the study.

DISCUSSION

In this double-blind, placebo-controlled randomized study of 300 dyslipidemic patients with type II diabetes, we observed highly significant modifications in plasma concentrations of Lp-PLA_2, total cholesterol, LDL-C, HDL-C, triglycerides, and non–HDL-C in addition to a trend toward reduction of hsCRP by the combination therapy of simvastatin and fenofibrate. Combination therapy was not more effective in modifying levels of hsCRP and Lp-PLA_2 than either simvastatin or fenofibrate monotherapy; however, it was superior in reducing total cholesterol, LDL-C, and non–HDL-C concentrations compared with fenofibrate and in reducing triglyceride levels compared with simvastatin.

Four points contribute to the clinical relevance and importance of this study. 1) The magnitude of reduction by fenofibrate, simvastatin, and combination therapy was greatest when concentrations of hsCRP and Lp-PLA_2 were increased >2.0 mg/l and the median value of 320.9 ng/ml, respectively. 2) The ability of fenofibrate to lower hsCRP was comparable with simvastatin and combination therapy. 3) Reductions of hsCRP were not correlated with any other lipid parameter or Lp-PLA_2 by any treatment. 4) Reduction of Lp-PLA_2 was significantly correlated with reductions in total cholesterol, LDL-C, and non–HDL-C by simvastatin. The extent of correlation to the reduction of LDL is similar

to that reported by Albert et al. (12) in the PRINCE (Effect of Statin Therapy on C-Reactive Protein Levels: The Pravastatin Inflammation/CRP Evaluation) study.

The important reported relationship between hyperlipidemia, chronic inflammation, and cardiovascular risk, as demonstrated by the strong association among concomitant reductions in lipids (LDL-C to <70 mg/dl) and inflammatory markers (hsCRP to <2 mg/l) and cardiovascular risk (13), deserves further investigation, as also does the potentially vascular specific inflammatory marker and direct vascular toxin Lp-PLA_2. Little is known regarding the effect of combination therapy on inflammatory biomarkers, including hsCRP, but particularly for Lp-PLA_2. Koh et al. (9) examined the effect of atorvastatin, fenofibrate, and the combination of atorvastatin and fenofibrate on hsCRP in patients with hyperlipidemia. Our study, as well as the study by Koh et al. (9), found all therapies reduced hsCRP levels from baseline; however, the magnitude of the reduction was similar among all therapies. Our study is the first to report reductions of Lp-PLA_2 by combination therapy. As with hsCRP, all treatments significantly reduced Lp-PLA_2 concentrations from baseline to 12 weeks, with reductions being similar among treatments. Why there was no greater effect on these inflammatory markers from combination compared with either monotherapy is not known. Although statins and fibrates have different mechanisms of action in relationship to lipid metabolism, it is possible that they both exert a similar non–dose-responsive effect on inflammation. Therefore, the combination therapy would have no greater effect than either monotherapy.

CONCLUSIONS

Among type II diabetic patients with mixed dyslipidemia, fenofibrate, simvastatin, and combination therapy, the use of each lowered hsCRP and Lp-PLA_2. Of interest, combination therapy was no more effective than either form of monotherapy. These anti-inflammatory effects were most pronounced among patients with elevated baseline inflammation levels. Likewise, combination therapy significantly altered lipid concentrations, with combination therapy exerting a greater positive combined effect on total cholesterol, triglycerides, and non–HDL-C than either monotherapy.

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