

Early effects of lipid lowering treatment in subjects with metabolic syndrome and acute coronary syndromes

Carlos M.C. Monteiro, Luciene Oliveira, Maria C.O. Izar, Andreza O. Santos, Rui M.S. Póvoa, Simone M. Fischer, Sahna W. Barros, Antonio C.C. Carvalho, Francisco A.H. Fonseca

Abstract

Background: Patients with metabolic syndrome are at high-risk for cardiovascular events. This study compared early effects of usual lipid-lowering treatment on several metabolic parameters after an acute coronary syndrome. **Methods and results:** Patients (n=116) of both sexes with acute coronary syndrome and LDL-C <130 mg/dL on hospital admission with metabolic syndrome criteria (NCEP/ATP III) were randomly assigned to double blind 6-wk therapy with atorvastatin 10 mg/day, fenofibrate 200 mg/day, atorvastatin 10 mg/day plus fenofibrate 200 mg/day or placebo, in addition to nutritional counseling based on the therapeutic lifestyle changes. The active drug treatment promoted significant changes in lipid profile, however optimal targets for LDL-C, HDL-C, triglycerides, non-HDL-C and ApoB/ApoA1 ratio were achieved only in nearly half of these subjects. At the end of the study, we found lower serum levels of high-sensitivity C-reactive protein, fibrinogen, von Willebrand factor, D-Dimer, and thiobarbituric acid-reactive species, regardless of treatments. **Conclusions:** In these high-risk patients, partial improvement in several non-lipid risk factors was found to be part of the healing process after acute coronary syndromes, and a more aggressive lipid approach seems necessary for additional benefits and achievement of current lipid goals.

Key words: Metabolic syndrome; Acute coronary syndrome; Hemostasis, C-reactive protein; Lipids

Introduction

Metabolic syndrome (MetS) rate is rising worldwide and has been associated with high risk for cardiovascular morbidity and mortality^{1,2}. In addition, MetS was reported as a strong predictor of 30-day and 1-year mortality among patients with non-clinically diagnosed diabetes with recent myocardial infarction³. Therefore, therapeutic strategies aimed at stabilizing coronary heart disease in patients with MetS should be identified to improve outcomes.

Limited information is available regarding the impact of lipid-lowering treatment in patients with MetS after recent myocardial infarction or unstable angina, usually pre-

senting high triglycerides and low HDL-C serum levels. Changes in lifestyle have been proposed for the treatment of these patients due to their potential benefit of several parameters such as oxidative stress, insulin resistance, dyslipidemia and hemostasis disturbances^{4,5}. However, the early changes induced by lifestyle are less reported among these individuals, as well as the additional improvement, by pharmacologic treatment, in the healing process that occurs naturally after the acute insult. The best lipid-lowering regimen for these subjects has not yet been established, since residual cardiovascular morbidity and mortality risk persists, despite effective LDL-C lowering by statins. On

Department of Medicine, Cardiology Division, the Federal University of Sao Paulo, UNIFESP

Correspondence: Francisco Antonio Helfenstein Fonseca, Lipids, Atherosclerosis and Vascular Biology Section, Cardiology Division, Federal University of São Paulo, Rua Pedro de Toledo 276, 04039-030 São Paulo, SP, Brazil, Phone: 55-11- 50848777, Fax: 55-11- 55750052, e-mail: fahfonseca@terra.com.br

Received: 07.30.2008 Revision accepted: 10.28.2008

the other hand, lipid changes provided by fibrates appear insufficient to obtain desired results^{6,7}. Based on these aspects, combined lipid-lowering agents have been proposed for the management of the typical dyslipidemia in these patients⁸.

Therefore, our study aimed to evaluate the early effects of three usual lipid-lowering strategies over placebo on metabolic disturbances commonly present in these patients.

Material and methods

This randomized, double-blind, placebo-controlled study was conducted at the Federal University of Sao Paulo. Informed consent was obtained from all patients, and this study was approved by the local ethics committee.

Patients

Subjects aged 30 to 75 years, of both sexes (n=116) were prospectively included if they shared the following criteria: recent documented acute coronary syndrome (acute myocardial infarction or unstable angina pectoris requiring hospitalization), MetS according to the National Cholesterol Education Program / Adult Treatment Panel (NCEP /ATP III)⁹, LDL-C levels <130 mg/dL (obtained in the first 24h from hospital admission), and stable he-

modynamic conditions in the first 1–3 days after hospital discharge. Patients were excluded if they had a prior diagnosis of diabetes mellitus, heart failure class III or IV (New York Heart Association), any form of coronary revascularization (CABG or percutaneous intervention) planned for the next six weeks, or were in use of hypolipidemic drugs in the last 30 days. The major characteristics of the study population are shown in Table 1.

Drugs and randomization

Subjects started study medication 1–3 days after hospital discharge. They were randomized to receive for a 6-wk period atorvastatin (10 mg/day, Lipitor[®], Pfizer Inc) plus fenofibrate placebo, micronized fenofibrate (200 mg/day, Lipidil[®], Farmalab Chiesi) plus atorvastatin placebo, combined treatment (atorvastatin 10 mg/day plus fenofibrate 200 mg/day) or double-placebo. For all patients, the dietitian provided specific counseling based on the Therapeutic Lifestyle Changes (TLC) recommended by NCEP/ATP III⁹. Drug compliance was higher than 80% for all patients.

Measurements

Anthropometric measurements for BMI and waist circumference were recorded. Seated blood pressure in the right upper arm was determined by an average of three

Table 1. Baseline characteristics of study population.

Variable	Placebo n=30	Atorvastatin n=30	Atorvastatin + fenofibrate n=30	Fenofibrate n=26	p
Age, years	56 (2)	55 (1)	57 (1)	55 (2)	0.68
Male/female	21/9	17/13	21/9	16/10	0.65
UA/AMI	16/14	20/10	15/15	11/15	0.31
Thrombolysis, y/n	2/28	2/28	3/27	2/24	0.87
PI, y/n	12/18	7/23	15/15	12/14	0.32
Waist circumf, cm	104 (2)	105 (2)	106 (2)	100 (2)	0.22
BMI, kg/m ²	30 (1)	31 (1)	30 (1)	29 (1)	0.30
Total cholesterol	191 (7)	191 (7)	189 (7)	194 (8)	0.97
LDL-C	116 (5)	115 (7)	118 (7)	116 (7)	0.99
HDL-C	39 (2)	41 (2)	40 (2)	39 (2)	0.64
Triglycerides	179 (15)	183 (16)	158 (7)	190 (16)	0.45
Glucose, mg/dL	132 (10)	121 (8)	123 (7)	125 (9)	0.84
SBP, mm Hg	124 (5)	135 (6)	135 (4)	133 (4)	0.23
DBP, mm Hg	80 (4)	91 (3)	86 (3)	87 (3)	0.07
ACEI	63%	87%	80%	77%	0.18
Beta-blockers	83%	77%	90%	88%	0.49
Aspirin	83%	90%	93%	88%	0.67
Clopidogrel	30%	13%	40%	46%	0.04

Results shown as mean (SEM) or n; lipids are mg/dL; UA=unstable angina; AMI=acute myocardial infarction; y/n=yes/no; PI=in-hospital percutaneous intervention; BMI=body mass index; ACEI=angiotensin-converting enzyme inhibitors. Data are compared by ANOVA.

measurements after 5 min rest. Fasting blood samples were obtained before and six weeks after lipid-lowering treatment for measurement of cholesterol and triglycerides using an automated enzymatic kit (LDL-C was estimated by the Friedewald formula)¹⁰. Apolipoprotein B (apo B), apolipoprotein A1 (apo A1), Lp (a), and high-sensitivity C-reactive protein (hsCRP) were measured by nephelometry. Thiobarbituric acid-reactive species (TBARS) was estimated by spectrophotometry. Fibrinogen, D-Dimer, and factor VII by automated methods. Von Willebrand factor (vWf), and plasminogen-activator inhibitor-1 (PAI-1) were determined by enzyme-linked immunosorbent assay (ELISA). Oral glucose tolerance test (OGTT, 75 g glucose in 200 mL water) was performed 1-3 days after hospital discharge and after 6-wk of lipid lowering treatment. The homeostasis model assessment of insulin resistance (HOMA-IR) was calculated as $\text{insulin (mU/L)} \times (\text{glucose (mg/dL)} \times 0.055) / 22.5^{12}$. For this calculation we used the mean of three consecutive samples of fasting insulin. The insulinogenic index was calculated as the difference between the 30 min and 0 min OGTT plasma insulin values divided by the difference between the corresponding plasma glucose values ($\Delta I_{30} / \Delta G_{30}$). The area under the curve (AUC) for glucose and insulin were determined based on the blood samples obtained before ($t=0$) and 30, 60, 90, and 120 min after oral glucose load. Adiponectin was measured by enzyme-linked immunosorbent assay (ELISA) using a commercial kit (Humam Adiponectin/Acrp30 Immunoassay – Quantiquine, R&D Systems). Glycated hemoglobin (HbA1c) was measured using high performance liquid chromatography.

Statistical analysis

The primary assessment included changes in parameters of lipids, oxidative stress, hemostasis, and inflammation from baseline and between the 4 treatment strategies using the General Linear Model (GLM) for repeated measures. When necessary, variables were log transformed. At baseline, continuous variables were compared by ANOVA. Categorical variables were compared using chi-square tests. All tests were 2-tailed, and a p value <0.05 defined statistical significance. All analyses were performed with SPSS 11.5 for Windows.

Results

Study population

Baseline characteristics of all treatment groups are shown in Table 1. Major clinical data and in-hospital procedures were similar in the four groups, including anthropo-

metric data, systolic and diastolic blood pressure, as well as biochemical variables, and extension of coronary disease. One patient died after hemorrhagic stroke in the beginning of the study and was excluded from the statistical analysis.

Lipids

Table 2 shows major changes in lipid serum levels 6 weeks after treatment. Total cholesterol was reduced by atorvastatin (191 ± 8 vs 143 ± 6 mg/dL, $p < 0.001$), fenofibrate (195 ± 8 vs 168 ± 8 mg/dL, $p < 0.001$), and by combined lipid-lowering treatment (190 ± 7 vs 145 ± 5 mg/dL, $p < 0.001$), whereas it was not changed by placebo (191 ± 7 vs 196 ± 8 mg/dL, ns). LDL-C was decreased by atorvastatin (115 ± 7 vs 72 ± 6 , $p < 0.001$), atorvastatin plus fenofibrate (118 ± 7 vs 79 ± 4 mg/dL, $p < 0.001$), and fenofibrate (116 ± 8 vs 97 ± 8 , $p < 0.004$). HDL-C was increased by fenofibrate alone ($p < 0.001$) and combined with atorvastatin ($p < 0.001$); while triglycerides were reduced by atorvastatin ($p < 0.001$), fenofibrate ($p < 0.001$) and fenofibrate plus atorvastatin ($p < 0.001$). Non HDL-C was reduced by atorvastatin ($p < 0.001$), fenofibrate ($p < 0.001$) and by atorvastatin plus fenofibrate ($p < 0.001$). Apo B was reduced by atorvastatin ($p < 0.001$), fenofibrate ($p < 0.001$), and by atorvastatin plus fenofibrate ($p < 0.001$), whereas ApoB/ApoA1 ratio was reduced by all lipid-lowering treatments ($p < 0.001$ vs baseline). Lp (a) levels decreased after six weeks ($p = 0.003$ vs baseline) without differences between treatments. Percentages of patients achieving lipid goals are shown in Table 3.

Hemostasis

Fibrinogen and D-Dimer plasma levels decreased after 6 weeks ($p < 0.001$ vs baseline), but these changes were not influenced by the treatment. Plasma levels of vWf also decreased ($p = 0.013$ vs baseline) without differences between treatments. PAI-1 and factor VII concentrations were neither influenced by time nor by treatment (Table 2).

High sensitivity C-reactive protein (hsCRP) and leukocyte count

As shown in Table 2, an impressive decrease in plasma hsCRP was observed after 6-wk treatment ($p < 0.001$ vs baseline), without differences between regimens. In addition, leukocyte count significantly diminished after treatments ($p < 0.001$ vs baseline) but this decrease did not differ among lipid-lowering strategies.

Thiobarbituric acid reactive species (TBARS)

After 6-wk treatment, there was a significant reduction in plasma TBARS ($p < 0.001$ vs baseline), but this change was not affected by the lipid-lowering regimen (Table 2).

Table 2. Changes in lipid and non-lipid variables according to the hypolipidemic treatment after six weeks.

	Placebo N=30			Atorvastatin N=30			Atorvastatin + fenofibrate N=30			Fenofibrate N=26		
	Baseline	6-wk	Δ%	Baseline	6-wk	Δ%	Baseline	6-wk	Δ%	Baseline	6-wk	Δ%
Cholesterol**	191 (7)	196 (8)	3	191 (8)	142 (6)	-26	189 (7)	145 (5)	-23	194 (9)	167 (8)	-4
Non HDL-C†	152 (7)	156 (8)	3	150 (7)	100 (6)	-50	150 (7)	100 (5)	-50	155 (8)	119 (8)	-23
LDL-C*‡	116 (6)	122 (7)	5	115 (7)	72 (5)	-37	118 (7)	79 (4)	-33	116 (8)	97 (8)	-17
Apo A1	105 (4)	113 (4)	8	110 (5)	120 (4)	9	107 (3)	125 (5)	17	107 (3)	125 (4)	17
Apo B*§	117 (5)	120 (7)	3	112 (6)	79 (5)	-30	115 (4)	79 (4)	-31	114 (6)	91 (5)	-20
ApoB/ApoA*‡	1.2 (0.1)	1.1 (0.1)	-8	1.1 (0.1)	0.7 (0.1)	-36	1.1 (0.1)	0.7 (0.1)	-36	1.1 (0.1)	0.7 (0.1)	-36
Lp (a)	52 (8)	41 (7)	-21	43 (9)	34 (7)	-21	36 (8)	36 (8)	0	62 (11)	55 (10)	-11
Glucose	221 (23)	186 (16)	-16	229 (19)	212 (16)	-8	235 (21)	230 (21)	-2	220 (23)	201 (21)	-9
HbA1c	6.5 (0.4)	6.3 (0.3)	0	6.4 (0.3)	6.1 (0.3)	0	6.6 (0.4)	6.5 (0.3)	0	6.6 (0.4)	6.5 (0.4)	0
Insulin	13 (1)	13 (2)	0	17 (1)	18 (2)	6	17 (3)	16 (3)	-6	13 (2)	11 (1)	-15
HOMA-IR	5 (1)	4 (1)	-20	5 (1)	5 (1)	0	6 (1)	5 (1)	-17	4 (1)	4 (1)	0
ΔI ₃₀ /ΔG ₃₀	117 (20)	125 (21)	7	110 (18)	93 (14)	-16	106 (22)	63 (8)	-40	105 (20)	130 (27)	24
Glucose _{AUC}	1400 (105)	1240 (82)	-11	1450 (88)	1380 (85)	-5	1460 (102)	1470 (103)	0.7	1400 (103)	1330 (117)	-15
Insulin _{AUC}	9843 (1428)	9156 (1118)	-10	13231 (1602)	12090 (1540)	-8	10429 (1085)	9162 (793)	-18	10121 (1526)	10726 (1694)	10
Adiponectin	6.4 (1.1)	5.4 (0.7)	-14	7.0 (0.8)	5.8 (0.7)	-14	5.4 (0.6)	6.2 (0.8)	0	6.6 (1.0)	5.9 (0.7)	-14
hs-CRP	14.2 (2.3)	4.4 (0.5)	-14	17.0 (3.5)	4.9 (0.7)	-70	18.4 (4.5)	8.6 (2.8)	-55	14.0 (2.8)	6.7 (7.0)	-23
TBARS	1.7 (0.1)	1.5 (0.2)	-12	1.7 (0.2)	1.3 (0.1)	-23	1.7 (0.1)	1.3 (0.1)	-23	1.7 (0.2)	1.4 (0.1)	-18
Fibrinogen	400 (23)	350 (20)	-13	408 (30)	350 (25)	-14	427 (22)	375 (28)	-12	425 (25)	300 (16)	-30
Factor VII	119 (12)	117 (10)	-1.7	122 (10)	117 (11)	-4	105 (8)	100 (5)	-5	130 (17)	104 (6)	-20
D-Dimer	1120 (240)	450 (65)	-60	970 (160)	480 (70)	-50	1060 (170)	480 (77)	-55	990 (160)	450 (60)	-55
vWf	100.6 (5.5)	96.4 (5.7)	-3	99.2 (7.0)	91.4 (6.6)	-8	89.0 (6.3)	81.2 (6.4)	-9	101.5 (5.8)	94 (0.6)	-7
PAI-I	32 (4)	36 (5)	13	40 (5)	33 (4)	-18	35 (4)	33 (4)	-6	35 (4)	30 (3)	-14
FMD	13 (2)	11 (1)	-15	14 (2)	15 (1)	7	13 (2)	13 (1)	0	15 (2)	12 (2)	-20

Results are mean (SEM) baseline and after 6 weeks; Δ%=percentage changes; FMD=flow-mediated dilatation; Lp (a)=apolipoprotein (a); ΔI₃₀/ΔG₃₀=insulinogenic index; Units: total cholesterol, lipoproteins, glucose and fibrinogen (mg/dL), HbA1C, factor VII, vWf, and FMD (%), insulin (μU/mL), HOMA-IR (μUmmol/L), ΔI₃₀/ΔG₃₀ (pmol/mmol), glucose 120=OGTT (oral glucose tolerance test) at 120 min.; glucose AUC=area under curve (mmol L min), insulin AUC=area under curve (μU mL min), adiponectin (μg/mL), hs-CRP (mg/L), TBARS (nmol/L), D-Dimer and PAI-1 activity (ng/mL); total cholesterol: atorvastatin and atorvastatin+fenofibrate < placebo (p=0.0001), †fenofibrate < placebo (p=0.007); non HDL-C: †atorvastatin, atorvastatin+fenofibrate and fenofibrate < placebo (p=0.0001); LDL-C: †atorvastatin and atorvastatin+fenofibrate < placebo (p=0.0001), †fenofibrate < placebo (p=0.004); apo B: †atorvastatin and atorvastatin+fenofibrate < placebo (p=0.0001), †fenofibrate < placebo (p=0.004); apoB/apoA ratio: †atorvastatin and atorvastatin+fenofibrate < placebo (p=0.0001), †fenofibrate < placebo (p=0.001). Comparisons were made by ANOVA.

Glucometabolic parameters

As shown in Table 2, fasting glucose, fasting insulin, glycated hemoglobin (HbA1C), adiponectin, HOMA-IR, insulinogenic index (ΔI₃₀/ΔG₃₀), glucoseAUC, and insulinAUC did not differ significantly after 6-wk, regardless of treatment.

Metabolic syndrome parameters

Changes in the MetS parameters after treatment are reported in Table 4.

As could be expected, waist circumference did not change after treatment, however we found lower diastolic blood pressure in the atorvastatin group as compared to the placebo group (p=0.039), and higher HDL-C levels were observed for the fenofibrate group (p=0.005

vs atorvastatin; p=0.008 vs placebo). Triglycerides were reduced by atorvastatin (p<0.048 vs placebo), and by atorvastatin+fenofibrate (p=0.001 vs placebo), and by fenofibrate alone (p=0.001 vs placebo). Glucose levels remained unchanged after 6-wk, regardless of treatment.

Discussion

This study aimed at comparing the role of standard lipid-lowering strategies in several metabolic abnormalities commonly present in patients with MetS after an acute coronary syndrome.

In spite of relatively low LDL-C levels (115–118 mg/dL) at baseline, and the expected decrease in lipids after ACS, a large number of patients treated with atorvastatin

Table 3. Percentages of patients achieving optimal lipid goals after treatment.

Treatment	LDL-C <70	HDL-C ≥40	TG <150	Non-HDL-C <100	ApoB/ApoA1 <0.7
Placebo	0%	43%	47%	3%	10%
Atorvastatin	50%	67%	63%	50%	50%
Atorvastatin + fenofibrate	33%	63%	90%	53%	57%
Fenofibrate	27%	73%	85%	35%	46%

Lipid values (mg/dL) achieved after 6 weeks of treatment.

Table 4. Changes in the metabolic syndrome parameters according to the treatment after six weeks.

	Placebo N=30			Atorvastatin N=30			Atorvastatin + fenofibrate N=30			Fenofibrate N=26		
	Baseline	6-wk	Δ%	Baseline	6-wk	Δ%	Baseline	6-wk	Δ%	Baseline	6-wk	Δ%
Waist, cm	104 (2)	102 (1)	-2	105 (2)	104 (1)	-1	106 (2)	105 (1)	-1	100 (2)	99 (2)	-1
SBP, mm Hg	124 (5)	135 (5)	9	135 (5)	137 (5)	2	135 (4)	135 (5)	0	133 (4)	139 (5)	5
DBP*, mm Hg	80 (4)	88 (3)	10	91 (3)	89 (3)	-2	86 (3)	88 (3)	2	87 (3)	88 (3)	1
Glucose, mg/dL	132 (10)	122 (11)	-7	122 (8)	117 (7)	-4	123 (7)	120 (9)	-2	125 (9)	120 (11)	-4
TG*†, mg/dL	179 (16)	174 (13)	-3	183 (17)	141 (12)	-23	159 (7)	102 (7)	-35	191 (16)	108 (9)	-43
HDL-C†† mg/dL	39 (2)	40 (2)	3	42 (2)	43 (2)	2	40 (2)	45 (2)	13	39 (2)	48 (2)	23

Results are mean (SEM) at baseline and after 6 weeks; Δ%=percentage change. SBP=systolic blood pressure; DBP=diastolic blood pressure; TG=triglycerides. *DBP atorvastatin < placebo (p=0.039); TG: †atorvastatin < placebo (p=0.048); †atorvastatin+fenofibrate, and fenofibrate < placebo (p=0.001); HDL-C: †fenofibrate > atorvastatin (p=0.005), †fenofibrate > placebo (p=0.008). Results were compared by ANOVA.

alone or combined with fenofibrate did not achieve the primary objective by current guidelines (LDL-C <70 mg/dL) (Table 3).

Other common lipid alterations in patients with MetS are low levels of HDL-C, high levels of triglycerides, and increased apoB/apoA1 ratio, abnormalities linked to high coronary risk^{11,12}. As these abnormalities are less effectively modified by statins, the use of fibrates has been proposed, mainly in combination with statins^{13,14}. In fact, a recent review of post hoc analyses of several fibrate trials has shown that subjects with features of MetS, particularly those overweight with high plasma triglyceride levels and low levels of HDL-C had a large reduction in their cardiovascular risk¹⁵. In our study, treatment with either atorvastatin or fenofibrate, alone or combined, markedly reduced apoB/apo A1 ratio. The optimal level of apoB/apoA1 ratio is not established, however recently a level <0.7 for this ratio in subjects at low coronary risk was suggested¹⁶. Considering this level a target for apoB/apoA1 ratio, we observed that only half of our patients using lipid-lowering drug treatment achieved this target (Table 3).

Patients with the MetS in secondary prevention should obtain a target LDL-C <70 mg/dL¹⁷. In our study, only 50% of patients receiving atorvastatin 10 mg achieved this LDL-C goal, and other strategies were less effective (Table 3). Furthermore, we observed a significant increase

in serum HDL-C levels only among those patients receiving fenofibrate alone or combined with atorvastatin.

As expected, beyond dyslipidemia, we found several metabolic alterations at baseline: high levels of hsCRP and TBARS and hemostasis disturbances. Some of these parameters decreased after six weeks, as part of the healing process after an acute coronary insult regardless of the lipid-lowering strategy. However, hsCRP remained high. Previous studies have shown that persistent elevation of hsCRP plasma levels in patients with acute coronary syndromes are associated with recurrent coronary events^{18,19}. In the Pravastatin or Atorvastatin Evaluation and Infection Therapy - Thrombolysis In Myocardial Infarction 22 (PROVE IT-TIMI 22) trial²⁰, a more efficient decrease in hsCRP was seen after 4-wk treatment with atorvastatin 80 mg/day in comparison with pravastatin 40 mg/day, suggesting the need for more intensive treatment to obtain better results. Fibrates have also some benefits beyond lipid changes, including reduction in markers of inflammation and oxidative stress^{20,21}.

Early improvement in the risk of thrombosis is also desirable for clinical stabilization of these patients. A recent study showed that atorvastatin 40 mg/day, simvastatin 40 mg/day, fenofibrate 160 mg/day, and quinapril 10 mg/day were all able to increase clot permeability and susceptibility to fibrinolysis in coronary heart disease (CHD) patients

receiving aspirin, after approximately one month of treatment²². We observed marked alterations in parameters of hemostasis at baseline, and significant improvement in the majority of these markers, but with little influence by the hypolipidemic strategy (Table 2). Early changes in parameters of hemostasis appear important since fibrinogen and vWf were both identified as predictors of CHD among persons with diabetes in the Atherosclerosis Risk in Communities (ARIC) study²³. Despite initial negative results with gemfibrozil, early benefits to hemostasis were reported after the use of micronized fibrates²⁴.

Finally, abnormal fasting glycemia and undiagnosed diabetes mellitus were observed in a large number of our patients. Altered carbohydrate metabolism is associated not only with lipid alterations, but also with increased oxidative stress, inflammation, and thrombotic risk. A recent US survey showed that individuals with diabetes and cardiovascular disease (CVD) are at the highest risk. Even those with 1 or 2 MetS risk factors are at a 2-fold-greater risk of CHD and CVD mortality, suggesting that risk is not optimal unless all MetS risk factors are absent²⁵. In our study several glucometabolic abnormalities, including an expressive number of subjects with impaired glucose tolerance or diabetes mellitus were identified in the early phase of acute coronary syndromes, but these abnormalities were not modified by the hypolipidemic treatment. In addition, relatively few changes in the MetS components were observed, suggesting the need of a more extensive strategy in order to reduce the attributable cardiovascular risk linked to this syndrome.

Limitations

When the study was proposed, it was based on the NCEP/ATP III guidelines⁹ that allowed TLC counselling without the need of lipid lowering agents, for those patients with coronary disease with LDL-C <130 mg/dL. These guidelines have changed substantially in the last years, based on recent trials showing early benefits by the use of more aggressive lipid lowering strategy for these patients, and now an LDL-C <70 mg/dL is suggested for secondary prevention with or without MetS^{16,26,27}.

In conclusion, for subjects with MetS on secondary prevention, common hypolipidemic therapy is clearly insufficient to achieve current lipid goals. In addition, our study showed that significant improvement in inflammatory and hemostatic markers can be observed over six weeks following hypolipidemic treatment and lifestyle counseling. However, more aggressive therapeutic strategies seem to be required to improve short- and long-term outcomes related to lipid and non-lipid parameters in this high-risk population and the potential benefits tested in larger clinical trials.

Acknowledgments: This study was supported by FAPESP (The State of São Paulo Research Foundation, grant # 04/00325-8). Dr. Monteiro is also a recipient of a research fellowship from CNPq (National Counsel of Technological and Scientific Development). Atorvastatin and fenofibrate were a gift from Pfizer Brazil and Farnalab-Chiesi Brazil, respectively.

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