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Targeting vascular risk in patients with metabolic syndrome but without diabetes

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Abstract

There are no prospective data on the effect of a multitargeted treatment approach on cardiovascular disease (CVD) risk reduction in nondiabetic patients with metabolic syndrome (MetS). Furthermore, the optimal hypolipidemic drug treatment in these patients remains controversial. In this prospective, randomized, open-label, intention-to-treat, and parallel study, 300 nondiabetic patients with MetS, free of CVD at baseline, were studied for a period of 12 months. Age- and sex-matched subjects without MetS (n = 100) acted as controls. All patients received lifestyle advice and a stepwise-implemented drug treatment of hypertension, impaired fasting glucose, and obesity. For hypolipidemic treatment, the patients were randomly allocated to 3 treatment groups: atorvastatin (n = 100, 20 mg/d), micronized fenofibrate (n = 100, 200 mg/d), and both drugs (n = 100). Clinical and laboratory parameters, including the lipid profile and C-reactive protein (CRP), were assessed at the baseline and at the end of the study. The primary end point was the proportion of patients not having MetS or its component features at the end of the 12-month treatment period. The secondary end points were the difference in 10-year CVD risk (Prospective Cardiovascular Munster risk calculator) and the degree of CRP reduction. By the end of the study, 76% of the patients no longer had MetS, and 46% had only one diagnostic MetS factor. The estimated 10-year (Prospective Cardiovascular Munster) risk of all patients with MetS at baseline was 14.6%. This was reduced in the atorvastatin group to 6.4%, in the fenofibrate group to 9.2%, and in the combination group to 5.5% ($P < .0001$ for all vs baseline). The 10-year risks of the atorvastatin and combination groups were not different from that of the control group (5.0%). C-reactive protein was significantly reduced in all treatment groups, with the atorvastatin and combination groups having the greatest reduction (65% and 68%, respectively, $P < .01$ vs the fenofibrate group, 44%). Lipid values were significantly improved in all 3 treatment groups, with those on the combined treatment attaining lipid targets to a greater extent than those in the other 2 groups. A target-driven and intensified intervention aimed at multiple risk factors in nondiabetic patients with MetS substantially offsets its component factors and significantly reduces the estimated CVD risk. The atorvastatin-fenofibrate combination had the most beneficial effect on all lipid parameters and significantly improved their CVD risk status. Atorvastatin and combination treatment were more effective than fenofibrate alone in reducing CRP levels.

1. Introduction

The clustering of risk factors called the metabolic syndrome (MetS) confers an increased risk of cardiovascular disease (CVD)–related morbidity and mortality [1,2] and all-cause mortality [2], even in the absence of clinically

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evident CVD and/or diabetes mellitus (DM) [2,3]. The National Cholesterol Education Program (NCEP) Adult Treatment Panel III (ATP III) provided an easy to use definition of the MetS [4]. However, the NCEP ATP III does not specify whether subjects with the MetS should receive more intense therapy for underlying conditions (ie, hypertension or dyslipidemia) other than that called for by their estimated risk on the basis of the Framingham Study.

The placebo data from the Scandinavian Simvastatin Survival Study (4S) and the Air Force/Texas Coronary Atherosclerosis Prevention Study [5] showed that in nondiabetic subjects, the long-term relative risk of major coronary events associated with MetS was higher than for those without MetS. This increased risk was irrespective of the calculated Framingham 10-year risk score [5]. Likewise, the 14-year follow-up of the San Antonio Heart Study [6] showed that nondiabetic subjects with MetS had about a 2-fold increase in risk for CVD (adjusted for age, sex, and ethnicity) compared with those without MetS.

Type 2 DM and MetS are diseases of considerable heterogeneity [7]. The Steno 2 Trial showed a significant clinical benefit from multifactorial treatment of type 2 DM [8]. Probably, the same is valid for the MetS, given that 85% of patients with DM have the MetS [9], although up to two thirds of those with MetS do not have DM [10,11]. However, no clinical trial addressed this issue.

There has also been a controversy about the appropriate hypolipidemic drug treatment in subjects with the MetS. Fibrates are effective in normalizing lipid levels (mainly, triglycerides [TG] and high-density lipoprotein cholesterol [HDL-C]) in patients with MetS and may improve insulin resistance [12]. In favor of statin therapy (mainly reducing low-density lipoprotein cholesterol [LDL-C]) is the fact that simvastatin was more effective in the 4S subjects with the lipid triad (high LDL-C, high TG and low HDL-C) than in the subjects with isolated elevated LDL-C levels [13].

The present prospective, open-label, randomized, intention-to-treat study addressed 2 issues. Firstly, can multitargeted treatment in nondiabetic subjects with MetS, free of CVD at baseline, substantially decrease prevalent MetS, thus, reducing CVD risk? Secondly, which is the most appropriate treatment of the lipid abnormalities associated with the MetS (ie, statins, fibrates, or their combination)?

2. Study design and methods

Three hundred consecutive subjects with MetS free of DM and CVD were included. We selected this population with MetS (according to the NCEP ATP III definition) because subjects with DM and CVD have already been well studied and are considered as high-risk patients [4]. Thus, the degree of CVD risk and the LDL-C goal for patients with DM have been clearly defined by the NCEP ATP III [4]. In contrast, the NCEP ATP III guidelines are vague in defining the CVD risk status of subjects with MetS but no DM (ie, nearly two thirds of subjects with MetS [10,11]). Subjects with impaired renal function (serum creatinine [SCr] >115 mmol/L, 1.5 mg/dL), serum TG levels more than 500 mg/dL (5.6 mmol/L), with high transaminases or creatinine kinase (3-fold and 5-fold the upper normal limit, respectively), were excluded. Subjects without the MetS (n = 100), matched for age and sex with the patients, acted as controls. The study received ethical approval, and informed consent was obtained from all subjects before enrollment.

2.1. Definition of the MetS

Participants having 3 or more of the following criteria (according to the NCEP ATP III report [4]) were defined as having the MetS:

1. Abdominal obesity: waist circumference larger than 102 cm in men and larger than 88 cm in women,
2. Hypertriglyceridemia: TG 1.7 mmol/L (150 mg/dL) or more,
3. Low HDL-C: less than 1.0 mmol/L (40 mg/dL) in men and less than 1.3 mmol/L (50 mg/dL) in women,
4. High blood pressure: 130/85 mm Hg or more, or use of antihypertensive medication,
5. High fasting plasma venous glucose: 6.1 mmol/L (110 mg/dL) or more, or treatment of DM.

2.2. Definition of DM

The 1997 American Diabetes Association criteria [14] were used to define DM. We considered a subject to have DM when the fasting plasma venous glucose was 7 mmol/L (126 mg/dL) or more in 2 consecutive assessments, or if they were on treatment of DM.

2.3. Definition of CVD

This included coronary heart disease (CHD), stroke, and/or peripheral arterial disease. Diagnosis was based on personal history and clinical as well as other diagnostic noninvasive criteria.

2.4. Study population—Study protocol

Consecutive patients (n = 300) with MetS without overt DM or CVD at baseline were recruited. All patients were treated by targeting the MetS diagnostic criteria. One hundred age- and sex-matched subjects without MetS, randomly selected from the general population, acted as controls. Controls were used to establish the calculated CVD risk in subjects without MetS living under the same social, economic, and environmental milieu.

2.4.1. Lifestyle advice

All subjects received lifestyle advice. This included exercise (walking for at least 30 minutes 5 days a week or equivalent exercise) and low-fat (NCEP ATP III) hypocaloric diet. After estimating the appropriate energy intake for a specific subject (according to his/her job and leisure time activity), we provided him/her (according to the

suggestions of a dietician) with a computer-generated diet (taking into consideration his/hers dietary preferences) with a daily energy intake of 2092 J less than that estimated as appropriate. The compliance to the diet was established at every visit with a 3-day food intake questionnaire.

2.4.2. Treatment of arterial hypertension

Arterial hypertension was treated in a stepwise manner with angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARB). If these were not enough to reach the 130/85 mm Hg target, a low dose (12.5 mg/d) of hydrochlorothiazide was added (in a fixed combination with ACE inhibitor or ARB). If another antihypertensive was required, a calcium channel blocker was added. Finally, any other antihypertensive agent was added to reach treatment targets, but the intention was to avoid any metabolic side effects of antihypertensive drug treatment.

2.4.3. Treatment of obesity

In patients with obesity (>30 kg/m^2), orlistat (360 mg/d) was prescribed.

2.4.4. Treatment of impaired fasting glucose

Impaired fasting glucose (IFG) was treated with metformin. The starting dose was 850 mg/d, and this was increased to 1700 mg/d if fasting glucose levels remained more than 6.1 mmol/L (110 mg/dL).

2.4.5. Treatment of dyslipidemia

Subjects were randomly allocated to 3 treatment groups (each, n = 100). The first received atorvastatin 20 mg/d, the second micronized fenofibrate 200 mg/d, and the third both drugs.

2.5. End points

The primary end point of the study was the proportion of patients not having MetS or component criteria by the end of the 12-month treatment period. The secondary end points were the difference in the 10-year CVD risk (Prospective Cardiovascular Munster [PROCAM] risk calculator [15]) of patients with MetS and the degree of CRP level reduction.

2.6. Framingham and PROCAM 10-year CVD risk calculator estimates

The PROCAM Trial risk calculator is appropriate to estimate the risk in MetS subjects, free of CHD at baseline [15]. It calculates risk taking into consideration, age, LDL-C, HDL-C, TG, smoking habit (including ex-smokers), fasting blood glucose, systolic blood pressure (SBP), antihypertensive treatment, and family history of premature CVD. The Framingham risk scoring does not consider IFG, ex-smoking, high TG, and family history of premature CVD as risk factors when calculating the 10-year risk. Moreover, when the 10-year probability is greater than 30%, the program does not provide an exact number. Thus, from the 5 components of the MetS, only HDL-C and arterial hypertension are considered if the Framingham risk scoring is used, probably providing falsely low results [5]. Neither risk engines considers abdominal obesity.

2.7. Laboratory-based assessments

After an overnight fast, total cholesterol (TC), HDL-C, TG, SCr, serum uric acid (SUA), aspartate amino transferase, alanine amino transferase, γ-glutamyl transpeptidase, and alkaline phosphatase were assessed, for all patients, using an Olympus AU 560 autoanalyzer and respective reagents (Olympus Diagnostica GmbH, Clare, Ireland). Low-density lipoprotein cholesterol was calculated by the Friedewald formula (LDL-C [mg/dL] = TC [mg/dL] − {TG [mg/dL]/5 + HDL-C [mg/dL]}). The non–HDL-C value was obtained by subtracting the HDL-C value from that of TC. Fasting blood glucose was measured with the GOD-PAP method using an Olympus AU 560 autoanalyzer and respective reagents (Medicon Hellas, Athens, Greece). Serum creatinine was measured using the Jaffe's method (normal range, 55-115 μmol/L, 0.6-1.5 mg/dL), and SUA with an enzymatic colorimetric test (uricase) (normal range, 150-415 μmol/L, 2.5-7.0 mg/dL). Serum creatinine levels were adjusted for age, sex, and body mass index (BMI). Plasma fibrinogen was assessed by the Clauss method, using the Fibrindex test (Ortho Diagnostic, Raritan, NJ). C-reactive protein measurements were performed using a high-sensitivity standardized enzyme-linked immunosorbent assay (Alpha Diagnostic International, San Antonio,

Table 1
Baseline demographic and clinical characteristics of the 3 treatment groups

	Atorvastatin, 20 mg/d (n = 100)	Fenofibrate, 200 mg/d (n = 100)	Combination treatment (n = 100)	Difference, *P*
Age (y)	59 ± 9	60 ± 10	59 ± 10	NS
Sex, male (%)	64	62	63	NS
BMI (kg/m^2)	30 ± 6	31 ± 5	31 ± 6	NS
Current smokers (%)	37	34	39	NS
Ex-smokers (%)	25	27	26	NS
Never smokers (%)	38	39	35	NS
IFG (%)	44	45	42	NS
AH (%)	82	84	83	NS
High TG (%)	66	64	67	NS
Low HDL-C (%)	55	56	55	NS
Central obesity (%)	89	88	89	NS
MetS (%)	100	100	100	NS

Age represented in years and BMI in kilograms per meter squared are expressed in mean values ± standard deviation. High TG >1.7 mmol/L (150 mg/dL); Low HDL-C <1.0 mmol/L (40 mg/dL) for men and <1.3 mmol/L (50 mg/dL) for women; central obesity, waist circumference >102 cm for men and >88 cm for women; MetS, ≥3 of IFG, AH, High TG, Low HDL-C, or central obesity.
AH indicates arterial hypertension (blood pressure ≥ 130/85 mm Hg).

Table 2
Measured laboratory and clinical parameters at baseline in the 3 treatment groups

	Atorvastatin, 20 mg/d (n = 100)	Fenofibrate, 200 mg/d (n = 100)	Combination treatment (n = 100)	Difference, *P*
TC (mmol/L)	6.0 ± 1.0	5.9 ± 0.9	6.0 ± 1.0	NS
LDL-C (mmol/L)	3.9 ± 1.0	3.8 ± 1.1	3.9 ± 1.0	NS
HDL-C (mmol/L)	1.0 ± 0.3	1.1 ± 0.3	1.0 ± 0.3	NS
Non–HDL-C (mmol/L)	5.0 ± 0.8	4.8 ± 0.7	4.9 ± 0.8	NS
TG (mmol/L)	2.2 ± 1.0	2.1 ± 1.1	2.2 ± 1.0	NS
Fasting glucose (mmol/L)	5.6 ± 0.9	5.7 ± 1.0	5.5 ± 0.8	NS
SCr (μmol/L)	92 ± 13	94 ± 12	93 ± 14	NS
SUA (μmol/L)	481 ± 68	492 ± 74	486 ± 75	NS
CRP (mg/L)	4.4 ± 0.7	4.3 ± 0.8	4.5 ± 0.8	NS
Fibrinogen (mg/dL)	403 ± 42	415 ± 51	410 ± 44	NS
SBP (mm Hg)	145 ± 9	143 ± 12	146 ± 11	NS
DBP (mm Hg)	89 ± 6	88 ± 5	90 ± 8	NS
Waist circumference (cm)	106 ± 12	107 ± 14	107 ± 15	NS
Body weight (kg)	94 ± 14	95 ± 13	94 ± 12	NS
MetS (%)	100	100	100	NS
10-y risk Framingham (%)	11.4	11.2	11.3	NS
10-y risk PROCAM (%)	14.6	14.4	14.8	NS

The 10-year risk for the Framingham and PROCAM [15] risk calculator was used.
To convert data from millimoles per liter to milligrams per deciliter, multiply total cholesterol, LDL-C, HDL-C, and non–HDL-C values by 38.7 and triglycerides by 88.6. To convert SCr and SUA values from micromoles per liter to milligrams per deciliter, divide by 76.29 and 59.48, respectively.

Tex; sensitivity, 0.35 ng/mL). Physical examination and assessment of lipid profile and fasting blood glucose were performed every 6 weeks, whereas plasma fibrinogen, SCr, SUA, and CRP were assessed at baseline and at the end of the study.

2.8. Safety

A clinical and laboratory (transaminases and creatinine kinase) assessment was performed every 6 weeks.

2.9. Statistical analyses

An intention-to-treat analysis of all patients randomized to the 3 treatment groups was performed. Clinical and laboratory findings within groups were compared by unpaired Student *t* tests for parametric data and by χ^2 tests for categorical data. Parametric data of the 3 groups were compared using analysis of variance, whereas nonparametric data were compared using the Kruskal-Wallis test. A 2-tailed *P* value less than .05 was considered significant. All analyses were carried out using the SPSS 11.01 software package (SPSS, Inc, Chicago, Ill).

3. Results

Characteristics of the study population are shown in Table 1 and lipid values in Table 2. There were no significant differences in smoking habits among the groups (Table 1).

3.1. Medications used in the study population

The medications used in the study population are listed in Table 3.

3.2. Measured laboratory and clinical parameters (Tables 2 and 4)

The lipid values of patients with MetS significantly improved in all 3 treatment groups (Table 4). The percentage of patients from each treatment group with LDL-C or

Table 3
All medications used in the study population

	Atorvastatin, 20 mg/d (n = 100)	Fenofibrate, 200 mg/d (n = 100)	Combination group (n = 100)	Difference, *P*
Atorvastatin (%)	100	0	100	<.0001
Fenofibrate (%)	0	100	100	<.0001
Metformin (%)	53	54	52	NS
ACE inhibitors or ARBs (%)	64	67	65	NS
Hydrochlorothiazide (%)	45	43	47	NS
CCBs (%)	42	40	44	NS
Other antihypertensive (%)	15	18	16	NS
Orlistat (%)	38	36	36	NS

All those on metformin had fasting glucose impairment and all those on antihypertensive drugs were hypertensive.
CCB indicates calcium channel blockers.

Table 4
Measured laboratory and clinical parameters at the end of the study

	Atorvastatin, 20 mg/d (n = 100)	Fenofibrate, 200 mg/d (n = 100)	Combination treatment (n = 100)	Control group (n = 100)
TC (mmol/L)	4.2 ± 0.7 (−30)*	5.2 ± 0.9 (−12)*	4.1 ± 0.6 (−32)*	5.2 ± 0.9
LDL-C (mmol/L)	2.5 ± 0.5 (−35)*	3.4 ± 0.6 (−11)*	2.4 ± 0.4 (−39)*	3.1 ± 0.7
HDL-C (mmol/L)	1.1 ± 0.4 (9)*	1.3 ± 0.4 (20)*	1.3 ± 0.3 (24)*	1.5 ± 0.3
Non–HDL-C (mmol/L)	3.1 ± 0.6 (−38)*	3.9 ± 0.6 (−19)*	2.8 ± 0.5 (−43)*	3.7 ± 0.8
TG (mmol/L)	1.5 ± 0.6 (−32)*	1.3 ± 0.5 (−40)*	1.2 ± 0.5 (−46)*	1.3 ± 0.5
Fasting glucose (mmol/L)	4.8 ± 0.5 (−14)*	4.8 ± 0.6 (−15)*	4.7 ± 0.5 (−15)*	4.2 ± 0.4
SCr (μmol/L)	81 ± 7 (−12)*	101 ± 14 (8)*,**	90 ± 12 (−3)**	78 ± 8
SUA (μmol/L)	428 ± 47 (−11)*	417 ± 52 (−15)*	403 ± 49 (−17)*	380 ± 42
CRP (mg/L)	1.5 ± 0.6 (−65)*,**	2.4 ± 0.5 (−44)*,**	1.4 ± 0.5 (−68)*,**	0.6 ± 0.3
Fibrinogen (mg/dL)	382 ± 37 (−5)*,**	344 ± 31 (−17)*	336 ± 29 (−18)*	338 ± 35
SBP (mm Hg)	121 ± 6 (−17)*	123 ± 5 (−14)*	120 ± 4 (−18)*	118 ± 4
DBP (mm Hg)	74 ± 3 (−17)*	75 ± 4 (−15)*	74 ± 4 (−18)*	72 ± 3
Waist circumference (cm)	98 ± 7 (−8)*	97 ± 8 (−9)*	98 ± 10 (−8)*	94 ± 3
Body weight (kg)	84 ± 8 (−11)*	83 ± 6 (−13)*	84 ± 7 (−11)*	78 ± 6
MetS (%)	25 (−75)*,**	24 (−76)*,**	23 (−77)*,**	0
10-y risk Framingham (%)	6.1 (−46)*	8.9 (−21)*,**	5.2 (−54)*	4.6
10-y risk PROCAM (%)	6.4 (−56)*	9.2 (−36)*,**	5.5 (−63)	5.0

Percent reduction vs baseline in parenthesis.
* $P < .05$ vs baseline.
** $P < .05$ vs the control group.

non–HDL-C on target and with recommended levels of HDL-C or TG is reported in Fig. 1. Waist circumference, SBP, diastolic blood pressure (DBP), fasting blood glucose, SUA, and fibrinogen were significantly reduced in all 3 treatment groups (Table 4). Serum creatinine was reduced in the atorvastatin group, remained unchanged in the combination group, and increased in the fenofibrate group (Table 4).

3.3. End points

3.3.1. Percentage of subjects not having MetS by the end of the study

At the end of the study, 76% of the patients no longer had MetS and 46% had only one MetS component factor (Table 4). The rest of the patients (24%, all with 5 MetS components at baseline) had 2 component factors less than at baseline.

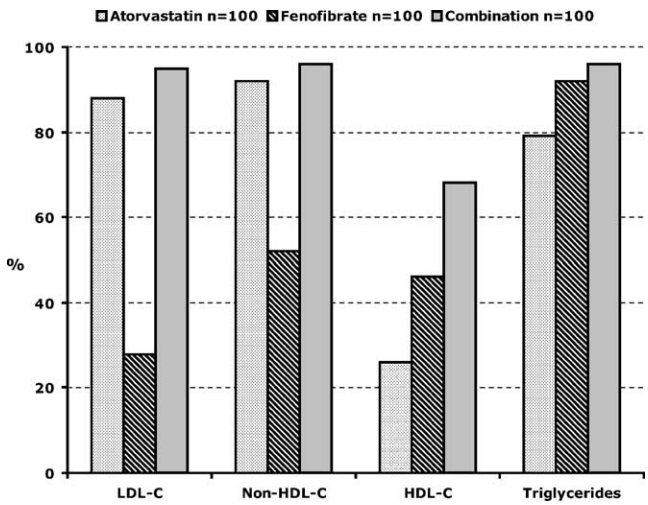

Fig. 1. Percentage of patients in each treatment group at LDL-C target (<2.6 mmol/L, 100 mg/dL), non–HDL-C target (<3.4 mmol/L, 130 mg/dL), and desirable levels of HDL-C (>1.0 mmol/L, 40 mg/dL, for men and >1.3 mmol/L, 50 mg/dL, for women) or triglycerides (<1.7 mmol/L, 150 mg/dL).

3.3.2. Framingham and PROCAM risk estimates

The estimated 10-year risk of all patients at baseline was 11.3% according to the Framingham estimate and 14.6% according to the PROCAM estimate. Even after adjustment for family history of premature CVD, the Framingham risk was significantly lower than the PROCAM estimate ($P = .02$). The PROCAM 10-year probability for a CVD event was reduced in the atorvastatin group to 6.4%, in the fenofibrate group to 9.2%, and in the combination group to 5.5% ($P < .0001$ for all vs baseline). The 10-year risk of the atorvastatin and combination treatment groups was not different from that of the control group (5.0%) at the end of the study (Table 4). Both risk estimates (Framingham and PROCAM) were similar after the multifactorial intervention (Table 4).

3.3.3. C-reactive protein

C-reactive protein was significantly reduced in all treatment groups with the atorvastatin and combination groups having the greatest reduction (65% and 68%, respectively, $P < .01$ vs the fenofibrate group [44%]) (Table 4). The reduction in CRP in all 3 treatment groups paralleled the reduction in the estimated 10-year risk.

3.4. Safety

There was no case of myopathy. One patient from the atorvastatin group and 2 from the combination group had to discontinue treatment because of myalgia without elevated SCr kinase activity. One patient from the atorvastatin group had alanine amino transferase levels more than 3-fold the

upper limit of normal. Because this was an intention-to-treat study, all patients are included in the final analysis. Alanine amino transferase, aspartate amino transferase, alkaline phosphatase, and γ-glutamyl transpeptidase values were significantly reduced during the study. These were elevated at baseline, probably because a number of patients had liver function tests indicative of nonalcoholic fatty liver disease.

4. Discussion

Our results suggest that a target-driven intervention aimed at multiple risk factors in nondiabetic patients with MetS, free of CVD at baseline, substantially reduces the MetS component criteria and the estimated CVD risk. The atorvastatin and the combination (atorvastatin + fenofibrate) treatment also reduced CRP more than fenofibrate by at least 20% ($P < .01$ for both). A CRP lowering effect could be clinically relevant in view of the recent evidence, suggesting that CRP levels should also be a treatment target in high-risk patients [16,17].

The mean 10-year probability for CVD of the entire MetS population was 14.6% (PROCAM calculation). According to the recent NCEP ATP III guidelines [18], these are medium high-risk subjects that would benefit from achieving LDL-C levels less than 2.6 mmol/L (100 mg/dL). This criterion justifies lipid-lowering intervention in patients with MetS.

During the 12-month study period, no patient developed DM. This might be partially attributed to the multitargeted intervention because lifestyle measures [19,20], metformin [20], ACE inhibitor [21], and ARBs [22] have been shown to reduce incident DM. These interventions may be one way of preventing DM, a CHD equivalent [23,24].

After the 12-month multitargeted intervention, 76% of patients no longer had MetS, whereas 46% had only one MetS diagnostic component. The remaining patients (24%) had 2 component factors less than that at baseline. Because there is an association between the number of MetS features and CVD mortality [25,26], all participants probably benefited from our intervention.

Metformin has been administered in prediabetic subjects [20], and there was a 31% reduction in the risk of developing DM and a significant decline in body weight [20]. However, intensive lifestyle also caused a 58% relative reduction in progression to DM [20]. Therefore, it is interesting to speculate on the potential benefit of combining intensive lifestyle modification, metformin, and other interventions. Metformin inhibits endogenous glucose production [27], and it has been administered in insulin-resistant women with the polycystic ovary syndrome (PCOS) [28]. A substudy of the United Kingdom Prospective Diabetes Study Group showed that treating overweight patients with DM who had metformin alone was associated with a decreased risk of combined diabetes-related end points, all-cause deaths, and myocardial infarction compared with conventionally treated patients [29]. It was also shown that metformin treatment has a beneficial effect on multiple, nontraditional, CVD risk factors in patients with type 2 DM [30]. This might also be the case for subjects with IFG in our study.

Angiotensin-converting enzyme inhibitors and ARBs reduce CVD risk in hypertensive patients whether they have diabetes or not [31]. In addition, these drugs probably reduce the risk of developing diabetes [31]. Thus, ACE inhibitors and ARBs may have reduced CVD risk to a greater extent than we estimated (using the PROCAM calculation) by exerting beneficial effects on insulin resistance.

In the cross-sectional epidemiological study METS-GREECE (n = 4753) [32], we showed that MetS identifies a substantial additional CVD risk, above and beyond the individual components, even in those without DM. After adjustment for LDL-C or non–HDL-C, the odds ratios for CVD in subjects with MetS (especially those without DM) were not significantly higher than those of subjects without MetS. This finding supports the need to reduce LDL-C and non–HDL-C to the NCEP ATP III treatment targets [4]. A projection of pooled observational data [33] suggested that optimal control of LDL-C in subjects with MetS prevented 46.2% and 38.1% of the CHD-related events, in men and women, respectively. Indeed, the Anglo-Scandinavian Cardiac Outcomes Trial—Lipid Lowering Arm [34] (hypertensive patients), Collaborative Atorvastatin Diabetes Study [35] (subjects with type 2 DM free of CVD at baseline), and Greek Atorvastatin and Coronary-Heart-Disease Evaluation (GREACE) (patients with CHD) [36-38] trials showed that treatment with atorvastatin can substantially reduce CVD events in patients who have, or are likely to have, MetS.

Fibrates may also be beneficial in patients with MetS. In the Veterans Affairs HDL Cholesterol Intervention Trial, the occurrence of new CVD events and the benefit of fibrate therapy were much less dependent on levels of HDL-C or TG than on the presence of insulin resistance [39]. Moreover, in the Helsinki Heart Study (primary prevention with gemfibrozil) [40] and Bezafibrate Infarction Prevention (BIP) Study (secondary prevention with bezafibrate) [41], the subgroups with features of the MetS had a significant reduction in the primary end point [40,41].

Atorvastatin and fenofibrate monotherapy significantly improve different aspects of the lipid profile in patients with type 2 DM and combined hyperlipidemia [42]. However, combination treatment is probably the optimal approach in these patients because of the beneficial effect on all lipid parameters [42]. Thus, CVD morbidity and mortality in 525 primary or secondary prevention patients with combined hyperlipidemia on 4 different statin-fibrate combinations were significantly lower than in other end point studies evaluating statin or fibrate monotherapy [43]. The safety of such combination treatments, in carefully selected and closely monitored patients, appears to be good [44,45]. The present findings and those of an earlier study [46]

suggest that if the statin-fibrate combination is not tolerated, monotherapy with atorvastatin is an effective alternative with high safety standards, lower treatment cost, and good compliance in patients with combined hyperlipidemia.

In the Helsinki Heart Study [47], SCr increased over time in the placebo and gemfibrozil subgroups. Dyslipidemia and hypertension accelerated this change [47]. Subjects with an LDL-C/HDL-C ratio greater than 4.4 had a 20% faster decline than those with a ratio less than 3.2. Both the contribution of the lipoprotein ratio and the protective effect of HDL-C alone remained significant in multiple regression analyses. Therefore, a high SCr could represent a CVD risk factor. This hypothesis is supported by the findings of an observational study [48]. It showed that higher SCr levels, mostly within normal range, were a strong and independent predictor of CHD adverse outcomes and stroke after first myocardial infarction in 2677 patients (follow-up = 3.4 years). In the present study and the GREACE trial, atorvastatin significantly improved renal function, thus, potentially offsetting an additional CHD risk factor [49].

Serum uric acid levels are probably related to adverse CVD outcome. This concept is supported by the results of studies [50,51] that included middle-aged dyslipidemic patients with CHD, with normal SCr levels at baseline, and the findings of the First National Health and Nutrition Examination Survey follow-up study [52]. A recent study reported that SUA levels are a strong predictor of CVD mortality in healthy middle-aged men, independent of variables commonly associated with gout or MetS [53]. This population-based prospective cohort study was performed at 1423 middle-aged Finnish men initially without CVD or DM. Moreover, in dyslipidemic patients with CHD, there is an increase in SUA levels over 3 years if they are not treated with a statin [51]. Atorvastatin treatment to NCEP targets significantly reduced SUA levels in these patients. This reduction correlated with a decrease in CVD events [51]. Fenofibrate also reduces SUA levels [54,55], mainly by a uricosuric effect [54]. Atorvastatin may reduce SUA levels by a different mode of action (probably by improving renal function [49]). This could explain the greater reduction in SUA levels seen in the combination treatment group. In the few patients on losartan (n = 14), which also reduces SUA levels [55], there was a further reduction (data not shown).

Metabolic syndrome may be associated with elevated CRP levels [56]. Subjects with 1, 2, 3, 4, and 5 MetS diagnostic criteria, compared with those who had no components of the MetS, were, respectively, 1.48, 1.84, 1.92, 3.42, and 4.17 times more likely to have mildly elevated CRP levels (>1.0 mg/L) (trend $P < .001$) [57]. C-reactive protein levels in these patients, indicative of a low-grade inflammatory state, correlated with practically all components of the MetS [56]. The results of a prospective study, including 14719 initially healthy women [58], confirmed that MetS is a high-risk state, because those with MetS had significantly worse CVD event-free survival than those without MetS. Moreover, this study [58] also demonstrated that at all levels of severity of the MetS, CRP added important and independent prognostic information in terms of CVD risk. This additive effect was present in all the study groups and evident with several definitions of the MetS [58]. In the present study, the reduction in CRP levels in the 3 treatment groups paralleled the reduction in the estimated 10-year risk.

Metformin reduces CRP levels in women with PCOS [59]. Serum concentrations of CRP were significantly higher in obese than in nonobese subjects with PCOS at baseline and correlated with the BMI suggesting that the elevated CRP levels may be related to obesity and not only to PCOS itself [59]. Thus, it is plausible that weight reduction and control of glucose levels induced by metformin might be one of the mechanisms by which this biguanide contributed to CRP reduction in our patients. Fenofibrate also reduced CRP levels in subjects with combined hyperlipidemia [60]. However, the results of the ATOrvastatin versus bezafibrate MIXed hyperlipidermia (ATOMIX) Study [61] showed that atorvastatin reduces CRP more than bezafibrate in patients with combined hyperlipidemia, whereas the Myocardial Ischemia Reduction with Aggressive Cholesterol Lowering (MIRACL) Trial [62] showed an association between CRP level decrease and event reduction in patients with acute coronary syndromes treated with atorvastatin. It has also been demonstrated that visceral obesity (a significant component of the MetS) is associated with raised plasma CRP levels [63] and that treatment with atorvastatin or atorvastatin with fish oil, but not fish oil alone, reverses this abnormality [63]. Recent data show that CRP might be an important marker of the reduction in clinical events. The recently published A-Z Trial [64] failed to show a significant reduction in the primary end point in subjects with acute coronary syndromes on a high simvastatin dose vs those on placebo/low simvastatin dose, despite significant differences in LDL-C levels. The editorial discussing this paper [65] suggests that the relatively small effect of high dose simvastatin on CRP (−17%) might be the reason for this failure. Thus, in trials showing substantial clinical benefit, there was a more pronounced effect of atorvastatin on inflammation (CRP reduced by 34% in the MIRACL Trial [62] and 38% in the Pravastatin or Atorvastatin Evaluation and Infection Therapy Trial [66]). In our patients, there was a significant reduction in CRP in all 3 treatment groups. Several factors (ie, metformin [59], weight loss [59], fall in SBP [67], increase of physical activity [68], and hypolipidemic drug use [61,62]) may have contributed to that. A CRP lowering effect could be clinically relevant in view of the recent evidence suggesting that CRP levels should also be a treatment target in high-risk patients [16,17].

It is plausible that the actual clinical benefit in our patients was greater than that estimated by the PROCAM or Framingham risk calculators, because the reductions in plasma fibrinogen, CRP, SCr, and SUA levels are not included in these risk engines.

4.1. Conclusions

A target-driven and intensified intervention aimed at multiple risk factors in nondiabetic patients with MetS is realistic and substantially offsets MetS component criteria reducing the estimated CVD risk by more than 60%. The atorvastatin-fenofibrate combination has a highly beneficial effect on all lipid parameters in these patients and substantially improves CVD risk status. All treatments induced significant reductions in CRP levels, but the atorvastatin and combination treatment were more effective than fenofibrate alone. In all 3 treatment groups, the reduction in CRP paralleled the fall in the estimated 10-year risk suggesting that inflammation is a component of the MetS. Finally, the CVD risk reduction in these subjects may be greater than estimated because the modification of several potential risk factors (fibrinogen, CRP, SCr and SUA) is not taken into consideration by the PROCAM and Framingham risk engines.

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