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Fibrates but not statins increase plasma selenium in dyslipidemic aged patients - The EVA study

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Short title: Lipid lowering drugs and selenium

Abstract

This secondary analysis of EVA ("Etude du Vieillissement Artériel") study reports the effect of fibrates and statins on plasma selenium concentration and its 9-year change in free-living dyslipidemic elderly. Dyslipidemic **patients** were categorized in three sub-groups according to final LDL-cholesterol level or hypolipidemic treatment: non treated dyslipidemic (LDL-

Cholesterol > 4.41 mmol/l, n=84); dyslipidemic who were treated exclusively by fibrates (n=47) or by statins (n=25) whatever their serum LDL-Cholesterol concentration. The influence of lipid lowering treatments on plasma selenium concentrations and its 9-year change was evaluated by ANOVA and multivariate linear regression models taking into account cardiovascular risk and changes in lipid profile parameters. Multivariate linear regression indicated that the plasma selenium decline was associated with the longitudinal variation in LDL ($\beta=-0.039\pm0.019$, $p=0.04$) and HDL-cholesterol concentrations ($\beta=0.187\pm0.059$, $p=0.002$) but not with triglycerides ($\beta=-0.018\pm0.031$, $p=0.57$). During the 9-year follow-up, similar plasma selenium declines were observed in all the sub-groups ($p=0.33$) despite plasma selenium levels were higher in fibrate users and lower in statin users ($p=0.0004$). The mechanisms underlying these data are not yet totally understood but considering the risk of selenium deficiency in the elderly and its relationship with poor health status, [further clinical trial is needed to verify the proposed hypotheses](#).

Key words: selenium; fibrates; statins; dyslipidemia; older adults

Introduction

Dyslipidemia is a well established risk factor for diseases occurring in older adults such as cardiovascular diseases, metabolic syndrome and diabetes. Peroxisome proliferator-activated receptor (PPAR) alpha activators (fibrates) and 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors (statins) are the backbone of pharmacologic hypercholesterolemia and dyslipidemia treatment [1, 2]. Parts of their clinical effects, remain still enigmatic and could be related to selenium metabolism [3]. Fibrates decrease triglycerides and increase weakly HDL-cholesterol [1, 2] whereas statins reduce LDL-cholesterol [2]. In addition, both drugs have anti-inflammatory properties [2], statins modulate oxidative stress and NO synthase [2], whereas fibrates act as antioxidants [4] but have also been reported to oxidize DNA [2].

Selenium plays an important role in the redox balance and its deficiency is commonly observed in the European elderly [5]. Plasma or serum selenium concentration has been reported to predict mortality [6, 7] and to be associated with higher cancer risk [8, 9], cardiovascular disease risk [10, 11] and cognitive decline [12, 13]. The relationships between serum lipids and selenium, [10, 11, 14, 15] and between poor selenium status and cardiovascular diseases and diabetes remain highly controversial [9].

A previous report on the 1389 participants in EVA (Etude du Vieillissement arteriel) study at baseline has evidenced an increase in plasma selenium in dyslipidemic patients compared to normolipidemic participants. This increase was more pronounced in lipid-lowering drug users, particularly in those who took fibrates [16, 17]. In this context, we aimed to investigate the association between long-term lipid lowering drug treatment and long-term longitudinal plasma selenium change as well as to further investigate the cross-sectional effect of lipid lowering drugs on plasma selenium concentrations in the sub-population of free-living dyslipidemic elderly of the EVA study.

Material and methods

Design and participants

The EVA study is a 9-year longitudinal study which has been largely described elsewhere [6, 18]. Briefly, 1389 volunteers (575 men and 814 women, age range: 59-71 years) residing in the town of Nantes (western France) were recruited from electoral rolls, and to a lesser extent, via information campaigns from 1991 to 1993. All participants were community residents. They underwent a complete examination in the EVA study centre where they spent half a day every other year for eight years and nine year after inclusion (end of the study). Characteristics of the 1389 participants included have been previously described [16, 17]. Six hundred and eight participants dropped out during the study. Comparison of drop out subjects and volunteers who completed the study have also been presented elsewhere [19]. The study protocol was approved by the Ethical Committee of University Center Hospital of

Kremlin-Bicêtre, (France). Signed, informed consent was obtained from all participants at enrolment.

The present analysis focused on the dyslipidemic subgroup at the end of the study (n=233) (Figure 1). Dyslipidemia was characterized by an LDL-cholesterol concentration > 4.1 mmol/l or the use of lipid-lowering drugs. In order to evaluate the association between fibrates or statins treatment and longitudinal plasma selenium evolution, the 156 older-adults who neither received lipid lowering treatment (with the exception of nutritional advice) or who received the same treatment during the whole follow-up were finally included in the analysis (Figure 1). Data from men and women were not examined separately as no gender difference was evidenced for plasma selenium concentrations in the three studied groups (see below). In addition, previous analyses conducted in the EVA study did not report any effect of gender on plasma selenium concentrations [6, 16, 17, 20-22] and on plasma selenium longitudinal decline [19].

Data collection

At each follow-up wave, a general questionnaire allowed us to obtain updated information on socio-demographic factors, life style habits such as tobacco status and medical events. In addition, two independent measures of systolic and diastolic blood pressure were made with a digital electronic tensiometer after a 10-minute rest. At inclusion, year 2, year 4 and at the end of the study, blood samples were drawn between 8.30 am and 9.30 am after a 12-hour fast. Determination of total, HDL- and LDL-cholesterol, triglycerides and glucose concentrations were performed according to previously described methods [18]. Plasma selenium was measured at baseline, year 2 and at the end of the study by electrothermal atomic absorption spectrometry according to a previously described method [6]. Briefly, selenium was determined using electrothermal atomic absorption spectrometry (Perkin Elmer 5100 ZT, Norwalk, CT, USA). A selenium electrode-less discharge lamp and a Zeeman longitudinal background correction were used. Serum was diluted in a solution containing 0.1 M nitric acid and 0.2% (w/v) Triton X 100 and matrix modifier was introduced

onto the platform of a pyrolytic graphite furnace. Concentration was obtained using an addition calibration. Seronorm[®] trace element serum was chosen as internal quality control (Sero[®], Billingstad, Norway). The tolerance limits were $\pm 10\%$ of the batch target value in use. Precision varied from 1.4% (within-run, n=20) to 8% (between-run, n=22) at a concentration of 1.30 $\mu\text{mol/l}$. In addition, the laboratory took part in two external quality assessment schemes and its annual scores were acceptable (values higher than 60%).

Statistical analysis

The characteristics of dyslipidemic patients at the end of the study were described and compared according to their lipid lowering treatment group, taking into account plasma selenium concentrations, serum lipid profile and cardiovascular risk factors associated with dyslipidemia : age and sex (men older than 50 years or women older than 60 years), smoking habits (current smokers or former smokers since less than three years), HDL cholesterol lower than 1.0 mmol/l, diabetes (defined as plasma glucose level ≥ 7.00 mmol/l or use of anti-diabetic drugs at least at two consecutive waves), cardiovascular diseases antecedents, hypertension (defined as systolic or diastolic blood pressure ≥ 140 or ≥ 90 mm Hg respectively, or use of hypertensive drugs at least at two consecutive waves) or protective factors : HDL cholesterol equal or higher than 1.5 mmol/l (Table 1). Results were expressed by percentage or means with their standard deviation (SD) and to test differences between the three groups, Chi square test and Fisher's test were used.

To take into account the cumulative or compensatory effect of respectively cardiovascular risk and protective factors associated with dyslipidemia during the whole study, we built a risk factor score according to HAS recommendations [23] (Table 1). Plasma selenium and lipid profile changes defined by the difference between baseline and end of EVA study, were normally distributed. To study the association between plasma selenium change during the 9-year follow-up and lipid lowering treatments in dyslipidemic patients we used first a classical variance analysis ANOVA and then we performed multivariate linear regression

model to take into account the cardiovascular risk and protective factors associated with dyslipidemia as well as changes in lipid profile parameters. Results of linear regression models were expressed by the regression coefficients with their standard deviation (SD). Statistical significance was defined by $p \leq 0.05$. Statistical analyses were performed using SAS software version 9.1 (SAS Institute, Inc. Cary, North Carolina).

Results

The present analyses focused on the 156 participants who were selected as described in Figure 1 divided in three groups: non treated dyslipidemic group included participants who were never treated before or during the whole study and had a LDL-cholesterol >4.1 mmol/l ($n=84$); fibrates group corresponded to patients who received only fibrates as lipid lowering treatment before or during the 9-year follow-up ($n=47$) and the statins group was similarly defined ($n=25$). Characteristics of these 156 participants were compared between each of these 3 groups (Table 2). At the end of the study, the sex ratio and age did not differ significantly between these three groups. In addition, plasma selenium concentrations were similar in both gender in the three groups (non treated dyslipidemic group: men 1.02 ± 0.22 $\mu\text{mol/l}$, women: 1.02 ± 0.16 $\mu\text{mol/l}$, $p=0.96$; fibrate users: men 1.12 ± 0.19 $\mu\text{mol/l}$, women 1.11 ± 0.17 $\mu\text{mol/l}$, $p=0.85$; statin users: men 0.92 ± 0.18 $\mu\text{mol/l}$, women 0.96 ± 0.17 $\mu\text{mol/l}$, $p=0.55$). We showed that smoking habits were significantly different between the three groups, with a lower percentage of current and former smokers in non treated group than in lipid lowering treatment groups. Percentages of diabetic patients, participants with cardiovascular disease events or permanent hypertension were not significantly different between the three groups. Taken as a whole, population was not at high risk of cardiovascular diseases as the mean risk score value varied between 1.11 to 1.36, the most frequently additional risk factor being age and hypertension counteracted by a high frequency of HDL-cholesterol concentrations equal or higher than 1.5 mmol/l. Regarding biological parameters, as expected, we found significantly lower LDL and total cholesterol

concentrations in lipid lowering treated groups than in non treated group and triglycerides concentrations were lower in the fibrates group. No significant difference appeared for HDL cholesterol. Plasma selenium concentrations both at baseline and at the end of the study for each of the three groups are reported in Figure 2. During the 9-year follow-up, plasma selenium decreased in the three groups (Table 2) but the 9-year longitudinal selenium [decline](#) did not show significant differences between the three groups. The relationship between the 9-year plasma selenium decrease and the lipid lowering treatments was studied using linear regression models controlling for cumulative cardiovascular risk factors associated with dyslipidemia score and for the 9-year lipid parameter [evolution](#). The results of these multivariate models confirmed that the plasma selenium decrease during the 9-year follow-up was not related to the treatment (Table 3). Furthermore, the multivariate linear regression models also showed that 9-year plasma selenium [decline](#) was significantly and negatively related to 9-year LDL-cholesterol level [evolution](#) and significantly and positively related to 9-year HDL-cholesterol level [evolution](#), whereas no relationship was evidenced with triglycerides level [evolution](#). Interestingly, at the end of EVA study, plasma selenium concentrations were significantly higher in the fibrate group and lower in the statin group (Table 2).

Discussion and conclusion

As part of a clinical longitudinal trial that examined the role of oxidative stress on vascular and cognitive aging, the present analysis aimed at examining the influence of two lipid lowering groups of drugs on longitudinal variation of plasma selenium taking into account the other cardiovascular disease risk in EVA dyslipidemic [patients](#). This analysis was performed because cross-sectional analyses [conducted separately in men and women](#) at baseline have evidenced a significant increase in plasma selenium [concentrations](#) in fibrate users , [whereas non treated dyslipidemic participants exhibited similar plasma selenium concentrations than volunteers without major chronic diseases or risk factors](#) [16]. At that time, statin users were not considered. In the present sub-EVA population, a higher number

of patients were treated by fibrates which was the main lipid lowering group of drugs used in the nineties. Cross-sectional analysis after 9 years confirmed the higher plasma selenium concentrations in fibrate users observed in the EVA population at baseline [16, 17]. In addition, the statin users exhibited lower plasma selenium concentrations, while EVA volunteers without major chronic diseases or risk factors plasma selenium concentrations were found to be $0.99 \pm 0.17 \mu\text{mol/l}$ ($n=162$) (data not reported). Various factors have been reported to modify plasma selenium [5, 24-26], sometimes with discrepant conclusions according to the studies. In this secondary analysis, only factors strongly related to dyslipidemia follow-up [23] have been taken into account. In particular, impact of dietary selenium intake, which is strongly related to plasma selenium [24, 25], was not evaluated. However, biochemical mechanisms could support an impact of lipid lowering drugs on plasma selenium concentrations. Indeed, regarding statins, this observation could be related to the inhibition of selenocystein t RNA by statins [27, 28]. Moreover, coenzyme Q10 depletion during statin therapy [29, 30] might be associated with selenium deficiency. Indeed, it has been reported that the ubiquinol-10 is regenerated by selenoenzyme [31, 32]. As regard fibrates, several hypothesis might explain the beneficial effect on plasma selenium concentrations. Induction of glutathione peroxidase has been reported in chick and hamster liver [33, 34] though not in rats or crustaceans [34, 35]. A sparing effect of selenium related to PPAR activation by fibrates may be hypothesized as PPARs act as antioxidants [36]. Nonetheless, cross-sectional results were not statistically confirmed by longitudinal variation of plasma selenium concentrations. Plasma selenium decline was similar in the three studied groups as well as in the volunteers without major chronic diseases or risk factors ($-0.07 \pm 0.21 \mu\text{mol/l}$ ($n=162$), data not reported) and is probably related to aging as previously described [5, 37]. As a secondary analysis, the small number of dyslipidemic participants might contribute to the lack of power of the analysis as the larger decrease in plasma selenium in the statin group did not reach the statistical significance. Previous reports conducted on a short period and on a limited number of patients did not show any effect of statins on plasma selenium variations [38, 39]. It can also be hypothesized that the response

of plasma selenium to lipid lowering drugs, observed on cross-sectional analysis, reach a plateau and then is up-regulated by the changes in HDL- and LDL-cholesterol concentrations as suggested by the multiple linear regression models. The observed relationships may reinforce the antioxidant role of selenium as an increase in plasma selenium is associated to a decrease in LDL particles, more susceptible to oxidation, and to an increase in HDL particles, that may inhibit the oxidation of LDL. To our knowledge, this is the first report dealing on long-term longitudinal relationships between plasma selenium and lipid profile variations in dyslipidemic patients, therefore these results must be interpreted cautiously. Indeed, previous cross-sectional associations between lipid profile and selenium largely depend on studied populations [40-42]. In the general population, positive association between HDL and selenium have been reported in agreement with our results [10, 11], but were not reported by others [14, 15]. Among the confounding factors, age [41], sex [16, 17], lipid concentrations [42] have been evidenced.

In conclusion, the mechanisms underlying our results probably involved both redox balance and selenoprotein synthesis. Considering the high risk of selenium deficiency in the European elderly and its relationship with poor health status [5-7], as well as side effects of lipid lowering drugs, further large clinical trial is needed to verify the proposed hypotheses.

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Table 1: Cardiovascular risk factors associated with dyslipidemia score according to HAS recommendation [23]

Factors	Definition	Score
Age and sex	Male ≥ 50 y or Female ≥ 60 y	1
Cardiovascular diseases	Personal cardiovascular disease episode before or during the study	2
Diabetes	Plasma glucose concentration ≥ 7.00 mmol/l or use of anti-diabetic drugs at least at two consecutive waves	1
Hypertension	Systolic or diastolic blood pressure ≥ 140 or ≥ 90 mm Hg respectively, or use of hypertensive drugs at least at two consecutive waves	1
Mean HDL cholesterol	<1.0 mmol/l	1
on the whole follow-up	between 1.0 and 1.5 mmol/l	0
	≥ 1.5 mmol/l	-1
Smoking	Smoker or former smoker since less than 3 years	1
	Non smoker or former smoker since more than 3 years	0

Table 2: Characteristics of the three dyslipidemic [patient](#) groups

Parameters		Non-treated N=84	Fibrates N=47	Statins N=25	P- value
Men/Women ratio		26/58	16/31	13/12	0.15
Age, mean (SD) y		73.5 (2.9)	72.6 (2.70)	74.2 (3.0)	0.07
Smoker or former smoker since less than 3 years, %		1.2	8.7	8.3	0.05
Diabetes, %		2.4	2.1	4.0	0.88
Hypertensive patients , %		46.3	66.0	44.0	0.07
Personal history of CVD, %		10.7	8.5	20.5	0.33
HDL-cholesterol	HDL mean < 1 mmol/l, %	2.5	2.4	No subject	0.90
	HDL mean ≥ 1.5 mmol/l, %	63.8	76.2	56.5	
Cardiovascular risk factors associated with dyslipidemia, mean (SD) score		1.11 (1.05)	1.19 (1.08)	1.36 (1.29)	0.63
HDL-cholesterol, mean (SD) mmol/l	HDL-cholesterol at EVA6,	1.62 (0.42)	1.72 (0.38)	1.53 (0.37)	0.12
	9-year HDL-cholesterol change (HDL at EVA6 – HDL at EVA0)	-0.01 (0.32)	-0.05 (0.28)	-0.07 (0.33)	
LDL-cholesterol, mean (SD) mmol/l	LDL-cholesterol at EVA6,	4.57 (0.36)	3.36 (0.55)	3.65 (1.42)	<10 ⁻⁴
	9-year LDL-cholesterol change (LDL at EVA6 – LDL at EVA0)	0.04 (0.71)	-1.08 (1.06)	-0.88 (1.64)	
Triglycerides (TG), mean (SD) mmol/l	TG at EVA 6	1.30 (0.50)	0.95 (0.39)	1.39 (1.09)	0.002
	9-year TG change (TG at EVA6 – TG at EVA0)	0.04 (0.59)	-0.12 (0.47)	0.18 (1.06)	
Total Cholesterol (TC), mean (SD) mmol/l	TC at EVA6	6.77 (0.50)	5.51 (0.70)	5.74 (1.59)	<10 ⁻⁴
	9-year TC change (TC at EVA6 – TC at EVA0)	0.64 (0.74)	-1.18 (1.14)	-1.00 (1.67)	
Selenium (Se), mean (SD) μmol/l	Plasma Se at EVA6	1.02 (0.18)	1.11 (0.18)	0.94 (0.17)	0.0004
	9-year Plasma Se change (Se at EVA6 – Se at EVA0)	-0.07 (0.21)	-0.06 (0.25)	-0.14 (0.18)	

Table 3: Influence of lipid lowering treatment on 9-year longitudinal plasma selenium [evolution](#).

	Plasma selenium change			Plasma selenium change			Plasma selenium change		
	(Se EVA6- Se EVA0)			(Se EVA6- Se EVA0)			(Se EVA6- Se EVA0)		
	β^*	SD*	p-value	β^*	SD*	p-value	β^*	SD*	p-value
Fibrates vs non treated	-0.048	0.048	0.31	0.005	0.042	0.91	-0.008	0.044	0.85
Statins vs non-treated	-0.096	0.057	0.10	-0.053	0.053	0.31	-0.063	0.055	0.25
Cardiovascular risk factors associated with dyslipidemia score	-0.005	0.018	0.76	-0.001	0.017	0.97	0.002	0.017	0.89
LDL-cholesterol change (end-baseline)	-0.039	0.019	0.04						
HDL-cholesterol change (end-baseline)				0.187	0.059	0.002			
Triglycerides change (end-baseline)							-0.018	0.031	0.57

* Results of adjusted linear regression model expressed by the regression coefficient (with their standard deviation) of plasma selenium

[evolution](#) according to lipid lowering groups, adjusted for all variables listed on the table.

The model was performed on 143 [patients](#).

Figure 1 : Selection of the three groups of dyslipemic **patients** at the end of the EVA study according to their current and previous lipid lowering drug treatment.

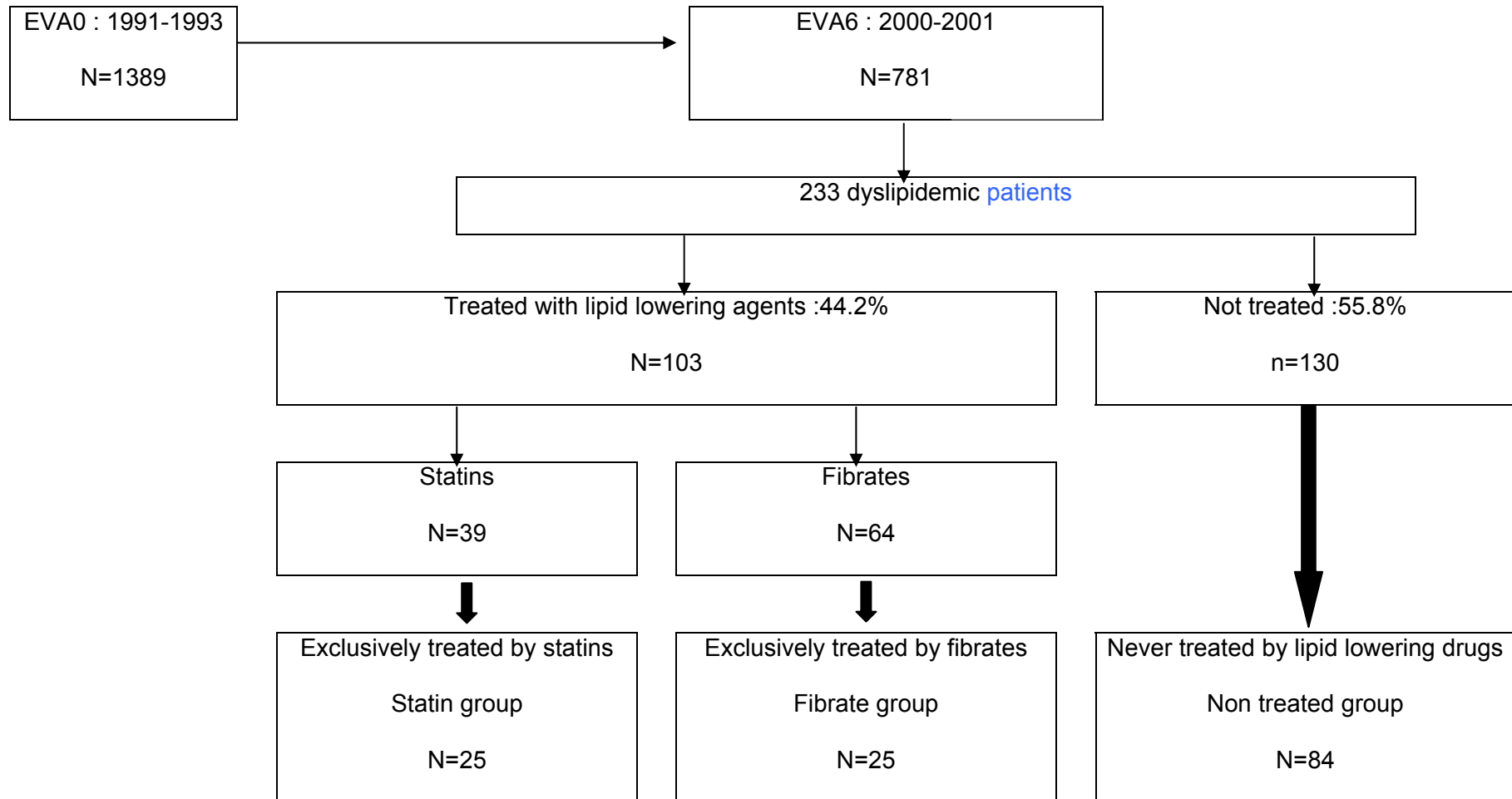
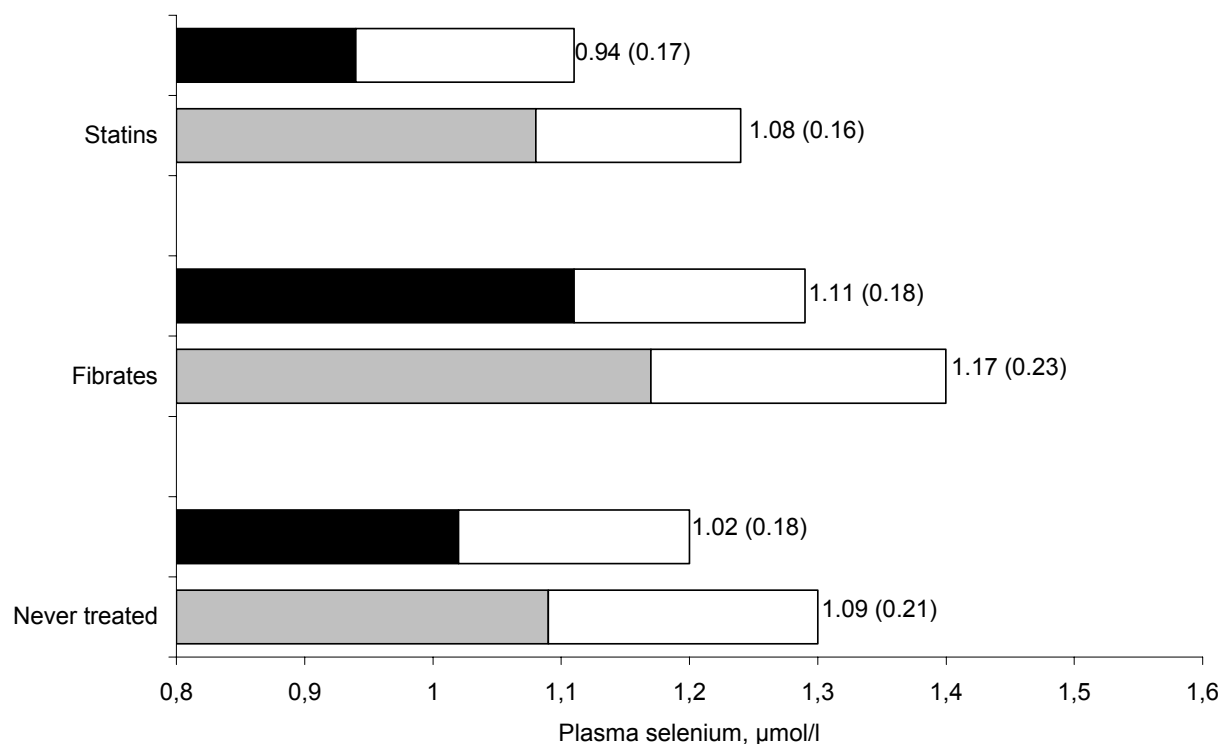


Figure 2 : Plasma selenium at baseline and at the end of the study according to the treatment groups.



Never treated = Non treated group with a LDL cholesterol concentration >4.1 mmol/l (n=84);

Fibrates: Group exclusively treated with fibrates (n=47); Statins: Group exclusively treated with statins (n=25)

Results expressed as mean plasma selenium concentrations at baseline, nine years after, Standard deviation