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Long-Term Therapy with Cuban Policosanol on Hypercholesterolemic Elder Patients: Analysis by Gender

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***Abstract*— *Background**: Cardiovascular Disease is the leading cause of morbidity and mortality in the adult population. End-point based studies have been demonstrated a direct relationship between coronary artery disease and elevated serum levels of low density lipoprotein cholesterol (LDL-C) and total cholesterol, as well as the benefits of lowering LDL-C and increasing high density lipoprotein cholesterol (HDL-C) on clinical end-points. Cuban policosanol is a mixture of saturated long-chain fatty alcohols, purified from sugarcane wax, which exhibits effects on the control of dyslipidemia, with demonstrated effectiveness, safety and tolerability in numerous clinical trials. **Objectives**: To investigate whether the results of policosanol treatment show any difference by sex in the elderly. **Methods**: In a previous long-term study old patients of both sexes with type II hypercholesterolemia, between 60 to 80 years old with ≥ 1 non-lipid coronary risk factors were randomized in two groups. The patients were treated with policosanol or placebo, during 3 years. The incidence of vascular side adverse events (SAE) occurred during the study was considered as a primary efficacy variable. Changes on lipid profile were considered secondary efficacy variables. In the present report it is analyzed differences of policosanol effects between genders. The analysis of variables was by Intention-to-treat method. **Results**: The frequency of all SAE was lower in the policosanol group compared with placebo in both sexes. There were 63 SAE in placebo (10.8 %) and 17 in policosanol treated women (3.0 %) ($p<0.00001$). In turn, there were 20 SAE in placebo (13.2 %) and 9 in policosanol treated men (5.4 %) ($p<0.01$). Policosanol reduced all vascular SAE in both sexes. Thus, there were 34 vascular SAE in placebo (5.8 %) and 9 in policosanol treated women (1.6 %) ($p<0.0001$), while 15 vascular SAE occurred in placebo (9.9 %) and 6 in policosanol treated men (3.6 %) ($p<0.01$). Policosanol reduced cardiovascular SAE in both sexes. Thus, 21 cardiovascular SAE (3.6 %) occurred in placebo and 4 in policosanol treated women (0.7 %) ($p<0.001$), whereas 12 events (7.9 %) occurred in placebo and 3 (1.8 %) in policosanol treated men ($p<0.01$). Benefits were evident in both sexes, but greater in women. At study completion, the changes induced by policosanol in LDL-C, total cholesterol, triglycerides and HDL-C with respect to baseline were similar by gender. **Conclusions**: The present results demonstrate that treatment with policosanol significant lower amount of vascular SAE, produce relevant positive changes on serum lipid profile and lower frequency of total AE in older hypercholesterolemic patients. Clinical impact was evident in both sexes, but greater in woman. These findings support the recommendation of policosanol use as treatment in primary or secondary prevention program for older patients at cardiovascular risk.*

***Keywords*—** *Policosanol, elderly, hypercholesterolemia, serious adverse events, cholesterol-lowering, genders.*

I. INTRODUCTION

Cardiovascular Disease (CVD) is the leading cause of morbidity and mortality in the adult population.[1] It is called CVD primary prevention when risk factors, as LDL high serum concentration, are treated in individuals who has not previously experienced an atherosclerotic vascular event. The rationale for treatments focused on LDL-C reduction are based upon epidemiologic data documenting a continuous, positive, and graded relationship between LDL-C concentration and CVD events and mortality, and the evidence that lowering of LDL-C in patients across a broad range of LDL-C levels, reduces the risk in patients with and without CVD.[2,3]

Patients without known CVD are generally at much lower baseline risk of cardiovascular events than patients with known CVD. The decision as to whether LDL-C treatment should be recommended depends on a determination of global cardiovascular disease risk, as the potential absolute risk reduction with treatment for hypercholesterolemia will usually be smaller than for patients with established CVD.[2,3]

End-point based studies have demonstrated a direct relationship between coronary disease and elevated serum levels of LDL-C and total cholesterol[2], as well as the benefits of lowering LDL-C with statins on clinical end-points.[4-9]

Hypercholesterolemia management in the elderly had been questioned because elevated LDL-C and total cholesterol levels reduces its predictive value in ageing patients, because the relative decline of coronary risk with age.[10] However, does plasma lipid determinations still remains as strong predictors for absolute coronary risk in the elderly[11] and the evidence obtained from strata analyses of older patients included in statin trials had shown the clinical benefits in this population.[4-9]

On the other hand, increased HDL is considered a cardio protective factor. A multivariable analysis, the largest of its

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kind to date, has confirmed the inverse, independent, strong and graded relationship between HDL-C and both CVD and CHD mortality.[12]

Policosanol is a mixture of high molecular weight alcohols purified from sugar cane *(Saccharum officinarum, L)* wax[13] with cholesterol-lowering effects due to the inhibition of cholesterol synthesis by regulating the activity of hydroxymethyl glutaryl Coenzyme (HMG CoA) through the increase of AMP kinase activity.[14-17]

The cholesterol-lowering effects of policosanol have been demonstrated in patients with type II hypercholesterolemia[18,19] The efficacy and tolerability of policosanol in the elderly have been investigated in several clinical trials, being effective, safe and well tolerated in older individuals.[20-27]

Policosanol shows also relevant pleiotropic effects, such as the inhibition of platelet aggregation[28-30] and the susceptibility of LDL to be oxidised.[31,32] Clinical studies and long-term post marketing surveillance studies have proven that policosanol is safe and well tolerated.[13,18-35]

This background supported the conduction of a long-term study with policosanol in hypercholesteraemic elders

II. Patients and Methods

Study design: The presented analysis by gender were obtained from the data of all patients treated with policosanol included in a previous prevention study.[36] It was a prospective, randomized, double-blinded, placebo-controlled study including 1470 older patients after randomization treated with placebo or policosanol for 3 years. In brief, an independent Ethics Committee approved the study protocol. Patients were recruited at four Polyclinic Centres and followed by a medical staff of the Surgical Medical Research Centre after providing informed written consent.

Patients were advised to follow a step one cholesterol-lowering diet for 5 weeks, after which lipid profile and safety laboratory indicators were assessed and the next week they attended to visit 2. Laboratory values obtained at the end of baseline period and safety physical indicators obtained at visit 2 were considered as baseline values for respective parameters.

Enrolment criteria: Patients of both sexes aged 60 to 80 with documented coronary disease, hypercholesterolemia, and others coronary risk factors were enrolled. The rationale for the lowest age was to include older subjects with a considerable life expectancy.

Inclusion criteria: Patients were included for randomization if after the diet-only period they showed total cholesterol ≥ 5.2, LDL-C ≥ 3.4 and triglycerides <4.52 mmol/L and exclusion criteria were not present.

Exclusion criteria: Patients were excluded if active renal disease, diagnosed neoplastic disease, severe hypertension (diastolic blood pressure≥120 mm Hg), uncontrolled diabetes or poor cognitive function were present. In addition, patients who had had episodes of unstable angina, myocardial infarction, stroke or any serious AE (SAE) within the 3 months previous to being enrolled in the study were also excluded.

Withdrawal criteria: Any SAE or any AE justifying such decision, unwillingness to follow-up by any cause, major violations of study protocol, including > 6 consecutive weeks without taking the study medications. In addition, alert lipid laboratory values (total cholesterol > 9.0 mmol/L and triglycerides > 10 mmol/L) during the study.

Treatment: Tablets must be taken 5 mg once a day with evening meal. Patients should be titrated to 2 tablets oid if their total cholesterol levels after 6 or 12 months on therapy were ≥ 7 mmol/L.

Compliance assessment:—Compliance being assessed by patient questioning and tablet counts and defined as ≥ 85 % of the scheduled tablets having been consumed since the prior visit.

Concomitant medications: Consumption of lipid-lowering drugs was forbidden from the time of enrolment to study completion, but no other restriction of concomitant therapy was done. Cases at secondary prevention were encouraged to take aspirin and/or β-blockers.

Assessments: Lipid profile and safety laboratory tests were performed at baseline and after 1, 2 and 3 years of randomization. At each visit dietary reinforcement and physical examination were done.

Efficacy analyses

Primary efficacy variables: The incidence of vascular serious adverse events (SAE) that occurred during the study was considered as a primary efficacy variable. Vascular SAE included all cardiovascular, cerebrovascular and peripheral events that led to the hospitalization or death of the patient.

Cardiovascular SAE included coronary disease death, non-fatal myocardial infarction or angina, congestive heart failure and seriously uncontrolled hypertension. Cerebrovascular SAE included stroke or ischemic transient attacks.

To conduct the study in conditions near to Cuban clinical practice, serious adverse events were evaluated through the official records of the hospitals, Death Registry and Family Doctors. At each visit, the occurrence of any event was documented from patients' recall, but information was verified with hospitals and Family Doctors. The events were diagnosed by personnel not only blinded to treatment allocation, but also not involved in the study.

Death certificates were requested for all deaths occurring during the study and the cause of death was ascertained from hospital records and official certificates, helped by interviews with Family Doctors and relatives. Whether the patients were alive was confirmed at each visit by contact with patients. In case of patients travelling abroad or moving to other towns, household and Family Doctors were contacted.

Secondary efficacy variables: The incidence of total SAE (vascular and non-vascular) and mortality as well as changes on lipid profile (LDL-C, total cholesterol, HDL-C and triglycerides) were considered a secondary efficacy variable.

Safety and tolerability analyses: Adverse event (AE) defined as any new unfavourable change in function, structure or laboratory data or the worsening of any pre-existing condition occurring through the study, independent of its relationship

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with treatment were considered in the safety and tolerability analysis.

AE were classified according to their intensity as mild, moderate or serious. Mild AE were those not requiring treatment or withdrawal of study medication, moderate AE required withdrawal of study medication and/or treatment of the AE.

Mild and moderate AE were also included for safety and tolerability analysis. Each AE was classified as having a causal relationship with treatment using the categories of definitely, probably, possibly, probably not, or definitively not drug-related.

Also, physical indicator (body weight, pulse rate, blood pressure) and laboratory test values (glucose, creatinine, aspartate aminotransferase –AST-, alanine aminotransferase –ALT-) were analysed.

Laboratory analysis: Blood samples were drawn after 12 hours overnight fasting at Policlinics and transported within the next 2 hours to the Surgical Medical Research Center for processing and analysis. Lipid profile and laboratory test values were determined by enzymatic methods using reagent kits (Roche). Laboratory analyses were performed in a Hitachi 719 autoanalyzer. Determinations were done on the same sampling day. A quality control was performed throughout the study, so that precision (within and between-day variations) and accuracy versus reference standards were controlled.

Statistical Analysis: Statistical analysis for the whole study was planned in study protocol and amendments. All data were analysed according to intention to-treat principle, so that analyses were based on data of all randomised patients, as randomised.

Continuous values were compared using t test for paired (within group comparisons) and independent (between group comparisons) samples. Categorical data were compared with the $\chi 2$ test. All statistical tests were two-tailed, with significance at $\alpha = 0.05$. Statistical analyses were performed using Statistics for Windows (Release 4.2; Copyright StatSoft, Inc. US) and SAS/STAT (Stat Soft, Version 8, US).

III. Results

Baseline patient characteristics: An analysis of baseline characteristics by gender reveals that 108/317 men (34.1 %) and 189/1153 women (16.4 %) were smokers ($p < 0.0001$), whereas 768/1153 (66.6 %) women and 175/317 (55.2 %) men were hypertensive ($p < 0.001$). All baseline characteristics, however, were similar in placebo and policosanol subgroups by sex (Table 1).

The frequency of withdrawals was greater ($p<0.0001$) in placebo group (189, 25.8 %) than in policosanol group (88, 11.9 %) and similar by gender. The same was true ($p<0.0001$) for withdrawals due to AE and other reasons, these last ones being mainly related with patients showing alert values (total cholesterol ≥ 9.0 mmol/L). Two hundred and seventy-seven patients (18.8 %) withdrew from the study. Of them, 109 discontinued because of SAE and another 12 (9 placebos, 1.2 % and 3 policosanol 0.4 %) because of mild or moderate AE (data not shown in Table for simplicity).

Compliance: Compliance within the study drugs was good and similar by gender, since 721/737 (97.8 %) policosanol patients and 715/733 (97.5 %) of placebo adhered to compliance criterion (> 85 % of dose taken at the end of treatment) during the time that they received treatment.

Dosage: Most policosanol patients (665/737, 90.2 %) were treated with 5 mg/d during the study. Three hundred eight (308) patients: 72 (9.8 %) policosanol and 236 placebos (32.2 %) were titrated to 2 tablets oid with the evening meal. The frequency needing titration was different in both groups ($p<0.01$), and similar by gender.

Effects on primary efficacy variables: The analysis by gender is shown in Table 2. There were 63 SAE in placebo (10.8 %) and 17 in policosanol women (3.0 %) ($p<0.00001$). In turn, there were 20 SAE in placebo (13.2 %) and 9 in policosanol men (5.4 %) ($p<0.01$).

Policosanol reduced all vascular SAE in both sexes. Thus, there were 34 vascular SAE in placebo (5.8 %) and 9 in policosanol treated women (1.6 %) ($p<0.0001$), while 15 vascular SAE occurred in placebo (9.9 %) and 6 in policosanol treated men (3.6 %) ($p<0.01$).

Policosanol reduced cardiovascular SAE in both sexes. Thus, 21 cardiovascular SAE (3.6 %) occurred in placebo and 4 in policosanol treated women (0.7 %), ($p<0.001$), whereas 12 events (7.9 %) occurred in placebo and 3 (1.8 %) in policosanol treated men ($p<0.01$). Also, policosanol lowered cerebrovascular SAE in women, occurring 9 (1.5 %) in placebo and 3 in policosanol (0.5 %) ($p<0.05$).

Only 11/1153 women (1.0 %), 10 placebos (1.7 %) and 1 policosanol (0.2 %) died. Of them, 7 women, all placebo (1.2 %), but not policosanol-treated, died because of cardiovascular causes, 1 placebo woman died due to cerebrovascular cause, while other 3 (2 placebos, 1 policosanols) died from nonvascular causes. Twelve of 317 men (3.8 %) (9 placebos, 6.0 %; 3 policosanols, 1.8 %) died. Of them, 6 placebos (4.0 %) and 1 policosanol (0.6 %) died because of cardiovascular causes, 2 placebos due to stroke, while other 3 (1 placebo, 2 policosanols) because of nonvascular causes.

As expected, policosanol did not increase the frequency of nonvascular SAE, but surprisingly reduced its frequency. Thus, there were 11 (1.5 %) nonvascular SAE in policosanol and 34 (4.6 %) in placebo ($p<0.001$), in treated women (8 events, 1.4 %) compared with placebo (29 events, 5.0 %) ($p<0.001$), whereas in men the risk was similar in both groups (data not shown in Table for simplicity).

Effects on lipid profile: Table 3 summarized the effects on lipid profile. After 6 months of therapy with policosanol, at which point all patients were still consuming 5 mg/d, total cholesterol was reduced by 15.0 %. At study completion, the changes induced by policosanol in LDL-C, total cholesterol, triglycerides and HDL-C in woman were -33.7 %, -22.9 %, -19.8 % and +15.6 %, respectively, and in men -31.0 %, -20.9 %, -19.8 % and +14.9 %, respectively.

Safety and tolerability

Policosanol did not modify safety indicators (data not shown in Table for simplicity). Thus, it did not raised ALT,

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AST, glucose or creatinine values, body weight and pulse rate were unchanged, but systolic and diastolic pressure were significantly ($p<0.0001$) reduced compared with baseline and placebo.

On the other hand, the report during the study, of mild and moderate adverse events was also significantly lower in the policosanol group than in the placebo group ($p <0.01$) (data not shown in Table for simplicity).

TABLE 1. Main baseline characteristics by gender

Women				
Characteristics	**Placebo (n = 571)**		**Policosanol (n=582)**	
Age (years) (X ± SD)	66 ± 6		66 ± 6	
Risk factors	**n**	**%**	**n**	**%**
Hypertension	391	67.2	377	66.0
CHD	158	27.2	151	26.4
Diabetes mellitus	109	18.7	109	19.1
Smoking	97	16.7	92	16.1
Cerebrovascular (CBV) disease	26	4.5	22	3.9
Concomitant medications				
Diuretics	154	26.5	160	28.0
Calcium antagonists	131	22.5	121	21.2
Anxyolytics	106	18.2	107	18.7
Aspirin	99	17.0	88	15.4
β-blockers	85	14.6	79	13.8
Vasodilators	81	13.9	74	13.0
Vitamins	61	10.5	74	13.0
Myorelaxants	57	9.8	67	11.7
Oral hypoglycemic drugs	68	11.7	53	9.3
Dypiridamole	37	6.4	35	6.1
Men	**Placebo (n=151)**		**Policosanol (n=166)**	
Age (years) (X ± SD)	66 ± 6		66 ± 6	
Risk factors	**n**	**%**	**n**	**%**
Hypertension	82	54.3	93	56.0
CHD	43	28.5	56	33.7
Diabetes mellitus	23	15.2	22	13.3
Smoking	55	36.4	53	31.9
Cerebrovascular (CBV) disease	8	5.3	14	8.4
Concomitant medications				
Calcium antagonists	28	18.5	33	19.9
Aspirin	31	20.5	30	18.1
Diuretics	26	17.2	28	16.9
β-blockers	22	14.6	19	11.5
Vasodilators	14	9.3	16	9.6
Vitamins	18	11.9	14	8.4
Anxyolytics	12	8.0	14	8.4
Oral hypoglycemic drugs	11	7.3	12	7.2

n Number of patients; X mean, SD standard deviation, CHD* coronary heart disease, (myocardial infarction, angina, coronary surgery); CBV (stroke, ischemic transient attacks). The table include CM consumed by > 6 % of study patients. All between group comparisons were not significant

TABLE 2 Effects on efficacy variables by gender

All SAE (fatal + nonfatal)					
Women	**Placebo (n = 582)**		**Policosanol (n = 571)**		**p value***
	n	**%**	**n**	**%**	
All SAE	63	10.8	17	3.0	p < 0.001
All vascular SAE	34	5.8	10	1.6	p < 0.001
Cardiovascular SAE	21	3.6	4	0.7	p < 0.001
Coronary EAS	19	3.3	3	0.5	p < 0.001
All deaths	10	1.7	1	0.2	p < 0.05
Men	**n = 151**		**n = 166**		
All SAE	20	13.2	9	5.4	p < 0.001
All vascular SAE	15	9.9	6	3.6	p < 0.01
Cardiovascular SAE	12	7.9	3	1.8	p < 0.01
Coronary EAS	11	1.9	3	1.8	p < 0.01
All deaths	9	6.0	3	1.8	p < 0.05
Nonvascular SAE					
Women	29	5.0	8	1.4	p < 0.001
Men	5	3.3	3	1.8	ns

SAE serious adverse events, ns no significant, *Comparison with placebo ($\chi 2$ test)

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TABLE 3. Effects of policosanol on lipid profile (X ± SD): Analyses by gender

Treatment	Baseline	1 year	2 years	3 years
CT (mmol/L)				
Women				
Policosanol	6.82±0.91	5.69±0.69^{++}	5.42±0.70^{++}	5.26±0.63^{++}
Placebo	6.71±0.84	6.65±0.83	6.70±0.81	6.60±0.73
Men				
Policosanol	6.56±0.83	5.58±0.67^{++}	5.39±0.62^{++}	5.19±0.49^{++}
Placebo	6.63±0.97	6.47±0.94	6.55±0.94	6.49±0.80
LDL-C (mmol/L)				
Women				
Policosanol	4.78±0.88	3.75±0.65^{++}	3.39±0.69^{++}	3.17± 0.57^{++}
Placebo	4.67±0.85	4.69±0.80	4.82±0.77	4.74± 0.72
Men				
Policosanol	4.51±0.86	3.66±0.67^{++}	3.42±0.64^{++}	3.11±0.69^{++}
Placebo	4.60±0.89	4.57±0.87	4.68±0.94	4.65±0.83
HDL-C (mmol/L)				
Women				
Policosanol	1.22±0.34	1.28±0.25^{+}	1.34±0.27^{+}	1.41±0.23^{+}
Placebo	1.24±0.33	1.18±0.29	1.11±0.20	1.11±0.17
Men				
Policosanol	1.21±0.33	1.26±0.24^{+}	1.30±0.23^{+}	1.39±0.25^{+}
Placebo	1.19±0.31	1.13±0.23	1.11±0.22	1.08±0.12
Triglycerides (mmol/L)				
Women				
Policosanol	2.22±0.91	1.77±0.56^{+}	1.81±0.48^{+}	1.78±0.41^{+}
Placebo	2.22±0.99	2.09±0.72	2.08±0.54	2.03±0.51
Men				
Policosanol	2.27±0.89	1.82±0.61^{+}	1.78±0.44^{+}	1.82±0.53^{+}
Placebo	2.26±0.98	2.11±0.92	2.09±0.66	2.04±0.40

X mean, SD standard deviation, +p < 0.0001, ++p < 0.00001 Comparison with placebo (t-test for independent samples)

IV. Discussion

Policosanol inhibits cholesterol synthesis in the firth step of its metabolic pathway through activation of Adenosine Monophosphate Protein Kinase (AMPK), which in turn inhibit Hydroxyl-Methyl-Glutaryl-Coenzyme A-Reductase, a key enzyme for cholesterol synthesis.[14-17] AMPK, once activated, also inhibit Acetyl CoA Carboxylase (ACC). The inhibition of ACC increases fatty acid oxidation and reduces lipid synthesis, protecting in this way, muscle, heart, and others tissues from lipotoxicity.[37,38] In addition, AMPK activation is associated with a wide array of beneficial effects,[39] that could explain the low level of side effect and compliance in the treated group versus placebo.

After intestinal absorption, very long chain fatty alcohols are up taken by the liver and partially converted into carboxylic acids.[40] These results indicated that higher intake of VLCFA is significantly associated with favorable metabolic status including lower levels of circulating triglycerides.[41] An study confirmed that circulating serum VLCSFAs were independently associated with favorable profiles of blood lipids (lower triglycerides and increase HDL-C); others cardio vascular disease risk markers, and a lower CVD risk by 52 %.[42]

On the other hand, fatty alcohols, derive from fatty acid in endothelial reticulum are substrates for the synthesis of plasmalogens in peroxisomes, which are potent endogenous antioxidants. Plasmalogens are released from the liver as component of lipoproteins thus protecting them from oxidation, and favoring its functionability.[43]

The mean age of study patients was 66 years at randomization, which indicates that many study patients still were enough young to apply preventive measures that improve their quality and expectancy of life.

The larger proportion of women respect to men is a particular characteristic of the study, which does not reflect an objective of study protocol, but a characteristic of the patients assisting to the Policlinics visits of this area of Havana.[44]

The disproportion between genders in the study participants could be a limitation of the study results, nevertheless, percentages of participants by sex, but in the opposite sense, it means a larger proportion of men occurs in women/men participating in 4S, CARE, LIPID, WOSCOPS and AFCAPS/TexCAPS[5–9] studies, been 18/82 %, 14/86 %, 17/83 %, 15.1/84.9 % and 0/100 %, respectively; in contrast with the 78/22 % relationship here occurred. Thus, although CHD is their leading cause of death,[45] women had been misrepresented from lipid trials, principally because of the earlier onset of CHD in men has led to the perception that it is a men disease. However, after menopause, the low oestrogen production contributes to the increase on CHD in women.[46] Thus, increased oxidation of LDL and platelet aggregation documented for postmenopausal women[46,47] can contribute to explain, at least partly, the greater clinical impact of policosanol in this sex.

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The beneficial impact on clinical outcomes was better in women, despite the lipid-lowering response was similar in both sexes.

The present study demonstrates that policosanol reduce the incidence of serious vascular adverse events (fatal and non-fatal), as well as total SAE and mortality, compared with placebo in old aged patients.

Contribution of other effects, beyond its lipid-lowering properties of policosanol, such as antiplatelet effects [28-30] and inhibition of LDL lipid peroxidation[31,32] must contributes to the obtained results. Moreover, according with recent results, policosanol seems to present regeneration abilities via enhancement of HDL functionability.[48]

Policosanol, not placebo, modestly, but significantly reduced blood pressure, consistently with some previous data,[23-26] contributing in these way to reduction of coronary events, cerebrovascular events and mortality in the elderly.[49,50]

Since the mean age of the study population is within a range wherein life expectancy is still considerable and study conditions were similar to routine clinical practice, preventive measures based on the present results obtained with policosanol could improve the quality and extent of life in these age group of this population.

V. CONCLUSIONS

The present results demonstrate that treatment with policosanol significant lower amount of vascular SAE, produce relevant positive changes on serum lipid profile and lower frequency of total AE in older hypercholesterolemic patients. Clinical impact was evident in both sexes, but greater in woman. These findings support the recommendation of policosanol use as treatment in primary or secondary prevention program for older patients at cardiovascular risk.

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