

Long-term effects with policosanol on lipid profile according to hypercholesterolemia severity in older patients

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Abstract

Background: End-point based studies have demonstrated a direct relationship between coronary disease and elevated serum levels of low density lipoprotein cholesterol (LDL-C) and total cholesterol, as well as the benefits of lowering LDL-C with statins on clinical end-points.

Policosanol is a mixture of very long chain fatty alcohols purified from sugar cane wax, with dislipidemia controlling effects, proved in numerous clinical assays in which patients with different conditions were included. The efficacy and tolerability of policosanol in the elderly have been also investigated in several clinical trials, being effective, safe and well tolerated.

Objectives: To investigate the effects of policosanol treatment during three years on lipid profile with a proportional intensity to the initial dislipidemia severity in older hypercholesterolemic patients.

Methods: The present analysis was obtained from the data of all patients treated with policosanol included in a previous prevention study. One thousand, four hundred seventy old patients of both sexes, between 60 to 85 years old, with type II hypercholesterolemia, and ≥ 1 non-lipid coronary risk factors, were randomized in two groups and treated with policosanol or placebo, during three years. Significant changes on lipid profile with a proportional intensity to the initial dislipidemia severity were considered primary efficacy variables. The analysis was done by Intention-to-treat method.

Results: An analysis of the response intensity show that after treatment, reductions of LDL-C, total cholesterol and triglycerides were greater, and according to the initial hypercholesterolemia severity, so that, patients with severe hypercholesterolemia showed the better responses, followed by moderate and mild hypercholesterolemia. An opposite pattern, however, was observed for HDL-C serum concentration. Triglycerides did not respond in the same way.

The frequency of vascular serious adverse events was lower in the policosanol group (15 events) compared with those on placebo group (49 events). There were 109 patients who experienced serious adverse events: 83 (11.3 %) in placebo and 26 (3.5 %) in policosanol group ($p < 0.0001$). Twenty-three deaths occurred up to study completion: 19 patients belonging to placebo group (2.6 %) and 4 to the policosanol group (0.5 %).

Conclusions: The treatment with policosanol produce positive changes on serum lipid profile according to hypercholesterolemia severity and with a significant lower amount of vascular serious adverse events, mortality, and frequency of total adverse events in older patients.

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1. Introduction

The management of cardiovascular risk factors, like elevated LDL-C, is called primary prevention when patients had not previously experienced a cardiovascular event. The focalization on primary prevention on LDL reduction is based on epidemiologic data documenting a continuous, positive and graded relationship between LDL-C concentration and cardiovascular disease events and mortality, evidencing that lowering LDL-C in patients, reduces the risk in patients with or without cardiovascular disease across a broad range of concentration [1-3].

Patients without known cardiovascular disease are generally at much lower baseline of cardiovascular events risk than patients with known cardiovascular disease. The decision to recommend LDL treatment depend on the global cardiovascular disease risk because the potential absolute risk reduction by treating hypercholesterolemia will usually be smaller for patients with established cardiovascular disease [2,3].

End-point based studies have demonstrated a direct relationship between coronary disease and elevated serum levels of LDL-C and total cholesterol², as well as the benefits of lowering LDL-C on clinical end-points [4-9].

Hypercholesterolemia management in the elderly had been questioned because, according with some opinions, 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, plasma lipid determinations still remain 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 large and prolonged multivariable analysis, had confirmed the inverse, independent, strong and graded relationship between HDL-C in both cardiovascular disease and coronary disease mortality [12].

Policosanol is a mixture of high molecular weight alcohols purified from sugar cane (*Saccharum officinarum*, L) wax [13]. exhibiting a 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].

A total cholesterol, and LDL-C lowering, the HDL concentration increment and a constant but less effective reduction on triglycerides concentration 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 many and relevant pleiotropic effects, such as the inhibition of platelet aggregation [28-30]. and the susceptibility inhibition of LDL to be oxidised between many others [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 hypercholesterolemic elders with the objective to investigate its effects on lipid profile according to different degree of hypercholesterolemia severity in older patients during three years.

2. Patients and Methods

2.1. Study design

The data of hyperlipidaemia severity used in the present analysis on policosanol effect, was obtained from the results of all patients treated with policosanol included in a previous prospective, randomized, double-blinded, placebo-controlled study which included 1470 older patients [36]. treated with placebo or policosanol for three years after randomization.

An Independent Ethics Committee approved the study protocol. Patients were recruited at four Polyclinic Centre 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 five 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.

2.1.1. 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 an appropriate life expectancy which, in Cuba is around 80 years.

2.1.2. 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.

2.1.3. 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 adverse events within the three months previous to being enrolled in the study were also excluded.

2.1.4. Withdrawal criteria

Any serious adverse events or any adverse events justifying such decision, unwillingness to follow-up by any cause, major violations of study protocol, including > 6 consecutive weeks without taking the study medications.

2.2. Treatment

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

2.2.1. 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.

2.2.2. 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.

2.2.3. 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.

2.3. Efficacy analyses

2.3.1. Primary efficacy variables

Changes on lipid profile (LDL-C, total cholesterol, HDL-C and triglycerides) according to hypercholesterolemia severity were considered a primary efficacy variable in this analyses. Treatment was considered as effective if LDL-C was significantly reduced by $\geq 15\%$ [37].

2.3.2. Secondary efficacy variables

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

2.3.3. 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 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 [38].

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 definitely 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.

2.3.4. 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.

2.4. 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 χ^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).

3. Results

3.1. Baseline patient characteristics

Of the 1612 patients recruited, 1470 were eligible and randomized to policosanol (n=737) or placebo (n=733). The main causes to be not eligible were total cholesterol and LDL-C values after diet period below inclusion criteria (n=76); triglycerides > 4.52 mmol/L (n=36) and unwillingness to continue participating (n=30).

Table 1 summarizes the main baseline characteristics of study patients. Both groups were well matched at randomisation. Of 1470 randomised subjects, 466 (31.7 %) were at secondary prevention, while most were at primary prevention (1004, 68.3 %), but with ≥ 1 concomitant coronary risk factor. The prevalence of arterial hypertension, diabetes and current smoking was 64.1 %; 17.9 % and 20.2 %, respectively. Most patients (917, 62.3%) showed isolated hypercholesterolemia (elevated total cholesterol, normal triglycerides), while 553 (37.6 %) showed combined hypercholesterolemia (elevated total cholesterol and triglycerides).

Table 1 Main baseline characteristics of study patients

Characteristics	Placebo (n = 733)	Policosanol (n=737)
Age (years) (X±SD)	66 ± 6	66 ± 6
Body mass index (kg/m²) (X±SD)	26.5 ± 5.3	26.7 ± 4.8
Total cholesterol (mmol/L) (X±SD)	6.70 ± 0.87	6.76 ± 0.90
LDL-C (mmol/L) (X±SD)	4.65 ± 0.86	4.72 ± 0.88

HDL-C (mmol/L) (X±SD)	1.21 ± 0.33		1.22 ± 0.34	
Triglycerides (mmol/L) (X±SD)	2.23 ± 0.99		2.23 ± 0.90	
Systolic blood pressure (mm Hg) (X±SD)	136 ± 17		137 ± 20	
Diastolic blood pressure (mm Hg) (X±SD)	82 ± 10		82 ± 10	
	N	%	n	%
Gender: Female	582	79.4	571	77.5
Male	151	20.6	166	22.5
Isolated hypercholesterolemia	465	63.4	452	61.3
Combined hypercholesterolemia	268	36.6	285	38.7
Risk factors				
Arterial hypertension	473	64.5	470	63.8
Smoking	152	20.7	145	19.7
Coronary disease*	201	27.4	207	28.1
Diabetes mellitus	132	18.0	131	17.8
Obesity (kg/m ² > 30)	66	9.0	63	8.5
HDL-C < 0.9 mmol/L	51	7.0	59	8.0
Cerebrovascular disease**	34	4.6	36	4.9
Family history of coronary disease	362	49.4	366	50.0
Concomitant medications (CM)***				
Diuretics	181	24.7	187	25.4
Calcium antagonists	158	21.6	155	21.0
Aspirin	129	17.6	119	16.1
Anxiolytics	118	16.1	121	16.4
β-blockers	107	14.6	98	13.3
Vasodilators	95	13.0	90	12.2
Oral hypoglycemic drugs	79	10.8	65	8.8

n Number of patients; X mean, SD standard deviation, *myocardial infarction, unstable angina, coronary surgery. **stroke, ischemic transient attacks; ***CM consumed by > 6 % of study patients.

3.2. All comparisons were not significant

Table 2 lists the frequency of withdrawals, which was greater ($p < 0.0001$) in placebo group (189, 25.8 %) than in policosanol group (88, 11.9 %). The same was true ($p < 0.0001$) for withdrawals due to adverse events 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 serious adverse events and another 12 (9 placebos, 1.2 % and 3 policosanol treated, 0.4 %) because of mild or moderate adverse events.

Compliance within the study drugs was good, 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.

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 o.d. with the evening meal. The frequency of needing titration was different in both groups ($p < 0.01$).

Table 2 Withdrawal analysis

Withdrawals due to AE	Placebo (n = 733)	Policosanol (n = 737)	p value*	Total
Vascular SAE	49	15	p < 0.0001	64
SAE from other causes	34	11	p < 0.001	45
Mild and moderate AE	9	3	ns	12
Subtotal due to all AE	92	29	p < 0.0001	121
Withdrawals due to other reasons				
Unsatisfactory efficacy	37	7	p < 0.0001	44
Travels abroad+changes to other towns or living areas	16	13	ns	29
Unwillingness to follow-up	30	30	ns	60
Protocol violations	14	9	ns	23
Subtotal due to other reasons	97 (13.2 %)	59 (8.0 %)	p < 0.01	156 (10.6 %)
Total of withdrawals	189 (25.8 %)	88 (11.9 %)	p < 0.0001	277 (18.8 %)

AE adverse event, SAE serious adverse events, *Comparison with placebo (χ^2 test)

3.3. Effects on primary efficacy variables

Table 3 shows the effects of policosanol on lipid profile variables according to the severity of hypercholesterolemia at baseline. These data revealed a difference from placebo response of LDL-C, total cholesterol, HDL-C and triglycerides in all strata of hypercholesterolemia severity.

Table 3 Long-term effects of policosanol on lipid profile ($x \pm SD$) according to hypercholesterolemia severity in older patients

Study groups	Baseline	1 year	2 years	3 years
Total cholesterol (TC) (mmol/L)				
Mild hypercholesterolemia (TC ≥ 5, but < 6.1)				
Policosanol (n=200)	5.79 $\pm$ 0.22	5.21 $\pm$ 0.53 ⁺	5.19 $\pm$ 0.64 ⁺	5.16 $\pm$ 0.67 ⁺
Placebo (n=207)	5.76 $\pm$ 0.22	5.97 $\pm$ 0.55	5.99 $\pm$ 0.50	5.93 $\pm$ 0.52
Moderate hypercholesterolemia (TC ≥ 6.1, but < 7.8)				
Policosanol (n=424)	6.80 $\pm$ 0.47	5.71 $\pm$ 0.59 ⁺	5.41 $\pm$ 0.60 ⁺	5.26 $\pm$ 0.57 ⁺
Placebo (n=435)	6.80 $\pm$ 0.48	6.64 $\pm$ 0.63	6.72 $\pm$ 0.63	6.72 $\pm$ 0.60
Severe hypercholesterolemia (TC ≥ 7.8)				
Policosanol (n=113)	8.31 $\pm$ 0.55	6.25 $\pm$ 0.75 ⁺	5.78 $\pm$ 0.89 ⁺	5.42 $\pm$ 0.66 ⁺
Placebo (n=91)	8.33 $\pm$ 0.38	7.80 $\pm$ 0.91	7.88 $\pm$ 0.84	7.82 $\pm$ 0.84
LDL-C (mmol/L)				
Mild hypercholesterolemia (TC ≥ 5, but < 6.1)				
Policosanol (n=200)	3.89 $\pm$ 0.45	3.33 $\pm$ 0.49 ⁺	3.16 $\pm$ 0.63 ⁺	3.13 $\pm$ 0.59 ⁺
Placebo (n=207)	3.85 $\pm$ 0.45	4.11 $\pm$ 0.58	4.18 $\pm$ 0.55	4.14 $\pm$ 0.54
Moderate hypercholesterolemia (TC ≥ 6.1, but < 7.8)				
Policosanol (n=424)	4.77 $\pm$ 0.59	3.77 $\pm$ 0.59 ⁺	3.42 $\pm$ 0.59 ⁺	3.19 $\pm$ 0.58 ⁺
Placebo (n=435)	4.75 $\pm$ 0.59	4.71 $\pm$ 0.67	4.86 $\pm$ 0.65	4.85 $\pm$ 0.65

Severe hypercholesterolemia (TC ≥ 7.8)				
Policosanol (n=113)	5.98 ± 0.77	4.23 ± 0.71 ⁺	3.71 ± 0.88 ⁺	3.21 ± 0.62 ⁺
Placebo (n=91)	6.07 ± 0.60	5.64 ± 0.87	5.87 ± 0.80	5.89 ± 0.35
HDL-C (mmol/L)				
Mild hypercholesterolemia (TC ≥ 5, but < 6.1)				
Policosanol (n=200)	1.15 ± 0.31	1.28 ± 0.23 ⁺	1.34 ± 0.29 ⁺	1.35 ± 0.23 ⁺
Placebo (n=207)	1.17 ± 0.27	1.16 ± 0.29	1.11 ± 0.21	1.10 ± 0.15
Moderate hypercholesterolemia (TC ≥ 6.1, but < 7.8)				
Policosanol (n=424)	1.21 ± 0.33	1.27 ± 0.24 ⁺	1.31 ± 0.24 ⁺	1.40 ± 0.21 ⁺
Placebo (n=435)	1.25 ± 0.33	1.16 ± 0.26	1.10 ± 0.18	1.11 ± 0.17
Severe hypercholesterolemia (TC ≥ 7.8)				
Policosanol (n=113)	1.35 ± 0.39	1.36 ± 0.28 ⁺	1.39 ± 0.28 ⁺	1.48 ± 0.28 ⁺
Placebo (n=91)	1.30 ± 0.39	1.24 ± 0.33	1.17 ± 0.28	1.07 ± 0.17
Triglycerides (mmol/L)				
Mild hypercholesterolemia (TC ≥ 5, but < 6.1)				
Policosanol (n=200)	2.00 ± 0.81	1.67 ± 0.54 ⁺	1.72 ± 0.38 ⁺	1.74 ± 0.53 ⁺
Placebo (n=207)	2.02 ± 0.93	1.92 ± 0.60	1.91 ± 0.48	1.89 ± 0.50
Moderate hypercholesterolemia (TC ≥ 6.1, but < 7.8)				
Policosanol (n=424)	2.24 ± 0.90	1.80 ± 0.57 ⁺	1.82 ± 0.50 ⁺	1.77 ± 0.30 ⁺
Placebo (n=435)	2.24 ± 0.98	2.09 ± 0.69	2.10 ± 0.52	2.06 ± 0.49
Severe hypercholesterolemia (TC ≥ 7.8)				
Policosanol (n=113)	2.61 ± 0.95	1.88 ± 0.60 ⁺	1.84 ± 0.43 ⁺	1.90 ± 0.62 ⁺
Placebo (n=91)	2.67 ± 1.00	2.49 ± 1.15	2.33 ± 0.77	2.27 ± 0.35

X mean, SD standard deviation, ⁺p < 0.001 Comparison with placebo (t-test for independent samples)

3.4. Intensity of response versus degree of dislipidemia

An analysis of the responses intensity of the showed that reductions in LDL-C, total cholesterol and triglycerides after one year of treatment were greater according to the degree of hypercholesterolemia severity, so that patients with severe hypercholesterolemia showed the better responses, followed by moderate and mild hypercholesterolemia. An opposite pattern, however, was observed for HDL-C. With the exception of triglycerides, the other responses were improved during the study. These changes are summarized and simplified in Tables 4 and 5 showing absolute values and percent changes, respectively.

3.5. Effects on secondary efficacy variables

The frequency of vascular serious adverse events was lower in the policosanol group (15 events) as compared with placebo (49 events) (p<0.0001) (Table 6).

The amount of cardiovascular serious adverse events compared to placebo (33) was significantly lower in the policosanol group (7) (p<0.0001). Also, there were 12 cerebrovascular serious adverse events (1.6 %) in the placebo and 5 (0.7 %) in the policosanol group (p<0.05).

There were 109 patients who experienced serious adverse events (fatal + non-fatal): 83 (11.3 %) in placebo and 26 (3.5 %) in policosanol group (p<0.0001).

Twenty-three deaths occurred up to study completion: 19 taking placebos (2.6 %), and 4 policosanol (0.5 %). The frequency of deaths due to cardiovascular events with policosanol (1 death, 0.1 %) was lower ($p < 0.01$) than with placebo (13 deaths, 1.8 %). Also, 3 patient taking placebo (0.4 %), but any patient under policosanol treatment died because of cerebrovascular events. The deaths due to nonvascular causes (6/ 23, 26.1 %) were similar in both groups.

On the other hand, the frequency of non-vascular serious adverse events in the policosanol group (11 events, 1.5%) was significantly lower ($p < 0.001$) than in placebo (34 events, 4.6%) (data not shown in Table for simplicity).

3.5.1. Safety and tolerability

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

Table 4 Summary of the changes on lipid profile variables in policosanol group according to hypercholesterolemia (HC) severity

Study groups	Baseline	1 year	2 years	3 years
Total cholesterol (mmol/L) ($\bar{x} \pm SD$)				
Mild HC (n=200)	5.79 $\pm$ 0.22	5.21 $\pm$ 0.53	5.19 $\pm$ 0.64	5.14 $\pm$ 0.67
Moderate HC (n=424)	6.80 $\pm$ 0.47	5.71 $\pm$ 0.59	5.41 $\pm$ 0.60	5.26 $\pm$ 0.57
Severe HC (n=113)	8.31 $\pm$ 0.55	6.25 $\pm$ 0.75	5.78 $\pm$ 0.89	5.42 $\pm$ 0.66
LDL-C (mmol/L)				
Mild HC (n=200)	3.89 $\pm$ 0.45	3.33 $\pm$ 0.49	3.16 $\pm$ 0.63	3.13 $\pm$ 0.59
Moderate HC (n=424)	4.77 $\pm$ 0.59	3.77 $\pm$ 0.59	3.42 $\pm$ 0.59	3.19 $\pm$ 0.58
Severe HC (n=113)	5.98 $\pm$ 0.77	4.23 $\pm$ 0.71	3.71 $\pm$ 0.88	3.21 $\pm$ 0.62
HDL-C (mmol/L)				
Mild HC (n=200)	1.15 $\pm$ 0.31	1.28 $\pm$ 0.23	1.34 $\pm$ 0.29	1.35 $\pm$ 0.23
Moderate HC (n=424)	1.21 $\pm$ 0.33	1.27 $\pm$ 0.24	1.31 $\pm$ 0.24	1.40 $\pm$ 0.21
Severe HC (n=113)	1.35 $\pm$ 0.39	1.36 $\pm$ 0.28	1.39 $\pm$ 0.28	1.48 $\pm$ 0.28
Triglycerides (mmol/L)				
Mild HC (n=200)	2.00 $\pm$ 0.81	1.67 $\pm$ 0.54	1.72 $\pm$ 0.38	1.74 $\pm$ 0.53
Moderate HC (n=424)	2.24 $\pm$ 0.90	1.80 $\pm$ 0.57	1.82 $\pm$ 0.50	1.77 $\pm$ 0.30
Severe HC (n=113)	2.61 $\pm$ 0.95	1.88 $\pm$ 0.60	1.84 $\pm$ 0.43	1.90 $\pm$ 0.62

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 5 Lipid profile % changes in policosanol group (according to hypercholesterolemia- HC- severity)

Study groups	1 year	2 years	3 years
Total cholesterol			
Mild HC (n=200)	- 11	- 11	- 11
Moderate HC (n=424)	- 16	- 20	- 23
Severe HC (n=113)	- 25	- 30	- 35
LDL-C			
Mild HC (n=200)	- 14	- 19	- 20
Moderate HC (n=424)	- 21	- 28	- 33

Severe HC (n=113)	- 29	- 38	- 46
HDL-C			
Mild HC (n=200)	+ 11	+ 17	+ 17
Moderate HC (n=424)	+ 5	+ 8	+ 16
Severe HC (n=113)	+ 1	+ 3	+ 10
Triglycerides			
Mild HC (n=200)	- 17	- 14	- 13
Moderate HC (n=424)	- 20	- 19	- 19
Severe HC (n=113)	- 28	- 30	- 27

Table 6 Effects on secondary efficacy variables

	Placebo (n= 733)		Policosanol (n = 737)		p value*
Primary efficacy	n	%	n	%	
Vascular SAE	49	6.7	15	2.0	p < 0.0001
Cardiovascular SAE	33	4.5	7	0.9	p < 0.0001
Cerebrovascular SAE	12	1.6	5	0.7	p < 0.05
Secondary efficacy					
SAE (fatal + non-fatal)	83	11.3	26	3.5	p < 0.0001
Non vascular SAE	34	4.6	11	1.5	p < 0.01
All mortality	19	2.6	4	0.5	p < 0.001

SAE serious adverse events, *Comparison with placebo (χ^2 test)

4. Discussion

The present analysis demonstrates that long-term treatment with policosanol produce positive changes on lipid profile according to hypercholesterolemia severity in older patients.

Both groups were well balanced at baseline. Most subjects were at primary prevention with one or more risk factors, but secondary prevention patients with a generally stable condition were also included. Hence, the study results should be extrapolated mainly to patients with similar conditions.

Among the most relevant baseline characteristics must be noted that the mean age of study patients was 66 years at randomization, indicating that many subjects still were young enough to apply preventive measures that might improve their quality and expectancy of life. The frequency of concomitant medications was high, consistent with their risk condition and common in the elderly [11].

LDL-C is considered the most important variable among lipid profile parameters. As compared with placebo, policosanol reduced LDL-C, total cholesterol and triglycerides, whereas it increased HDL-C. These changes were consistent with those expect response to policosanol, being potentially useful for risk reduction [12,17-26].

The responses were maintained, or even enhanced, throughout the study. The changes here reported for LDL-C; total cholesterol and HDL-C are consistent with the expected response to policosanol long-term therapy. Reductions on triglycerides, however, were superior that those reported in previous studies, a finding without any conclusive explanation. No significant change of any lipid profile variable occurred in placebo group.

The analysis of the cholesterol-lowering response according to hypercholesterolemia severity at randomization revealed that reductions in LDL-C, total cholesterol and triglycerides after one year of treatment were greater in severe and moderate hypercholesterolemia compared with mild hypercholesterolemia, while the opposite pattern was observed for HDL-C. These findings, agree with previous results. With the exception of triglycerides, which showed a similar response throughout the trial, the other responses were enhanced during the study when we analysis the data according to hypercholesterolemia strata.

The different withdrawal rate in both groups was a consequence of the discontinuations due to serious adverse events and those due to unsatisfactory efficacy for achieving levels over those considered as upper cut-off for premature discontinuations. Thus, the frequency of all vascular serious adverse events, cardiovascular, cerebrovascular, all deaths to vascular causes and all deaths was lower ($p < 0.05$) than in placebo, consistently with LDL-C lowering and pleiotropic effects of policosanol, all beneficial for vascular function, thus preventing the occurrence of vascular events.

It was demonstrated that policosanol inhibits cholesterol synthesis in the first step of its metabolic pathway through activation of Adenosine Monophosphate Protein Kinase (AMPK), which in turn inhibit Hydroxyl-Methyl-Glutaryl-Coenzyme A-Reductase [13-16]. 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 [39]. In addition, AMPK activation is associated with a wide array of beneficial effects, [40]. 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 [41]. These results indicated that higher intake of VLCFA is significantly associated with favorable metabolic status including lower levels of circulating triglycerides [42]. Other study confirmed that circulating serum VLCFAs were independently associated with favorable profiles of blood lipids (lower triglycerides and increase HDL-C); others cardiovascular disease risk markers, and a lower cardiovascular disease risk by 52 % [43].

On the other hand, fatty alcohols 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 [44].

Thus, the contribution of other effects, beyond its lipid-lowering properties, must be present in the benefits here demonstrated for policosanol. In particular, the contribution of its antiplatelet effects could be relevant, taking into account the effects reported for antiplatelet therapy on risk reduction in patients at high vascular risk [45]. Moreover, according with recent results, policosanol seems to present regeneration abilities via enhancement of HDL functionability [46].

Policosanol was safe and well tolerated. Unexpectedly, policosanol reduced nonvascular serious adverse events, a finding that could to be explained in basis of its pleiotropic effects, including those described and others yet unknown. The analysis of the overall frequency of any adverse events also discards any increase in particular adverse events due to policosanol.

Overall frequency of mild and moderate adverse event was lower in the policosanol group than in the placebo group. This result, together with serious adverse events and withdrawal analysis, eliminates any increase in particular adverse event due to policosanol.

No drug-related impairment of any safety indicator was observed. Policosanol, not placebo, modestly, but significantly reduced blood pressure, consistently with some previous data.^{22,24,25} Such decreases could have contributed to the presents results, since lowering systolic pressure significantly reduces coronary events and total mortality in the elderly. [47]. Specific on the effect of policosanol on hypertension studies confirm these results [48-50].

5. Conclusion

Elder patients with documented coronary disease, hypercholesterolemia, and others coronary risk factors, once treated with policosanol, reported relevant positive changes on serum lipid profile and a significant lower amount of vascular serious adverse events, frequency of total adverse events and mortality.

Compliance with ethical standards

Financial Disclosure

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Conflict of interest

The authors declare that there is no conflict of interest in relation to this work.

Statement of informed consent

Informed consent was obtained from all individual participants included in the study.

References

- [1] Virani SS, Alonso A, Benjamin EJ, Bittencourt MS, Callway CW, Carson AP, et al. American Heart Association Council on Epidemiology and Prevention Statistics Committee and Stroke Statistics Subcommittee. Heart Disease and Stroke Statistics-2020 Update: A Report from the American Heart Association. *Circulation*. 2020; 141(9):e139-e596.
- [2] Ference BA, Ginsberg HN, Graham I, et al. Low-density lipoproteins cause atherosclerotic cardiovascular disease. Evidence from genetic, epidemiologic, and clinical studies. A consensus statement from the European atherosclerosis society consensus panel. *Eur Heart J*. 2017; 38: 2459–2472.
- [3] Reiter-Brennan C, Osei AD, Uddin MI, Orimoloye OA, Obisesan OH, Mirbolouk M, et al. ACC/AHA lipid guidelines: Personalized care to prevent cardiovascular disease. *Cleveland Clinic Journal of Medicine*. 2020; 87(4): 231-239.
- [4] Packard CJ, Ford I. Long-term follow-up of lipid-lowering trials. *Curr Opin Lipidol*. 2015; 26: 572-575.
- [5] Kazi DS, Penko JM, Bibbins-Domingo K. Statins for primary prevention of cardiovascular disease: Review of Evidence and Recommendations for Clinical Practice. *Med Clin North Am*. 2017; 101(4): 689-699.
- [6] Kim K, Le SH. Effects of Statins for Primary Prevention in the Elderly: Recent Evidence. *J Lipid Atheroscler*. 2020; 9(1): 1-7.
- [7] Ford I, Murray H, Mc Cowan C, Packard CJ. Long-term safety and efficacy of lowering low-density lipoprotein cholesterol with statin therapy: 20-year follow-up of West of Scotland Coronary Prevention Study. *Circulation*. 2016; 133: 1073-1076.
- [8] Heart Protection Study Collaborative Group. MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20,536 high-risk individuals: a randomized placebo-controlled trial. *Lancet*. 2002; 360: 7-22.
- [9] Lloyd SM, Stott DJ, de Craen AJ, Kearney PM, Sattar N, Perry I, et al. Long-term effects of statin treatment in elderly people: extended follow-up of the prospective study of pravastatin in the elderly at risk (PROSPER). *PloS ONE*. 2013; 8: e72642.
- [10] Arnett DK, Blumenthal RS, Albert MA, Buroker AB, Goldberger ZD, Hahn EJ, et al. 2019 ACC/AHA Guideline on the Primary Prevention of Cardiovascular Disease: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Am Coll Cardiol*. 2019; 74(10): e177-e232.
- [11] Jellinger PS, Handelsman Y, Rosenblit PD, Bloomgarden ZT, Fonseca VA, Garber AJ, et al. American association of clinical endocrinologists and american college of endocrinology guidelines for management of dyslipidemia and prevention of cardiovascular disease. *Endocr Pract*. 2017; 23(2): 1-87.
- [12] Cooney MT, Dudina A, De Bacquer D, Wilhelmsen L, Sans S, Menotti A, & Whincup P. HDL cholesterol protects against cardiovascular disease in both genders, at all ages and at all levels of risk. *Atherosclerosis*. 2009; 206(2): 611-616.
- [13] Mas R. Policosanol Drugs of the Future. 2000; 25: 569-586.
- [14] Menéndez R, Amor AM, Rodeiro I, Gonzalez RM, Acosta P, Alfonso J, Más R. Policosanol modulates HMG-CoA reductase activity in cultured fibroblast. *Arch Med Res*. 2001; 32: 8-13.
- [15] Sing DK, Li Li, Poter TD. Policosanol inhibits cholesterol synthesis in hepatoma cells by activation of AMP-kinase. *J Pharmacol Ther*. 2006; 318: 1020-1025.

- [16] Banerjee S, Ghoshal S, Porter TD. Activation of AMP-kinase by policosanol requires peroxisomal metabolism. *Lipids*. 2011; 46(4): 311-321.
- [17] Oliaro-Bosso S, Calcio E, Mantegna S, Maniet P, Rolie S. Regulation of HMG Co A reductase activity by policosanol and octacosadienol, a new synthetic analogue of octacosanol. *Lipids*. 2009; 44: 907-916.
- [18] Canetti M, Morera MS, Mas R, Illnait J, Fernández L, Fernández JC, et al. Effects of policosanol on primary hypercholesterolemia: A 3-year open follow-up. *Curr Ther Res Clin & Exptl*. 1997; 58: 868-875.
- [19] Más R, Castaño G, Illnait J, Fernández L, Fernández JC, Alemán C, et al. Effects of policosanol in patients with type II hypercholesterolemia and additional coronary risk factors. *Clin Pharmacol Ther*. 1999; 65(4): 439-447.
- [20] Castaño G, Canetti M, Moreira M, Tula L, Más R, Illnait J, et al. Efficacy and tolerability of policosanol in elderly patients with type II hypercholesterolemia: A 12 months study. *Curr Ther Res*. 1995; 56(8): 819-828.
- [21] Ortensi G, Gladstein H, Valli H, Tesone PA. A comparative study of policosanol versus simvastatin in elderly patients with hypercholesterolemia. *Curr Ther Res*. 1997; 58: 390-401.
- [22] Castaño G, Más R, Arruzazabala ML, Noa M, Illnait J, Fernández JC, et al. Effects of policosanol and pravastatin on lipid profile, platelet aggregation and endothelemia in older hypercholesterolemic patients. *Int J Clin Pharm Res*. 1999; 19: 105-116.
- [23] Castaño G, Más R, Fernández JC, Illnait J, Fernández L, Alvarez E. Effects of policosanol in older patients with type II hypercholesterolemia and high coronary risk. *J. Gerontol Sci Med Sci*. 2001; 56(3): 186-192.
- [24] Fernández JC, Más R, Castaño G, Menéndez R, Amor AM, González RM, Alvarez E. Comparison of the efficacy, safety and tolerability of policosanol versus fluvastatin in elderly hypercholesterolemic women. *Clin Drug Invest*. 2001; 21(2): 103-113.
- [25] Más R, Castaño G, Fernández L, Illnait J, Fernández J, Alvarez E. Effects of policosanol on lipid profile and cardiac events in older hypercholesterolemic patients with coronary disease. *Clin Drug Invest*. 2001; 21(1): 485-497.
- [26] Castaño G, Más R, Fernández J, Fernández L, Illnait J, López E. Effects of policosanol on older patients with hypertension and type II hypercholesterolemia. *Drugs R&D*. 2002; 3(3): 159-172.
- [27] Castaño G, Mas R, Fernández L, Illnait J, Mesa M, Alvarez E, Lezcay M. Comparison of the efficacy, safety and tolerability of policosanol versus atorvastatin in elderly patients with Type II hypercholesterolemia. *Drugs & Aging*. 2003; 20: 153-163.
- [28] Arruzazabala ML, Valdés S, Más R, Fernandez L, Carbajal D. Effect of policosanol successive dose increases on platelet aggregation in healthy volunteers. *Pharmacol Res*. 1996; 34: 181-185.
- [29] Arruzazabala ML, Mas R, Molina V, Carbajal D, Mendoza S, Fernandez L, Valdes S. Effect of policosanol on platelet aggregation in type II hypercholesterolemic patients. *Int J Tiss React*. 1998; 20: 119-124.
- [30] Arruzazabala ML, Molina V, Mas R, Fernandez L, Carbajal D, Valdes S, Castaño G. Antiplatelet effects of policosanol 20 and 40 mg/d in healthy volunteers and dyslipidemic patients. *Clin Exp Pharmacol Physiol*. 2002; 29: 891-897.
- [31] Menéndez R, Más R, Amor AM, González RM, Fernández JC, Rodeiro I, et al. Effects of policosanol treatment on the susceptibility of low density lipoprotein (LDL) isolated from healthy volunteers to oxidative modification in vitro. *Brit J Clin Pharmacol*. 2000; 50: 255-262.
- [32] Menéndez R, Mas R, Amor AM, Fernández JC, González RM. Effects of policosanol on the low density lipoprotein (LDL) isolated on hypercholesterolemic patients at high coronary risk to in vitro copper-mediated lipid peroxidation. A Randomised, Double-Blinded Pilot Study. *Curr Ther Res Clin & Exptl*. 2000; 61: 609-620.
- [33] Fernández L, Más R, Illnait J, Fernández JC. Policosanol: results of a postmarketing surveillance control on 27 879 cases. *Curr Ther Res*. 1998; 59: 717-722.
- [34] Más R, Rivas P, Izquierdo JE, Hernández R, Fernández L, Fernández JC, et al. Pharmacoeconomic study of policosanol. *Curr Ther Res*. 1999; 60: 458-467.
- [35] Fernández S, Mas R, Gámez R, Díaz A, Fernández J, Orta SD, et al. A pharmacological surveillance of policosanol tolerability in the elderly. *Am J Gerontol Pharmacother*. 2004; 2: 11-16.
- [36] Illnait J, Fernández JC, Fernández L, Gámez R, Mendoza S, Mas R, Alvarez E, López LE, Gutiérrez JA, Lesacy M, Orta SD. Benefits of a long-term therapy with policosanol on hypercholesterolemic elder patients: a controlled study. *Int J of Med Sci and Curr Res*. 2019; 2(2): 383-395.

- [37] Karalis DG, Subramanya RD, Hessen SE, Liu L, Victor MF. Achieving optimal lipid goals in patients with coronary artery disease. *Am J Cardiol*. 2011; 107(6): 886-890.
- [38] Requerimientos para la notificación y el reporte de eventos adversos graves e inesperados en los ensayos clínicos. Regulación No. 45-2007, Centro para el Control Estatal de los Medicamentos, Equipos y Dispositivos Médicos (CECMED), MINSAP, La Habana, Cuba. 2007.
- [39] Munday MR, Campbell DG, Carling D, Hardie DG. Identification by amino acid sequencing of three major regulatory phosphorylation sites on rat acetyl-CoA carboxylase. *Eur J Biochem*. 1988; 175(2): 331-338.
- [40] Steinberg GR, Kempt BE. AMPK in Health and Disease. *Physiol Res*. 2009; 4: 1025-1078.
- [41] Rizzo WB, Craft DA, Somer T, Carney G, Trafrova J, Simon M. Abnormal fatty alcohol metabolism in cultured keratinocytes from patients with Sjögren-Larsson syndrome. *J Lipid Res*. 2008; 49(2): 410-419.
- [42] Youn Sue Lee, Yoonsu Cho, Min-Jeon Shin. Dietary long chain Saturated Fatty Acids and metabolic Factors: Findings from the Korea National Health and nutrition examination Survey 2013. *Food Sci & Biotech*. 2016; 25(3): 899-904.
- [43] Malik VS, Chiuve SE, Campos H, Rimm EB, Mozaffarian D, Hu, FB, et al. Circulating very-long chain saturated fatty acids and incident coronary heart disease in US men and women. *Circulation* (2015). Downloaded from <http://circ.ahajournals.org/> by guest on November 23, 2016.
- [44] Nagan N, Zoeller RA. Plasmalogens: Biosynthesis and functions. *Progress in Lipid Research*. 2001; 40(3): 199–229.
- [45] EUROASPIRE II Study Group. Lifestyle and risk factor management and use of drug therapies in coronary patients from 15 countries. Principal results from EUROASPIRE II. *Eur Heart J*. 2001; 22: 554-572.
- [46] Lee EY, Yoo JA, Lim SM, Cho KH. Anti-aging and tissue regeneration ability of policosanol along with lipid-lowering effect in hyperlipidemic zebrafish via enhancement of high-density lipoprotein functionality. *Rejuvenation Research*. 2016; 19(2): 149-158.
- [47] Antithrombotic Trialists' Collaboration. Collaborative meta-analysis of randomised trials of antiplatelet therapy for prevention of death, myocardial infarction and stroke in high/risk patients. *BMJ*. 2000; 324: 71-86.
- [48] Kim SJ, Yadav D, Park H J, Kim J R, Cho KH. Long-term consumption of Cuban policosanol lowers central and brachial blood pressure and improves lipid profile with enhancement of lipoprotein properties in healthy Korean participants. *Front Physiol*. 2018; 9: 412.
- [49] Denker MG, Cohen DL. What is an appropriate blood pressure goal for the elderly: review of recent studies and practical recommendations. *Clin Interv Aging*. 2013; 8: 1505-1517.
- [50] Kim, J Y, Kim, SM, Kim SJ, Lee EY, Kim JR, Cho KH. Consumption of policosanol enhances HDL functionality via CETP inhibition and reduces blood pressure and visceral fat in young and middle-aged subjects. *International Journal of Molecular Medicine*. 2017; 39(4): 889-899.