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Benefits of a Long-Term Therapy with Policosanol On Hypercholesterolemic Elder Patients: A Controlled Study

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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 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: Investigate whether policosanol administered for 3 years was able to reduce the incidence of vascular serious adverse events (SAE) in older hypercholesterolemic patients.

Methods: We randomized 1470 old patients of both sexes with type II hypercholesterolemia, between 60 to 85 years old with ≥ 1 non-lipid coronary risk factors. They were treated with policosanol or placebo, for 3 years. The incidence of vascular SAE occurred during the study was considered as a primary efficacy variable, while the total of SAE (vascular and non-vascular), mortality, and the changes on lipid profile were considered secondary efficacy variables. Analysis was done by Intention-to-treat.

Results: The frequency of vascular SAE was lower in the policosanol group (15 events) compared with placebo (49 events). The amount of cardiovascular SAE compared to placebo (33 events) was significantly lower in the policosanol group (7 events). Also, there were 12 cerebrovascular SAE (1.6 %) in the placebo and 5 (0.7 %) in the policosanol group. There were 109 patients who experienced SAE: 83 (11.3 %) in placebo and 26 (3.5 %) in policosanol group ($p<0.0001$). Twenty-three (23) deaths occurred up to study completion: 19 in the group of placebo patients (2.6 %), and 4 in the policosanol group (0.5 %). At study completion, the changes induced by policosanol in LDL-C, total cholesterol, triglycerides and HDL-C with respect to baseline were -30 %, -22 %, -20 % and +15 %, respectively.

Conclusions: The group treated with policosanol reported a significant lower amount of vascular SAE and mortality, relevant positive changes on serum lipid profile and lower frequency of total AE. 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

INTRODUCTION

The leading cause of morbidity and mortality in the adult population is cardiovascular disease (CVD).[1] The management of the risk factors for atherosclerotic CVD, of which elevated LDL-C is one, is called primary prevention, if this process is done in someone who has not previously experienced an atherosclerotic vascular event. The rationale for activities focused on LDL-C reduction is based upon epidemiologic data documenting a continuous, positive, graded relationship between LDL-C concentration and CVD events and mortality and 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 decline with age, as predictors, of the relative coronary risk.[10]. However, still it is a strong predictor 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]

Policosanol is a mixture of high molecular weight alcohols purified from sugar cane *(Saccharum officinarum, L)* wax[12] 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.[13-16]

The cholesterol-lowering effects of policosanol have been demonstrated in patients with type II hypercholesterolemia[17,18] 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.[19-26]

Policosanol shows also relevant pleiotropic effects, such as the inhibition of platelet aggregation[27-29] and the susceptibility of LDL to be oxidised.[29,30] Clinical studies and long-term post marketing surveillance studies have proven that policosanol is safe and well tolerated.[12,17-34]

This background supported the conduction of a long-term study with policosanol in elder with hypercholesterolemia. This study was undertaken to investigate whether policosanol administered for 3 years was able to reduce the incidence on vascular serious adverse events (SAE) in older hypercholesterolemic patients.

PATIENTS AND METHODS

Study Design: This 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 (visit 1).

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.

Eligible patients (1470) were randomized, under double-blind conditions, to policosanol 5 mg or placebo tablets. Concomitant medications were recorded. The patients were followed every 3 months during the first year (visits 3 to 6) and at 6 months intervals thereafter (visits 7-10).

Enrolment criteria: Patients of both sexes aged 60 to 80 with documented coronary disease, hypercholesterolemia, hypertension, smoking habits or/and diabetes 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

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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: Study medications were identical in appearance. The only difference was in the composition between policosanol and placebo tablets since in the latter, 5 mg of active ingredient was replaced by the same amount of lactose. Treatments were administered in identical packages identified by a code number and the number of treatment assigned at each Policlinic by progressive inclusion. Study medications were randomised through a random allocation generated in the Database centre, consisting of balanced block of size ten, with a randomization ratio 1:1. Tablets must be taken once a day (oid) 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: Were performed from visits 3 to 10, 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. The changes on lipid profile (LDL-C, total cholesterol, HDL-C and triglycerides) were also 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 with treatment.

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, being recorded from visits 3 to 10. 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.

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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).

RESULTS

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 (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 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 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.

Compliance: 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 takenat 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 ($p<0.01$).

Effects on primary efficacy variables: The frequency of vascular serious adverse events (SAE) was lower in the policosanol group (15 events) compared with placebo (49 events) ($p<0.0001$) (Table 3).

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

The analysis revealed that episodes of unstable angina were more frequent in the placebo (15 events, 2.0 %) than in the policosanol group (5 events, 0.7 *%).* Likewise, there were 15 myocardial infarctions (fatal + non-fatal) in the placebo (1.9 %) and 1 (0.1 %) in the policosanol group ($p<0.0001$).

Effects on secondary efficacy variables: There were 109 patients who experienced SAE (fatal+non-fatal): 83 (11.3 %) in placebo and 26 (3.5 %) in policosanol group ($p<0.0001$) (Table 3).

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Twenty-three (23) deaths occurred up to study completion: 19 placebos (2.6 %), 4 policosanol (0.5 %), (Table 4). 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 placebos (0.4 %), but no policosanol patient died because of cerebrovascular events. The deaths due to nonvascular causes (6/ 23, 26.1 %) were similar in both groups (3 /group).

On the other hand, the frequency of non-vascular SAE 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).

Effects on lipid profile: Table 5 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 %. After 1 year, policosanol lowered LDL-C, total cholesterol and triglycerides by 21 %, 16 % and 20 %, respectively, whereas raised HDL-C by 6 %. At study completion, the changes induced by policosanol in LDL-C, total cholesterol, triglycerides and HDL-C were – 30 %, -21 %, - 20 % and + 15 %, respectively. The corresponding values in placebo were + 1 %, - 2 %, - 9 % and – 4 %, respectively.

Safety and tolerability

Policosanol reduced moderately systolic and diastolic blood pressure, but significantly ($p<0.0001$) compared with placebo, without affecting pulse rate. Other variables were not modify (ALT, AST, glucose or creatinine values) (Table 6).

On the other hand, the report during the study, of mild and moderate AE was also significantly lower in the policosanol group than in the placebo group ($p <0.01$) (Table 7).

DISCUSSION

It was demonstrated that 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.[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.[35,36] In addition, AMPK activation is associated with a wide array of beneficial effects,[37] 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.[38] These results indicated that higher intake of VLCFA is significantly associated with favorable metabolic status including lower levels of circulating triglycerides.[39] Other 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 %.[40]

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.[41]

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.

In line with updated guidelines, LDL-C values were used as a criterion for study entry. Compared with placebo, policosanol produced a significant decrease in this variable versus placebo as well as decreases in total cholesterol, modest reduction of triglycerides and increase in HDL-C. These changes are consistent with those expected, being potentially useful for risk reduction.

The progressive improvement of LDL-C and HDL-C values agrees with some previous long-term studies,[17-19] being less pronounced for total cholesterol values.

It was demonstrated the clinical benefits of policosanol in randomized, placebo-controlled and comparative clinical studies in high-risk populations, after 6 months on therapy, the frequency of SAE among policosanol patients was reduced in more than 50 % *versus* placebo.[22,24,25]

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As expected in a large study, both groups were well balanced at baseline. Most subjects were at primary prevention with 1 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.[42]

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.[43] Moreover, according with recent results, policosanol seems to present regeneration abilities via enhancement of HDL functionability.[44]

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. All the changes were consistent with the expected response to policosanol.[12,17-26]

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

Overall frequency of mild and moderate AE were lower in the policosanol group than in the placebo group. This result, together with SAE and withdrawal analysis, eliminates any increase in particular AE 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.[45] Specific on the effect of policosanol on hypertension studies confirm these results.[46,47]

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 of this population.

CONCLUSIONS

The group treated with policosanol reported a significant lower amount of vascular SAE and mortality, relevant positive changes on serum lipid profile and lower frequency of total AE. 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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Table 1: Main baseline characteristics of study patients

Characteristics	Placebo (n = 733)		Policosanol	
Age (years) (X±SD)	66 ± 6		66 ± 6	
Body mass index (kg/m^2) (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)	136 ± 17		137 ± 20	
Diastolic blood pressure (mm Hg)	82 ± 10		82 ± 10	
	n	**%**	**n**	**%**
Gender: Female	582	79.4	571	77.5
Male	151	20.6	166	22.5
Isolated HC	465	63.4	452	61.3
Combined HC	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
HDLC< 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

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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
Anxyolytics	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.

All comparisons were not significant

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 ($\chi 2$ test)

Table 3: Effects on efficacy variables

	Placebo (n=		Policosanol (n =		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					

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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

Table: 4 Deaths occurred during the study

Causes	**Placebo (n = 733)**		**Policosanol (n = 737)**		**p value***
Vascular causes	**n**	**%**	**n**	**%**	
Myocardial infarction	12	1.6	1	0.1	ns
Sudden cardiac arrest	1	0.1	0	0.0	ns
Stroke	2	0.3	0	0.0	ns
Cerebral edema	1	0.1	0	0.0	ns
Subtotal	**16**	**2.2**	**1**	**0.1**	**p < 0.001**
Other causes					
Cancer	2	0.3	1	0.1	ns
Pneumonia	1	0.1	0	0.0	ns
Septicemia	0	0.0	1	0.1	ns
Car accident	0	0.0	1	0.1	ns
Subtotal	**3**	**0.4**	**3**	**0.4**	ns
Total	**19**	**2.6**	**4**	**0.5**	**p < 0.001**

*Comparison with placebo ($\chi 2$ test)

Table 5: Long-term effects on lipid profile (X ± SD) of older patients

Treatment	**Baseline**	**1 year**	**2 years**	**3 years**
Total cholesterol (mmol/L)				
Policosanol	6.76 ± 0.90	5.67 ± 0.68^{+}	5.41 ± 0.69^{+}	5.26 ± 0.62^{+}
Placebo	6.70 ± 0.87	6.62 ± 0.85	6.67 ± 0.84	6.57 ± 0.75
LDL-C (mmol/L)				
Policosanol	4.72 ± 0.88	3.73 ± 0.65^{+}	3.40 ± 0.68^{+}	3.18 ± 0.59^{+}
Placebo	4.65 ± 0.86	4.67 ± 0.82	4.79 ± 0.81	4.71 ± 0.76
HDL-C (mmol/L)				
Policosanol	1.22 ± 0.34	1.28 ± 0.24^{+}	1.33 ± 0.26^{+}	1.40 ± 0.23^{+}
Placebo	1.21 ± 0.33	1.17 ± 0.28	1.14 ± 0.20	1.14 ± 0.16
Triglycerides (mmol/L)				
Policosanol	2.23 ± 0.90	1.78 ± 0.57^{+}	1.80 ± 0.46^{+}	1.79 ± 0.43^{+}
Placebo	2.23 ± 0.99	2.10 ± 0.77	2.08 ± 0.56	2.03 ± 0.49

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

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Table 6: Long-term effects on safety indicators (X ± SD) of older patients

Treatment	Baseline	1 year	2 years	3 years
Weight (kg)				
Policosanol	66.97 ± 12.56	66.90 ± 11.81	66.85 ± 11.84	66.75 ± 11.70
Placebo	66.90 ± 13.02	67.07 ± 12.45	67.43 ± 12.29	67.79 ± 12.24
Pulse (beats/min)				
Policosanol	72.85 ± 7.17	72.48 ± 7.06	72.28 ± 5.81	71.71 ± 4.77
Placebo	73.01 ± 6.96	72.11 ± 6.37	72.18 ± 6.25	72.23 ± 4.95
Diastolic pressure (mm Hg)				
Policosanol	81.92 ± 10.26	80.92 ± 7.68	80.49 ± 6.11	80.04 ± 5.65^{+}
Placebo	81.84 ± 9.84	81.13 ± 7.15	81.64 ± 6.10	82.06 ± 6.17
Systolic pressure (mm Hg)				
Policosanol	136.95 ± 19.60	131.50 ± 14.32	130.40 ± 13.75^{+}	128.93 ± 13.01^{+}
Placebo	136.01 ± 17.48	133.80 ± 14.43	133.41 ± 13.24	133.34 ± 11.38
ALT (U/L)				
Policosanol	19.81 ± 9.29	19.84 ± 11.37	18.86 ± 6.34	19.32 ± 5.87
Placebo	19.88 ± 9.54	21.96 ± 8.50	21.65 ± 6.63	22.28 ± 5.91
AST (U/L)				
Policosanol	21.82 ± 7.86	19.29 ± 8.49	18.81 ± 6.61	18.51 ± 9.12
Placebo	22.44 ± 8.66	21.56 ± 7.23	22.19 ± 6.30	22.03 ± 6.30
Creatinine (μmol/L)				
Policosanol	91.52 ± 17.63	87.78 ± 13.05	89.84 ± 11.31^{+}	90.61 ± 10.58
Placebo	91.33 ± 17.11	89.84 ± 15.66	91.46 ± 12.74	90.99 ± 9.88
Glucose (mmol/L)				
Policosanol	5.35 ± 1.11	5.37 ± 1.25	5.26 ± 0.85	5.35 ± 1.05
Placebo	5.43 ± 1.54	5.56 ± 1.62	5.45 ± 1.42	5.45 ± 0.85

X mean, SD standard deviation, ALT alanin amino transferase, AST aspartate amino transferase

$^{+}p < 0.0001$ Comparison with placebo (t-test for independent samples)

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Table 7: Moderate and mild adverse events (AE) reported during the study

Body System	Placebo (n = 733)		Policosanol (n = 737)	
Skin and appendages disorders	24	3.3	13	1.8
Muscle-skeletal system disorders	70	9.5	41	5.6^{+}
Central and peripheral nervous system disorders Subtotal	69	9.4	34	4.6^{+}
Psychiatric disorders	2	0.3	1	0.1
Gastrointestinal system disorders	35	4.8	24	3.3
Liver and biliary system disorders	8	1.1	10	1.4
Endocrine disorders	24	3.3	9	1.2^{+}
Cardiovascular disorders	30	4.1	29	3.9
Heart rate and rhythm disorders	6	0.8	7	0.9
Respiratory system disorders	11	1.5	11	1.5
Red blood disorders	1	0.1	0	0
White cell and RES disorders	1	0.1	1	0.1
Urinary system disorders	23	3.1	14	1.9
Reproductive disorders, female	1	0.1	1	0.1
Body as a whole, general disorders	37	5	36	4.9
Total of mild and moderate AE	**342**	**47.1**	**231**	**31.3^{++}**
Total of patients with moderate or mild AE	**190**	**25.9**	**134**	**18.2^{++}**

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