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Concomitant Use Of Policosanol And Diuretics In Older Patients With Type Ii Hypercholesterolemia

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Presentation letter:

A: Editor IOSR Journal of Pharmacy:

We hereby request the evaluation of the work for publication, bearing in mind that it has not been previously published, nor is it being reviewed by any other journal.

The instructions for the authors and the ethical responsibilities have been taken into account, among them, that all the authors meet the requirements of authorship and all have declared not to have a conflict of interest.

Contribution to the scientific literature:

The present study was conducted with the aim of having new evidence and to corroborate the excellent safety and tolerability profile of policosanol in elderly people who consume concomitantly diuretic medications, without the risk of relevant drug interactions.

The implication of the results obtained for clinical practice, research and health policies is that the study demonstrated the lipid-lowering efficacy of policosanol when administered long-term in the elderly population that consumes concomitant diuretics, without inducing adverse drug interactions, as well as produced beneficial effects in these high-risk patients, without affecting the safety indicators investigated and without increasing any adverse experience with respect to the placebo group.

Authorship declaration:

The authors have been involved in the conception and design of the work, or in the collection of data, or in the analysis and interpretation of the data, as well as in the writing of the article or in its critical review and in the approval of the final version for publication.

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Conflict of interests:

All authors have declared no conflict of interest.

Abstract

Objective: The objective of the present analysis as a part of a Prevention Study, we investigated whether concomitant administration of policosanol with diuretics induces some specific adverse event or disturbance on any safety indicator in older patients.

Methods: We randomised 1470 elderly patients at high coronary risk to policosanol 5 mg/day or placebo for 3 years. For this analysis, the records of all patients (368) taking diuretics were included. Analysis was by Intention-to-treat.

Results: Both groups were well matched at baseline. Policosanol effects persisted during the whole study. At study completion, policosanol reduced low-density lipoprotein cholesterol (LDL-C) (29.1 %), total cholesterol (19.6 %), triglycerides (22.5 %) and raised high-density lipoprotein cholesterol (HDL-C) (13.8 %). Of 368 patients consuming diuretics, 76 (20.7 %) discontinued the study, 49/181 placebo (27.1 %) and 27/187 policosanol (14.4 %) patiens. Of them, 37 patients (25 placebo, 12 policosanol) discontinued prematurely the study because of some adverse event. No disturbance of any safety indicator was found. Diastolic and systolic blood pressures, however, was lowered in policosanol group compared with placebo. The extent of serious adverse events, most vascular, in policosanol patients (9/187, 4.8 %) taking diuretics was lesser than in placebo (23/181, 12.7 %). Policosanol did not increase the frequency of mild and moderate adverse events compared with placebo.

Conclusion: It is concluded that policosanol therapy added to older hypercholesterolemic patients taking diuretics produced relevant benefits on lipid profile, blood pressure and the frequency of serious adverse events respect to placebo, then indicated concomitant with diuretic in elderly, without increase any adverse event.

Key words: policosanol, diuretics, elderly, hypercholesterolemia, drug interactions

RESUMEN

Objetivo: El objetivo del presente estudio como parte de un Estudio de Prevención fue investigar si la administración concomitante de policosanol con diuréticos induce algún evento adverso específico o alteraciones en los indicadores de seguridad de estos pacientes.

Métodos: Fueron aleatorizados 1470 ancianos con alto riesgo coronario los cuales recibieron policosanol 5 mg/día o placebo durante 3 años. Para el análisis se tomaron los registros de todos los pacientes incluidos que tomaban diuréticos (368). El análisis fue realizado según el método de intención de tratar.

Resultados: Ambos grupos fueron homogéneos al inicio del tratamiento. Los efectos del policosanol se mantuvieron durante todo el tiempo de tratamiento. Al finalizar el estudio, el policosanol redujo el colesterol asociado a lipoproteínas de baja densidad LDL-C (29,1 %), el colesterol total (19,6 %) y los triglicéridos (22,5 %), así como incrementó el colesterol asociado a lipoproteínas de alta densidad HDL-C (13,8 %). De los 368 pacientes que consumían diuréticos, 76 (20,7 %) causaron baja del estudio, 49/181 placebo (27,1 %) y 27/187 policosanol (14,4 %). De ellos, 37 pacientes (25 placebo y 12 policosanol) descontinuaron prematuramente del estudio debido a algún evento adverso. No se afectaron los indicadores de seguridad, solo la presión arterial se redujo en el grupo policosanol en comparación con el placebo. La frecuencia de eventos adversos severos, sobre todo vasculares, en los pacientes tratados con policosanol (9/187, 4,8 %) que tomaban diuréticos fue menor que el grupo placebo (23/181, 12,7 %). El policosanol no incremento la frecuencia de eventos adversos leves y moderados respecto al grupo placebo.

Conclusión: Se concluye que la terapia con policosanol añadida a pacientes ancianos hipercolesterolémicos que tomaban diuréticos produce beneficios relevantes sobre el perfil lipídico, sobre la presión arterial y sobre la frecuencia de eventos adversos severos respecto al placebo, por lo tanto, puede ser indicado conjuntamente con diuréticos en ancianos, sin incrementar la aparición de eventos adversos.

Palabras claves: policosanol, diuréticos, ancianos, hipercolesterolemia, interacción medicamentosa

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I. INTRODUCTION

Coronary events are the leading cause of morbidity and mortality in middle-aged and elderly individuals.[1] End-point based clinical studies have shown a direct relation between coronary events and increased serum levels of low-density lipoprotein cholesterol (LDL-C) and total cholesterol, as well as that lowering LDL-C with statins reduces coronary risk.[2,3]

Hypercholesterolemia treatment in older individuals had been controversial because the contribution of elevated LDL-C levels as predictors of the relative coronary risk decreases with age.[4] By the other hand, increased LDL-C levels, however, are strong predictors for absolute coronary risk in the elderly.[11] and subgroup analyses of older patients included in landmark statin trials have demonstrated the benefits of lowering LDL-C values in the coronary risk of such patients.[2,3]

Older individual shows impairment of hepatic and renal drug clearance, and commonly consume several concomitant drugs as a consequence of their co-morbid status. Then, the frequency of drug-related adverse events (AE) in the elderly is greater than in younger adults.[4]

Policosanol is a mixture of high molecular weight alcohols purified from sugar cane *(Saccharum officinarum, L.)* wax with cholesterol-lowering effects demonstrated in patients with type II hypercholesterolemia and in patients with dyslipidemia due to Type 2 diabetes mellitus. Policosanol (5-20 mg/d) significantly lowers LDL-C and total cholesterol, raises high-density lipoprotein cholesterol (HDL-C), while its effects on triglycerides are modest and not consistent.[5] In particular, the effects of policosanol in older patients have been investigated, policosanol being supported as an effective, safe and well tolerated cholesterol-lowering drug in the elderly.[6-9]

Policosanol inhibits cholesterol biosynthesis in a step between acetate consumption and mevalonate production, by suppressing HMG-CoA reductase up-regulation, so that its inhibitory effects can be explained, at least partially, by a depression of *de novo* synthesis of HMG-CoA reductase and/or stimulation of its degradation.[10,11] Also, policosanol significantly increases LDL receptor-dependent processing, enhancing LDL catabolic rate.[12] Policosanol also shows important pleiotropic effects that can reinforce its effects on atherosclerosis development, such as inhibition of platelet aggregation,[13] and of the susceptibility of LDL to be oxidised.[14]

Clinical and post-marketing studies have demonstrated that policosanol is safe and well tolerated[15-17] in populations with high use of concomitant therapy, suggesting that the risk of adverse events (AE) coming from drug interactions is low.

Drug interactions come from pharmacokinetic and/or pharmacodynamic link between drug processing and/or drug actions.[18] Experimental studies showed that policosanol does not interact with drugs metabolised through the cytochrome P450 hepatic system. Thus, policosanol orally administered for 21 days did not change both antipyrine and theophylline pharmacokinetics, and given orally for 30 days to male rats did not affect the activities of hepatic drug-metabolising enzymes.[19] Since cytochrome P450 hepatic system is the major metabolic route of most drugs, the probability of pharmacokinetic interactions with policosanol is reduced.

Nevertheless, pharmacodynamic interactions between policosanol and other drugs cannot be discarded. In such regard, some short and long-term clinical studies have demonstrated that policosanol lowered arterial pressure respect to placebo. In particular, experimental data have previously shown that policosanol increase the antihypertensive effects of β-blockers, without affecting pulse rate values.[20] Then, it is rationale to investigate the potential drug interactions between policosanol and other commonly used antihypertensive drugs, such as diuretics.

Based in prospective clinical studies, experts recommend diuretics and β-blockers as first-line therapy for hypertension management.[21] Diuretics are attractive for use in elderly individuals because of their efficacy in reducing volume and lowering systolic pressure. Numerous prospective clinical studies have documented that diuretic-based therapy is effective in reducing morbidity and mortality in hypertensive patients, their effects being marked in the elderly, mainly for the risk reduction of stroke.[22] Diuretics, however, can disturb lipid and glucose homeostasis.[23]

This background supported to assess the potential interaction between policosanol and diuretics from the analysis of the data of the long-term prevention study with policosanol in the elderly. Then, the present analysis was conducted to determine whether concomitant administration of policosanol with diuretics impairs some safety indicator or increase the report of some AE. In addition, we also investigated if cholesterol-lowering efficacy of policosanol was evident and persistent in older patients consuming diuretics and if the addition of policosanol to diuretic consumption improved the control of arterial pressure in such patients.

II. PATIENTS AND METHODS

Study Design. The present analysis was based on data of a prospective, randomized, double-blinded, placebo-controlled study conducted in 1470 older patients treated with placebo or policosanol for 3 years after randomization.[24] In brief, patients were recruited at 4 Policlinical Centers, "Ramón González Coro"; "Elpidio Berovides," "Educational" and "26 de Julio" from Marianao, Lisa and Playa and followed by medical staff of the Surgical Medical Research Centre.

The personnel involved in patients follow up were blinded respect to treatment allocation during the whole study. A Steering Committee was responsible for the study, a Clinical Coordination Group followed the patients, an End-point Committee reviewed and categorized endpoint data and a Data Safety Monitoring Committee (DSMC) monitored study conduction and reviewed reports from investigators.

An independent Ethics Committee approved the study protocol and patients were recruited after providing informed written consent. Study conduction was done preventing the study patients from any prejudice, ensuring benefits and underlying that they decided to start or continue in the study in a voluntary and free manner.

Initially subjects aged 60 to 80 were invited, through Family Doctors, to assess their risk factors. A total of 1612 patients were recruited after confirming that exclusion criteria were absent (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.

Lab 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).

Enrollment criteria. Subjects of both sexes aged 60 to 80 with documented past history of coronary (myocardial infarction, angina pectoris and/or surgery), cerebrovascular disease, hypertension, dyslipidemia, smoking habits or/and diabetes were enrolled in the study. The rationale for the lowest age was to include older individuals with a considerable life expectancy.

Inclusion criteria. Patients were randomized if after the baseline period they showed total cholesterol ≥ 5.2, LDL-C ≥ 3.4 and triglycerides < 4.52 mmol/L, if exclusion criteria were not present.

Exclusion criteria. Patients were excluded if had active renal or diagnosed neoplastic diseases, severe hypertension (diastolic pressure ≥ 120 mm Hg), uncontrolled diabetes or poor cognitive function. Patients who had experienced unstable angina, myocardial infarction, stroke or any serious AE (SAE) within the 3 months prior to enrollment were also excluded.

Withdrawal criteria. Any SAE or AE justifying such decision, unwillingness to follow-up, patients with TC ≥ 9 mmol/l according to central lab report, major violations of study protocol, including > 6 weeks without taking the study medications.

Treatment. Study medications were identical in appearance. 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 center, consisting of balanced block of size ten, with a randomization ratio 1:1. Tablets must be taken once a day (oid) with evening meal. Participants in both groups should be titrated to 2 or 4 tablets oid if their TC levels after 6 or 12 months on therapy were ≥ 7 mmol/L.

Compliance assessment. Compliance with study medications was assessed at each visit by tablet counts and patient request, including such data in the Case Report Forms.

Concomitant medications. Consumption of lipid-lowering drugs was forbidden from the enrolment. No other restriction for concomitant drugs was done. Cases at secondary prevention were encouraged to take aspirin. Following on concomitant therapy was controlled through patient interview. In cases with chronic diseases, additional questioning was done to Family Doctors, since except for aspirin, medications for chronic diseases in Cuba are controlled by individual cards.

Assessments. TC was determined at baseline and every 6 months, while lipid profile and safety laboratory tests were performed at baseline and after 1, 2 and 3 years of randomization. Laboratory tests included lipid profile, glucose, creatinine, aspartate aminotransferase (AST) and alanine aminotransferase (ALT).
At each visit dietary reinforcement and physical examination were done. Compliance assessment and request for AE were performed from visits 3 to 10, compliance being assessed by tablet counts and defined as ≥ 85 % of the scheduled tablets having been consumed since the prior visit.

Effects on lipid profile. Changes on LDL-C were considered as the primary efficacy variable to assess whether diuretics or calcium channel blockers affect policosanol efficacy in older patients. Treatment was considered as effective if LDL-C was significantly reduced by ≥ 15 %,[25] changes on other lipid profile variables being secondary variables.

Safety and tolerability analyses. Patient records were reviewed and information about concomitant medication collected and analyzed. All patients taking diuretics or calcium channel blockers were included in the analysis. Physical (body weight, pulse rate, blood pressure) and laboratory safety indicators (glucose, creatinine, AST, ALT) were analyzed. Safety and tolerability analysis included all data on AE. Special attention was addressed to explore if policosanol increased the report of any AE respect to placebo group.
An adverse event (AE) was defined as any new undesirable experience or change in physical or laboratory data or the worsening of any pre-existing condition occurred through the trial, being or not drug-related. AE were classified according to their intensity in mild, moderate and serious. Mild AE were those AE not requiring treatment or withdrawal of study medication, moderate AE required withdrawal of study medication and/or specific treatment of the AE.[26]

A serious AE (SAE) was considered any AE leading to patient hospitalisation or death, independently of their nature. They included all mortality, as well as fatal and non-fatal coronary, cardiovascular, cerebrovascular and vascular SAE. For the whole study, events were analysed according by time of first event, but for the present analysis, the sample size and event number was too small for survival and hazard ratio analyses, the groups being compared by relative proportions.
To conduct the study in conditions similar to Cuban clinical practice, end-points were evaluated through the official records of the hospitals, death Registry and Family Doctors. At each visit, any event was documented from patients' recall, information verified with hospitals and Family Doctors.

The End-point Committee of the whole study blindly reviewed and categorized endpoint information, the events being diagnosed and classified by personnel blinded to treatment allocation and not involved in the study. For each category, events with definite + suspect causes were included, so that if diagnosis was not definite, they were recorded as suspected. Death certificates were requested for all deaths and the causes of death ascertained from hospital data and official certificates, helped by requests to Family Doctors and relatives. Whether the patients were alive or not was corroborated by contact with patients. In case of patients travelling abroad, household and Family Doctors were contacted.

Laboratory analysis. Blood samples were drawn after 12 hours overnight fasting. Serum total cholesterol and triglycerides were assessed by enzymatic methods using reagent kits. HDL-C levels were determined as the cholesterol content present in the supernatant obtained after β-lipoproteins precipitation.[27] LDL-C values were calculated using the Friedewald equation.[28] Laboratory tests were performed in the Hitachi 719 autoanalyzer (Tokyo, Japan) located at the Medical Surgical Research Centre. Determinations were done at the same day of sampling. A quality control was performed, so that within day and between-day variations as well as accuracy vs 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.
ANOVA test was used to compare continuous variables during the study. Comparisons between groups of categorical data were made using the Fisher´s Exact Probability test and corroborated with chi square test. All statistical tests were two-tailed, with significance at $\alpha = 0.05$. Statistical analyses were performed using Statistica for Windows (Release 4.2; Copyright StatSoft, Inc. US) and SAS/STAT (Stat Soft, Version 8, US).

III. RESULTS

Baseline patient characteristics. Both groups of patients taking diuretics were comparable at baseline (Table 1). Most patients were women (> 85 %) and hypertensive (> 98 %) Study patients also showed a high frequency of coronary events (> 30 %), the frequency of diabetics (> 20 %) being also relatively high. In turn, the frequency of concomitant medications was also high, the other CM most consumed being anxyolytics, β-blockers, anti-platelets, calcium channel blockers, vasodilators, vitamins, digitalics and oral hypoglycemic drugs. CM consumption was well matched in both groups.

Withdrawal analysis. Table 2 shows withdrawals analysis. The total number of withdrawals in policosanol group was significantly lower than in placebo. Of 368 patients consuming diuretics, 76 (20.7 %) discontinued the study, 49/181 placebo (27.1 %) and 27/187 policosanol (14.4 %) patients. Of them, 37 patients (25 placebo, 12 policosanol) discontinued prematurely the study because of some AE, the frequency of policosanol patients who discontinued the study due to AE being also lower than in placebo, a fact consistent with the frequency of SAE in both groups.

Compliance. Compliance with study medications, assessed by tablet count and patient interviews was good as defined by compliance criterion. Compliance was greater in policosanol than in placebo, the main difference being attributable to the withdrawals, since once a patient withdrew from the study, it did not continue on treatment.

Effects in serum lipid profile. Table 3 shows the effects on lipid profile. After one year, policosanol lowered significantly ($p < p<0.00001$ vs placebo) LDL-C (19.3 %), total cholesterol (15.2 %) and triglycerides (TG) (22.5 % $p <0.00001$), while raised ($p<0.001$ vs placebo) HDL-C levels (4.1 %). Policosanol effects persisted during the whole study. At study completion, policosanol reduced ($p<0.00001$ vs placebo) LDL-C (29.1 %), total cholesterol (19.6 %), ($p < 0.05$) triglycerides (22.5 %) and raised ($p < 0.00001$ vs placebo) HDL-C (13.8 %).

Safety and tolerability. No impairment of safety indicators was observed (Table 4). Policosanol added to diuretics, however, reduced diastolic blood pressure values compared with placebo.
Table 5 shows the frequency of AE occurred during the study. The extent of serious adverse events (SAE), most vascular, in policosanol patients taking diuretics (9/187, 4.8 %) was lesser than in placebo (23/181, 12.7 %). Policosanol did not increase the frequency of mild and moderate AE compared with placebo.

IV. DISCUSSION

The whole prevention study demonstrated that lowering LDL-C with policosanol in older hypercholesterolemic patients reduced the risk of all SAE, the primary endpoint, all mortality as well as vascular, cardiovascular and coronary SAE respect to placebos. The study also showed that policosanol, did not increased the frequency of non-vascular SAE.

The present analysis demonstrates that policosanol administered to elderly patients taking diuretics induced additional reductions on both systolic and diastolic pressure, without affecting any safety indicator or increasing the report of AE. In addition, the efficacy of policosanol was consistent with that expected.

Both groups were comparable at baseline, which supports their homogeneity. The mean age of study patients was around 66 years at baseline, being still young for preventive measures and related effects on life quality and expectancy. The larger proportion of women is a characteristic of the patients attending to the Policlinics of this area of Havana City[29] who are also more motivated to participate in clinical studies than men.

The frequency of concomitant medications was high, which is characteristic in the elderly. Taking into account this fact the analyses here reported are not related with a population only treated with diuretics and placebo or diuretics and policosanol, but receiving other therapies. The other concomitant drugs consumed by patients were well matched in both groups and those most frequent were consistent with the risk condition of study patients. Consumption of anxyolytics, most benzodiazepines, was high since they are frequently indicated in Cuba as adjuvant of hypertension management and for the management of anxiety in older patients. The consumption of inhibitors of angiotensin converting enzyme (IACE) was absent, which reflects the limited introduction of IACE in Cuban market, the doctors being more familiar to prescribe other antihypertensive drugs.

The frequency of patients consuming antiplatelet drugs (25 %), most of them consuming aspirin alone, was slightly lower than that expected according to the frequency of cases with coronary disease (31.5 %).

The present results support that policosanol efficacy is evident also in patients taking diuretics and are consistent with previous report of the concomitant use of policosanol and β-blockers.[30]

Thus, policosanol lowered LDL-C, the primary efficacy variable, total cholesterol and triglycerides, while raised HDL-C levels. 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, but 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 different withdrawal rate in both groups was a consequence of the discontinuations due to SAE 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, cardiovascular and coronary SAE was lower in policosanol 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.

The frequency of SAE here reported is relatively low compared with other trials,[2,3] a fact related with some study characteristics, such as the higher frequency of women and cases at primary prevention as well as that study patients were younger than older subjects. Also, some program routinely put in practice for Cuban subjects ≥ 60 years old also contribute to such low event rate. Thus, these subjects are commonly included in a program organized by health areas, including regular practice of physical exercise. As a result of all prevention measures, a decline on coronary heart disease has occurred in Cuba in the last years.[29]

Policosanol did not affect any safety indicator, with the exception of the reduction of diastolic and systolic pressure compared with placebo, an effect that could contribute to a lower frequency of vascular SAE. The mechanistic explanation for such interaction is beyond the objective of the present study, but policosanol effects on endothelial function could provide an independent contribution to the antihypertensive effects of diuretics. Hypotension was not reported in policosanol group, which limits the possibility of a potential risk resulting from the interaction between policosanol and diuretics.

Policosanol did not increase the frequency of AE compared with placebo, thus minimizing any potential risk derived from the concomitant use of policosanol and diuretics.

V. CONCLUSIONS

Policosanol was very well tolerated in elderly hypercholesterolemic patients consuming diuretics. Cholesterol-lowering efficacy of policosanol was persistent, even enhanced, during the whole study and additional reduction of diastolic blood pressure was observed in policosanol patients. The frequency of SAE was lower in policosanol than in placebo, suggesting that policosanol can contribute to reduce the risk of older patients consuming diuretics. Policosanol did not increase the frequency of AE in such patients. These results support that policosanol is effective for lowering LDL-C and TC in patients taking diuretics, providing

advantages in reducing blood pressure and the frequency of SAE respect to placebo, without increase any AE, even in older patients at high coronary risk, highly medicated with concomitant therapy and sensitive to drug-related AE and drug/drug interactions.

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Table 1. Main baseline characteristics of study patients

Characteristics	Placebo (n = 181)		Policosanol (n =	
Age (years) (X ± SD)	66 ± 6		66 ± 6	
Body mass index (kg/m^2) (X ± SD)	27.60 ± 4.82		27.20 ± 4.74	
	n	%	n	%
Gender: Female	155	85.6	159	85.0
Male	26	14.4	28	15.0
Risk factors:				
Arterial hypertension	180	99.4	184	98.4
Smoking	27	14.9	29	15.5
Coronary heart disease*	56	30.9	60	32.1
Diabetes mellitus	38	21.0	42	22.5
Obesity (kg/m^2 > 30)	11	6.1	16	8.6
Cerebrovascular disease**	9	5.0	8	4.3
Other concomitant medications***				
Anxyolytics	31	17.1	37	19.8
β-blockers	44	24.3	32	17.1
Antiplatelet	45	24.9	47	25.1
Calcium antagonists	48	26.5	55	29.4
Vasodilators	28	15.5	24	12.8
Vitamins	12	6.6	13	6.9
Digitalics	14	7.7	18	9.6
Oral hypoglycemic drugs	20	11.0	23	12.3
Myorelaxants	22	12.1	25	13.4

n number of patients; X mean, SD standard deviation, *myocardial infarction, unstable angina, coronary surgery, **stroke, ischemic transient attacks; ***consumed by > 6 % of study patients.
All comparisons were not significant

Table 2. Withdrawal analysis of study patients

Withdrawals due to AE			
	Placebo (n = 181)	**Policosanol (n = 187)**	**P value ***
Withdrawals due to vascular SAE	17	5	**p < 0.01**
Withdrawals due to SAE from other causes	6	4	**ns**
Subtotal due to SAE	23	9	**p < 0.01**
Withdrawals due to mild and moderate AE	2	3	**ns**
Subtotal due to all AE	25	12	**p < 0.05**

Withdrawals due to other reasons			
Unsatisfactory efficacy	12	1	**p < 0.01**
Travels abroad + changes to other towns or living areas	2	6	**Ns**
Unwillingness to follow-up	5	7	**Ns**
Protocol violations	5	1	**Ns**
Subtotal due to other reasons	24	15	**p < 0.05**
Total of withdrawals	49	27	**p < 0.01**

*Comparison with placebo (χ2 test)

Table 3. Long-term effects on lipid profile of study patients

Study groups	Baseline	1 year	2 years	3 years
Total cholesterol (mmol/L) (x ± SD)				
Policosanol	6.69 ± 0.83	5.67 ± 0.73^{++++}	5.42 ± 0.57^{++++}	5.38 ± 0.72^{++++}
Placebo	6.73 ± 0.84	6.68 ± 0.94	6.66 ± 0.86	6.67 ± 0.83
LDL-C (mmol/L)				
Policosanol	4.60 ± 0.83	3.71 ± 0.65^{++++}	3.34 ± 0.63^{++++}	3.26 ± 0.64^{++++}
Placebo	4.67 ± 0.86	4.67 ± 0.88	4.76 ± 0.82	4.70 ± 0.81
HDL-C (mmol/L)				
Policosanol	1.23 ± 0.34	1.28 ± 0.24^{++}	1.37 ± 0.29^{++++}	1.40 ± 0.24^{++++}
Placebo	1.21 ± 0.30	1.17 ± 0.28	1.10 ± 0.18	1.12 ± 0.19
Triglycerides (mmol/L)				
Policosanol	2.35 ± 1.01	1.82 ± 0.66^{+++}	1.85 ± 0.65^{++}	1.82 ± 0.57^{+}
Placebo	2.46 ± 1.15	2.27 ± 0.99	2.16 ± 0.63	2.03 ± 0.54

$^{+}$p < 0.05; $^{++}$p < 0.001; $^{+++}$p < 0.0001, $^{++++}$p < 0.00001 Comparison with placebo (ANOVA test)

Table 4. Long-term effects on safety indicators of patients

Study groups	Baseline	1 year	2 years	3 years
Weight (kg)				
Policosanol	68.03 ± 12.69	67.98 ± 11.58	67.57 ± 11.75	67.17 ± 11.33
Placebo	68.04 ± 13.36	67.27 ± 12.66	66.38 ± 12.24	69.23 ± 12.22
Pulse (beats/min)				
Policosanol	73.11 ± 7.41	72.14 ± 7.19	71.67 ± 6.35	70.38 ± 5.38
Placebo	73.01 ± 7.41	72.04 ± 6.89	72.47 ± 7.96	71.58 ± 5.59
Diastolic pressure (mm Hg)				
Policosanol	84.50 ± 10.32	82.59 ± 8.47^{+}	81.26 ± 7.36^{+}	80.63 ± 5.59^{++}
Placebo	83.11 ± 8.89	82.28 ± 7.24	83.13 ± 6.63	83.04 ± 6.27
Systolic pressure (mm Hg)				
Policosanol	142.07 ± 18.47	134.65 ± 14.11	133.59 ± 16.37^{+}	131.60 ±
Placebo	139.31 ± 17.09	136.87 ± 18.54	135.93 ± 13.90	132.66 ± 11.18
ALT (U/L)				
Policosanol	20.82 ± 10.42	19.43 ± 6.38	19.58 ± 5.99	19.91 ± 6.04
Placebo	20.41 ± 9.78	21.42 ± 8.46	22.35 ± 7.79	22.37 ± 5.73
AST (U/L)				
Policosanol	20.91 ± 7.64++	19.09 ± 7.99	19.71 ± 6.67	20.06 ± 15.37
Placebo	23.97 ± 8.80	20.76 ± 6.88	22.86 ± 7.72	22.65 ± 6.47
Creatinine (μmol/L)				
Policosanol	91.76 ± 18.38	86.69 ± 12.30	90.06 ± 12.03	91.59 ± 11.73
Placebo	92.61 ± 17.71	89.36 ± 16.86	92.03 ± 15.46	92.74 ± 10.85
Glucose (mmol/L)				
Policosanol	5.57 ± 1.13	5.54 ± 1.58	5.41 ± 1.05	5.54 ± 1.27
Placebo	5.51 ± 1.31	5.69 ± 2.10	5.57 ± 1.39	5.44 ± 0.76

X mean, SD standard deviation, ALT alanin aminotransferase, AST aspartate aminotransferase
$^{+}$p < 0.05; $^{++}$p < 0.01 Comparison with placebo (ANOVA test)

Table 5. Adverse events (AE) in study patients

AE	Placebo (n = 181)		Policosanol (n	
Serious AE	**n**	**%**	**n**	**%**
All cardiovascular SAE	13	7.2	2	1.1^{+}
All vascular SAE	17	9.4	5	2.7^{++}
All deaths	4	2.2	2	1.1
SAE (fatal + non fatal)	23	12.7	9	4.8^{++}
Moderate and mild AE				
Skin and appendages disorders	5	2.8	1	0.5
Nervous system disorders	15	8.5	13	6.9
Muscle-skeletal system disorders	16	8.8	12	6.4
Cardiovascular disorders	9	5.0	7	3.7
Heart rate and rhythm disorders	1	0.6	2	1.1
Gastrointestinal system disorders	13	7.4	10	5.3
Liver and biliary system	0	0.0	1	0.5
Endocrine	6	3.3	0	0.0^{+}
Respiratory system	4	2.2	3	1.6
Urinary system	5	2.8	3	1.6
Reproductive	0	0.0	1	0.5
Body as a whole	14	7.7	14	7.5
Patients reported Moderate or mild AE	**48**	**26.5**	**38**	**20.3**

$^{+}p < 0.05$, $^{++}p < 0.01$ Comparison with placebo ($\chi 2$ test)

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