Research Article

Effects of Policosanol (5 and 10 Mg/Day) in Adults with Serum Cholesterol Levels ≤ 5.9 MMOL/L

José Illnait, Ernesto López[2], Lilia Fernández[1], Rosa Mas[1], Rafael Gámez[1], Meilis Mesa[2], Sarahi Mendoza[1]*, Julio César Fernández[1]
1. Centre of Natural Products, National Centre for Scientific Research Research (CNIC), Havana City, Cuba.
2. Medical Surgical Research Centre, Playa, Havana City, Cuba.
***Corresponding author's E-mail:** sarahi.mendoza@cnic.edu.cu

Accepted on: 28-08-2013; **Finalized on:** 30-09-2013.

ABSTRACT

Hypercholesterolemia is a coronary risk factor. Lowering serum low-density lipoprotein-cholesterol (LDL-C) benefits individuals with a broad range of serum total cholesterol (TC) values. Then, subjects are encouraged to decrease LDL-C to targets according to their individual coronary risks. Policosanol, purified from sugar cane wax, has been shown to lower LDL-C in subjects with "normal to mildly elevated TC", but new evidences on this population are required. Objective of the present study to investigate the efficacy and tolerability of policosanol 5 and 10 mg/day in subjects with serum TC ≤ 5.9 mmol/L. After a 4 week diet-only period, 90 subjects of both sexes (mean age: 57 years) were double-blinded to placebo, policosanol 5 mg/day or policosanol 10 mg/day for 12 weeks. Lipid profile, safety indicators, adverse events (AE) and compliance with study treatments were assessed. Policosanol (5 and 10 mg/day) significantly ($p < 0.00001$) lowered LDL-C (17.6% and 19.7%, respectively) and TC (13.1% and 17.4%), raised ($p<0.00001$) high-density lipoprotein-cholesterol (HDL-C) (11.3% and 14.8%), and unchanged triglycerides. Lipid profile unchanged in placebo. The frequency of policosanol-treated subjects who reached LDL-C targets (54/70, 5 mg/day) (60/70, 10 mg/day) was greater ($p < 0.001$) than in placebo (4/70). Policosanol was well tolerated. Seven subjects (4 placebo, 2 policosanol-5mg, 1 policosanol-10mg) discontinued the trial, two (placebo) due to AE (dizziness, diarrhoea). This study demonstrates that policosanol (5 and 10 mg/day) for 12 weeks lowered serum LDL-C and TC, and raised HDL-C in subjects with serum TC ≤ 5.9 mmol/L, being well tolerated.

Keywords: Borderline cholesterol, LDL-C, Policosanol, cholesterol lowering.

INTRODUCTION

Elevated serum levels of low-density lipoprotein-cholesterol (LDL-C) and total cholesterol (TC) are major risk factors for coronary heart disease (CHD).[1, 2] Intervention clinical studies have demonstrated that lowering LDL-C reduces coronary risk in subjects at secondary and primary prevention stages, [2 –7] so that LDL-C is a primary target inside coronary prevention programs. [8-10]

Guidelines emphasize that lipid-modifying treatments must lower LDL-C values to reach targets according to the individual coronary risk estimated through algorithms that establish "desirable" rather than "normal" LDL-C and TC, so that values accepted as "normal" 10 years ago, currently could be high in accordance to the individual risk of the subjects. Recommended LDL-C goals for high risk and very high-risk persons are <100 and <70 mg/dL, respectively, although this last goal may be used for both cases. [8- 10] The LDL-C goal for persons with moderate high-risk (≥ 2 concomitant risk factors and 10-year risk 10% to 20%) is <130 mg/dL, but a more restricted target (<100 mg/dL) may be optimal. In low-risk subjects the recommended LDL-C goal is <160 mg/dL.[9] In addition, although LDL-C is the primary lipid target for CHD risk reduction, high-density lipoprotein cholesterol (HDL-C) and triglycerides (TG) have also emerged as CHD risk factors, so that increases of HDL-C or decreases of TG can provide additional benefits. [10 – 14]

Subjects should be educated to reach LDL-C targets firstly through therapeutic lifestyle changes (TLC). The adherence to a low-fat, low-cholesterol diet is the cornerstone of TLC and allows achieve the goals in many individuals, mainly those with borderline and mildly elevated values. Nevertheless, in many individuals with non-lipid risk factors, TLC alone is not enough to reach these targets required, and different cholesterol-lowering interventions are recommended, in addition to the TLC strategy.

Policosanol, a mixture of higher aliphatic primary alcohols purified from sugar cane wax with cholesterol-lowering effects, [15] has been shown to inhibit cholesterol synthesis by regulating HMG-CoA reductase activity through the activation of AMP-kinase phosphorylation, a mechanism that requires the peroxisomal metabolism of the fatty alcohols to the corresponding fatty acids. [16 - 19] Also, policosanol significantly increases LDL receptor-dependent processing, increasing LDL catabolic rate. [20]

Most clinical studies have demonstrated the cholesterol-lowering effects of policosanol in patients with type II hypercholesterolemia[21 – 28] and dyslipidemia associated to type 2 diabetes, [29 - 31] and only a few trials supported such evidences in subjects with "normal, borderline and mildly" elevated serum TC and normal TG values: [32 – 35] One of these studies was conducted in subjects with TC < 5.7 mmol/L treated with 10 or 20 mg/day for only 4 weeks, [32] another investigated the effects of 5 and 10 mg/day administered for 8 weeks to individuals with serum TC < 5.2 mmol/L, [33] while a third one investigated the effects of 5 mg/day given for 8 weeks to individuals with a broad serum TC range (4.8 – to 6.0 mmol/L). [34] A

more recent study assessed demonstrated the efficacy of 10 mg/day administered for a longer period (12 weeks) to subjects with serum TC ≥4.5; ≤5.9 mmol/L. [35] These data, however, are still relatively limited considering the current trends of cholesterol management.

In light of these issues, this study was undertaken to investigate the short-term efficacy and tolerability of policosanol 5 and 10 mg/day in subjects with serum TC ≤5.9 mmol/L.

PARTICIPANTS AND METHODS

Study design

Study was conducted in accordance to the ethical principles of the Declaration of Helsinki. The independent Ethics Committee from the Medical Surgical Research Centre (Havana, Cuba) approved the study protocol. Subjects were enrolled after providing their informed written consent.

This randomised, double-blinded, parallel-group, comparative study was conducted at the Medical Surgical Research Centre, patients being enrolled at Ramon Gonzalez Coro, Elpidio Berovides and 19 de Julio Policlinical Centres (Havana City, Cuba).

At recruitment (visit 1) a complete medical history including physical examination was performed, and patients entered in a 4 week run-in period, during which followed a low-fat, low-cholesterol diet, with a daily consumption of cholesterol < 300 mg/day, total fat (saturated, polyunsaturated and monounsaturated) from 8 to 10 %, carbohydrates ≥ 55% and protein for about 15 % of total calories. [8] After this diet-only period, laboratory determinations (lipid profile and assessment of safety indicators) were done. Eligible patients were randomized, under double-blind conditions, to policosanol (5 mg) or placebo tablets (Visit 2) for 12 weeks. Physical examination and laboratory tests were done at baseline and at the end of the study. At visit 3 subjects were requested about AE and compliance with study medications was assessed.

After therapy, a final check-up was performed (visit 4).

The placebo group was included as a parallel control to detect any systematic factor that could affect the results, since data supporting the efficacy of policosanol on subjects with "normal" to mildly elevated serum TC is relatively limited. Since all subjects were on TLC regimen and treatment duration was short, placebo subjects were not at special risk status as compared to clinical practice.

Study subjects

Women and men (37-75 years) with serum TC < 6.2 mmol/L were enrolled in the study. To be randomized to active treatment they should have serum TC ≤ 5.9 mmol/L at the end of the baseline diet-only period.

Subjects with TG ≥ 2.4 mmol/L, active renal diseases, diagnosed neoplastic diseases, severe hypertension (diastolic pressure ≥ 120 mm Hg) and uncontrolled diabetes (serum glucose > 7.5 mmol/L) were excluded from the study. Also, those with a history of myocardial infarction, stroke, or any major surgery prior to the study were also excluded.

The study protocol predefined the following reasons as causes of premature withdrawals: adverse events (AE) justifying such decision, unwillingness to follow-up b, major violations of study protocol, including > 5 consecutive days without taking the study medications.

Treatment

Study medications were identical in appearance and administered in identical packages identified with a code number and the number of treatment assigned by successive progressive inclusion. Study medications were randomised by a fixed randomisation method using blocks of regular sizes and allocation ratio 1:1. Subjects were instructed to take study medications once a day with the evening meal for 12 weeks

Compliance with study treatments (placebo or policosanol) were done by tablet count and confirmed by patient interviews.

Study outcomes

The primary study outcome was to obtain a significant serum LDL-C reduction of at least 15% versus placebo. [36] Changes on others lipid profile markers (TC, HDL-C and TG) and comparison of the frequencies of subjects achieving LDL-C targets were secondary outcomes.

Since most randomized subjects were at low CHD risk (no previous coronary or cerebrovascular events, no 2 or more non lipid risk factors), we considered that individuals who reach LDL-C values ≤ 160 mg/dL achieved the recommended goals. In the cases that concomitant risk factors evidenced a moderate risk we consider a target value of ≤130 mg/dL.

Safety and tolerability analyses

Data from the physical examination (bodyweight, pulse and blood pressure), laboratory tests and AE were included for the safety and tolerability analyses. Laboratory tolerability tests included determinations of glucose, creatinine, aspartate aminotransferase (AST) and alanin aminotransferase (ALT).

An AE was any new undesirable experience appearing during the study or any worsening of habitual symptoms. "Serious" AE were those leading to hospitalisation and/or deaths. "Moderate" AE were those requiring discontinuation of therapy and/or specific treatment, and "mild" AE were those not requiring discontinuation of study treatments nor specific therapy for the AE. Also, AE were classified as unlikely, doubtfully, possibly or probably treatment-related according to Naranjo algorithm. [37]

Laboratory determinations

Blood samples were drawn after 12 hours overnight fast and aliquots were taken for laboratory determinations. Serum TC, TG and HDL-C were determined by enzymatic methods using reagent kits (Roche, UK). LDL-C values were calculated using the Friedewald equation. [38]

Determinations of safety indicators were performed by routine laboratory tests based in enzymatic methods using reagent kits (Roche, UK). All laboratory tests were performed in the Hitachi 719 autoanalyzer (Tokyo, Japan) of the Centre for Surgical and Medical Research (Havana City, Cuba).

Quality control was performed throughout the study. The precision was assessed according to repeatability (r) (within-day variations) and reproducibility (R) (between-day variations); and the accuracy was evaluated against standard references for each parameter. The differences against the standard reference were < 4% for TC and < 5% for TG. The assay bias of such parameters was constant throughout the trial.

Statistical analysis

All data were analysed by Intention-to-Treat approach, meaning that data of all randomised patients, as randomised, including those who withdrew from the trial, were included for the analyses.

The sample size estimation assumed that the final reduction of LDL-C from baseline induced by policosanol 10 mg/day should be ≥15% as compared to placebo. Then, 30 subjects per treatment arm would be enough to detect such difference with 80% power and $\alpha = 0.05$. We assume a permissible dropout rate of 10%, so that about 100 subjects should be enrolled.

Continuous variables were analysed with the t test for paired samples (within group comparisons) and with the t test for independent samples (between group comparisons). Categorical variables were compared by using the Fisher's Exact Probability Test. All tests were two tailed.

A value of $\alpha = 0.05$ was assumed for statistical significance. Statistical analyses were performed using the Statistics for Windows package program (Release 4.2, Stat Soft, Inc USA).

RESULTS

Baseline characteristics

Baseline characteristics of the three groups were well matched (Table 1). Study patients had a relative high frequency (≥ 20%) of non-lipid coronary risk factors, most non-modifiable, like postmenopausal status in women (36.7%), family history of CHD (56.7%), age ≥ 45 years in men (31.1%). Nevertheless, the frequency of cigarette smoking (33.3%), a modifiable risk factor, was also high.

Table 1: Baseline characteristics of study patients

Characteristics (n = 30)	Placebo		Policosanol 5 mg		Policosanol 10 mg	
Age (years)(X ± SD)	59 ± 10		58 ± 10		54 ± 9	
Body mass index (kg/m^2)(X ± SD)	28.3 ± 6.1		29.2 ± 6.0		28.8 ± 5.6	
Sex	**n**	**%**	**n**	**%**	**n**	**%**
Women	20	66.7	21	70.0	20	66.7
Men	10	33.3	9	30.0	10	33.3
Personal history						
Postmenopausal women	11	36.7	12	40.0	10	33.3
Male older than 45 years old	10	33.3	8	26.7	10	33.3
Smoking	10	33.3	10	33.3	10	33.3
Hypertension	10	33.3	10	33.3	10	33.3
Diabetes mellitus	1	3.3	1	3.3	2	6.7
Family history of CHD	16	53.3	17	56.7	18	60.0
Concomitant therapy						
Diuretics	6	20.0	5	16.7	5	16.7
Calcium channel blockers	4	13.3	6	20.0	4	13.3
Inhibitors of angiotensin converting enzyme	1	3.3	2	6.7	2	6.7
Antiplatelets	3	10.0	5	16.7	5	16.7
β - blockers	2	6.7	2	6.7	1	3.3
Oral hypoglycemic drugs	1	3.3	1	3.3	1	3.3

n: Number of patients; (X ± SD) (mean ± standard deviation)

Eighty- three (83) of 90 randomised patients (92.2%) concluded the study. There were 7 study withdrawals: 4 (13.3%) from placebo, 2 (6.7%) from policosanol 5 mg/day and 1 (3.1%) from policosanol 10 mg/day groups. Only two placebo-treated subjects discontinued the study due to AE (dizziness and diarrhoea, respectively), meanwhile the other dropouts were due to unwillingness to follow-up (4) (1 placebo, 2 policosanol 5 mg/day, 1 policosanol 10 mg/day) and travels abroad (1 placebo).

Efficacy

Compliance with study medications was very good, since according to tablet count and interviews, with the exception of the study withdrawals, > 90% of study population consumed all required tablets.

After 12 weeks on treatment, policosanol (5 and 10 mg/day) significantly ($p< 0.00001$) lowered serum LDL-C by 17.6% and 19.7%, respectively (Table 2). In addition, policosanol significantly ($p<0.00001$) lowered TC (11.3% and 14.8%) and raised ($p<0.01$) HDL-C (16.7% and 19.6%), whereas unaffected TG levels. Lipid profile unchanged in placebo. The frequency of policosanol-treated subjects who reached LDL-C targets (25/30, 83.3%; 5 mg/day) (26/30, 86.7%; 10 mg/day) was greater ($p < 0.001$) than in placebo (5/30, 16.7 %).

Safety and tolerability

Policosanol was safe and well tolerated. The treatment did not impair physical or lab safety indicators, and individual values remained within normal ranges (Table 3)

Twelve subjects (8 placebo, 2 policosanol-5mg and 2 policosanol-10mg) reported some AE (Table 4). Except the two AE causing the withdrawals, which were moderate, all other AE were mild. All AE, disregarding if they happened in placebo or policosanol subjects, were considered as possibly treatment-related.

Table 2: Effects of policosanol (5 and 10 mg/day) on the lipid profile of study subjects

Treatment	Baseline	12 weeks	% changes
LDL-C (mmol/L) (X ± SD)			
Placebo	4.23 ± 0.37	4.41 ± 0.51	**+4.2**
Policosanol 5 mg	4.27 ± 0.38	3.52 ± 0.63^{++**}	**-17.6**
Policosanol 10 mg	4.21 ± 0.34	3.38 ± 0.53^{+++**}	**-19.7**
CI 95 %			
Placebo	4.09 - 4.37	4.22 - 4.60	
Policosanol 5 mg	4.13 - 4.40	3.29 - 3.76	
Policosanol 10 mg	4.08 - 4.33	3.18 - 3.58	
TC (mmol/L) (X ± SD)			
Placebo	5.59 ± 0.22	5.65 ± 0.61	**+1.1**
Policosanol 5 mg	5.64 ± 0.15	5.00 ± 0.41^{++**}	**-11.3**
Policosanol 10 mg	5.60 ± 0.17	4.77 ± 0.71^{+++**}	**-14.8**
CI 95 %			
Placebo	5.50 - 5.67	5.42 - 5.88	
Policosanol 5 mg	5.58 - 5.70	4.85 - 5.16	
Policosanol 10 mg	5.53 - 5.66	4.50 - 5.03	
HDL-C (mmol/L) (X ± SD)			
Placebo	1.06 ± 0.28	0.95 ± 0.28	**-10.4**
Policosanol 5 mg	0.96 ± 0.23	1.12±0.40^{+*}	**+16.7**
Policosanol 10 mg	0.97 ± 0.20	1.16 ± 0.39^{+*}	**+19.6**
CI 95 %			
Placebo	0.96 - 1.17	0.85 - 1.06	
Policosanol 5 mg	0.88 - 1.05	0.97 - 1.28	
Policosanol 10 mg	0.89 - 1.04	1.01 - 1.30	
Triglycerides (TG) (mmol/L) (X ± SD)			
Placebo	1.82 ± 0.65	1.80 ± 0.73	**-1.1**
Policosanol 5 mg	1.83 ± 0.77	1.75 ± 0.69	**-4.4**
Policosanol 10 mg	2.01 ± 0.89	1.84 ± 0.67	**-8.5**
CI 95 %			
Placebo	1.58 - 2.07	1.52 - 2.07	
Policosanol 5 mg	1.54 - 2.12	1.49 - 2.01	
Policosanol 10 mg	1.68 - 2.34	1.59 - 2.09	

CI 95%: Confidence intervals (± 95%), X: mean, SD: standard deviation; *p < 0.01; **p < 0.00001. Comparison with baseline (t test for paired samples); $^{+}$p < 0.05; $^{++}$p < 0.0001; $^{+++}$p < 0.00001. Comparison between groups (t test for independent samples)

Table 3: Effects of policosanol (5 and 10 mg/day) on safety indicators of study subjects

Treatment	Baseline	Week 12
Physical safety indicators		
Body weight (kg) (X ± SD)		
Placebo	74.0 ± 10.0	74.1 ± 10.0
Policosanol 5 mg	73.6 ± 6.7	73.5 ± 6.8
Policosanol 10 mg	75.7 ± 7.5	75.8 ± 7.0
Pulse rate (beats/min) (X ± SD)		
Placebo	73.9 ± 9.3	73.2 ± 8.1
Policosanol 5 mg	73.5 ± 8.6	74.1 ± 8.2
Policosanol 10 mg	74.7 ± 8.8	74.8 ± 7.9
SBP (mm Hg) (X ± SD)		
Placebo	134.8 ± 16.0	136.0 ± 15.4
Policosanol 5 mg	135.0 ± 17.1	130.0 ± 14.9
Policosanol 10 mg	133.0 ± 14.1	128.3 ± 11.4
DBP (mm Hg) (X ± SD)		
Placebo	85.5 ± 6.2	83.4 ± 8.4
Policosanol 5 mg	84.5 ± 9.9	81.8 ± 10.2
Policosanol 10 mg	84.3 ± 7.9	81.0 ± 9.2
Blood biochemistry safety indicators		
ALT (U/L) (X ± SD)		
Placebo	22.00 ± 14.58	21.68 ± 14.22
Policosanol 5 mg	19.47 ± 5.90	18.59 ± 6.85
Policosanol 10 mg	22.44 ± 8.48	18.86 ± 6.79
AST (U/L) (X ± SD)		
Placebo	21.61 ± 5.71	20.68 ± 10.54
Policosanol 5 mg	20.17 ± 6.76	17.90 ± 5.27
Policosanol 10 mg	22.22 ± 7.0	18.96 ± 6.89
Glucose (mg/dL) (X ± SD)		
Placebo	5.30 ± 1.09	5.00 ± 1.02
Policosanol 5 mg	4.84 ± 0.85	4.72 ± 0.87
Policosanol 10 mg	4.86 ± 0.84	4.93 ± 1.02
Creatinine (μmol/L) (X ± SD)		
Placebo	83.92 ± 17.02	83.27 ± 14.82
Policosanol 5 mg	82.55 ± 15.15	81.67 ± 12.78
Policosanol 10 mg	78.32 ± 13.87	78.26 ± 14.04

X: mean, SD: standard deviation, SBP: systolic blood pressure, DBP: diastolic blood pressure, ALT: alanine aminotransferase, AST: aspartate aminotransferase.

DISCUSSION

This study demonstrates that policosanol (5 and 10 mg/day) given for 12 weeks was effective to lower LDL-C in subjects with serum TC ≤ 5.9 mmol/L. Also, the treatment produced additional benefits on the lipid profile of study subjects, lowering TC and increasing HDL-C levels.

Table 4: Adverse events (AE) reported during the study

AE	Placebo	Policosanol 5 mg	Policosanol 10 mg
	n (%)		
Nervous system			
Headache	0 (0.0)	0 (0.0)	0 (0.0)
Dizziness/vertigo	1 (3.3)*	1 (3.3)	0 (0.0)
Paresthesia	1 (3.3)	0 (0.0)	0 (0.0)
Somnolence	1 (3.3)	1 (3.3)	1 (3.3)
Bone and skeletal muscle			
Arthralgia	0 (0.0)	0 (0.0)	0 (0.0)
Cardiovascular			
Dyspnea	2 (6.7)	0 (0.0)	0 (0.0)
Gastrointestinal			
Heartburn	0 (0.0)	0 (0.0)	1 (3.3)
Diarrhoea	1 (3.3)*	0 (0.0)	0 (0.0)
Genitourinary - Body as a whole			
Weight loss	1 (3.3)	0 (0.0)	0 (0.0)
Anorexia	1 (3.3)	0 (0.0)	0 (0.0)
AE reported	**8 (26.7)**	**2 (6.7)**	**2 (6.7)**
Patients reporting AE	**8 (26.7)**	**2 (6.7)**	**2 (6.7)**

* Withdrawals

Policosanol 5 and 10 mg/day produced LDL-C reductions of 17.6% and 19.7%, respectively. These values are comparable with those produced by some nutraceutical or functional foods alternatives, like plant sterols, which lower serum LDL-C by up to about 15%. [36]

In turn, the rates of achieving target LDL-C levels in subjects treated with policosanol 5 and 10 mg/day (83.3% and 86.7%, respectively) are consistent with those expected in low-risk patients, [39, 40] as those included in this study.

In addition, policosanol 5 and 10 mg/day produced reductions of TC (11.3% and 14.8%, respectively) and increases of HDL-C (16.7% and 19.6%, respectively), which supports a beneficial on these other variables of the lipid profile. Policosanol did not change TG values, which agrees with most clinical data. [21-35]

The lipid-lowering effects of policosanol 5 and 10 mg/day here seen are consistent with those obtained in three of the four previous short-term (8 weeks) studies conducted on of subjects with "normal, borderline and mildly elevated" TC levels, in which policosanol (5 - 10 mg/day) have produced average reductions of LDL-C (16.7% - 22.1%) and TC (10.5% - 12.4%); and HDL-C increases (9% - 15.2%).[33-35] An early study, however, found a lower efficacy of policosanol 10 mg/day on normocholesterolemic subjects, since this dose only reduced significantly TC (10.7%), not LDL-C and HDL-C. [32] Such discrepancy could be related to the shorter duration

(4 weeks) of the treatment in that study as compared to further studies (8 – 12 weeks). [33-35] Nevertheless, even with such short-term treatment 20 mg/day was able to lower significantly TC (11.3%), LDL-C (22.9%) and to raise HDL-C (29%) in such individuals. [32] In addition, the present results are coherent with those obtained in patients with type II HC and type 2 diabetes. [21-31]

Policosanol was very well tolerated, as reflects the low withdrawal rate, the unchanged safety indicators and the low frequency of AE, a result consistent with all previous safety and tolerability profile documented for policosanol. [21-35, 41 - 43]

CONCLUSION

The present study demonstrates that policosanol (5 and 10 mg/day) administered for 12 weeks to individuals with serum TC ≤ 5.9 mmol/L effectively reduced LDL-C and TC, whereas raised HDL-C, and that it was safe and well tolerated.

REFERENCES

1. Lipid Research Clinics Program, The lipid research clinics coronary primary prevention trial results I, Reduction in the incidence of coronary heart disease, JAMA 251, 1984, 351-364.
2. Lipid Research Clinics Program, The lipid research clinics coronary primary prevention trial results II, The relationship of reduction in the incidence of coronary heart disease to cholesterol-lowering, JAMA , 251, 1984, 365-374.
3. Scandinavian Simvastatin Survival Study Group, Randomised trial of cholesterol lowering in 4 444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Study (4S), Lancet, 344, 1994, 1 383-389.
4. Sacks FM, Pfeffer MA, Moy LA et al, for the Cholesterol and Recurrent Events Trial Investigators, The effect of pravastatin on coronary events after myocardial infarction in patients with average cholesterol levels, N Engl J Med, 335, 1996, 1001-1009.
5. Tonkin A, Aylward P, Colqhoun D, Prevention of cardiovascular events and deaths with pravastatin in patients with coronary heart disease and a broad range of initial cholesterol levels. New Eng J Med, 339, 1998, 1349-1357
6. Downs JR, Clearfield M, Weiss S, for the AFCAPS/TexCAPS Research Group. Primary prevention of acute coronary events with lovastatin in men and women with average cholesterol levels: results of AFCAPS/TexCAPS, JAMA, 279, 1998, 1615 – 1622.
7. Shepherd S, Cobbe SM, Ford I, et al, Prevention of coronary heart disease with pravastatin in men with hypercholesterolemia, N Engl J Med, 333, 1995, 1301-1307.
8. Expert Panel of Detection, Evaluation and Treatment of High Blood Cholesterol in Adults: Executive Summary of the Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III), JAMA, 285, 2001, 2486-2497.
9. Grundy SM, et al, Implications of recent clinical trials for the National Cholesterol Education Program Adult Treatment Panel III guidelines, Circulation, 110, 2004, 227–239.
10. Teramoto T, Sasaki J, Ueshima H, Executive summary of Japan Atherosclerosis Society (JAS) guideline for diagnosis and prevention of atherosclerotic cardiovascular diseases for Japanese, J Atheroscler Thromb, 14, 2007, 45-50.
11. Sherbet DP, Garg P, Brilakis ES, Banerjee S, Low-density lipoprotein cholesterol: how low can we go? Am J Cardiovasc Drugs, 2013, Apr 23. [Epub ahead of print]
12. Brown TM, Tanner RM, Carson AP, Yun H, Rosenson RS, Farkouh ME, Woolley JM, Thacker EL, Glasser SP, Safford MM, Muntner P, Awareness, treatment, and control of LDL cholesterol are lower among United States adults with undiagnosed diabetes versus diagnosed diabetes, Diabetes Care, 2013, May 1. [Epub ahead of print]
13. Gao F, Zhou YJ, Hu da Y, Zhao YX, Liu YY, Wang ZJ, Yang SW, Liu XL, Contemporary management and attainment of cholesterol targets for patients with dyslipidemia in China. PLoS One, 8, e47681.
14. Takahashi E, Moriyama K, Yamakado M, Status of dyslipidemia treatment in Japanese adults: an analysis of the 2009 Japan Society of Ningen Dock database, Intern Med, 52, 2013, 295-301.
15. Mas R, Policosanol, Drugs of the Future 25, 2000, 569-586.
16. Menéndez R, Amor A, Rodeiro I, González RM, Acosta P, Alfonso J, Mas R, Policosanol modulates HMGCoA reductase activity in cultured fibroblasts, Arch Med Res, 32, 2001, 8-12.
17. Singh DK, Li Li, Porter TD, Policosanol inhibits cholesterol synthesis in hepatoma cells by activation of AMP-kinase, J Pharmacol Ther, 318, 2006, 1020-1025.
18. Oliaro Rosso S, Calcio E, Mantegna S, Regualtion of HMGCoA reductase by policosanol and octacosadienol, a new synthetic analogue of octacosanol, Lipids, 2009, DOI 10.1007/s11745-009-3338-y.
19. Banerjee S, Ghoshal S, Porter TD, Activation of AMP-kinase by policosanol requires peroxisomal metabolism, Lipids, 2011 Feb 27. [Epub ahead of print]
20. Menéndez R, Arruzazabala ML, Más R, del Río A, Amor AM, González RM, Carbajal D, Fraga V, Molina V, Illnait J, Cholesterol-lowering effect of policosanol on rabbits with hypercholesterolemia induced by a wheat starch-casein diet, Brit J Nutr, 77, 1997, 923-932.
21. Más R, Castaño G, Illnait J, Fernández L, Fernández JC, Alemán C, Pontigas V, Lescay M, Effects of policosanol in patients with type II hypercholesterolemia and additional coronary risk factors, Clin Pharmacol Ther, 65, 1999, 439-447.
22. Castaño G, Más R, Fernández L, Fernández JC, Illnait J, López LE, Alvarez E, Effect of policosanol on postmenopausal women with type II hypercholesterolemia, Gynecol Endocrinol, 14, 2000, 187-195.
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 Med Sci, 56, 2001, M186-M192.

24. Más R, Castaño G, Fernández L, Illnait J, Fernández J, Alvarez E, Effects of policosanol in older hypercholesterolemic patients with coronary disease, Clin Drug Invest, 21, 2001, 485-497.
25. Nikitin IP, Slepchenko NV, Gratsianskii NA et al, Results of the multicenter controlled study of the hypolipidemic policosanol in Russia, Ter Arkh, 72, 2000, 7 – 10.
26. 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, 20, 2002, 153 – 163.
27. Wang Y, Kuanman KE, Wang Hia L, Jiao Y, Zhao X, Sun N, Yang X, Sun R, Efficacy and safety of policosanol and pravastatin in treatment of hyperlipidemia in Chinese patients, J New Drugs Clin Res, 2, 2008, 124-129.
28. Liu S, Tan MY, Zhao SP, Rong H, Effects of policosanol on serum lipids and heme oxygenase-1 in patients with hyperlipidemia, Zhonghua Xin Xue Guan Bing Za Zhi, 40, 2012, 840-843.
29. Torres O, Agramonte AJ, Illnait J, Más R, Fernández L, Fernández JC, Treatment of hypercholesterolemia in NIDDM with policosanol, Diabetes Care, 18, 1995, 393-397.
30. Crespo N, Illnait J, Mas R, Fernández L, Castaño G, Comparative study of the efficacy and tolerability of policosanol and lovastatin in patients with hypercholesterolemia and non insulin dependent diabetes mellitus, Int J Clin Pharmacol Res, 19, 1999, 105-116.
31. Castaño G, Fernández L, Mas R, Comparison of the effects of policosanol and atorvastatin on lipid profile and platelet aggregation on patients with dyslipidemia and Type 2 diabetes mellitus, Clin Drug Invest, 23, 2000, 639 – 650.
32. Hernández F, Illnait J, Mas R, Effects of policosanol on serum lipids and lipoproteins in healthy volunteers, Curr Ther Res, 51, 1992, 568-575.
33. Menéndez R, Mas R, Amor AM, 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, 50, 2000, 255-262.
34. Castano G, Mas R, Fernandez J, Effects of policosanol on patients with borderline to mildly increased serum cholesterol levels: A prospective,_double-blinded placebo-controlled study, Curr Ther Res Clin & Exp, 64, 2003, 522 – 536.
35. López E, Illnait J, Fernández JC, Fernández L, Gámez R, Mesa M, Mendoza S, Mas R, Ruiz D, Jardines Y, Effects of sugarcane wax alcohols in subjects with normal or borderline serum cholesterol levels, Rev CENIC Cien Biol, 41, 2010, 31-37.
36. Patch CS, Tapsell LC, Williams PG, Gordon M, Plant sterols as dietary adjuvants in the reduction of cardiovascular risk: theory and evidence, Vasc Health Risk Manag, 2, 2006, 157-162.
37. Naranjo CA, Busto U, Sellers EM, A method for estimating the probability of adverse drug reactions, Clin Pharmacol Ther, 30, 1981, 239-245.
38. Friedewald WT, Levy RI, Friederickson SD, Estimation of the concentration of low-density-lipoprotein cholesterol in plasma without of the preparative ultracentrifuge, Clin Chem, 18, 1972, 499-502.
39. Ambegaonkar B, Chirovsky D, Tse HF, Lau YK, Tomlinson B, Li SK, Yue CS, Wong TH, Choi MC, Tunggal P, Sazonov V, Attainment of normal lipid levels among patients on lipid-modifying therapy in Hong Kong, Adv Ther, 29, 2012, 427-441.
40. Lee JA, Sunwoo S, Kim YS, Oh HJ, Kang HC, Park KC, Sin DH, Lee SY, Yang YJ, Yu BY, Kim CM, Achieving recommended low density lipoprotein cholesterol goals and the factors associated with target achievement of hypercholesterolemia patients with rosuvastatin in primary care, Curr Med Res Opin, 29, 2013, 751-760.
41. Fernández L, Mas R, Illnait J, Policosanol: results of a post-marketing surveillance control on 27 879 cases, Curr Ther Res, 59, 1998, 717-722.
42. Mas R, Rivas P, Izquierdo JE, Pharmacoepidemiologic study of policosanol, Curr Ther Res, 60, 1999, 458-467.
43. Fernández S, Mas R, Gamez, R, A pharmacological surveillance of policosanol tolerability in the elderly, Am J Ger Pharmacotherapy, 2, 2004, 219 – 229.

Source of Support: Nil, **Conflict of Interest:** None.