IOSR Journal Of Pharmacy *www.iosrphr.org*
(e)-ISSN: 2250-3013, (p)-ISSN: 2319-4219
Volume 9, Issue 5 Series. I (May 2019), PP. 57-65

Concomitant Use of Policosanol and Oral Hypoglycemic Drugs in Older Diabetic Patients

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Abstract: **Introduction:** Coronary disease is the major complication and leading cause of death among patients with diabetes mellitus. Hyperlipidemia is common in patients with diabetes mellitus and the high frequency of coronary disease in diabetics is partly a consequence of the abnormalities of lipid metabolism. Policosanol is a cholesterol-lowering drug with concomitant antiplatelet effects. The efficacy and safety of policosanol have been investigated in clinical studies and post-marketing surveillance, included diabetic patients. Policosanol is very safe and no drug-related adverse events have been demonstrated, even in population subsets with high consumption of concomitant therapy, indicating that the potential risk of drug-drug interaction (DDI) for policosanol is low. This background supported to assess the potential interaction between policosanol and oral hypoglycemic drugs from the analysis of the data of the long-term prevention study with policosanol in the diabetic elderly.
Objective: The objective of the present analysis as a part of a prevention study, we investigated whether concomitant administration of policosanol with oral hypoglycemic drugs induces some specific adverse event or disturbance on any safety indicator in older diabetic patients with hypercholesterolemia.
Methods: We randomised 1470 elderly patients at high coronary risk to policosanol or placebo for 3 years. For this analysis, the records of all diabetic patients (144) taking oral hypoglycemic drugs were included. Analysis was by Intention-to-treat.
Results: Both groups were well matched at baseline. At study completion, policosanol significantly reduced low-density lipoprotein cholesterol (LDL-C) (32.7 %), total cholesterol (24.8 %), triglycerides (31.7 %) and raised high-density lipoprotein cholesterol (HDL-C) (9.6 %). Of 144 diabetic patients consuming oral hypoglycemic drugs, 36 (25 %) discontinued the study, 28/79 placebo (35.4 %) and 8/65 policosanol (12.3 %) patients. Of them, 22 patients (19 placebo, 3 policosanol) ($p<0.01$) discontinued prematurely the study because of some adverse event. No disturbance of any safety indicator was found. Policosanol no modify control of glucose of these patients. The serious vascular adverse events in policosanol patients taking oral hypoglycemic drugs (1/65, 1.5 %) was lesser ($p<0.01$) than in placebo (18/79, 22.8 %). Also, the frequency of moderate and mild adverse events reported in the policosanol group was lower ($p<0.05$) compared with placebo group.
Conclusion: It is concluded that policosanol therapy added to older hypercholesterolemic diabetic patients taking oral hypoglycemic drugs produced relevant benefits on lipid profile and the frequency of serious adverse events respect to placebo, then indicated concomitant with oral hypoglycemic drugs in elderly, without increase any adverse event.

Key words: policosanol, diabetic, elderly, hypercholesterolemia, oral hypoglycemic, drug interactions

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Date of Submission: 25-04-2019 Date of acceptance: 06-05-2019

I. INTRODUCTION

Coronary events are the leading cause of morbidity and mortality in middle-aged and elderly individuals.[1] Coronary heart disease (CHD) is the major complication and leading cause of death among patients with diabetes mellitus.[2-4] Hyperlipidemia is common in patients with diabetes mellitus and the high frequency of CHD in diabetics is partly a consequence of the abnormalities of lipid metabolism, as hypercholesterolemia, especially when a high level of low density lipoprotein cholesterol (LDL-C) is present.[5,6]

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.[7]

A combination of lifestyle changes, including glycemic control, is the first-choice therapy for dyslipidemia management in diabetes mellitus. Nevertheless, adherence to these measures alone is often not sufficient and lipid-lowering drugs must be prescribed.[8-11]

Policosanol is a mixture of high molecular weight primary aliphatic alcohols isolated and purified from sugar cane (*Sacharum officinarum)*, wax with cholesterol-lowering effects.[12] Policosanol inhibits cholesterol synthesis, modulating the activity of hydroxymethyl glutaryl Coenzyme (HMG CoA) through the increase of AMP kinase activity,[13-16] increasing LDL receptor-dependent processing and catabolic rate of LDL.[17-19]

Policosanol also shows important pleiotropic effects that can reinforce its effects on atherosclerosis development, such as inhibition of platelet aggregation,[20] and of the susceptibility of LDL to be oxidised.[21]

Previous studies conducted in older diabetic patients with hypercholesterolemia treated with policosanol showed that policosanol was effective and well tolerated in these patients.[22-26]

Clinical and post-marketing studies have demonstrated that policosanol is safe and well tolerated[27-29] 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.[30,31] Nevertheless, pharmacodynamic interactions between policosanol and other drugs cannot be discarded.[32-35]

This background supported to assess the potential interaction between policosanol and oral hypoglycemic drugs from the analysis of the data of the long-term prevention study with policosanol in the diabetic elderly. Then, the present analysis was conducted to determine whether concomitant administration of policosanol with oral hypoglycemic drugs 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 diabetic patients consuming oral hypoglycemic drugs and if the addition of policosanol to oral hypoglycemic drugs consumption improved the control of glucose values 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. In brief, patients were recruited at four Policlinical Centres 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 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.

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).

Enrollment criteria. Patients of both sexes aged 60 to 80 with documented past history of coronary (myocardial infarction, unstable angina 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 serious adverse events (SAE) or AE justifying such decision, unwillingness to follow-up, patients with total cholesterol ≥ 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. Patients should be titrated to 2 or 4 tablets oid if their total cholesterol 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. 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. 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. Treatment was considered as effective if LDL-C was significantly reduced by ≥ 15 %,[36] 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 oral hypoglycemic drugs were included in the analysis. Physical (body weight, pulse rate, blood pressure) and laboratory safety indicators (aspartate aminotransferase (AST), alanine aminotransferase (ALT), glucose, creatinine) 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.[37]

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. Lipid profile and laboratory safety indicators were assessed by enzymatic methods using reagent kits (Roche). 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 $\chi 2$ 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 diabetic patients taking oral hypoglycemic drugs were comparable at baseline (Table 1). Most patients were women (84 %) and hypertensive (73.6 %) Study patients also showed a high frequency of coronary events (38.9 %). In turn, the frequency of concomitant medications was also high, the other concomitant medications most consumed being angiotensin converting enzyme inhibitors, diuretics, anti-platelets, calcium antagonists, vasodilators, β-blockers, anxyolytics and digitalics. Concomitant medications 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 ($p<0.05$) than in placebo. Of 144 patients consuming oral hypoglycemic drugs, 36 (25 %) discontinued the study, 28/79 placebo (35.4 %) and 8/65 policosanol (12.3 %) patients. Of them, 22 patients (19 placebo, 3 policosanol) ($p<0.01$) 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 ($p<0.0001$ vs placebo) LDL-C, total cholesterol and triglycerides, while raised ($p<0.001$ vs placebo) HDL-C levels. Policosanol effects persisted during the whole study. At study completion, policosanol reduced ($p<0.0001$ vs placebo) LDL-C (32.7 %), total cholesterol (24.8 %), triglycerides (31.7 %) and raised ($p<0.0001$ vs placebo) HDL-C (9.6 %).

Safety and tolerability. No impairment of safety indicators was observed (Table 4). Policosanol no modify control of glucose of these patients.

Table 5 shows the frequency of AE occurred during the study. The serious vascular adverse events in policosanol patients taking oral hypoglycemic drugs (1/65, 1.5 %) was lesser ($p<0.01$) than in placebo (18/79, 22.8 %). Also, the frequency of moderate and mild AE reported in the policosanol group was lower ($p<0.05$) compared with placebo group.

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 placebo. The study also showed that policosanol, did not increased the frequency of non-vascular SAE.

The present analysis demonstrates that policosanol administered to elderly diabetic patients taking oral hypoglycemic drugs no 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[38] 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 oral hypoglycemic drugs and placebo or oral hypoglycemic drugs 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.

The frequency of patients consuming antiplatelet drugs (24.3 %), most of them consuming aspirin alone, was slightly lower than that expected according to the frequency of cases with coronary disease (38.9 %).

The present results support that policosanol efficacy is evident also in older diabetic patients taking oral hypoglycemic drugs and are consistent with previous report of the concomitant use of policosanol and others drugs.[32-35]

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 SAE, cardiovascular, cerebrovascular, all deaths to vascular causes and all deaths was lower ($p<0.05$) than in placebo, consistently with LDL-C lowering and pleiotropic effects of policosanol, all beneficial for vascular function, thus preventing the occurrence of vascular events.

Policosanol was very well tolerated in elderly hypercholesterolemic diabetic patients consuming oral hypoglycemic drugs. The frequency of SAE was lower in policosanol than in placebo, suggesting that policosanol can contribute to reduce the risk of older diabetic patients consuming oral hypoglycemic drugs. Policosanol did not increase the frequency of AE compared with placebo, thus minimizing any potential risk derived from the concomitant use of policosanol and oral hypoglycemic drugs.

These results support that policosanol is effective for lowering LDL-C and total cholesterol in patient taking oral hypoglycemic drugs, providing advantages in reducing the frequency of SAE respect to placebo, without increase any AE, even in older diabetic patients at high coronary risk, highly medicated with concomitant therapy and sensitive to drug-related AE and drug/drug interactions.

V. CONCLUSIONS

It is concluded that policosanol therapy added to older hypercholesterolemic diabetic patients taking oral hypoglycemic drugs produced relevant benefits on lipid profile and the frequency of serious adverse events respect to placebo, then indicated concomitant with oral hypoglycemic drugs in elderly, without increase any adverse event.

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Table 1. Main baseline characteristics of study diabetic patients taking oral hypoglycemic drugs

Characteristics	**(n = 79)**		**(n = 65)**	
Age (years) (X ± SD)	66 ± 6		66 ± 6	
Body mass index (kg/m^2) (X ± SD)	26.90 ± 6.09		28.01 ± 4.98	
	n	**%**	**n**	**%**
Gender: Female	68	86.1	53	81.5
Male	11	13.9	12	18.5
Risk factors:				
Arterial hypertension	57	72.1	49	75.4
Coronary heart disease*	31	39.2	25	38.5
Smoking	18	22.8	13	20.0
Obesity (kg/m^2 > 30)	7	8.9	4	6.1
Cerebrovascular disease**	2	2.5	4	6.1
Other concomitant medications (CM)***				
Angiotensin converting enzyme inhibitors	21	26.6	23	35.4
Diuretics	20	25.3	23	35.4
Anti-platelets	19	24.0	16	24.6
Calcium antagonists	18	22.8	14	21.5
Anxyolytics	11	13.9	6	9.2
Digitalics	10	12.7	7	10.8
Vasodilators	10	12.7	6	9.2
β-blockers	9	11.4	6	9.2
Myorelaxants	7	8.9	4	6.1
Thyroid hormones	6	7.6	4	6.1

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 of study

Withdrawals due to AE	**Placebo (n = 79)**	**Policosanol (n = 65)**	**P value***	**Total**
Withdrawals due to vascular SAE	13	1	p<0.01	14
Withdrawals due to SAE from other causes	5	2		7
Subtotal due to SAE	**18**	**3**	**p<0.01**	**21**
Withdrawals due to mild and moderate AE	1	0		1
Subtotal due to all AE	**19 (24.0)**	**3 (4.6)**	**p<0.01**	**22**
Withdrawals due to other reasons				
Unsatisfactory efficacy	5	0	p<0.05	5
Travels abroad + changes to other towns	2	1		3
Unwillingness to follow-up	1	2		3
Protocol violations	1	2		3
Subtotal due to other reasons	**9 (11.4)**	**5 (7.7)**	**ns**	**14 (9.7)**
Total of withdrawals	**28 (35.4)**	**8 (12.3)**	**p<0.05**	**36 (25.0)**

*Comparison with placebo (χ2 test)

Table 3 Long-term effects of policosanol on lipid profile (X±SD)

Study groups	Baseline	1 year	2 years	3 years
Total cholesterol (mmol/L)				
Policosanol	6.81 ± 0.90	5.30 ± 0.45^{+++}	5.20 ± 0.44^{+++}	5.12 ± 0.36^{+++}
Placebo	6.73 ± 0.89	6.63 ± 0.91	6.57 ± 0.82	6.70 ± 0.75
LDL-C (mmol/L)				
Policosanol	4.56 ± 0.84	3.57 ± 0.87^{+++}	3.21 ± 0.48^{+++}	3.07 ± 0.35^{+++}
Placebo	4.57 ± 0.88	4.61 ± 0.89	4.72 ± 0.87	4.77 ± 0.75
HDL-C (mmol/L)				
Policosanol	1.25 ± 0.34	1.32 ± 0.23^{++}	1.35 ± 0.27^{+++}	1.37 ± 0.20^{+++}
Placebo	1.22 ± 0.31	1.18 ± 0.35	1.10 ± 0.17	1.12 ± 0.21
Triglycerides (mmol/L)				
Policosanol	2.71 ± 0.90	2.03 ± 0.73^{+}	1.93 ± 0.37^{++}	1.85 ± 0.31^{+++}
Placebo	2.69 ± 1.17	2.72 ± 1.22	2.74 ± 0.57	2.67 ± 0.67

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

Table 4. Long-term effects of policosanol on safety indicators (X ± SD)

Study groups	Baseline	1 year	2 years	3 years
Weight (kg)				
Policosanol	68.74 ± 13.50	67.93 ± 12.80	68.21 ± 13.01	70.88 ± 13.72
Placebo	66.86 ± 13.03	66.34 ± 11.96	66.54 ± 11.82	67.19 ± 10.97
Pulse (beats/min)				
Policosanol	72.61 ± 7.08	71.29 ± 6.44	72.21 ± 5.83	70.68 ± 6.13
Placebo	73.75 ± 6.99	72.18 ± 5.20	71.55 ± 4.21	70.73 ± 5.17
Diastolic pressure (mm Hg)				
Policosanol	82.62 ± 10.21	80.86 ± 5.39	80.35 ± 8.44	80.27 ± 6.48
Placebo	81.84 ± 7.73	80.86 ± 6.56	79.62 ± 4.79	81.18 ± 5.37
Systolic pressure (mm Hg)				
Policosanol	138.8 ± 20.95	133.6 ± 13.64	133.8 ± 11.05	134.5 ± 12.64
Placebo	136.7 ± 14.83	135.0 ± 16.93	133.4 ± 11.59	135.3 ± 10.80
Alanine amino transferase (U/L)				
Policosanol	20.39 ± 8.29	20.97 ± 8.38	19.89 ± 7.82	20.50 ± 7.64
Placebo	23.18 ± 11.88	23.34 ± 12.02	22.18 ± 7.61	23.29 ± 6.94
Aspartate amino transferase (U/L)				
Policosanol	19.95 ± 8.89	19.73 ± 7.81	19.52 ± 7.04	19.15 ± 7.14
Placebo	20.69 ± 10.49	20.29 ± 8.56	21.58 ± 7.25	22.06 ± 5.26
Creatinine (μmol/L)				
Policosanol	89.42 ± 17.77	88.86 ± 12.37	86.52 ± 12.03^{+}	88.80 ± 10.73
Placebo	88.80 ± 16.30	90.03 ± 16.60	91.79 ± 19.05	91.85 ± 11.27
Glucose (mmol/L)				
Policosanol	6.25 ± 1.38	6.19 ± 2.76	5.86 ± 1.44	5.91 ± 1.72
Placebo	6.67 ± 2.63	6.52 ± 3.43	6.34 ± 3.34	6.27 ± 1.36

X mean, SD standard deviation

Table 5. Adverse events (AE) in study patients

	Placebo (n = 79)		**Policosanol (n = 65)**	
Serious adverse events (SAE)	**n**	**%**	**n**	**%**
All cardiovascular SAE	7	8.9	0	0.0^{+}
All cerebrovascular SAE	4	5.1	1	1.5
All vascular SAE	**13**	**16.4**	**1**	**1.5**$^{++}$
All SAE (fatal + non fatal)	**18**	**22.8**	**1**	**1.5**$^{++}$
Fatal SAE (Deaths)				
Deaths to vascular causes	**4**	**5.1**	**0**	**0.0**
Deaths to non-vascular causes	**1**	**1.3**	**0**	**0.0**
All deaths	**5**	**6.3**	**0**	**0.0**$^{+}$
Moderate and mild AE				
Chest pain	4	5.1	0	0.0
Arthralgia	2	2.5	2	3.1
Moderately uncontrolled hypertension	1	1.3	0	0.0
Gastritis	2	2.5	0	0.0
Asthma	0	0.0	1	1.5
Renal sepsis	2	2.5	1	1.5
Acidity	2	2.5	0	0.0
Diarrhoea	2	2.5	1	1.5
Asthenia	2	2.5	0	0.0
Nervousness	0	0.0	1	1.5

Insomnia	0	0.0	1	1.5
Abdominal pain	2	2.5	0	0.0
Headache/Cephalea	4	5.1	4	6.1
Bursitis	0	0.0	1	1.5
Dyspepsia	1	1.3	0	0.0
Pruritus	2	2.5	0	0.0
Patients with moderate or mild AE	**26**	**32.9**	**12**	**18.5**$^{+}$

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

IOSR Journal of Pharmacy (IOSR-PHR) is UGC approved Journal with Sl. No. 3365, Journal No-62875

Dr. Julio César Fernández Travieso. "Concomitant Use of Policosanol and Oral Hypoglycemic Drugs in Older Diabetic Patients.". IOSR Journal of Pharmacy (IOSRPHR), vol. 9, no. 5, 2019, pp. 57-65.