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Efficacy and Safety of Policosanol (Sugarcane Wax Alcohols) 20 mg/Day in Cuban Prehypertensive Patients: A Randomized, Double-Blind, Multicentre Study

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ABSTRACT

Hypertension is the most common modifiable cardiovascular risk factor. Policosanol exhibits lipid-modifying and beneficial vascular pleiotropic effects. Some previous Cuban trials found that policosanol lowered blood pressure in hypercholesterolemic patients. Similar results were found recently in prehypertensive Asian subjects. The aim of this study was to report the effects of 20 mg/day of policosanol on blood pressure in Cuban patients with prehypertension. A double-blind multicenter trial randomized 400 eligible patients into two strata of 200 patients each (prehypertension and Grade 1 hypertension), treated with placebo or 20 mg/day of policosanol (100 patients/group/stratum) for 12 weeks. The primary outcome was to determine whether policosanol could achieve significant systolic blood pressure (SBP) reductions ≥10 mmHg versus placebo. Changes in diastolic blood pressure (DBP) and lipid profile were secondary outcomes. Safety indicators and adverse events (AE) were assessed. Statistical analyses were conducted by intention-to-treat (ITT). Here we report the results of the prehypertension stratum (SBP 120–139 mmHg, DBP 80–89 mmHg). Both groups were similar at randomization. At study completion, policosanol significantly lowered ($p < 0.001$) SBP and DBP values versus baseline and placebo. Also, more ($p < 0.0001$) policosanol patients (44%) reached SBP reductions ≥10 mmHg and DBP reductions ≥5 mmHg versus baseline (44% and 61%, respectively) than placebo patients (7% and 22%, respectively). Policosanol significantly lowered low-density lipoprotein cholesterol (LDL-C) and total cholesterol (TC) and increased low-density lipoprotein cholesterol (HDL-C). Policosanol was well tolerated. Nine patients (4.5%) discontinued the trial, none because of AE. Four patients (3 placebo, 1 policosanol) reported AE. It is concluded that policosanol 20 mg/day given for 12 weeks to Cuban patients with prehypertension lowered SBP and DBP and produced beneficial changes in the lipid profile, being well tolerated.

1 | Introduction

Hypertension is the most frequent modifiable cardiovascular risk factor, with more than 1 billion individuals living with high blood pressure worldwide [1]. Hypertension has been widely recognized as the leading cause of cardiovascular disease and the main contributor of global mortality [2].

Evidence has proven the impact of lowering blood pressure for improving cardiovascular outcomes and all-cause mortality [3], making clear the relevance of promoting knowledge, prevention, and treatment of high blood pressure levels.

Hypertension is divided into primary (also referred to as 'essential') and secondary forms. While the secondary form is due to specific causes, the exact etiology of primary hypertension, by far the larger percentage of the hypertensive population, remains unclear. Hypertension management involves non-pharmacological and pharmacological approaches, and despite the efficacy of current antihypertensive drugs, lifestyle adjustments remain an integral part of treatment [4–6].

According to Cuban [7] and international guidelines [4–6], hypertension is defined as SBP values ≥140 mmHg and/or DBP ≥90 mmHg, supported by repeated office measurements [4–7]. There are some variations in cut-off values in the different guidelines, the American being the strictest. Cuban hypertension guidelines [7] define prehypertension as when systolic blood pressure (SBP) is consistently between 120 and 139 mmHg, and diastolic blood pressure (DBP) is between 80 and 89 mmHg, and Grade 1 hypertension when SBP is between 140 and 159 mmHg, and DBP between 90 and 99 mmHg. All guidelines agree that at the prehypertension stage, doctors may choose to initially manage hypertension with lifestyle changes only but may add medication based on the patient's overall cardiovascular risk. Hence, to assess the potential benefits of a treatment for blood pressure, one should start on patients at the lowest risk stage.

Policosanol is a mixture of high molecular weight primary alcohols isolated from the sugarcane (*Saccharum officinarum*, L.) wax, with cholesterol lowering effects involving low-density lipoprotein cholesterol (LDL-C) and total cholesterol (TC) reductions, and modest to moderate increases of high-density lipoprotein cholesterol (HDL-C), as supported by studies conducted in Cuba and other countries [8–17]. Some published studies, however, dismissed the cholesterol-lowering effects of policosanol [18–20]. Nevertheless, an older [21] and recent meta-analyses [22, 23] have supported policosanol lipid-modifying effects, the last one considering that conflicting data could depend on many factors, including the diversity of products used in such trials.

The cholesterol-lowering mechanism of policosanol has been associated with the inhibition of cholesterol synthesis through a modulatory action in hydroxy-methyl-glutaryl coenzyme A (HMGCoA)-reductase triggered by the activation of AMP kinase [24–27], and an increase in LDL receptor processing [27].

In addition, policosanol exhibits pleiotropic effects beneficial in preventing atherothrombotic complications, such as the inhibition of LDL oxidation [28], and of platelet aggregation and reactivity [29–31].

Some trials conducted in Cuban patients at high cardiovascular risk but focused on LDL-C as primary outcome, found that policosanol (5–10 mg/day) lowered their blood pressure values [12, 13]. In line with these old results, recent clinical trials conducted in Korean and Japanese prehypertensive subjects have shown that policosanol 10 and 20 mg/day significantly lowered both SBP and DBP [32–34].

Pooling all the previous data, a meta-analysis concluded that policosanol could lower SBP and DBP in adults but that it is important to conduct further studies in different populations to confirm such results [35].

Since policosanol (5–20 mg/day) has an excellent safety profile [8-17, 28–31, 36, 37], it could be a useful option in contributing to the long-term control of blood pressure values in the prehypertension stage, whenever larger trials conducted in different populations confirm such benefit. This work aimed to report the effects of policosanol 20 mg/day on blood pressure values in Cuban patients with prehypertension.

2 | Participants and Methods

2.1 | Study Design

This study was a randomized, double-blind, placebo-controlled multicenter clinical trial. The patients were recruited in one of the main health institutions at Havana, namely, the Clinical Surgical Hospital "Calixto Garcia," while other centers, such as the National Institute of Hygiene and Epidemiology and the Surgical Medical Research Centre, were involved in study control and test processing, respectively.

The study followed the ethical principles established in the latest version of the Declaration of Helsinki and Tokyo. The study protocol was approved by the Institutional Review Board (IRB) (IRB-120721) after receiving the inputs of the National Hypertension Group of the Cuban Ministry of Health and being registered in the Cuban Public Registry of Clinical Trials (RPCEC00000377). All participants provided written informed consent at enrolment.

Enrolled patients were eligible for randomization if they met inclusion criteria and had no exclusion criteria, being instructed to follow healthy lifestyle actions for hypertension management (healthy dietary advice with reduced salt and calorie intake, rich in vegetables and fruits along with advice to be physically active by systematic walking and exercise). Eligible patients were randomized in two strata of prehypertensive and Grade 1 hypertensive patients, respectively, in turn, randomized to receive either policosanol 20 mg or placebo tablets (Visit 2) for 12 weeks.

Patients were seen at baseline (Visit 2) and after 4, 8, and 12 weeks on therapy (Visits 3 to 5). Patients were examined every 4 weeks for blood pressure measurements, while laboratory analyses were conducted at baseline and at the end of the treatment period. At each visit, physical signs, compliance with study drugs and adverse events (AE) were assessed.

Clinic blood pressure values were measured at each visit by using manual aneroid sphygmomanometer (Gima, Italy) mea-

surements, with a maximum error tolerance for static pressure of ± 5 mmHg. Values were determined by the average of two recordings of SBP and DBP, obtained at 3-min intervals, after subjects were seated for 5 min in a quiet environment on a chair with their feet on the floor and arms supported at heart level. If differences in the measurements were ≥5 mmHg, a third measurement was taken, and its value averaged with the nearest one. Then, these results were corroborated with the support of ambulatory blood pressure monitoring (ABPM) to confirm the classification of the prehypertension or Grade 1 hypertension status before randomization.

The ethical premises in obviating any adverse outcomes by adding a placebo group in this trial was supported as follows. First, participants should be prehypertensive patients with 0–2 concomitant cardiovascular risk factors, none at the secondary prevention stage. Second, all patients were advised to follow the dietary approaches to control hypertension during the study, which was closely monitored. Third, treatment duration (12 weeks) agreed with the time proposed by the guidelines which recommend lifestyle interventions for 3–6 months initially in patients with prehypertension who do not have high cardiovascular risk factors. If the blood pressure remained poorly controlled after implementing these measures, then medication could be commenced, subject to physician opinion [38].

2.2 | Study Participants

Enrolled participants in the whole study were women and men between 20 and 60 years of age (including the threshold values), diagnosed with prehypertension (SBP: 120–139 mmHg; DBP: 80–89 mmHg) or Grade 1 hypertension (SBP: 140–159 mmHg; DBP: 90–99 mmHg) with 0–2 cardiovascular risk factors, such as smoking, dyslipidemia, overweight, sedentarism, and males older than 55 years. This study, however, reports the results obtained for the prehypertension stratum only.

Exclusion criteria included having other grades of hypertension [Grade 2 hypertension (SBP: 160–179, DBP: 100–109 mmHg) or Grade 3 hypertension (SBP ≥ 180, DBP ≥ 110 mmHg)], isolated systolic hypertension (SBP ≥ 140, DBP < 90 mmHg), diagnosed vascular diseases (cardiovascular, cerebrovascular, peripheral), serious mental illness, malignant neoplastic diseases, pregnant women or those planning a pregnancy, nursing mothers, suspected or definite allergy to any ingredient of the study medications, and any condition which could pose a risk for study patients. Inclusion criteria were defined simply as patients who complied with the enrollment criteria and did not show any exclusion criteria would be eligible for randomization. Study withdrawals were pre-defined as due to AE perceived by the patient and/or by medical criteria; unwillingness to continue in the trial; major protocol violations such as failure in treatment compliance where patients had not consumed the study medications for more than 7 consecutive days; and/or the intake of antihypertensive or cholesterol-lowering drugs other than study drugs.

2.3 | Treatment and Randomization

Treatments were randomized by strata and then by using the permuted block technique, being assigned by computer generated balanced block randomization, with a 1:1 ratio for each treatment group. Treatments were given to the patients according to their consecutive inclusion in the trial.

To guarantee blinding, none of the researchers involved in the study knew the randomization code, which was independently managed by the National Clinical Trials Coordinating Centre (CENCEC, Spanish acronym) (Havana, Cuba). Sealed participant specific code break envelopes were made, being kept at the quality unit in a secure, accessible location.

As stated, eligible patients on this stratum were randomized to receive either policosanol 20 mg or placebo for 12 weeks. Both policosanol 20 mg and placebo tablets were manufactured by Laboratorios MedSol (Havana, Cuba). The placebo tablets had similar composition to policosanol tablets, except for the content of the active ingredient, which was replaced by lactose, the inert filler of the formulation. Policosanol and placebo tablets were identical in outer packaging, color, shape, and flavor. If the investigators considered an adverse event to be of such severity as to require specific knowledge of the identity and dose of the relevant product, the investigator was allowed to break the study code for that participant only.

Compliance with study drugs was assessed by tablets counts and patients' self-reporting in daily charts. It was defined as good if each patient consumed ≥85 % of the scheduled tablets. Overall, compliance was good if > 90% of patients adhered to such criterion.

2.4 | Concomitant Medications

Consumption of antihypertensive and/or lipid-lowering drugs was forbidden, including any drug which could affect such values, such as corticosteroids, except for emergency situations, if these happened.

2.5 | Study Outcomes

The primary outcome of this study was to determine whether policosanol was able to significantly lower SBP as assessed in conditions of routine clinical practice in Cuba. The study predefined that, to be effective, policosanol should achieve significant reductions of SBP ≥10 mmHg versus baseline.

This assumption was based on the results of a networks meta-analysis of 42 clinical trials involving 144,220 patients with various risk comorbidities, age ranges, and blood pressure levels at baseline which found a linear association between SBP reductions and the risk of cardiovascular disease and all-cause mortality, so that lowering SBP by 10 mmHg to reach a target of 120 to 124 mmHg, the risk of cardiovascular disease was reduced by 29% (95% CI, 17%–40%) [39].

Changes in lipid profile values were considered as secondary study outcomes. Reductions of LDL-C and TC, as well as increases of HDL-C as compared to baseline and placebo were determined. The study protocol established that to be considered effective, final LDL-C values in the policosanol group should be signifi-

cantly different from baseline and placebo group values, and ≥15% as net difference versus placebo.

2.6 | Laboratory Variables and Analysis

Blood samples were drawn after a 12 h fast and aliquots were taken for laboratory determinations.

2.6.1 | Lipid Profile

Serum TC and triglycerides were determined by colorimetric enzymatic methods using reagent kits from Roche (Switzerland). Serum HDL-C levels were determined according to the cholesterol content present in the supernatant obtained after β-lipoproteins precipitation. LDL-C values were calculated using the Friedewald formula in mmol/L [40].

2.6.2 | Other Laboratory Tests

These included determinations of fasting glucose, alanine amino transferase (ALAT), aspartate amino transferase (ASAT), creatinine, and uric acid. All these were performed by routine laboratory tests based on enzymatic methods using reagent kits from Roche (Switzerland).

All tests were performed in Roche Cobas C311 autoanalyzer (Germany) located at the laboratory of the Centre for Surgical and Medical Research (Havana City, Cuba). Systematic quality control was performed throughout the study, so that the precision and accuracy of the methods were followed.

2.7 | Safety and Tolerability

Data from the physical examination, laboratory tests, and interview for AE were included for the analysis of treatment safety and tolerability. AE were predefined as any undesired subjective experience or laboratory adverse data occurring during the study which did not exist before or that was exacerbated during the trial, disregarding if they were treatment related or not. "Serious" AE were fatal or disabling experiences leading to, or prolonging, hospitalization, "moderate" AE were those requiring discontinuation of therapy according to the physician and/or specific treatment of the adverse event. Finally, "mild" AE were those not requiring withdrawal of study drugs and/or specific treatment of the AE [41]. According to their estimated relationship with study medications, AE were also classified as unlikely, doubtfully, possibly, or probably drug-related following the WHO-UMC system [42].

2.8 | Statistical Analysis

Data are presented as mean ± standard deviation of the mean. Statistical analysis was planned in the study protocol, all data being analyzed by intention-to-treat (ITT), so that data of all randomized patients were included in the analyses. Missing data were managed by a single imputation using the carry-forward method, using the last observation carried forward.

ANOVA was used to compare continuous variables throughout the study. Within-group comparisons of such data were conducted by the McNemar test once normal distribution of the data was confirmed. A Bonferroni adjustment for multiple comparisons in a single test was added post hoc for lipid profile comparisons [43].

Categorical data were compared by Chi square test, with Yates correction (Tables 2×2). The 95% confidence intervals (CI) for the study outcomes were estimated. Data management and statistical analysis were carried out in the Data Management and Processing Department of the CENCEC. For the analysis of the information, SPSS21.0 was used, and EPIDAT3.1 was used as a specific auxiliary method.

2.9 | Sample Size Estimation

The whole trial followed a typical ANOVA design in which the patients included in the prehypertension and Grade 1 hypertension strata cases were assigned to policosanol and placebo treatments, so that four groups were included in the whole analysis, here reporting the data of the prehypertensive patients only.

The reduction of SBP was the primary outcome chosen to determine the number of patients to be included, and the magnitude of the decrease considered as clinically relevant (10 mmHg) was based on a meta-analysis reporting that such a reduction in SBP was associated with a 29% decrease of the cardiovascular risk [39].

The planned sample size was based on 80% power at a two-sided α-level of 0.05 to detect a significant and clinically meaningful reduction of SBP of 10 mmHg in policosanol arms compared to placebo at Week 12. According to GPower, version 3.1.19.2 (2014), it was calculated that a total of 360 patients were necessary for the complete study with 180 in each stratum, allowing 90 patients to be included in each group. Assuming an approximate dropout rate of 10% over the trial period, the sample size was increased to 400 patients (200 patients per stratum, 100 patients per group). As explained above, this report includes the results of the prehypertension stratum only (200 patients).

3 | Results

3.1 | Baseline Characteristics

Of 424 patients enrolled in the whole study, 400 were randomized to policosanol 20 mg (n = 200) or placebo (n = 200), divided in two strata: prehypertensive patients (100 received policosanol 20 mg, 100 received placebo) and Grade 1 hypertensive patients (100 in each group also). Twenty-four (24) patients were not included in the whole study because 23 of these had failed to attend for lab testing and one more had missed the recruitment period deadline. Out of 212 prehypertensive patients enrolled in the whole study, 200 were randomized. Twelve (12) patients were

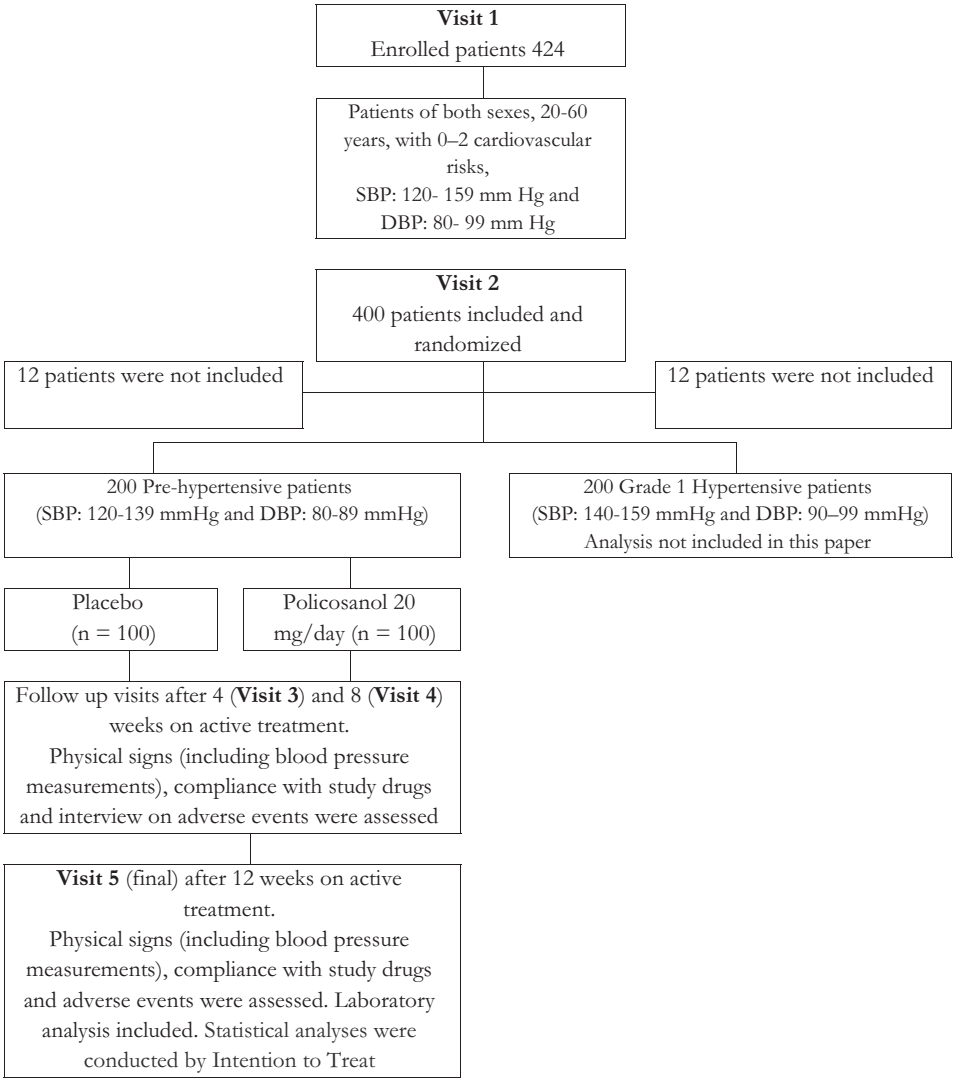

FIGURE 1 | Flow diagram of study participants. *Note:* In addition to statistical analysis by ITT, missing data was managed by simple imputation, including the last observation carried forward (LOCF).

not included because 11 did not attend for lab testing and other missed the recruitment period deadline (see Figure 1 for the study flow diagram).

Table 1 shows the baseline characteristics of the prehypertensive stratum, which were comparable in both groups. The average age of study patients was 43.8 ± 10.6 years, and the frequency of randomized women (74%) was higher than that of men (26%). Study patients had some additional cardiovascular risk factors. The most frequent (≥15%) cardiovascular risk factors were overweight, sedentary lifestyle, and smoking.

The most frequent medications consumed by the patients were antihistamines (14 patients, 3.5%) (8 placebo, 6 policosanol), oral hypoglycemic drugs (10 patients, 2.5%) (6 placebo, 4 policosanol) and analgesics, and paracetamol and/or non-steroidal anti-inflammatory drugs (8 patients, 2.0%) (4 in each group). The frequency of concomitant medications (not included in the table for simplicity) was statistically similar in both intervention groups in the whole population and at each stratum.

3.2 | Study Withdrawals

Out of 200 randomized prehypertensive patients, 9 (4.5%) (5 policosanol, 4 placebo) discontinued the trial prematurely (Table 2). The withdrawal rate was similar in both groups. No patient discontinued the trial due to AE.

3.3 | Efficacy Analysis

Compliance with treatment was very good over the study since, apart from the premature dropouts, all other patients consumed the scheduled tablets. This fact was controlled by counts of the scheduled remaining tablets and personal interviews based in auxiliary record charts for medication intake.

3.4 | Effects on SBP and DBP

Table 3 summarizes the effects of policosanol on blood pressure values. At study completion, policosanol significantly reduced (*p*

TABLE 1 | Baseline characteristics of study prehypertensive patients.

	Policosanol ($n = 100$)		Placebo ($n = 100$)		Total ($n = 200$)	
Age (years) ($X \pm SD$)	**44.6 ± 9.9**		**43.0 ± 11.1**		**43.8 ± 10.6**	
Body mass index (BMI) (kg/m^2) ($X \pm SD$)	**26.0 ± 4.5**		**26.6 ± 4.9**		**26.3 ± 4.7**	
	n	**%**	***n***	**%**	***n***	**%**
Women	73	73.0	75	75.0	148	74.0
Men	27	27.0	25	25.0	52	26.0
Overweight (BMI ≥ 25, < 30)	38	38.0	37	37.0	75	37.5
Smoking	16	16.0	28	28.0	44	22.0
Sedentary life	16	16.0	22	22.0	38	19.0
Salt rich diet	12	12.0	16	16.0	28	14.0
Postmenopausal women*	12	12.0	13	13.0	25	12.5
Obesity (BMI ≥ 30)	12	12.0	13	13.0	25	12.5
Dyslipidaemia	13	13.0	8	8.0	21	10.5
Diabetes mellitus	6	6.0	3	3.0	9	4.5

Abbreviations: *n*, number of cases; NSAIDs, non-steroidal anti-inflammatory drugs; *X*, mean; SD, standard deviation.
*Defined as those with ≥1 year of maintained amenorrhea. All comparisons were not significant (ANOVA, χ^2 test).

TABLE 2 | Study withdrawals among the prehypertensive patients included in the whole study.

	Policosanol ($n = 100$)		Placebo ($n = 100$)	
Withdrawal reasons	***n***	**%**	***N***	**%**
Unwillingness to follow-up	1	1.0	0	0.0
Protocol violation	2	2.0	1	1.0
Travels abroad	2	2.0	3	3.0
Subtotal	**5**	**5.0**	**4**	**4.0**

Note: All comparisons were not significant (χ^2 test). Protocol violations were due to intake of antihypertensive drugs.
Abbreviation: *n*, number of cases.

TABLE 3 | Effects on blood pressure values ($X \pm SD$) in study prehypertensive patients.

Treatment	Baseline	4 weeks	8 weeks	12 weeks
Systolic blood pressure (mmHg)				
Policosanol	127 ± 6	123 ± 10	123 ± 10	119 ± 9***,+++
95% CI	125–128	121–125	121–125	117–121
Placebo	125 ± 7	123 ± 8	123 ± 11	126 ± 9
95% CI	124–126	121–123	121–125	124–128
Diastolic blood pressure (mmHg)				
Policosanol	82 ± 3	80 ± 7	79 ± 7	77 ± 7***,+++
95% CI	81–83	79–81	78–81	76–78
Placebo	82 ± 3	80 ± 6	79 ± 7	81 ± 5
95% CI	82–84	79–81	78–80	80–82

Note: CI, confidence interval; SD, standard deviation; *X*, mean.
***$p < 0.001$ comparison with baseline (McNemar test, Bonferroni´s adjustment).
$^{++}p < 0.01$.
$^{+++}p < 0.001$ comparison with placebo group (ANOVA).

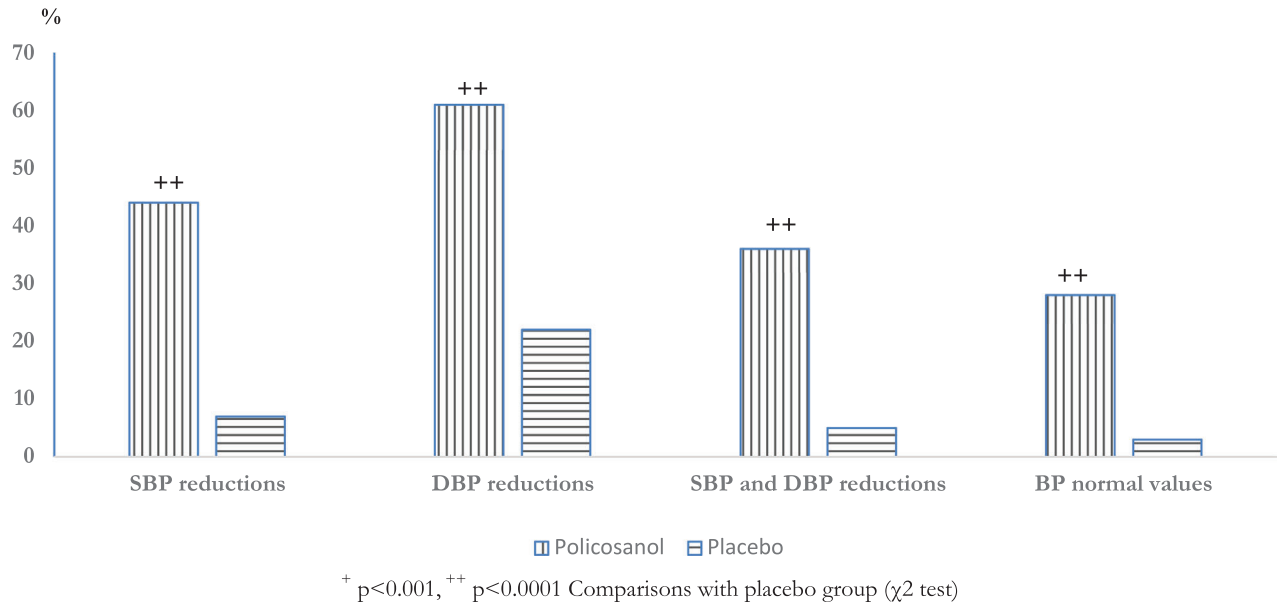

FIGURE 2 | Percent (%) of responders to the treatment.

< 0.0001) both SBP (primary outcome) and DBP values, compared to baseline and placebo groups, SBP and DBP reductions being significant only in Week 12. It should be noted that the final mean values of SBP and DBP were within the normal range.

The frequency of policosanol-treated patients with SBP reductions (≥10 mmHg vs. baseline) (44/100) was significantly higher ($p < 0.0001$) than in the placebo matched group (7/100) (Figure 2). In turn, the rate of policosanol responders according to DBP reductions (≥5 mmHg vs. baseline) (61/100) was significantly higher ($p < 0.0001$) than in the placebo group (22/100). Likewise, significantly ($p < 0.0001$) more policosanol patients (36/100) than placebo patients (5/100).

3.5 | Effects on the Lipid Profile

Table 4 lists the effects on the lipid profile. In prehypertensive patients, policosanol significantly lowered LDL-C ($p < 0.05$ vs. baseline, $p < 0.001$ vs. placebo) and TC ($p < 0.05$ vs. baseline, $p < 0.01$ vs. placebo), and significantly increased HDL-C ($p < 0.05$ vs. baseline and placebo). These changes account for net differences versus placebo of 23.5%, 14.5%, 5.8% for LDL-C, TC, and HDL-C, respectively. Triglycerides significantly ($p < 0.05$) increased in both groups, without differences between them. Data processing by the Pearson correlation analysis did not find a relationship between blood pressure and lipid profile variables.

3.6 | Safety and Tolerability

3.6.1 | Effects on Physical and Blood Safety Indicators

No significant within- or between-group differences were found regarding physical safety indicators (bodyweight, body mass index [BMI], and pulse rate). Also, no significant changes versus placebo were found for any laboratory variable, although significant reductions of blood glucose and significant increases of uric acid were found in both groups (table not included for simplicity). Since these changes occurred in both groups and individual values were within normal ranges, we exclude any clinically relevant meaning to this finding.

3.6.2 | AE

Only four patients reported some adverse event (1 from the policosanol group, 3 from the placebo group) (Table 5). As stated before, no adverse event was a cause for withdrawal. Only these three were classified as moderate because they required paracetamol for headache or for joint pain. All other AE were mild. All AE were classified, according to the potential causal relation with the treatment, as "doubtfully related."

4 | Discussion

This is the first report showing the blood pressure-lowering effects of policosanol (20 mg/day) in Cuban patients with prehypertension. Our results demonstrate that policosanol 20 mg/day given for 12 weeks was effective in significantly lowering SBP as compared to baseline and placebo, achieving the pre-determined mean SBP reductions of ≥10 mmHg compared to baseline, which were significantly different from the SBP changes in the placebo group also. Likewise, the treatment also achieved significant reductions of DBP ≥5 mmHg versus baseline and placebo.

Baseline characteristics were well matched in both groups, evidencing their homogeneity, thus supporting that the outcomes found here were not attributable to initial disparities in the comparison groups. The study patients were, on average, within the middle age range (mean age 43.8 years), in contrast to the Korean studies, in which patients were young prehypertensive patients (mean age around 30 years) [32, 33] but near to that of participants in the Japanese study (about 50 years as average) [34], and lower

TABLE 4 | Effects on the lipid profile ($X \pm SD$) in study prehypertensive patients.

Low-density lipoprotein cholesterol (LDL-C) (mmol/L)			
Policosanol	2.97 ± 0.83	2.52 ± 0.64*,+++	−15.2+++
95% CI	2.56–3.77	2.31–3.09	
Placebo	3.00 ± 0.80	3.25 ± 0.84	+8.3
95% CI	2.84–3.91	3.09–4.16	
Total cholesterol (TC) (mmol/L)			
Policosanol	4.34 ± 0.83	4.01 ± 0.69*,++	−7.6++
95% CI	4.18–5.12	3.75–4.74	
Placebo	4.35 ± 0.89	4.65 ± 0.96	+6.9
95% CI	4.17–5.18	4.46–5.52	
High-density lipoprotein cholesterol (HDL-C) (mmol/L)			
Policosanol	1.20 ± 0.40	1.29 ± 0.35*,+	+7.5+
95% CI	1.12–1.92	1.16–1.85	
Placebo	1.18 ± 0.39	1.20 ± 0.35	+1.7
95% CI	1.10–1.88	1.13–1.82	
Triglycerides (mmol/L)			
Policosanol	0.85 ± 0.43	1.01 ± 0.61*	+18.8
95% CI	0.78–1.76	0.89–2.20	
Placebo	0.84 ± 0.37	0.99 ± 0.55*	+17.9
95% CI	0.76–1.64	0.89–2.06	

Abbreviations: SD, standard deviation; *X*, mean.
*$p < 0.05$ comparison with baseline (McNemar test).
+$p < 0.05$.
++$p < 0.01$.
+++$p < 0.001$ comparisons vs. placebo (ANOVA).

TABLE 5 | Adverse events (AE) reported by prehypertensive patients during the study.

	Policosanol ($n = 100$)		**Placebo ($n = 100$)**	
AE	***n***	**%**	***n***	**%**
Lumbar pain	1	1.0	1	1.0
Headache	0	0.0	1	1.0
Polyuria	0	0.0	1	1.0
Total of AE	**1**	**1.0**	**3**	**3.0**
Total of patients referring AE	**1**	**1.0**	**3**	**3.0**

Abbreviation: *n*, number of patients.
All comparisons were not significant (χ^2 test).

than that of our early trials in populations at high vascular risk [12, 13].

The study population reflects the coexistence of other cardiovascular risk factors, some related with the patient's lifestyle (sedentarism, smoking, intake of salt rich diet) as well as other factors related with these, such as overweight, frequent among the participants. It should be noted that, albeit not required, all enrolled patients had not been treated with antihypertensive medications previously because they ignored having high blood pressure values until study enrolment.

Nine patients (4 placebo, 5 policosanol) withdrew prematurely from the study. So, the discontinuation rate was low (4.5%), which supports that study conduction was well managed. Indeed, reasons for withdrawals were few and none were associated with AE, which is consistent with the good safety profile of policosanol, as documented.

Factors such as the low rate of dropouts, the sample size of the study and that statistical analyses were made by the ITT approach in an independent center (CENCEC), support the validity of the present results.

The efficacy of policosanol was evidenced through the mean reductions of SBP and DBP values compared with baseline and placebo, which are closely comparable to those reported in the trials conducted in Korean and Japanese subjects [32–34], despite these being ethnically homogenous populations, different from the heterogenous Cuban one.

In addition, the efficacy of policosanol for lowering SBP and DBP was supported by the rate of responders per stratum according to the number of cases who reached the cutoff values of SBP and DBP established in the study protocol. Thus, the frequency of policosanol responders according to SBP reductions ≥10 mmHg versus baseline (44/100) was significantly greater than in the matched placebo group (7/100). Moreover, the rate of policosanol patients with DBP reductions ≥5 mmHg versus baseline (61/100) was significantly greater than that found in the placebo group (22/100).

Simultaneous reductions of both SBP ≥ 10 mm Hg and DBP ≥ 5 mm Hg, were also found in more policosanol patients (36/100) than in placebo cases (5/100); while 28/100 and 3/100 of policosanol and placebo patients, respectively, achieved normal blood pressure values at study completion.

The consistency of the blood pressure reductions, the magnitude of the SBP reduction and the rate of policosanol responders achieving the predefined goals, support the efficacy of policosanol 20 mg/day, given for 12 weeks, for lowering blood pressure in Cuban prehypertensive patients.

As mentioned earlier, a network meta-analysis which proved a linear association between SBP decreases and reduced cardiovascular disease and all-cause mortality, documented that an SBP reduction of 10 mmHg to reach values between 120 to 124 mmHg, should lower the cardiovascular disease risk by 29% [39]. Adding even more evidence on the magnitude of SBP decreases in ameliorating the cardiovascular disease risk, a large-scale analysis of randomized trials proved that just a simple SBP reduction of 5 mmHg lowered the risk of major cardiovascular events by about 10%, irrespective of previous diagnoses of cardiovascular disease and even at normal or high–normal blood pressure values [44]. Hence, obtaining an SBP reduction of ≥10mmHg in our study population would be expected to attract clinical interest.

Study patients were advised to follow lifestyle modifications, the core of hypertension management, including a healthy dietary pattern with low sodium intake, systematic physical activity, smoking cessation, and reduced alcohol consumption, all of which should enhance the benefit of pharmacological antihypertensive therapy. Nevertheless, the fact that bodyweight values did not decrease in any group over the study suggests that dietary advice was not well followed by study participants since a bodyweight reduction should be expected after 12 weeks on such a dietary regime. This suspicion is reinforced by the fact that triglycerides significantly increased in both groups.

Regarding the secondary outcomes, policosanol 20 mg/day produced positive changes in lipid profile variables, significantly lowering LDL-C and TC versus placebo by 23.5% and 14.5% respectively, and significantly increased HDL-C by 5.8 % versus placebo. In both groups, triglycerides significantly increased versus baseline, not between intervention groups. These increases suggest, as discussed previously, that the healthy dietary recommendations were not strictly followed by the subjects during the trial.

Despite the results of policosanol 20 mg/day from this study being promising, this study does not suggest, nor are we promoting, policosanol as a new antihypertensive drug. Such a goal will require several more studies, since although in some previous studies policosanol decreased blood pressure values [12, 13], these levels remained unchanged versus comparison groups in other trials [8–11, 14–17]. So, further studies investigating different dosages and effects on different populations will be required. To be clear, this study does not reveal new insights into the mechanism(s) whereby policosanol could reduce blood pressure, since this question was beyond the study objectives.

Some studies conducted with policosanol have found an association between blood pressure reductions and changes in lipid profile variables, as well as a decrease in aldosterone levels, without affecting the angiotensin converting enzyme [32, 33]. However, the analysis of our data failed to find a relationship between blood pressure and lipid profile variables. Therefore, it is logical to assume that other beneficial pleiotropic effects of policosanol could have contributed to the decrease in blood pressure reported here. The ability of policosanol to inhibit LDL oxidation (a trigger of endothelium damage), demonstrated a long time ago [28] and corroborated recently [32], could contribute to its blood pressure-lowering effects.

Also, policosanol has been reported to increase plasma prostacyclin (a vasodilator) and reduce thromboxane 2 (a vasoconstrictor) levels [26], effects beneficial in reducing endothelium damage, thus preventing one of the chain of events leading to high blood pressure. Nevertheless, although all these favorable effects could be associated with the purported blood pressure lowering effect of policosanol, the underlying mechanism(s) of this benefit remains speculative.

This study also corroborates the very good safety of policosanol. No treatment-related impairment of any safety indicator was observed. As expected, treatments were well tolerated by study patients. The AE reported were transient, and apart from the three declared as moderate because they required paracetamol for pain management, the others were classified as mild.

A limitation related to the population included in the study is the exclusion of older patients, when it is predicted that the population of older adults (60–79 years) will double from 800 million (2015) to 1.6 billion (2050). The risk for cardiovascular events doubles with each decade of aging, making good blood pressure control in the elderly a necessity [45, 46]. So, further studies including older patients (60–80 years old) are encouraged to investigate the potential benefits of policosanol in lowering blood pressure in this more vulnerable population. Another limitation related to study population was the inclusion of some diabetics, a population whose coronary risk should be carefully managed along with their other risk factors. Concomitant diabetes and hypertension put such patients at a high coronary risk [47]. These subjects were incorrectly included, thus representing protocol deviations, but, as we applied ITT for data analysis, their data

were included in this report, thus posing a slight impact in the risk categorization proposed for study participants. Since this factor was homogenously distributed between comparison groups, it did not affect the validity of the present results. In addition, it should be noted that the assessment of ABPM at the end of the treatment should improve the control of the blood pressure lowering effects obtained with blood pressure office assessment only, since all groups were managed in similar conditions, we should not expect that such an omission would affect the effects here attributed to the treatment. Despite these limitations, the study achieved the objective to demonstrate the effects of policosanol 20 mg/day on the blood pressure values of Cuban prehypertensive patients, being the first trial focused on blood pressure lowering effects in our population.

5 | Conclusions

This report demonstrates, for the first time, that policosanol given at 20 mg/day for 12 weeks was effective, as compared to placebo, for lowering SBP and DBP in Cuban patients with prehypertension, achieving the predefined reductions considered as clinically meaningful. The treatment also produced beneficial changes in the lipid profile, being safe and well tolerated. Further studies including different dosage, study designs, and populations, however, are required to extrapolate the present results to other populations of prehypertensive patients, including older people needing to have their blood pressure controlled.

Author Contributions

Moura Revueltas: conceptualization, investigation, and review. **Amarilys Jimenez Chiquet**: conceptualization, investigation, and review. **Yamile Valdes**: investigation and methodology. **Julio C. Fernández**: conceptualization, investigation, project administration, and writing–original draft. **Yenney Reyes**: investigation and methodology. **Yanay Fernández**: investigation and methodology. **Evelyn González**: investigation and methodology. **Sarahi Mendoza**: review and editing. **Pérez Yohani**: methodology and resources. **Manuel Delfin Pérez**: methodology and resources. **Daisy Navarro**: methodology and resources. **Yolanda Cruz**: methodology and resources. **Meilis Mesa**: methodology and resources. **Gladys Jiménez**: software and data analysis. **Carlos Sánchez**: software and statistical analysis. All authors have read and agreed to the published version of the manuscript.

Ethics Statement

We hereby request the evaluation of the work for publication, bearing in mind that it has not been previously published, nor it is being review by any other journal. The instructions for the authors and the ethical responsibilities have been take into account, among them, that all authors meet the requirements of authorship and all have declared not to have a conflict of interest. The authors who prepared the article are employees of a research institution. research activities.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The authors have nothing to report.

References

1. A. C. Flint, C. Conell, X. Ren, et al., "Effect of Systolic and Diastolic Blood Pressure on Cardiovascular Outcomes," *New England Journal of Medicine* 381 (2019): 243–251.

2. S. Brouwers, I. Sudano, Y. Kokubo, and E. M. Sulaica, "Arterial Hypertension," *Lancet* 398 (2021): 249–261.

3. M. Brunstrom and B. Carlberg, "Association of Blood Pressure Lowering With Mortality and Cardiovascular Disease Across Blood Pressure Levels: A Systematic Review and Meta-Analysis," *JAMA Internal Medicine* 178 (2018): 28–36.

4. T. Unger, C. Borghi, F. Charchar, et al., "2020 International Society of Hypertension Global Hypertension Practice Guidelines," *Hypertension* 75 (2020): 1334–1357.

5. G. Mancia, R. Kreutz, M. Brunstrom, et al., "ESH Guidelines for the management of Arterial Hypertension The Task Force for the management of Arterial Hypertension of the European Society of Hypertension," *Journal of Hypertension* 41, no. 12 (2023): 1874–2071.

6. S. Virani, L. K. Newby, S. V. Arnold, et al. AHA/ACC/ACCP/ASPC/NLA/PCNA Guideline for the Management of Patients with Chronic Coronary Disease: A Report of the American Heart Association/American College of Cardiology Joint Committee on Clinical Practice Guidelines; *Circulation* 148, no. 9 (2023): e9–e119.

7. M. D. Pérez, Y. Valdés, L. Pérez, et al. Hipertensión Arterial en el Adulto. Guía de Actuación para la Atención Primaria de Salud. Programa Nacional de Prevención, Diagnóstico, Evaluaciòn y Control de la Hipertensión Arterial de Cuba/HEARTS en las Américas. Representación en Cuba OPS/OMS; 2021.

8. G. Ortensi, H. Gladstein, H. Valli, and P. A. Tesone, "A Comparative Study of Policosanol versus Simvastatin in Elderly Patients With Hypercholesterolemia," *Current Therapeutic Research* 58 (1997): 390–401.

9. R. Mas, G. Castaño, J. Illnait, et al., "Effects of Policosanol in Patients With Type II Hypercholesterolemia and Additional Coronary Risk Factors," *Clinical Pharmacology & Therapeutics* 65 (1999): 439–447.

10. I. P. Nikitin, N. V. Slepchenko, N. A. Gratsianskii, et al., "Results of the Multicenter Controlled Study of the Hypolipidemic Policosanol in Russia," *Terapevticheskii Arkhiv* 72 (2000): 7–10.

11. A. Mirkin, R. Mas, M. Martinto, et al., "Efficacy and Tolerability of Policosanol in Hypercholesterolemic Postmenopausal Women," *International Journal of Clinical Pharmacology Research* 21 (2001): 31–42.

12. R. Mas, G. Castaño, L. Fernández, et al., "Effects of Policosanol on the Lipid Profile and Cardiac Events in Older Hypercholesterolemic Patients With Coronary Disease," *Clinical Drug Investigation* 21 (2001): 485–497.

13. G. Castaño, J. Mas R Fernández, et al., "Effects of Policosanol in Older Patients With Hypertension and Type II Hypercholesterolemia," *Drugs R & D* 3 (2002): 159–172.

14. Y. Wang, K. E. Kuanman, L. Wang Hia, et al., "Efficacy and Safety of Policosanol and Pravastatin in Treatment of Hyperipidemia in Chinese Patients," *Journal of New Drugs Clinical Research* 02 (2008): 124–129.

15. S. Liu, M. Y. Tan, S. P. Zhao, and H. Rong, "Effects of Policosanol on Serum Lipids and Heme Oxygenase-1 in Patients With Hyperlipidemia," *Zhonghua Xin Xue Guan Bing Za Zhi [Chinese Journal of Cardiovascular Diseases]* 40 (2012): 840–843.

16. D. Yu, "Efficacy and Safety of Policosanol in Lipid-regulating Therapy in Lipid Regulating Therapy for Elderly Cardiovascular Disease Patients," *Chinese Journal of Geriatric Heart Brain and Vessel Diseases* 17 (2015): 575–579.

17. T. N. Liu, C. T. Wu, F. He, et al., "Relationship Between the G75A Polymorphism in the Apolipoprotein A1 (ApoA1) Gene and the Lipid Regulatory Effects of pravastatin in Patients With Hyperlipidemia," *Genetics and Molecular Research* 15, no. 2 (2016): 1–6.

18. H. K. Berthold, S. Unverdorben, R. Degenhardt, M. Bulitta, and I. Gouni-Berthold, "Effect of Policosanol on Lipid Levels Among Patients

With Hypercholesterolemia or Combined Hyperlipidemia: A Randomized Controlled Trial," *Journal of American Medical Association* 295 (2006): 2262–2269.

19. M. F. Dulin, L. F. Hatcher, H. C. Sasser, and T. A. Barringer, "Policosanol Is Ineffective in the Treatment of Hypercholesterolemia: A Randomized Controlled Trial," *American Journal of Clinical Nutrition* 84 (2006): 1543–1548.

20. F. Francini-Pesenti, D. Beltramolli, S. Dall'acqua, and F. Brocadello, "Effect of Sugar Cane Policosanol on Lipid Profile in Primary Hypercholesterolemia," *Phytotherapy Research* 22 (2008): 318–322.

21. J. T. Chen, R. Wesley, R. D. Shamburek, et al., "Meta-analysis of Natural Therapies for Hyperlipidemia: Plant Sterols and Stanols versus Policosanol," *Pharmacotherapy* 25 (2005): 171–183.

22. M. P. Patrocinio, N. Paranas, J. A. Perez, et al., "The Effects of Sugar Cane Policosanol on the LDL, HDL, Triglyceride and Total Cholesterol Levels of Dyslipidemic Patients: A Meta-Analysis," *Anesthesia and Medical Practice Journal* (2017): AMPJ-117, 10.29011/AMPJ-117.100017.

23. J. Gong, X. Qin, F. Yuan, et al., "Efficacy and Safety of Sugarcane Policosanol on Dyslipidemia: A Meta-Analysis of Randomized Controlled Trials," *Molecular Nutrition & Food Research* 62, no. 1 (2018): 170028.

24. R. Menéndez, A. M. Amor, I. Rodeiro, et al., "Policosanol Modulates HMG-CoA Reductase Activity in Cultured Fibroblast," *Archives of Medical Research* 32 (2001): 8–13.

25. D. K. Singh, L. Li, and T. D. Porter, "Policosanol Inhibits Cholesterol Synthesis in Hepatoma Cells by Activation of AMP-kinases," *Journal of Pharmacology and Experimental Therapeutics* 106 (2006): 107–144.

26. S. Banerjee, S. Ghoshal, and T. D. Porter, "Activation of AMP-kinase by Policosanol Requires Peroxisomal Metabolism," *Lipids*. Published ahead of print, February 27, 2011.

27. F.-Y. He, J.i-P. Lu, and X.-M. Wei, "Effects and Mechanism of Action of Policosanol on Decreasing Cholesterol in Patients With Hypercholesterolemia," *World Journal of Pharmaceutical Sciences* 30 (2015): 660–662.

28. R. Menéndez, R. Mas, A. M. Amor, et al., "Effects of Policosanol Treatment on the Susceptibility of Low-density Lipoprotein (LDL) Isolated From Healthy Volunteers to Oxidative Modification in Vitro," *British Journal of Clinical Pharmacology* 50 (2000): 255–262.

29. D. Carbajal, M. L. Arruzazabala, S. Valdés, and R. Mas, "Effect of Policosanol on Platelet Aggregation and Serum Levels of Arachidonic Acid Metabolites in Healthy Volunteers," *Prostagl Leukotr Essent Fatty Acids* 58 (1998): 61–64.

30. M. L. Arruzazabala, V. Molina, R. Mas, et al., "Antiplatelet Effects of Policosanol 20 and 40 mg/D in Healthy Volunteers and Dyslipidemic Patients," *Clinical and Experimental Pharmacology & Physiology* 29 (2002): 891–897.

31. K. Xu, et al., "Safety and Efficacy of policosanol in Patients With High on-treatment Platelet Reactivity After Drug-eluting Stent Implantation: Two-year Follow-up Results," *Cardiovascular Therapeutics* 34 (2016): 337–342.

32. S. J. Kim, D. Yadav, H. J. Park, J. R. Kim, and K. H. Cho, "Long-Term Consumption of Cuban Policosanol Lowers central and Brachial Blood Pressure and Improves Lipid Profile With Enhancement of Lipoprotein Properties in Healthy Korean Participants," *Frontiers in Physiology* 9 (2018): 412–416.

33. H. J. Park, D. Yadav, D. J. Jeong, et al., "Short-Term Consumption of Cuban Policosanol Lowers Aortic and Peripheral Blood Pressure and Ameliorates Serum Lipid Parameters in Healthy Korean Participants: Randomized, Double-blinded, and Placebo-Controlled Study," *International Journal of Environmental Research and Public Health* 16, no. 5 (2019): E809, https://doi.org/10.3390/ijerph16050809.

34. K. H. Cho, H. S. Nam, S. H. Baek, et al., "Beneficial Effect of Cuban Policosanol on Blood Pressure and Serum Lipoproteins Accompanied With Lowered Glycated Haemoglobin and Enhanced High-Density Lipoprotein Functionalities in a Randomized, Placebo-controlled, and Double-blinded Trial With Healthy Japanese," *International Journal of Molecular Sciences* 24 (2023): 5185, https://doi.org/10.3390/ijms24065185.

35. M. Askarpour, E. Ghaediab, N. Roshanravanc, et al., "Policosanol Supplementation Significantly Improves Blood Pressure Among Adults: A Systematic Review and Meta-analysis of Randomized Controlled Trials," *Complementary Therapies in Medicine* 45 (2019): 89–99.

36. L. Fernández, R. Mas, J. Illnait, et al., "Policosanol: Results of a Post-Marketing Surveillance Control on 27 879 Cases," *Current Therapeutic Research* 59 (1998): 717–722.

37. S. Fernández, R. Mas, R. Gamez, et al., "Pharmacological Surveillance of Policosanol Tolerability in the Elderly," *American Journal of Geriatric Pharmacotherapy* 2 (2004): 219–229.

38. Y. Wang, Y. Liu, L. Liu, L. Hong, and H. Chen, "Comparative Analysis of Hypertension Guidelines: Unveiling Consensus and Discrepancies in Lifestyle Modifications for Blood Pressure Control," *Cardiology Research and Practice* 2023 (2023): 5586403, https://doi.org/10.1155/2023/5586403.

39. J. D. Bundy, C. Li, P. Stuchlik, et al., "Systolic Blood Pressure Reduction and Risk of Cardiovascular Disease and Mortality: A Systematic Review and Network Meta-Analysis," *JAMA Cardiology* 2, no. 7 (2017): 775–781.

40. W. T. Friedewald, R. I. Levy, and S. D. Friederickson, "Estimation of the Concentration of Low-Density Lipoprotein Cholesterol in Plasma Without of the Preparative Ultracentrifuge," *Clinical Chemistry* 18 (1972): 499–502.

41. National Institute on Aging (NIA), "Adverse Event and Serious Adverse + Event + Guidelines. NIA Adverse Event and Serious Adverse Event Guidelines.", (2007), https://wwww.nia.nih.gov.

42. "The Use of the WHO-UMC System for Standardised Case Causality Assessment." WHO, June 5, 2013, https://www.who.int/publications/m/item/WHO-causality-assessment.

43. P. C. O'Brien and M. A. Shampo, "Statistical Considerations for Performing Multiple Tests in a Single Experiment. Comparing Two Therapies With Respect to Several Endpoints," *Mayo Clinic Proceedings* 63 (1988): 1140–1143.

44. K. Rahimi, Z. Bidel, M. Nazarzadeh, et al., On Behalf of The Blood Pressure Lowering Treatment Trialists' Collaboration, "Pharmacological Blood Pressure Lowering for Primary and Secondary Prevention of Cardiovascular Disease Across Different Levels of Blood Pressure: An Individual Participant-Level Data Meta-Analysis," *Lancet* 397, no. 10285 (2021): 1625–1636.

45. R. Chaudhry, Y. A. Siddique, A. Sebai, et al., "The Efficacy of Antihypertensive Drugs in Lowering Blood Pressure and Cardiovascular Events in the Elderly Population: A Systematic Review and Meta-Analysis," *Cureus* 16, no. 1 (2024): e52053, https://doi.org/10.7759/cureus.52053.

46. B. M. Egan, H. J. Mattix-Kramer, J. N. Basile, and S. E. Sutherland, "Managing Hypertension in Older Adults," *Current Hypertension Reports* 26, no. 4 (2024): 157–167.

47. J. J. Joseph, P. Deedwania, and T. Acharya, on behalf of the American Heart Association Diabetes Committee of the Council on Lifestyle and Cardiometabolic Health; Council on Arteriosclerosis, Thrombosis and Vascular Biology; Council on Clinical Cardiology; and Council on Hypertension, "Comprehensive Management of Cardiovascular Risk Factors for Adults With Type 2 Diabetes: A Scientific Statement From the American Heart Association," *Circulation* 145 (2022): e722–e759.