Effect of Policosanol on Lipid Levels Among Patients With Hypercholesterolemia or Combined Hyperlipidemia
A Randomized Controlled Trial

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Policosanol is a mixture of long-chain primary alcohols isolated from sugar cane wax. Cuban sugar cane policosanol is sold in more than 40 countries mainly because of its supposed lipid-lowering effects. Other effects attributed to policosanol are antithrombotic, plaque stabilizing, and antioxidant actions. Numerous policosanol products from a variety of sources (sugar cane, wheat germ, rice bran, beeswax) are available over-the-counter and on the Internet in several countries. Advertising emphasizes predominantly its putative lipid-lowering effects.

Virtually all of the published scientific literature supporting the beneficial effects of policosanol on lipids has been authored by a single research group from Cuba. In 2002, we reviewed the existing literature and have stressed the need for independent confirmation of these results. A recent meta-analysis of natural therapies for hyperlipidemia concluded that policosanol has lipid-lowering properties more effective than plant sterols. In summary, the study shows that the low-density lipoprotein cholesterol (LDL-C) lowering effects of sugar cane–derived policosanol are similar to the effects of

Context  Policosanol is a natural substance derived from sugar cane that is advertised for its lipid-lowering effects as a nonprescription drug. More than 80 placebo-controlled or comparative trials, performed mostly by a single research institute, suggest that policosanol at doses of 5 to 40 mg/d has lipoprotein-lowering effects comparable with statins.

Objectives  To determine the lipoprotein-lowering effects of Cuban sugar cane–derived policosanol and to establish, if effective, dose-dependency up to 80 mg/d in patients with hypercholesterolemia or combined hyperlipidemia.

Design, Setting, and Participants  A multicenter (lipid outpatient clinics and general practitioners in Germany), randomized, double-blind, placebo-controlled, parallel-group trial conducted from September 29, 2000, to May 10, 2001, of patients with hypercholesterolemia or combined hyperlipidemia having baseline low-density lipoprotein cholesterol (LDL-C) levels of at least 150 mg/dL (≥3.88 mmol/L) and either no or 1 cardiovascular risk factor other than known coronary heart disease, or baseline LDL-C levels of between 150 and 189 mg/dL (3.88-4.89 mmol/L) and 2 or more risk factors.

Interventions  Open-label 6-week placebo and diet run-in phase followed by a double-blind 12-week treatment phase after randomization to 5 groups: 10, 20, 40, or 80 mg/d of policosanol or placebo.

Main Outcome Measure  The percentage change of LDL-C, with changes in other lipoproteins as secondary outcome measures.

Results  A total of 143 patients were randomized to 5 equal groups and were analyzed on an intention-to-treat basis. In none of the 5 treatment groups did LDL-C levels decrease more than 10% from baseline. No statistically significant difference between policosanol and placebo was observed. A nonparametric test analyzing dose-dependency yielded nonsignificant results. In none of the secondary outcome measures, namely total cholesterol, high-density lipoprotein cholesterol (HDL-C), very low-density lipoprotein cholesterol, triglycerides, lipoprotein(a), and ratio of total or LDL-C to HDL-C, were there any significant effects of policosanol. Policosanol was tolerated well without serious adverse events.

Conclusion  In patients with hypercholesterolemia or combined hyperlipidemia, the sugar cane–derived policosanol in usual and high doses does not demonstrate a reduction in lipid levels beyond placebo.

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HYPERCHOLESTEROLEMIA OR COMBINED HYPERLIPIDEMIA

Until 2004, trials outside of Cuba studying its effectiveness are lacking with the exception of 2 studies. All trials of the lipid-lowering effects have used policosanol manufactured by a company in Cuba and an astonishing consistency exists between the Cuban results of individual studies. Therefore, independent verification from studies outside Cuba on the Cuban policosanol is necessary. The Cuban findings have been challenged by a clinical trial from the Netherlands that showed that a standard dose (20 mg/d) of wheat germ–derived policosanol is ineffective in lowering total cholesterol and LDL-C.

Our trial was performed to corroborate the reported lipid-lowering effects of policosanol. The primary objective was to show a dose-dependent LDL-C level decrease in comparison with placebo in patients with hypercholesterolemia or combined hyperlipidemia. To comply with the requirement to meet the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use guideline, “Ethnic factors in the acceptability of foreign clinical data,” we tested the hypothesis of whether the lipid-lowering effects of policosanol are reproducible in patients by using sugar cane–derived policosanol produced in Cuba.

METHODS

Study Design and Protocol

Our trial was a multicenter (lipid outpatient clinics and general practitioners in Germany), placebo-controlled, randomized, double-blind trial with 5 in-dependent parallel treatment groups and was conducted from September 29, 2000, to May 10, 2001. After an open-and placebo run-in phase (no blinding intended) of 6 weeks, patients were randomized to receive either 10, 20, 40, or 80 mg/d of policosanol or placebo in a double-blind manner. The study medication was taken once daily, unchewed, with the evening meal. Policosanol was provided by Dalmer Laboratories (La Habana, Cuba) and film-coated tablets were manufactured by Madaus AG (Cologne, Germany). The placebo tablets contained lactose monohydrate and microcrystalline cellulose in equal amounts.

Blood was drawn after an overnight fast for lipid and lipoprotein analysis and safety parameters at screening visit 1 (–6 weeks), visit 2 and visit 3 (–2 or –1 weeks, respectively), visit 4 (day 0), and visits 5 and 6 (6 or 12 weeks, respectively). Dietary counseling was administered at visits 1 and 4. Patients had to adhere to the step I diet of the US National Cholesterol Education Program (The Third Report of the National Cholesterol Education Program Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults [Adult Treatment Panel III]). A 3-day food diary was performed before visits 4 and 6.

The primary outcome measure of our trial was to show the dose-dependent LDL-C level decrease with policosanol compared with placebo. Secondary outcome measures were to show dose-dependent total cholesterol, very low-density lipoprotein cholesterol (VLDL-C), lipoprotein(a), and triglyceride level decrease, the decrease of the ratios of total or LDL-C to high-density lipoprotein cholesterol (HDL-C), and HDL-C increase by policosanol vs placebo, as well as to show the tolerability of policosanol vs placebo.

The trial was performed according to the Declaration of Helsinki (current version), taking into account the current version of German drug legislation (Arzneimittelgesetz), and it was in accordance with the principles of Good Clinical Practice. The study protocol was approved by the ethics committee at each of the 14 participating centers across Germany, and written informed consent was obtained from all participants. The principal investigator (H.K.B.) and the statistician (M.B.) had complete access to the primary data.

Patients

Women and men aged 18 to 80 years with known or newly detected isolated hypercholesterolemia or combined hyperlipidemia attending a participating clinical trial center were eligible for enrollment. To enter the run-in phase, the participants had to have an LDL-C level of at least 150 mg/dL (≥3.88 mmol/L) at visit 1. Randomized patients were those patients whose mean LDL-C level on visits 2 and 3 (5 and 6 weeks after visit 1) was at least 150 mg/dL (≥3.88 mmol/L).

Inclusion criteria included the following characteristics: baseline LDL-C levels of at least 150 mg/dL (≥3.88 mmol/L) as described above and either no or 1 cardiovascular risk factor other than known coronary heart disease (CHD), or baseline LDL-C levels of between 150 and 189 mg/dL (3.88–4.89 mmol/L) for patients 2 or more risk factors. The following risk factors were considered: age (men >45 years and women >55 years or postmenopausal), known CHD, uncontrolled hypertension with systolic blood pressure of more than 140 mm Hg, HDL-C levels of less than 35 mg/dL (<0.91 mmol/L) for the mean of the values at visits 2 and 3, current cigarette smoking of more than 10 cigarettes per day, obesity (body mass index [BMI, calculated as weight in kilograms divided by height in meters squared] of >30), and family history of premature CHD.

Major exclusion criteria included myocardial infarction, percutaneous transluminal coronary angioplasty or coronary artery bypass grafting less than 1 year before trial inclusion, unstable angina pectoris, uncorrected hypothyroidism, diabetes mellitus, other endocrine or metabolic diseases, acute inflammatory diseases, severe gastrointestinal diseases, triglyceride levels of more than 500 mg/dL (≥5.65 mmol/L) at visits 2 or 3, use of systemic corticosteroids, anticoagulants, or lipid-lowering drugs, treatment within the previous 6 weeks with any medication that is known to affect lipoprotein levels, severe kidney or liver disease, or other severe diseases.
**Laboratory Analysis**

The LDL-C, VLDL-C, and HDL-C levels were determined by lipoprotein electrophoresis and subsequent quantitative cholesterol staining. Total cholesterol and triglyceride levels were determined enzymatically (cholesterol oxidase-β-aminophenazone or glycerol phosphate oxidase-β-aminophenazone methods, respectively; Boehringer Mannheim, Mannheim, Germany). Total mass of lipoprotein(a) was determined in serum by nephelometry (Beckmann Array, Fullerton, Calif), a method that depends on the measurement of the intensity of scattered laser light emanating from an illuminated volume of a dilute suspension of small particles. Biochemical and hematological safety parameters were determined by standard laboratory methods.

All analyses were performed in a central laboratory at the University of Freiburg im Breisgau, Germany. This laboratory applied Good Laboratory Practice standard and was certified according to International Organization for Standardization (ISO-9001) (http://www.iso.org), which defines quality management systems.

**Statistical Analysis**

Randomization was performed by using a 5 permutation block according to a list generated by means of the PROC PLAN procedure of the statistical package SAS version 6.0 (SAS Institute, Cary, NC). All randomized patients for whom at least 1 lipoprotein value was measured during treatment were evaluated in the intention-to-treat (ITT) group in terms of efficacy irrespective of any protocol violations. All patients of the ITT group who exhibited no major protocol violations and sufficient adherence were assessed for efficacy in the per-protocol group. Before the code was broken, a blind review was conducted to decide which protocol violations could be characterized as major. Safety and tolerability were assessed for all patients who had taken at least 1 dose of the trial medication, including placebo.

Patients were classified as nonadherent if they failed to take at least 80% or took more than 120% of the prescribed dose. Adherence was checked by pill count at visit 4 (day 0) for the placebo run-in phase and at visit 5 (6 weeks) and visit 6 (12 weeks) for the treatment phase. Patients found not to have adhered to the clinical trial regimen at visits 5 or 6 were not included in the per-protocol analysis.

The primary efficacy parameter, percentage change of LDL-C from baseline, was calculated as the percentage change at visit 5 and 6 from pooled baseline (mean value of visits 2, 3, and 4). A pooled baseline was calculated as the changes from pooled baseline to the last visit was performed (for completers, visit 6 and for randomized dropouts, visit 5 was taken as last visit, respectively). Descriptive results were also calculated for the changes from pooled baseline to visit 5 (6 weeks) and visit 6 (12 weeks).

The a priori statistical working hypothesis was that the highest dose is more effective in lowering LDL-C levels than the next lower dose and so on, the lowest dose being more effective than placebo. Multiple testing procedure was performed by using the trend test according to Jonckheere and Terpstra (JT test). One-sided level of significance was stipulated at $P_{1\text{JT}} = .025$. The treatment effects between policosanol and placebo were estimated by means of the nonparametric Hodges-Lehmann estimators with 95% confidence intervals. Descriptive and exploratory methods were used for the analysis of secondary variables. The statistical package SAS version 6.0 was used for general calculations. Sample size was calculated by using the software “N” version 2.2 (IDV-Data Analysis and Study Planning, Gauting, Germany). The JT test was calculated using StatXact-4 for Windows (Cytel Software Corp, Cambridge, Mass). Adverse events were coded according to World Health Organization–Adverse Reaction Terminology (WHO-ART).

Sample size estimation was based on the percentage change of LDL-C level from baseline, a level of significance of $P < .025$ (1-sided alternative), and a power of 80%. It was expected that the active treatment would result in an LDL-C level decrease of at least 10% (with an SD of 11%) compared with placebo. Thus, an effect size (Cohen d) of 0.91 (10/11) was expected. To achieve the calculated power, 20 patients had to be enrolled in each treatment group.

Predefined subgroups were analyzed in terms of different responses in the primary outcome parameter, percentage change in LDL-C. The subgroups included comparisons between men and women; patients younger or older than 65 years; baseline LDL-C levels of less than 165 mg/dL (<4.27 mmol/L), between 165 and 195 mg/dL (4.27-5.04 mmol/L), or more than 195 mg/dL (>5.04 mmol/L); BMI of less than or greater than 28; number of risk factors; smoker status; and medical care setting (lipid outpatient clinic vs general practitioner).

Diet protocols were evaluated using Prodi version 4.5 software (Wissenschaftliche Verlagsgesellschaft, Stuttgart, Germany). The following variables were compared between visits 4 and 6 with paired statistics: total calories, percentage of calories from fat (total, saturated, unsaturated), protein, carbohydrates, alcohol, intake of total cholesterol, and fiber intake.

**RESULTS**

The flow of participants through the trial is shown in the FIGURE. A total of 143 patients were randomized into the double-blind treatment phase. Nine of the patients terminated the trial prematurely. The reasons included not meeting inclusion criteria or meeting exclusion criteria in 4 patients, decision of patient in 3 cases (withdrawn), and adverse events in 2 patients. Five more patients had to be excluded from per-protocol...
analysis due to the following reasons: erroneously receiving interchanged trial medication (n = 2), completion of the trial but exclusion criteria were discovered afterward (n = 1), itraconazole treatment became necessary during the trial (n = 1), and insufficient adherence to trial medication (pill count) (n = 1). Thus, per-protocol analysis was performed in 129 patients.

**Patient Characteristics**

A total of 216 patients were enrolled in 14 trial centers, of which 143 patients were randomized and entered in the ITT analysis (Figure). Of the randomized patients, 114 (79.7%) were treated with policosanol and 29 (20.3%) received placebo, reflecting the anticipated allocation. A total of 134 of the randomized patients (93.7%) completed the trial. Fourteen randomized patients (9.8%) were excluded from the ITT analysis due to major protocol violations; therefore, 129 patients were analyzed per protocol.

Baseline characteristics of the randomized patients are shown in Table 1. Of the 143 randomized patients, 56 (39%) were men and 87 (61%) were women. Mean (SD) age was 56 (12) years (range, 23-78) and BMI was 27.2 (3.6). All patients were white and definition of race was by patient self-identification. A total of 26 patients (18%) were smokers and 4 (3%) were ex-smokers. Forty-two patients (29%) had a family history of premature CHD. All demographic data were equally distributed among the groups. Concomitant medications were also equally distributed among the groups and consisted of β-blockers (15%), angiotensin-converting enzyme inhibitors (10%), angiotensin II type 1 receptor antagonists (5%), diuretics (8%), calcium antagonists (4%), other antihypertensive medications (8%), thyroid hormones (13%), aspirin (10%), proton pump inhibitors (8%), nonsteroidal anti-inflammatory drugs (3%), hormone therapy (6%), benzodiazepines (4%), selective serotonin reuptake inhibitors (6%), and β agonists (4%).

Adherence was close to 100% in all treatment groups, as defined by the percentage of trial medication taken during treatment phase verified through pill count.

**Effects on Plasma Lipids and Lipoproteins**

The results of the lipid and lipoprotein measurements are shown in Table 2. Only data from the ITT analysis (as the more conservative statistical method) are presented because there were no differences between ITT and per-protocol analysis.

The mean (SD) LDL-C level of the total group of randomized patients at baseline was 187 (36) mg/dL (4.84 [0.93] mmol/L). There were no differences
Table 1. Baseline Characteristics of the Randomized Patients

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Placebo (n = 29)</th>
<th>10 mg (n = 28)</th>
<th>20 mg (n = 27)</th>
<th>40 mg (n = 27)</th>
<th>80 mg (n = 32)</th>
<th>P Value†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex, No. (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>16 (55)</td>
<td>9 (32)</td>
<td>7 (26)</td>
<td>11 (41)</td>
<td>13 (41)</td>
<td>.22</td>
</tr>
<tr>
<td>Female</td>
<td>13 (45)</td>
<td>19 (68)</td>
<td>20 (74)</td>
<td>16 (58)</td>
<td>19 (59)</td>
<td></td>
</tr>
<tr>
<td>Age, y</td>
<td>53.8 (13.8)</td>
<td>58.7 (11.5)</td>
<td>57.0 (10.2)</td>
<td>54.9 (9.9)</td>
<td>55.8 (11.8)</td>
<td>.55</td>
</tr>
<tr>
<td>Height, cm</td>
<td>170 (8)</td>
<td>168 (8)</td>
<td>166 (7)</td>
<td>171 (8)</td>
<td>169 (8)</td>
<td>.23</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>78 (13)</td>
<td>76 (12)</td>
<td>76 (11)</td>
<td>78 (12)</td>
<td>80 (13)</td>
<td>.67</td>
</tr>
<tr>
<td>BMI</td>
<td>27.1 (3.9)</td>
<td>26.8 (3.3)</td>
<td>27.5 (3.6)</td>
<td>26.8 (3.7)</td>
<td>27.7 (3.5)</td>
<td>.80</td>
</tr>
<tr>
<td>% of patients‡</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overweight</td>
<td>69</td>
<td>68</td>
<td>78</td>
<td>67</td>
<td>84</td>
<td>.02</td>
</tr>
<tr>
<td>Obese</td>
<td>28</td>
<td>14</td>
<td>37</td>
<td>15</td>
<td>25</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Smoker status, No. (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Smoker</td>
<td>4 (14)</td>
<td>3 (11)</td>
<td>8 (30)</td>
<td>4 (15)</td>
<td>7 (22)</td>
<td>.37</td>
</tr>
<tr>
<td>Ex-smoker</td>
<td>1 (3)</td>
<td>1 (4)</td>
<td>1 (4)</td>
<td>0 (0)</td>
<td>1 (3)</td>
<td>.91</td>
</tr>
<tr>
<td>Family history of premature</td>
<td>10 (35)</td>
<td>8 (29)</td>
<td>5 (19)</td>
<td>9 (33)</td>
<td>10 (31)</td>
<td>.71</td>
</tr>
<tr>
<td>cardiovascular disease, No. (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Abbreviation: BMI, body mass index, calculated as weight in kilograms divided by height in meters squared.
*Data are expressed as mean (SD) unless otherwise specified. See “Methods” section for definitions of characteristics.
†For sex, percentage of patients who are overweight or obese, smoker status, and family history of premature cardiovascular disease, P values were calculated by 2-sided χ² test; and for age, height, weight, and BMI, P values were calculated by analysis of variance.
‡Defined as BMI of at least 25 for overweight and at least 30 for obese.

Table 2. Results of Lipoprotein Measurements

<table>
<thead>
<tr>
<th>Lipids, mg/dL</th>
<th>Placebo Baseline</th>
<th>10 mg</th>
<th>20 mg</th>
<th>40 mg</th>
<th>80 mg</th>
<th>P Value†</th>
</tr>
</thead>
<tbody>
<tr>
<td>LDL-C</td>
<td>181 (36)</td>
<td>50 (16)</td>
<td>276 (39)</td>
<td>45 (18)</td>
<td>176 (65)</td>
<td>37 (46)</td>
</tr>
<tr>
<td>HDL-C</td>
<td>50 (16)</td>
<td>293 (65)</td>
<td>41 (14)</td>
<td>154 (49)</td>
<td>33 (31)</td>
<td>.61 (2.1)</td>
</tr>
<tr>
<td>Total Cholesterol</td>
<td>276 (39)</td>
<td>50 (16)</td>
<td>276 (47)</td>
<td>40 (15)</td>
<td>147 (59)</td>
<td>35 (32)</td>
</tr>
<tr>
<td>VLDL-C</td>
<td>45 (18)</td>
<td>154 (49)</td>
<td>35 (32)</td>
<td>147 (59)</td>
<td>35 (32)</td>
<td>8.8 (2.7)</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>176 (65)</td>
<td>37 (46)</td>
<td>147 (59)</td>
<td>35 (32)</td>
<td>8.8 (2.7)</td>
<td>3.9 (2.4)</td>
</tr>
<tr>
<td>Lipoprotein(a)</td>
<td>37 (46)</td>
<td>147 (59)</td>
<td>35 (32)</td>
<td>8.8 (2.7)</td>
<td>3.9 (2.4)</td>
<td></td>
</tr>
</tbody>
</table>

Mean (SD) [% Change From Baseline (SD)]

<table>
<thead>
<tr>
<th>Ratio</th>
<th>Placebo Baseline</th>
<th>10 mg</th>
<th>20 mg</th>
<th>40 mg</th>
<th>80 mg</th>
<th>P Value†</th>
</tr>
</thead>
<tbody>
<tr>
<td>LDL-C/HDL-C</td>
<td>6.0 (1.9)</td>
<td>4.0 (1.5)</td>
<td>.22</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HDL-C</td>
<td>6.0 (1.9)</td>
<td>4.0 (1.5)</td>
<td>.22</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; VLDL-C, very low-density lipoprotein cholesterol.

SI conversions: To convert HDL-C, LDL-C, VLDL-C, and total cholesterol to mmol/L, multiply by 0.0259; and triglycerides to mmol/L, multiply by 0.0113.

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between the groups at baseline. There was a slight decrease in some of the 5 treatment groups after 6 and 12 weeks compared with baseline. However, all these reductions were below 10% and therefore of limited clinical relevance. A statistically significant dose-dependent trend of LDL-C level decrease could not be demonstrated (P=.30, 1-sided JT test). The corresponding JT test for the per-protocol analysis was P=.39.

Table 3 shows the relative change, Hodges-Lehmann estimators, and the mean differences calculated by parametric tests for the pair-wise treatment differences regarding the percentage change in LDL-C levels for the 4 active treatment groups vs placebo. Hodges-Lehmann estimators, which are based on ranks, are more robust estimators of true differences than parametric estimators. Both approaches yielded similar results.

The results of the secondary outcome measures are also given in Table 2. Mean (SD) baseline levels were 51 (14) mg/dL (1.32 [0.36] mmol/L) for HDL-C, 282 (42) mg/dL (7.29 [1.09] mmol/L) for total cholesterol, 44 (16) mg/dL (1.14 [0.41] mmol/L) for VLDL-C, 175 (66) mg/dL (1.98 [0.75] mmol/L) for triglycerides, 37 (39) mg/dL (1.32 [1.39] µmol/L) for lipoprotein(a), 6.0 (1.8) for the ratio of total cholesterol to HDL-C, and 4.0 (1.4) for the ratio of LDL-C to HDL-C. There were no significant differences between the groups at baseline or in the changes from baseline at 6 or 12 weeks between the groups.

There were no differences in the effects on the primary outcome variable, percentage change in LDL-C, between predefined subgroups as defined in the Methods section (data not shown).

Diet Protocols

Food records (3 consecutive days at the end of the run-in phase and at the end of the treatment phase) were evaluated using computerized nutrient analysis. No significant differences between the 2 time points (paired statistics) or between treatment groups (analysis of variance) were found (data not shown).

### Table 3. Relative Change, Hodges-Lehmann Estimators, and Parametric Mean Differences for the Relative Change in LDL-C Levels vs Placebo

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Relative Change Mean (% SD)</th>
<th>Hodges-Lehmann Estimator</th>
<th>Mean Difference Calculated by Parametric Test</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>–8.1 (13.8)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Policosanol, mg/d</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>–5.2 (11.2)</td>
<td>–2.7 (–10.3 to 4.2)</td>
<td>–3.0 (–9.8 to 3.9)</td>
</tr>
<tr>
<td>20</td>
<td>–5.1 (12.3)</td>
<td>–3.0 (–10.2 to 5.0)</td>
<td>–3.1 (–10.2 to 4.1)</td>
</tr>
<tr>
<td>40</td>
<td>–2.0 (16.2)</td>
<td>–4.8 (–13.4 to 2.8)</td>
<td>–6.1 (–14.4 to 2.1)</td>
</tr>
<tr>
<td>80</td>
<td>–8.3 (12.4)</td>
<td>–0.8 (–7.2 to 6.6)</td>
<td>0.2 (–6.7 to 7.1)</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; LDL-C, low-density lipoprotein cholesterol.

**Safety and Adverse Events**

All 215 patients enrolled received at least 1 dose of trial medication and were included in the safety evaluation (172 patients received policosanol and 43 received placebo). The safety profile was excellent. In the double-blind phase, 45 patients experienced at least 1 adverse event. The proportion between the groups was not statistically significant (28% of patients received placebo, 21% received 10 mg, 37% received 20 mg, 3% received 40 mg, and 34% received 80 mg). The most commonly reported adverse events were bronchitis (13%), back pain (11%), pharyngitis (9%), upper respiratory tract infection (7%), and gastritis (5%). There were no differences in the frequencies between active treatment and placebo or between the dosage groups. No serious adverse events were found in all treatment groups.

Policosanol treatment resulted in no relevant changes in weight, vital signs (blood pressure, pulse rate), or routine chemistry and hematological laboratory parameters (data not shown).

**COMMENT**

Our rigorously controlled trial found no effect of Cuban sugar cane–derived policosanol on lipoprotein levels in patients with hypercholesterolemia or combined hyperlipidemia beyond placebo. Our goal was to corroborate the effectiveness of policosanol in lowering lipoprotein concentrations and to determine, if effective, the dose-dependency of effects and optimal doses. Two of the 5 treatment groups were treated with usual doses (10 and 20 mg/d), while 2 groups received high doses (40 and 80 mg/d) of policosanol. The study revealed no significant differences between the groups in all lipoprotein fractions examined, namely LDL-C, HDL-C, total cholesterol, VLDL-C, triglycerides, and lipoprotein(a). A nonparametric test (JT test) used to discover a possible dose-dependency as well as comparison of active treatment with placebo was not significant. The results are in contrast to a large number of published randomized controlled trials.

Recently, a systematic review of the literature up to June 2003 of randomized controlled trials using policosanol was published. Concerning the primary end point of reduction of LDL-C, this meta-analysis found 29 eligible studies with 1528 patients receiving treatment compared with 1406 patients receiving placebo. Twenty-eight of the 29 trials came from Cuba and 1 trial came from Argentina. Weighted estimates of percentage change in LDL-C were –23.7% for policosanol (mean dose of policosanol, 12 mg/d; range, 5-40 mg/d) vs –0.11% for placebo (P<.001). This LDL-C reduction is well in the order of magnitude that is achieved with commonly used doses of statins. In fact, some trials, again all but 1 from Cuba, directly compared the effects of policosanol...
policosanol with statins and found policosanol equally effective or better. Even a dose of policosanol as low as 2 mg/d was found to lower LDL-C significantly by more than 15%. It has been suggested that the lipid-lowering effects of policosanol are dose-dependent from 2 to 40 mg/d.

The reasons for the discrepant results between our trial and previous studies are unclear. As nearly all previous studies have been performed in Latin America (1 positive study was performed in Russia), it cannot be excluded that either ethnic or nutritional factors contribute to the impressively potent lipid-lowering effects of policosanol reported. Although ethnic and nutritional differences between European white and Latin American patients might play a role, the magnitude of differences reported (no effect vs a consistent 25% LDL-C reduction) makes this explanation unlikely. Furthermore, other lipid-lowering drugs, such as statins and ezetimibe, have been shown to have no ethnic-specific effects. The same holds true for responses to low-fat diet.

Almost all studies were supported by 1 sponsor, Dalmer Laboratories, a commercial enterprise founded by the Center of Natural Products, National Center for Scientific Research, La Habana, Cuba, to market policosanol. Our group and other studies have therefore suggested that independent studies should be performed to prove the efficacy of policosanol. Until now, independently performed studies are scarce. Our trial is the first study to investigate sugar cane-derived policosanol independently from the aforementioned Cuban research group but still using Cuban policosanol. A randomized placebo-controlled trial from the Netherlands of 58 patients found no effects when using wheat germ policosanol (20 mg/d) on lipoproteins in patients with normal to mildly increased cholesterol. Very few other studies outside Cuba exist but are not convincing in quality. An animal study performed in Canada in hamsters showed that sugar cane and rice wax policosanol have no effects on lipids, which is in contrast with findings of a variety of animal studies from Cuba. The putative mechanism of action of policosanol has not been clarified, although suppression of the 3-hydroxy-3-methylglutaryl coenzyme A reductase activity has been postulated.

There are several possible limitations to our study. Our study design is generally accepted for studies investigating lipid-lowering agents and our trial was a multicenter trial. Lipid and lipoprotein measurements were obtained on 3 different days at baseline (pooled baseline) to get reliable values. The measurements were performed in a central, certified laboratory. The trial consisted of a placebo and diet run-in phase with instructions to adhere to a National Cholesterol Education Program step I diet, initiated 4 to 6 weeks before baseline values were drawn. Diet had no influence on the results, as confirmed by comparison of food diaries at the end of the run-in phase and the treatment phase. The treatment duration was 12 weeks. It might be argued that lipid-lowering effects take longer to develop, although currently no known pharmacological intervention would support this notion. In the meta-analysis of Chen et al, the average treatment duration of the 29 studies was 30 weeks and a mean LDL-C level decrease of 23.7% was found. Extracting the subset of the 12 studies that had treatment durations of 12 weeks or less, the LDL-C lowering effect in these trials was still 24%. Furthermore, the published positive policosanol studies found lipid-lowering effects already after 4 to 6 weeks of treatment. Moreover, the putative lipid-lowering effect of policosanol has been reported to plateau after 10 weeks of administration.

We conclude therefore that trial duration cannot be made responsible for the observed absence of policosanol effects on lipids. We used Cuban sugar cane-derived policosanol that was provided as bulk from Dalmer Laboratories; therefore, a difference in the source of policosanol as a reason for the discrepant results is highly unlikely.

In general, it has been clearly demonstrated that cholesterol-lowering therapy reduces the risk of CHD and diminishes cardiovascular morbidity. Because CHD remains the leading cause of death in industrialized countries and some patients cannot be treated with statins, effective pharmacological lipid-lowering alternatives are greatly desired. The main target of treatment remains effective lowering of LDL-C levels, especially because a recent meta-regression analysis showed that LDL-C level decrease, and not the mechanism through which it is achieved, is important for reducing CHD risk. Our data clearly show that policosanol has no lipid-lowering effects beyond placebo. The policosanol-induced changes in LDL-C, all less than 10%, cannot be considered clinically relevant. When the Adult Treatment Panel III indicates that drug therapy is considered for LDL-C lowering, it is reasonable to use doses achieving a reduction in risk for major coronary events of 30 to 40%. The large intervention trials with statins have shown, however, that a risk reduction of this extent requires an approximate 30% reduction in LDL-C concentrations.

A considerable health food store and Internet market has extended the development of nonprescription policosanol, and worldwide sales are constantly increasing. A simple search in the Internet using the term policosanol gives about 640 000 items, with discount offers and bulk prices, for a substance that is marketed as “potent, natural and free of side effects.” A widely held belief among users is that policosanol is effectively lowering cholesterol. A national survey documented that alternative medicine use, such as herbal drugs, is increasing and is attributable primarily to an increase in the proportion of the population seeking alternative therapies. As justifiable as it may be to take patients’ wishes for herbal medicines into account, these drugs have to be scrutinized regarding their effectiveness, applying the same scientific criteria as standard drug therapies.

It is known from more than 80 trials performed so far that policosanol has an excellent safety profile. Also, in our study, the drug was tolerated well and no serious adverse events occurred.
frequency of adverse effects was comparable between placebo and the active treatment groups but more detailed information on the safety profile of policosanol is warranted, especially since it can be obtained as an over-the-counter drug.

In conclusion, policosanol is a well-tolerated substance derived from natural sources. Our results suggest that it is devoid of clinically relevant lipoprotein-lowering properties in white patients. Still, more independent studies are required to counterbalance the vast body of available positive trials. Although policosanol has been used for more than a decade in clinical trials, there are still no data on patient-related outcomes, such as cardiovascular morbidity and mortality. Moreover, independent information should be given to consumers who might take policosanol to improve their cardiovascular risk profile.

Author Contributions: Dr Berthold had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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Study supervision: Berthold.

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