

Bandolier Extra

Independent evidence-based thinking about health care

POLICOSANOL FOR LIPID-LOWERING

Clinical bottom line

Policosanol manufactured from Cuban sugar cane has been shown to lower total and LDL-cholesterol, and increase HDL-cholesterol levels in Hispanic populations with hypercholesterolemia, but only in studies conducted in Cuba that show worrying consistency. The results have not been replicated outside Cuba or with policosanol derived from other sources.

Background

Policosanol is a mixture of long-chain primary alcohols isolated from sugar cane wax. The main components are octacosanol (about 65%), triacosanol (about 12%), and hexacosanol (7%). Similar alcohols are found in other plant materials, such as wheat germ and rice bran, and in beeswax.

Cuban sugar cane policosanol, manufactured by Damler Laboratories, is patented and sold in over 40 countries, mainly in South America and the Caribbean. It is not available in the USA because of the trade embargo. The name "policosanol" is not patented, and numerous policosanol products are available world-wide, on the Internet, manufactured by different companies, and from a variety of different sources.

Search

The electronic databases PubMed, MEDLINE and EMBASE were searched for full, published reports of randomised controlled trials comparing policosanol with placebo or an active comparator for lipid lowering. The reference lists of reviews and retrieved articles were searched for additional trials. There were no language or date restrictions. Unpublished reports and abstracts were not considered. Authors were not contacted for original data.

Methods

For inclusion a trial had to have at least ten patients randomised to each treatment group, and report plasma lipid levels before and after treatment for each group.

Published reports of all potentially relevant trials were obtained, and those meeting the inclusion criteria were scored for quality [1]. Data were extracted on patients, treatments, changes in lipid levels, adverse events and discontinuations.

For the analysis of lipids, the weighted mean difference was calculated for total cholesterol (T-C), LDL-cholesterol (LDL-C) and HDL-cholesterol (HDL-C) levels, before and after treatment, in both policosanol and control groups.

Results

Most trials recruited patients with hypercholesterolemia, some specifically with or without established CHD or other risk factors. A few patients had normal lipid levels at enrolment, and one trial recruited patients with borderline to mildly elevated total cholesterol levels. Lipid levels at baseline were measured after a period of four to 12 weeks during which all lipid-lowering therapies were discontinued, and patients followed a low fat/low cholesterol diet and appropriate lifestyle advice.

Placebo controlled trials

Twenty-four reports of placebo controlled trials of Cuban sugar cane policosanol met the inclusion criteria. One report contained two trials of different doses of policosanol each with a placebo control, and is analysed here as two separate trials. Two trials did not report lipid levels but they were included in the adverse events analysis.

Details of the included trials are in the Appendix (available as a downloadable PDF from the Bandolier Internet site). All the studies were double blind, with the exception of one, which was single blind, but is included because lipid levels are unlikely to be affected by lack of blinding of the outcome assessor. The mean age of patients in the trials was 50 to 67 years, and there were more women than men.

The dose of policosanol used was 2 to 40 mg/day, with most patients receiving 5 to 10 mg/day. The duration of the studies ranged from 30 days to 24 months. For the two trials of 24 months, 12-month lipid levels are used in the analysis to make them more comparable with the other studies.

The effect of treatment on lipid levels in the individual trials is shown in the Appendix and in summary in Table 1. Table 3 at the end of the article gives a simplified breakdown of results by trial.

In 1410 patients treated with policosanol, there were clinically useful decreases in T-C and LDL-C levels (by about 1 mmol/L each) and an increase in HDL-C. There were no changes of note in 1308 patients treated with placebo. The effect was apparent by 6-8 weeks, and sustained for up to two years.

There was a considerable difference in effect between Cuban sugar cane policosanol, and wheat germ policosanol [2]. Figure 1 shows the difference in percentage reduction of total cholesterol with sugar cane policosanol and wheat germ policosanol, and Figure 2 shows the effects of placebo in the different trials.

Adverse events

Most adverse events were mild, and often transient, but there were fewer patients with any adverse event, or discontinuing treatment due to an adverse event, amongst those on policosanol (8% and 1%) than on placebo (24% and 6%) (Table 2).

Active controlled trials

Ten trials meeting the inclusion criteria used statins as active controls, of which five used lovastatin, and the others used simvastatin, pravastatin, fluvastatin, and atorvastatin.

Figure 1: Percentage reduction of total cholesterol with sugar cane policosanol (light fill) and wheat germ policosanol (dark fill)

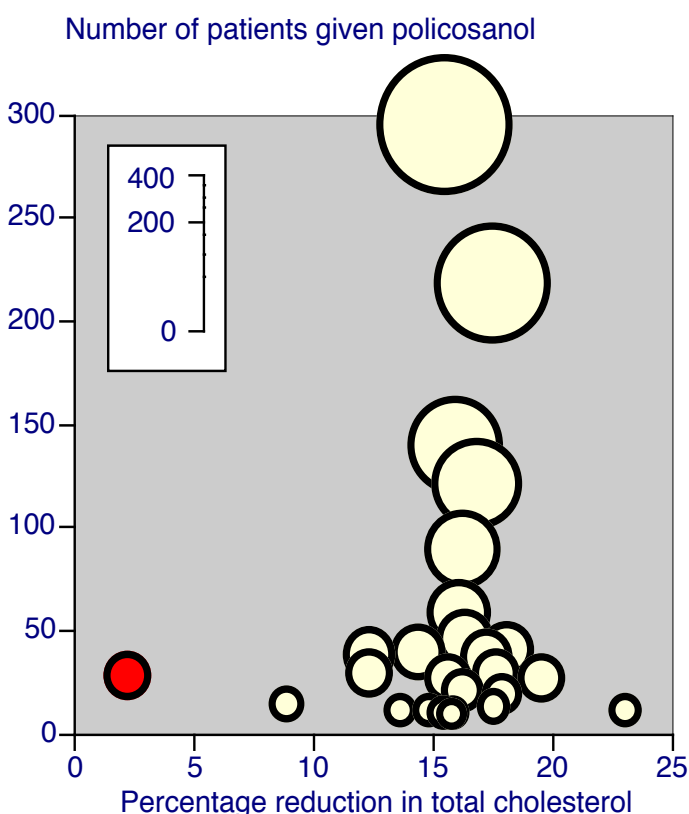
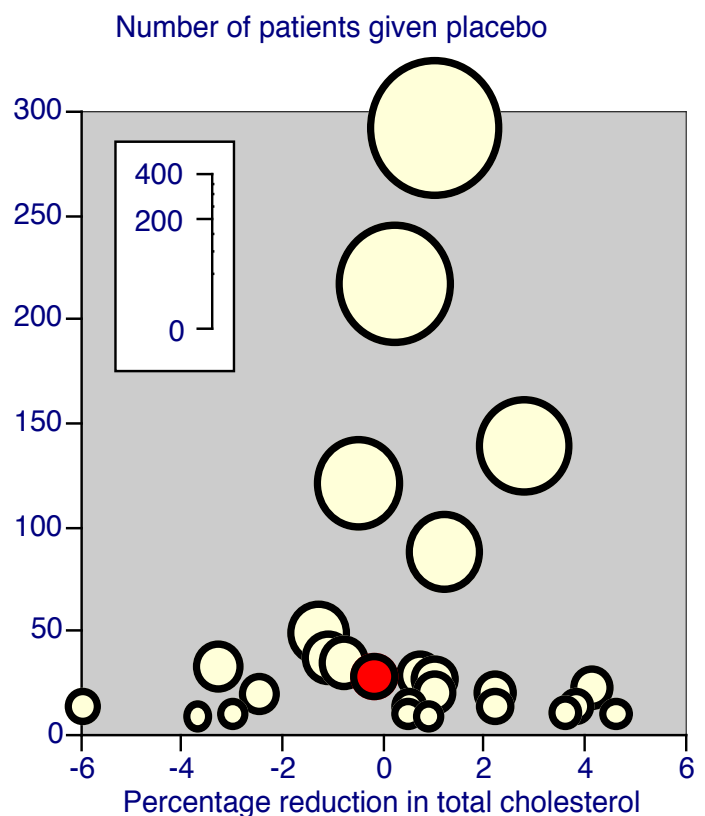


Figure 2: Percentage reduction of total cholesterol with placebo in sugar cane (light fill) and wheat germ (dark fill) trials



Details of these trials are in the Appendix on the Internet site.

Seven trials were double blind, and three were single blind. The mean ages of patients was 44 to 66 years, and again there were more women than men. The dose of policosanol was 10 mg/day, lovastatin 20 mg/day, simvastatin 10 mg/day, pravastatin 10 mg/day, fluvastatin 20 mg/day, and atorvastatin 10 mg/day. The duration of studies was 6 to 12 weeks.

In 279 patients treated with policosanol and 280 treated with a statin, there were clinically useful decreases in both TC and LDL-C, with statins giving a slightly greater reduction in TC. Policosanol also increased HDL-C, as in the placebo controlled trials, but statins had little effect on HDL-C. Separate analysis of the five trials using lovastatin gave the same result as for all statins combined (Table 1).

There were fewer patients with any adverse event, or discontinuing treatment due to an adverse event, amongst those on policosanol (6% and 0%) than on statin (20% and 6%) (Table 2).

Three other trials used different comparators: acipimox, Octa-60, and probucol. Details of these trials are in the Appendix. In each trial policosanol produced changes in lipid levels similar to those seen in the other trials, and greater than seen with the comparator. There were fewer patients with any adverse event in the policosanol groups than comparator groups, and only one discontinuation due to an adverse event, in the Octa-60 group.

Table 1: Pooled results for Cuban sugar cane policosanol for total, LDL, and HDL cholesterol as weighted mean percentage reductions or increase

	Trials	Patients	weighted mean difference		
			Total cholesterol reduction (%)	LDL cholesterol reduction (%)	HDL cholesterol increase (%)
Placebo-controlled trials					
Policosanol	25	1410	16.1	23.5	19.5
Placebo	25	1308	0.56	-0.4	-1.5
Statin-controlled trials					
Policosanol	10	279	13.3	25.4	12.3
Any statin	10	280	17.9	23.3	2.7
Lovastatin	5	115	17.2	22.7	3.1

Table 2: Percentages of patients experiencing any adverse event, or discontinuing because of an adverse event in Cuban sugar cane policosanol trials

	Trials	Patients	Patients with any adverse event (n/T; %)	Adverse event discontinuations (n/T; %)
Placebo-controlled trials				
Policosanol	25	1410	82/1001 (8)	14/1404 (1)
Placebo	25	1308	223/920 (24)	83/1308 (6)
Statin-controlled trials				
Policosanol	10	279	17/279 (6)	0/279 (0)
Any statin	10	280	56/280 (20)	16/280 (6)

Other outcomes

Some studies have examined outcomes other than lipid levels. These include platelet aggregation and susceptibility to lipid peroxidation, and important clinical end points such as intermittent claudication and cardiovascular events. In each case there was benefit with policosanol, but there are insufficient numbers to draw firm conclusions about reductions in vascular end points.

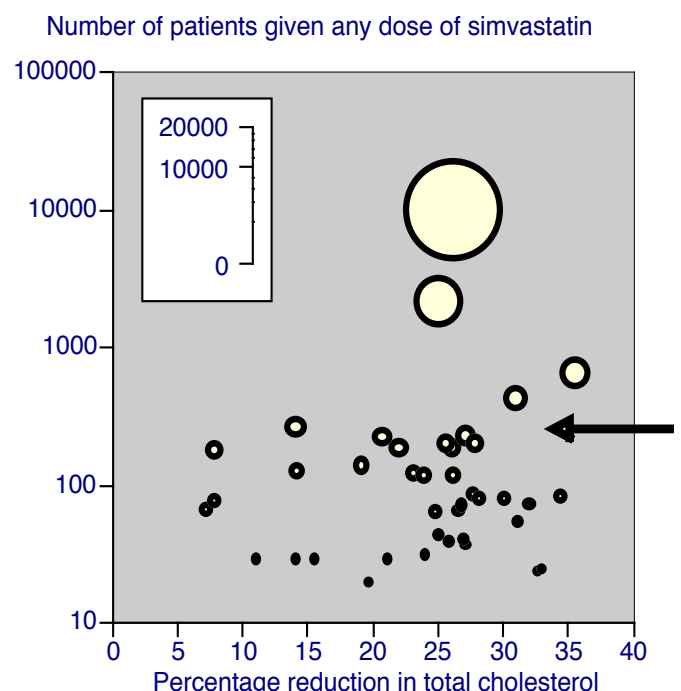
Comment

This set of trials shows that Cuban sugar cane policosanol reduces T-C and LDL-C by an amount equivalent to statins. In addition it increases HDL-C more than statins, and has fewer, less serious adverse events. For comparison, plant stanols (eg in Benecol) should reduce T-C by 6% and LDL-C by 10% (about 0.4 mmol/L) [3]. This sounds great, so why are we still using statins? What's the catch?

There are two catches:

The first catch is in the amazing consistency of the results for policosanol from Cuban sugar cane. As Figure 1 shows, all of the larger trials found exactly the same 15-16% reduction in total cholesterol. This was regardless of patient characteristics, duration of study (though most were longer than six weeks), or dose of policosanol. Moreover, almost all

Figure 3: Percentage reduction in total cholesterol in randomised studies on simvastatin (any dose) of 12 weeks or longer. The arrow shows the maximum group size in policosanol studies. Note the logarithmic scale for trial size



studies on Cuban policosanol come from a small number of researchers in a small number of institutions in Cuba.

On the other hand, we might expect consistency in lipid lowering trials, and so the results in Figure 1 (and similar ones for LDL-cholesterol and HDL-cholesterol) might be what we should expect. But take a look for a moment at Figure 3, showing a similar scatterplot for simvastatin (any dose) in studies of 12 weeks or longer [from 4]. This shows very considerable variation in percentage cholesterol reduction for group sizes below 300 patients, the range found in policosanol studies. The conclusion might then be that the consistency in the policosanol studies is rather special.

The second catch is that all these studies have used policosanol manufactured by one company. Policosanol manufactured from other sources such as wheat germ have not been effective in lowering cholesterol, despite having very similar chemical composition [2]. The mechanism of action is not understood.

To have any confidence we need:

- Independent verification from studies outside Cuba on the Cuban policosanol
- Studies of Cuban and other policosanols in non-Hispanic populations
- These studies should last at least 12 weeks, and compare policosanol with both placebo and statins.

Without this evidence, buyers of policosanol should beware. There can be no certainty that it is doing them any good.

References

1. AR Jadad et al. Assessing the quality of reports of randomized clinical trials: is blinding necessary? *Control Clin Trials* 1996 17:1-12.
2. Y Lin et al. Wheat germ policosanol failed to lower plasma cholesterol in subjects with normal to mildly elevated cholesterol concentrations. *Metabolism* 2004 53:1309-1314.
3. Phytosterol esters (plant sterol and stanol esters) [www.ifst.org/hottop29.htm]
4. JE Edwards, RA Moore. Statins in hypercholesterolaemia: A dose-specific meta-analysis of lipid changes in randomised, double blind trials. *BMC Family Practice* 2003, 4:18 (<http://www.biomedcentral.com/1471-2296/4/18>)

References to studies included in the review can be found on the Bandolier Internet site (www.ebandolier.com).

Table 3: Details of group size and percentage reduction in total and LDL cholesterol, and increase in HDL cholesterol for policosanol and placebo, in sugar cane and wheat germ studies

Cuban sugar cane studies

Sugar cane policosanol				Placebo			
n	T-C (% reduction)	LDL-C (% reduction)	HDL-C (% increase)	n	T-C (% reduction)	LDL-C (% reduction)	HDL-C (% increase)
12	23.0	31.2	8.7	10	0.9	2.9	-7.2
14	17.5	21.8	11.3	15	-6.0	-11.5	-8.8
30	17.6	26.9	21.1	15	0.5	1.4	-5.2
47	16.3	27.5	25.9	50	-1.3	0.8	-1.5
38	17.2	26.4	13.6	36	-0.8	-1.6	1.7
22	16.2	21.5	14.0	23	4.1	1.7	-6.3
28	15.6	23.1	8.0	34	-3.3	-5.0	-2.3
11	15.8	17.3	6.2	11	0.5	3.7	-7.4
12	14.8	15.6	0.0	11	-3.0	-5.5	0.0
15	8.8	12.6	2.8	15	2.2	-1.3	-4.4
12	13.6	19.1	11.5	12	3.6	4.0	-9.5
11	15.4	22.3	17.9	11	4.6	6.6	-3.4
40	14.3	22.1	24.0	20	-2.5	-2.0	3.6
219	17.4	25.6	28.4	218	0.2	0.4	2.9
122	16.8	25.4	29.3	122	-0.5	-0.4	3.3
10	15.7	19.6	5.4	10	-3.7	-3.3	-4.3
59	16.0	27.8	17.3	30	0.7	-7.8	-15.8
28	19.5	26.7	7.4	28	1.0	-1.0	-6.2
90	16.2	24.4	29.1	89	1.2	-0.4	-3.6
20	17.8	23.5	20.6	21	1.0	-0.2	-5.2
41	18.0	36.8	38.6	21	2.2	1.7	1.6
140	15.9	21.3	18.2	140	2.8	-1.5	-2.6
296	15.4	20.5	12.7	293	1.0	0.8	-2.7
30	12.3	16.4	5.2	15	3.8	2.5	0.8
39	12.3	19.9	10.5	38	-1.1	-1.1	0.0

Wheat germ study

Wheat germ policosanol				Placebo			
n	T-C (% reduction)	LDL-C (% reduction)	HDL-C (% increase)	n	T-C (% reduction)	LDL-C (% reduction)	HDL-C (% increase)
29	2.15	2.46	-1.57	29	-0.18	0.16	2.36