

Policosanol to Manage Dyslipidemia in Older Adults

Barbara Swanson and Joyce Keithley

Rush University College of Nursing, Chicago, IL, USA

Abstract

Policosanol (*Saccharum officinarum*) is a dietary supplement that is widely used in Latin America to normalize dyslipidemic profiles, as well as to reduce hypertriglyceridemia. Consisting of fatty alcohols derived from plant waxes, policosanol has shown comparable efficacy and better safety than statins for raising HDL and lowering LDL cholesterol levels. However, nearly all published trials of policosanol have been conducted by a single group of investigators in Cuba, and more recent studies outside of Cuba haven't replicated these findings. This chapter presents current information on the pharmacological properties of policosanol and reviews recent studies with a focus on those that target elderly populations. Additional studies are needed in elderly populations to further describe its efficacy, especially when directly compared with statins, and to characterize its mechanism of action and potential pleiotropic effects.

Keywords: *Policosanol, dietary supplements, plant waxes, cholesterol, triglycerides, older adults*

Policosanol is an over-the-counter dietary supplement that consists of fatty alcohols derived from plant wax, generally sugar cane (*Saccharum officinarum*). Widely used in Latin American countries to promote cardiovascular health, policosanol is a natural remedy that has been shown in several Cuban studies to be efficacious for normalizing dyslipidemic lipoprotein profiles, as well as for reducing hypertriglyceridemia. However, more recent studies from the United States, Europe, South Africa, and Canada have failed to replicate these findings, raising questions about the role of policosanol in the management of dyslipidemia.

PHARMACOLOGICAL PROFILE

Chemistry

Policosanol is also known as 32-C, dotriacontanol, heptacosanol, hexacosanol, nonacosanol, octacosanol, tetracosanol, tetratriacontanol, triacontanol.

It is composed of aliphatic primary alcohols that are isolated from purified sugar cane wax by hydrolytic cleavage. Its chemical formula is $\text{CH}_3-(\text{CH}_2)_n-\text{CH}_2\text{OH}$ with a chain length varying from 24 to 34 carbon atoms [1]. Most policosanols preparations contain aliphatic alcohols in the following proportions: 66–67% octacosanol, 12–14% triacosanol, 7–8% hexacosanol, and 11–15% other carbon alcohols [2].

Policosanols has been shown to melt without decomposition and to remain stable at temperatures up to 185°C [3]. It has low solubility in water. At temperatures of 25°C and 40°C , solubility has been reported to be 1.7×10^{-15} mg/ml and 2.5×10^{-15} mg/ml [3].

Mechanism of Action

The primary effect of policosanols is to reduce low-density lipoprotein (LDL) cholesterol concentration, although it has also been shown to raise high-density lipoprotein (HDL) cholesterol [4] and lower triglycerides (TG) [4–7]. Significant effects have been observed after 6–8 weeks of treatment [8–9]. Although the mechanism of action remains uncertain, policosanols is hypothesized to exert its lipid-altering effects via two mechanisms. First, a growing body of *in vitro* and animal studies suggest that policosanols inhibits cholesterol synthesis prior to the formation of mevalonate [10], thus suggesting a modulatory effect on 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase, the target for statin drugs (Fig. 7.1). Recent data suggest that policosanols inhibits *de novo* synthesis of HMG-CoA reductase and/or stimulates its degradation [11]. Other data suggest that policosanols upregulates hepatic

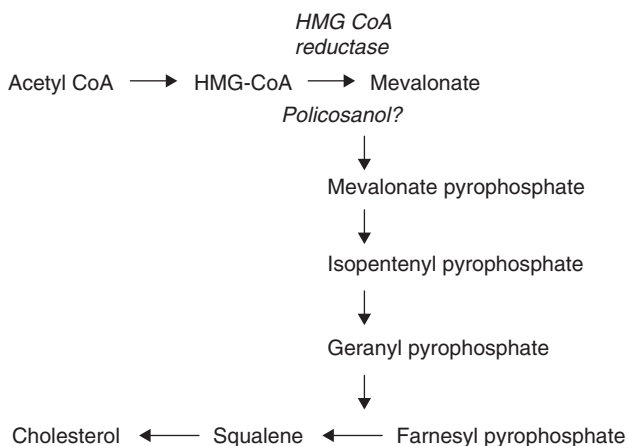


FIGURE 7.1 Cholesterol biosynthesis pathway.

AMP-kinase phosphorylation, an action known to suppress HMG-CoA activity [12]. Second, policosanol has been shown to increase receptor-mediated uptake of LDL in the liver [13]. A third mechanism, inhibition of bile acid absorption, has been reported, but additional data are needed to substantiate this finding [14]. Other effects of policosanol that are relevant to reducing atherogenic risk include inhibition of platelet aggregation, blocking the effects of cholesterol on smooth muscle proliferation, inhibition of foam cell formation, and prevention of LDL peroxidation [10, 15–17], although conflicting data exist on policosanol's antioxidant effects [14].

It is not clear if policosanol-induced inhibition of cholesterol synthesis is due to a single constituent or is the result of the interaction or synergy among multiple constituents. A study of cholesterol synthesis *in vitro* found that triacontanol, a minor component in most policosanol preparations, decreased HMG-CoA reductase activity in rat hepatoma cells, but not in microsomal fractions from Harlan Sprague–Dawley rats [12]. This suggests that triacontanol may be transformed to an active metabolite that inhibits cholesterol synthesis or, alternatively, it may act via intracellular pathways.

Pharmacokinetics

To date, there are no validated methods to measure plasma concentrations of long-chain alcohols or their metabolites in humans following therapeutic doses, thus restricting investigation of the pharmacokinetic properties of policosanol [1]. Studies of pharmacokinetics in animal models have involved measurement of total radioactivity following administration of radiolabeled octacosanol, rather than the parent drug, limiting the conclusions that can be drawn. Although the findings must be viewed cautiously, rat studies have found that the bioavailability of oral octacosanol ranges from 5% to 12% and that its half-life is 1–2 hours [18]. Orally administered octacosanol distributes to the tissues, with accumulations of greater than 1% of the administered dose in the liver and brown and white adipose tissues, and less than 0.4% in the spleen, kidney, heart, lung, brain, and muscle [13]. *In vitro*, octacosanol is metabolized to octacosanoic acid; *in vivo*, oral octacosanol is associated with the formation of shortened saturated and unsaturated fatty acids. This suggests that octacosanol and fatty acids are metabolized via shared pathways [19].

Toxicity

At doses that are between 100 and 3500 times greater than the recommended dosage, there have been no reports of policosanol-related toxicity in any published animal or human trials [1, 20]. A review of four clinical trials of policosanol in healthy volunteers and persons with dyslipidemia (total $N = 308$ persons treated with policosanol for between 8 weeks and 14 months) revealed the following adverse events: (a) significant, but mild, decrease in serum liver

transaminase levels that remained within normal limits and one case of abdominal pain with nausea [4], (b) significant decrease in serum creatinine levels, although no values were outside the normal range [21], (c) transient dizziness, nausea, and diarrhea in two participants [4], and (d) somnolence ($n = 1$) and headache ($n = 1$) [14]. A large surveillance study followed 27,879 policosan-ol-treated patients for an average of 2.7 years and found that only 86 (0.31%) patients reported adverse effects. The most commonly occurring adverse effects included weight loss (0.08%), polyuria (0.07%), insomnia (0.05%), and polyphagia (0.05%) [22].

There have been no reports of carcinogenicity associated with policosan-ol supplementation. In one study, mice who were administered excessive doses of policosan-ol (50–500 mg/kg) for 18 months did not show increased neoplastic disease compared with control mice [23]. This finding corroborated earlier animal studies that found no evidence of policosan-ol-related toxicities, including neoplasms, in doses of up to 500 mg/kg administered over a period of 12–24 months [24–26].

Several studies have shown that policosan-ol supplementation reduces platelet aggregation [5, 21, 27]. Although this could provide protection against thrombotic events, it could also be associated with bleeding tendencies. To date, no published clinical trials have reported the occurrence of bleeding or hemorrhagic events during policosan-ol supplementation.

There has been one published report on the perinatal and postnatal effects of policosan-ol in an animal model. In that study, pregnant Sprague-Dawley rats were administered policosan-ol at doses of up to 500 mg/kg/day from day 15 of pregnancy to day 21 post-parturition. No toxic effects were observed in the dams during pregnancy, while the pups showed no adverse effects related to postnatal growth, behaviors, or reproductive ability [28].

Drug Interactions

In clinical trials, policosan-ol has been concomitantly administered with a number of medications, including, but not limited to, calcium channel blockers, angiotensin-converting enzyme inhibitors, diuretics, antidepressants, oral hypoglycemics, and nonsteroidal anti-inflammatory drugs. There have been no reports of any adverse drug interactions with policosan-ol [1]. In one randomized controlled trial (RCT), two of three policosan-ol-treated participants (2mg/day for 14 months) who concomitantly received beta-adrenoceptor antagonists showed an increase in TG and no change in total cholesterol [29]. Beta-adrenoceptor antagonists are known to increase TG and very low-density lipoprotein (VLDL) cholesterol, and to decrease HDL cholesterol [30, 31]. Suprapharmacological doses of policosan-ol have been shown to significantly increase propranolol-induced hypotension in spontaneously hypertensive rats, while having no effect on blood pressure when concomitantly administered with nifedipine [32].

REVIEW OF STUDIES

Overview of Older Studies/Systematic Reviews

To our knowledge, two systematic reviews have evaluated the safety and efficacy of policosanol as a lipid-lowering agent. The first of these reviews [1] considered randomized double-blind placebo-controlled or randomized double-blind comparative trials in healthy volunteers, patients with hypercholesterolemia, and special populations, such as elderly patients and postmenopausal women. All 21 included studies reported significant changes in total cholesterol at doses of 10–20 mg/day, and 20 of the 21 studies reported significant changes in LDL cholesterol. Neither TG nor HDL cholesterol were significantly altered in the majority of studies. Most studies were done in the Caribbean using policosanol derived from Cuban sugar cane. The reviewers concluded that policosanol was well-tolerated and safe in reducing total and LDL cholesterol and that additional studies need to be conducted in other countries and research centers.

The second systematic review compared the safety and efficacy of plant sterols and stanols (e.g., fortified margarines) to policosanol for reducing LDL cholesterol [33]. Fifty-two randomized double-blind placebo-controlled studies (23 plant sterol and stanol; 29 policosanol) met all inclusion criteria. Similar to the first review, a variety of patient populations were studied, including patients with normal and elevated cholesterol levels, as well as patients with type 2 diabetes mellitus, post-myocardial infarction, and other disorders. In the 52 included studies, plant sterols and stanols and policosanol were significantly more effective than placebo ($p < 0.0001$) in reducing LDL cholesterol. Although none of the studies directly compared plant sterols and stanols to policosanol, policosanol was associated with greater reductions in LDL cholesterol than plant sterols and stanols ($p < 0.0001$). Among the authors' conclusions were that all three products – plant sterols and stanols and policosanol – were well-tolerated and safe, and that policosanol was more effective in reducing LDL cholesterol than plant sterols and stanols.

Review of Recent Studies: 2004–2007

Since the publication of the systematic reviews, 12 additional studies of policosanol for dyslipidemia have been published and are summarized in Table 7.1 [34–45]. Consistent with the findings reported in the systematic reviews, six studies showed that daily supplementation with policosanol produced significant reductions in some or all of the lipid parameters. Three of the six positive studies were conducted by the prominent Cuban research team; and three were conducted by researchers in Croatia, the United States, and Italy. With the exception of one retrospective, comparative study, all studies employed randomized, prospective, clinical trial designs. Study sample sizes ranged from 21 to 100 adults with hypercholesterolemia; and policosanol dosages ranged

TABLE 7.1 Recent Studies of Policosanol for Dyslipidemia: 2004–2007

Reference	Design	N	Dose/(Product source)	Duration	Results
Lin <i>et al.</i> (2004) (Netherlands) [34]	Randomized, double-blind, parallel placebo-controlled	58 adults with normal or mildly elevated cholesterol levels	20 mg wheat germ policosanols administered via chocolate pellets (Garuda Intl., Inc., USA, California; composition similar to sugar cane-derived policosanols)	4 weeks	No change in LDL, TC, HDL, TG No short-term adverse effects
Castano <i>et al.</i> (2005) (Cuba) [35]	Randomized, double-blind, comparative	90 patients with type II hypercholesterolemia	3 groups: 2 omega-3 fatty acids + placebo; 2 omega-3 fatty acids + 5 mg policosanols; 2 omega-3 fatty acids + 10 mg policosanols (Dalmar Labs, Havana, Cuba)	8 weeks	Decreased LDL, TC, TG, and increased HDL in both policosanols groups Only TG reduced in omega-3 fatty acids + placebo group Well-tolerated
Castano <i>et al.</i> (2005) (Cuba) [36]	Randomized, double-blind, comparative	100 patients with type II hypercholesterolemia	D-003, 5 or 10 mg, or policosanols, 5 or 10 mg (Dalmar Labs, Havana, Cuba; D-003 = mixture of high molecular weight aliphatic acids purified from sugar cane wax)	8 weeks	Decreased LDL, TC, and increased HDL in both groups at both dosages; with greater changes in both D-003 groups No change in TG Both agents well-tolerated

Reiner <i>et al.</i> (2005) (Croatia) [37]	Randomized, double-blind, placebo-controlled, crossover	67 patients with moderate hypercholesterolemia	Policosanol 10 mg (rice-derived policosanol)	8 weeks	Significant decrease in TC and increase in apoprotein A I No change in LDL, HDL, TG, homocysteine, CRP No adverse effects
Wright <i>et al.</i> (2005) (USA, Kentucky) [38]	Retrospective, comparative	21 adults with elevated cholesterol levels: 15 treated with policosanol and 6 treated with policosanol and statin therapy	Policosanol 10 mg/coenzyme Q 15 mg combination twice/day, or above + statin (product source not stated)	156 ± 63 days	Decreased LDL, $p < 0.001$ and TC, $p < 0.001$ in both groups No change in HDL, TG
Berthold <i>et al.</i> (2006) (Germany) [39]	Multi-center, randomized, double-blind, placebo-controlled	143 patients with hypercholesterolemia or combined hyperlipidemia	5 groups: 10, 20, 40, or 80 mg policosanol, or placebo (Dalmar Labs, Havana, Cuba)	12 weeks	No change in LDL, TC, HDL, TG, VLDL, lipoprotein a, LDL:HDL, TC:HDL All dosages well-tolerated
Castano <i>et al.</i> (2006) (Cuba) [40]	Randomized, double-blind, comparative	54 outpatients with atherosclerotic risk factors	1 omega-3 fatty acids + 10 mg policosanol, or 1 omega-3 fatty acids + placebo (Dalmar Labs, Havana, Cuba)	21 days	17% decrease in LDL, 10% decrease in TC, 18% increase in HDL No change in TG Policosanol + omega-3 fatty acids more effective in inhibiting platelet aggregation than omega-3 fatty acids alone

(Continued)

TABLE 7.1 (Continued)

Reference	Design	N	Dose/(Product source)	Duration	Results
Cubeddu <i>et al.</i> (2006) (USA, Florida) [41]	Randomized, double-blind, double dummy, placebo-controlled	99 patients with LDL levels 140–189 mg/dL	Four groups: policosanol 20 mg, atorvastatin 10 mg, combination therapy, placebo (Cholesstor, Pharmed Group, USA, Florida)	12 weeks	No change in LDL, TC, HDL, TG, either alone or as combination therapy Well-tolerated
Dulin <i>et al.</i> (2006) (USA, North Carolina) [42]	Randomized, double-blind, placebo-controlled	40 adults with mild hypercholesterolemia	Policosanol 20 mg per day (Garuda Intl., Inc., USA, California)	8 weeks	No change in LDL, TC, HDL, TG, C-reactive protein, NMRS-determined profiles
Greyling <i>et al.</i> (2006) (South Africa) [43]	Randomized, double-blind, placebo-controlled, cross-over	35 patients with hypercholesterolemia or familial hypercholesterolemia	Policosanol 20 mg per day (Garuda Intl., Inc., USA, California)	12 weeks	No change in LDL, TC, HDL, TG
Kassis and Jones (2006) (Canada) [44]	Randomized, double-blind, placebo-controlled, cross-over	21 hypercholesterolemic males and post-menopausal females	Policosanol 10 mg incorporated in margarine (Dalmar Labs, Havana, Cuba)	4 weeks	No change in LDL, TC, HDL, TG
Cicero <i>et al.</i> (2007) (Italy) [45]	Randomized, single-blind, parallel groups	40 patients with moderate dyslipidemias	Berberine (plant alkaloid) or combination of berberine, policosanol, red yeast extract, folic acid, astaxanthin	4 weeks	Decreased TC, LDL, TG, ApoB in both groups; increased HDL in both groups No adverse events in either group

Abbreviations: HDL, HDL-cholesterol; LDL, LDL-cholesterol; TC, total cholesterol; TG, triglycerides; VLDL, VLDL-cholesterol; CRP, C-reactive protein; NMRS, nuclear magnetic resonance spectroscopy

from 5 to 10mg, either alone or in combination with other agents, such as omega-3 fatty acids, coenzyme Q, or berberine. Policosanol source was sugar cane-derived in three studies, rice-derived in one study, and not identified in two studies. Study duration ranged from 4 weeks to 6 months. The majority of studies reported significant decreases in LDL-cholesterol, total cholesterol, and TG, and significant increases in HDL-cholesterol. Also similar to the systematic reviews, policosanol was well-tolerated and associated with no adverse effects in any of studies.

The other six studies reported results that were in marked contrast to the studies included in the systematic reviews. All six studies were double-blind, randomized, placebo-controlled clinical trials conducted with adults (*N* range, 40–143) who had normal or mild hypercholesterolemia or dyslipidemia. Policosanol dosages ranged from 10 to 80mg daily, either alone or in combination with other agents, primarily sugar-cane derived and from Dalmar Labs, Havana, Cuba or Garuda International, Inc., California. Study duration ranged from 4 to 12 weeks, and policosanol was well-tolerated. The majority of these studies found no change in any of the lipid parameters, including LDL-cholesterol, HDL-cholesterol, total cholesterol, and TG.

The divergence of these findings raises several questions: First, do differences in dietary patterns across countries affect policosanol bioavailability and subsequent efficacy? It has been shown, for example, that oleyl alcohol, a component of fish oil, inhibits absorption of long-chain alcohols in the rat gut [46]. Second, what is the variability in the composition of the policosanol products provided by Dalmar Laboratories, Havana, Cuba and Garuda International, Inc., California? It is well-established that plant-based supplements can vary from lot to lot and crop to crop. Third, do other differences in the composition of policosanol account for the disparate findings, such as the presence of other ingredients, or the use of other preparation or delivery techniques, such as chocolate pellets or margarine? Fourth, do genetic or other differences in the samples account for the discrepant findings? Or, fifth, do study duration, sample sizes, heterogeneous samples, or other limitations account for the variable findings?

Studies of Older Adults

Eight clinical trials and one surveillance study focusing on the aging population (>60 years) and including 3763 participants are summarized in Table 7.2 [47–55]. In dosages ranging from 5 to 20mg, policosanol was administered, either alone (*n* = 8 studies) or in combination with a beta-blocker (*n* = 1 study). Policosanol was compared against placebo, simvastatin, pravastatin, or atorvastatin. The studies encompassed a mix of small sample sizes and large multi-center samples and ranged in length from 8 weeks to 12 months. With the exception of one study conducted by researchers in Argentina, all studies were conducted by a Cuban research team. Policosanol was more effective

TABLE 7.2 Policosanol and Aging Studies

Reference	Design	N	Dose	Duration	Results
Castano <i>et al.</i> (1995) [47]	Multi-center, randomized, double-blind, placebo-controlled	62 patients (60–75 years) with hypercholesterolemia	Policosanol, 10 mg	12 months	Decreased LDL, TC, LDL:HDL, TC:HDL, $p < 0.00001$ HDL increased 8% No change in TG Mild/transient adverse effects
Ortensi <i>et al.</i> (1997) (Argentina) [48]	Randomized, double-blind, parallel-group, comparative	53 patients (60–77 years) with primary hypercholesterolemia	Policosanol or Simvastatin, 10 mg	8 weeks	Both drugs significantly/similarly decreased LDL, TC, TG, TC:HDL, LDL:HDL No change in HDL No serious adverse events
Castano <i>et al.</i> (1999) [49]	Randomized, double-blind	68 patients (60–80 years) with hypercholesterolemia	Policosanol, or Pravastatin, 10 mg	8 weeks	Policosanol decreased LDL, TC, LDL:HDL, TC:HDL, $p < 0.00001$ Pravastatin decreased LDL, TC, LDL:HDL, TC:HDL, $p < 0.00001$ Policosanol increased HDL, $p < 0.001$ and decreased TG, $p < 0.01$ Policosanol decreased platelet aggregation, $p < 0.05$ and endothelium levels, $p < 0.001$ Both agents well-tolerated

Castano <i>et al.</i> (2001) [50]	Multi-center, randomized, placebo-controlled	179 patients (60–78 years) with type II hypercholesterolemia and >1 concomitant atherosclerotic risk factor	Policosanol, 5 mg for 12 weeks; then 10 mg for 12 weeks	24 weeks	Both doses decreased LDL, TC, $p < 0.001$; and LDL:HDL, TC:HDL, $p < 0.01$ Both doses increased HDL, $p < 0.01$ and improved cardiovascular capacity, $p = 0.01$ No change in TG No serious adverse events, $p < 0.01$
Mas <i>et al.</i> (2001) [51]	Multi-centered, randomized, placebo-controlled	280 patients (≥ 60 years) with type II hypercholesterolemia and CHD	Policosanol 5 mg for 6 months; increased to 10 mg if pre- defined cholesterol goals not reached by 6 months	12 months	Decreased LDL, TC, TC:HDL, LDL:HDL, $p < 0.00001$ Decreased TG, $p < 0.001$ Increased HDL, $p < 0.001$ Decreased cardiac and vascular events and hospitalizations, $p < 0.001$ Well-tolerated
Castano <i>et al.</i> (2002) [52]	Multi-center, randomized, double- blind, placebo- controlled, parallel groups	589 patients (≥ 60 years) with hypertension and type II hypercholesterolemia	Policosanol 5 mg for 6 months; increased to 10 mg if pre- defined cholesterol goals not reached by 6 months	12 months	Decreased LDL, TC, TG, TC:HDL, LDL:HDL, $p < 0.00001$ Increased HDL, $p < 0.0001$ Decreased vascular and all-cause serious adverse events, $p < 0.05$, and total adverse events, $p < 0.01$

(Continued)

TABLE 7.2 (Continued)

Reference	Design	N	Dose	Duration	Results
Castano <i>et al.</i> (2003) [53]	Randomized, single-blind, parallel group	75 older patients (60–80 years) with type II hypercholesterolemia	Policosanol or Atorvastatin, 10 mg	8 weeks	Both agents decreased TC, LDL:HDL, TC:HDL, $p < 0.0001$, and TG, $p < 0.001$ Atorvastatin more effectively decreased LDL and TC Policosanol increased HDL, $p < 0.05$ Nine adverse events with Atorvastatin; none with policosanol
Castano <i>et al.</i> (2004) [54]	Randomized, placebo-controlled	205 patients (≥ 60 years) with hypercholesterolemia	Policosanol 5 mg plus beta-blocker, or placebo	3 years	Decreased LDL, TC, TG, $p < 0.00001$ Increased HDL, $p < 0.00001$ Decreased BP in policosanol/beta-blocker group Fewer adverse events in policosanol/beta-blocker group (3.1%) vs. placebo group (14.0%)
Fernandez <i>et al.</i> (2004) [55]	Multi-site surveillance for tolerability	2252 patients (≥ 60 years) with high coronary risk	Policosanol 5, 10, and 20 mg	Variable: 6–36 months	Serious adverse events: 1.4% Hospitalization: 0.6% Mild to moderate adverse events: 2.7%

Abbreviations: HDL, HDL-cholesterol; LDL, LDL-cholesterol; TC, total cholesterol; TG, triglycerides; CHD, coronary heart disease

than placebo in improving lipid parameters. Comparisons between policosanol and the three different statin agents suggested that policosanol was equivalent ($n = 2$) or superior ($n = 1$) in efficacy. With the exception of atorvastatin, policosanol and the other agents were associated with only mild or transient side effects. Because of the preponderance of studies conducted in one country with one type of policosanol, study findings may not be generalizable to other settings and populations and may be unique to the people of Cuba.

IMPLICATIONS FOR OLDER ADULTS

Although statins remain the cornerstone therapy for dyslipidemia, their high cost may preclude their use by persons on Medicare. For those individuals, policosanol may represent a cost-effective alternative. In November 2005, the average Medicare drug plan cost for a 1-month supply of simvastatin (Zocor®) was \$132 [56]. In contrast, a 1-month supply of policosanol costs \$12.00. Another consideration is older adult polypharmacy. With the exception of pravastatin and rosuvastatin, all statins are extensively biotransformed by the cytochrome P450 system and hence their plasma concentrations may be altered when P450 inducers or inhibitors are concomitantly administered. Competitive CYP inhibitors can increase statin plasma concentrations to potentially toxic levels, resulting in myopathy and rhabdomyolysis. CYP inhibitors that are commonly administered to the elderly include calcium channel blockers, warfarin, and sildenafil [57]. Digoxin can also increase the area under the curve (AUC) for statins through its effects on the P glycoprotein, a physiological drug transporter [58]. Given the interactions between statins and drugs commonly prescribed for older adults, policosanol may be a safer lipid-lowering alternative. Additional pharmacokinetic studies are needed to identify the effects of policosanol on CYP P450 isoforms and drug transporters.

Statin are characterized by cardioprotective pleiotropic actions that are independent of their lipid lowering effects. These pleiotropic actions include improved endothelial cell dysfunction, increased myocardial perfusion, increased bioavailability of nitric oxide, antioxidant and anti-inflammatory effects, and stabilization of plaque formation [59]. Additionally, statins have extrahepatic effects that may be beneficial to older adults. In the central nervous system, statins have been associated with reduced rates of Alzheimer's disease and other dementias, an effect not seen with non-statin lipid lowering therapies [60, 61]. One study found that persons receiving long-term statin therapy had lower depression and anxiety levels compared with statin-naïve persons [62]. However, the mechanisms underlying potential psychotropic effects of statins remain unknown. It is not known if policosanol shares these beneficial pleiotropic effects and additional studies are needed to characterize its pharmacodynamic spectrum.

Despite the widespread use of statins, it is unclear if they are associated with an increased or decreased risk of cancer. A recent meta-analysis of

23 statin treatment arms that encompassed 309,506 person-years of follow-up found an inverse relationship between achieved LDL-cholesterol levels and incidence of cancer [63]. However, other studies have either failed to find an association between statin use and cancer [64], or have concluded that statins reduce cancer risk [65]. While animal studies suggest no increased cancer risk with short-term suprapharmacological doses of policosanol, studies of long-term use in humans are needed.

CONCLUSIONS

There are conflicting findings on the efficacy of policosanol to normalize dyslipidemic profiles. The majority of studies that support policosanol's lipid-lowering properties have been conducted by the same team of Cuban researchers. Given the possibly unique properties of Cuban sugar cane or differences in sample/population characteristics, these findings must be viewed cautiously. Several recent studies conducted outside the Caribbean have failed to replicate the Cuban findings. However, direct comparisons of clinical trial findings have been limited by differences in regional dietary patterns and unknown variability in the composition of the policosanol products that were tested.

There is little disagreement that policosanol is safe, even when administered in amounts that exceed recommended doses. To date, there have been no published reports of serious toxic effects related to policosanol. This is significant because Americans' use of policosanol likely increased following the 2005 release of One-A-Day Cholesterol Plus®, a multivitamin that contains 10mg of policosanol.

It remains unclear whether policosanol is an effective alternative to conventional lipid lowering therapies. Additional studies are needed to further describe its efficacy, especially when directly compared with statins, and to further characterize its mechanism of action and potential pleiotropic effects. Moreover, clinical trials in elderly populations are needed to determine the safety and efficacy of policosanol within the context of polypharmacy and age-related reductions in drug biotransformation and elimination.

REFERENCES

1. Gouni-Berthold, I. & Berthold, H. K. (2002). Policosanol: Clinical pharmacology and therapeutic significance of a new lipid-lowering agent. *Am Heart J* **143**, 356–365.
2. Natural Medicines Comprehensive Database, online version (2007).
3. Uribarri, E., Laguna, A., Sierra, R. & Ricardo, Y. (2002). Physico-mechanical characterization of policosanol, a novel hypocholesterolemic drug. *Drug Dev Ind Pharm* **28**, 89–93.
4. Mas, R., Castano, G., Illnait, J., Fernandez, L., Fernandez, J., Aleman, C., Pontigas, V. & Lescay, M. (1999). Effects of policosanol in patients with type II hypercholesterolemia and additional coronary risk factors. *Clin Pharmacol Ther* **65**, 439–447.

5. Castano, G., Mas, R., Arruzazabala, M. L., Noa, M., Illnait, J., Fernandez, J. C., Molina, V. & Menendez, A. (1999). Effects of policosanol and pravastatin on lipid profile, platelet aggregation, and endothelium in older hypercholesterolemic patients. *Int J Clin Pharmacol Res* **19**, 105–116.
6. Castano, G., Mas, R., Fernandez, J. C., Lopez, L. E. & Fernandez, L. (1999). A long-term, open-label study of the efficacy and tolerability of policosanol in patients with high global coronary risk. *Curr Ther Res* **60**, 379–391.
7. Castano, G., Mas, R., Fernandez, J. C., Fernandez, L., Illnait, J. & Lopez, E. (2002). Effects of policosanol on older patients with hypertension and type II hypercholesterolemia. *Drugs R D* **3**, 159–172.
8. Illnait, J., Castano, G., Mas, R. & Fernandez, J. C. (1997). A comparative study on the efficacy and tolerability of policosanol and simvastatin for treating type II hypercholesterolemia [Abstract]. *Can J Cardiol* **13**(Suppl B), 342B.
9. Pons, P., Illnait, J., Mas, R., Rodriguez, M., Aleman, C., Fernandez, J. C., Fernandez, L. & Martin, M. (1997). A comparative study of policosanol versus probucol in patients with hypercholesterolemia. *Curr Ther Res* **58**, 26–35.
10. Menendez, R., Fernandez, S. I., Del Rio, A., Gonzalez, R. M., Fraga, V., Amor, A. M. & Mas, R. M. (1994). Policosanol inhibits cholesterol biosynthesis and enhances low density lipoprotein processing in cultured human fibroblasts. *Biol Res* **27**, 199–203.
11. Menendez, R., Amor, A. M., Rodeiro, I., Gonzalez, R. M., Gonzalez, P. C., Alfonso, J. L. & Mas, R. (2001). Policosanol modulates HMG-CoA reductase activity in cultured fibroblasts. *Arch Med Res* **32**, 8–12.
12. Singh, D. K., Li, L. & Porter, T. D. (2006). Policosanol inhibits cholesterol synthesis in hepatoma cells by activation of AMP-kinase. *J Pharmacol Exp Ther* **318**, 1020–1026.
13. Kabir, Y. & Kimura, S. (1993). Biodistribution and metabolism of orally administered octacosanol in rats. *Ann Nutr Metab* **37**, 33–38.
14. Ng, C., Leung, K. Y., Huang, Y. & Chen, Z. Y. (2005). Policosanol has no antioxidant activity in human low-density lipoprotein but increases excretion of bile acids in hamsters. *J Agric Food Chem* **53**, 6289–6298.
15. Menendez, R., Mas, R., Amor, A. M., Gonzalez, R. M., Fernandez, J. C., Rodeiro, I., Zayas, M. & Jimenez, S. (2000). Effects of policosanol treatment on the susceptibility of low density lipoprotein (LDL) isolated from healthy volunteers to oxidative modification in vitro. *Br J Clin Pharmacol* **50**, 255–262.
16. Noa, M., Mas, R. & Mesa, R. (1998). Effect of policosanol on intimal thickening in rabbit cuffed carotid artery. *Int J Cardiol* **67**, 124–132.
17. Noa, M., de la Rosa, M. C. & Mas, R. (1996). Effect of policosanol on foam-cell formation in carrageenan-induced granulomas in rats. *J Pharm Pharmacol* **48**, 306–309.
18. Kabir, Y. & Kimura, S. (1993). Biodistribution and metabolism of orally administered octacosanol in rats. *Ann Nutr Metab* **37**, 33–38.
19. Menendez, R., Maarrero, D., Mas, R., Fernandez, I., Gonzalez, L. & Gonzalez, R. M. (2005). *In vitro* and *in vivo* study of octacosanol metabolism. *Arch Med Res* **36**, 113–119.
20. Janikula, M. (2002). Policosanol: A new treatment for cardiovascular disease. *Altern Med Rev* **7**, 203–217.

21. Alcocer, L., Fernandez, L., Campos, E. & Mas, R. (1999). A comparative study of policosanol versus acipimox in patients with type II hypercholesterolemia. *Int J Tissue React* **21**, 85–92.
22. Fernandez, L., Mas, R., Illnait, J. & Fernandez, J. C. (1998). Policosanol: Results of a postmarketing surveillance study of 27,879 patients. *Curr Ther Res Clin Exp* **59**, 717–722.
23. Aleman, C., Puig, M. N., Elias, E. C., Ortega, C. H., Guerra, I. R., Ferreiro, R. M. & Brinis, F. (1995). Carcinogenicity of policosanol in mice: An 18-month study. *Food Chem Toxicol* **33**, 573–578.
24. Aleman, C. L., Mas, R., Hernandez, C., Rodeiro, I., Cerejido, E., Noa, M., Capote, A., Menendez, R., Amor, A., Fraga, V., Capote, A. & Jimenez, S. (1994). A 12-month study of policosanol oral toxicity in Sprague-Dawley rats. *Toxicol Lett* **70**, 77–87.
25. Mesa, A. R., Mas, R., Noa, M., Hernandez, C., Rodeiro, I., Gamez, R., Garcia, M., Capote, A. & Aleman, C. L. (1994). Toxicity of Policosanol in beagle dogs: One-year study. *Toxicol Lett* **73**, 81–90.
26. Aleman, C. L., Mas Ferreiro, R., Noa Puig, M., Rodeiro Guerra, I., Hernandez Ortega, C. & Capote, A. (1994). Carcinogenicity of policosanol in Sprague Dawley rats: A 24 month study. *Teratog Carcinog Mutagen* **14**, 239–249.
27. Valdes, S., Arruzazabala, M. L., Fernandez, L., Mas, R., Carbajal, D., Aleman, C. & Molina, V. (1996). Effect of policosanol on platelet aggregation in healthy volunteers. *Int J Clin Pharmacol Res* **16**, 67–72.
28. Rodriguez, M. D. & Garcia, H. (1998). Evaluation of peri- and post-natal toxicity of policosanol in rats. *Teratog Carcinog Mutagen*, **18**, 1–7.
29. Batista, J., Stusser, R., Saez, F. & Perez, B. (1996). Effect of policosanol on hyperlipidemia and coronary heart disease in middle-aged patients. A 14-month pilot study. *Int J Clin Pharmacol Ther* **34**, 134–137.
30. Brunton, L. L., Lazo, J. S. & Parker, K. L. (2006). *Goodman & Gilman's the Pharmacological Basis of Therapeutics*, 11th ed., McGraw-Hill, New York.
31. Katzung, B. G. (2004). *Basic and Clinical Pharmacology*, 9th ed., McGraw-Hill, Stamford, CT.
32. Molina Cuevas, V., Arruzazabala, M. L., Carbajal Quintana, D., Mas Ferreiro, R. & Valdes Garcia, S. (1998). Effect of policosanol on arterial blood pressure in rats. Study of the pharmacological interaction with nifedipine and propranolol. *Arch Med Res* **29**, 21–24.
33. Chen, J. T., Wesley, R., Shamburek, R. D., Pucino, F. & Csako, G. (2005). Meta-analysis of natural therapies for hyperlipidemia: Plant sterols and stanols versus policosanol. *Pharmacotherapy* **25**, 171–183.
34. Lin, Y., Rudrum, M., van der Wielen, R. P. J., Trautwein, E. A., McNeill, G., Sierksma, A. & Meijer, G. W. (2004). Wheat germ policosanol failed to lower plasma cholesterol in subjects with normal to mildly elevated cholesterol concentrations. *Metabolism* **53**, 1309–1314.
35. Castano, G., Fernandez, L., Mas, R., Illnait, J., Gamez, R., Mendoza, S., Mesa, M. & Fernandez, J. (2005). Effects of addition of policosanol to omega-3 fatty acid therapy on the lipid profile of patients with type II hypercholesterolaemia. *Drugs R D* **6**, 207–219.
36. Castano, G., Mas, R., Fernandez, L., Illnait, J., Mendoza, S., Gamez, R., Fernandez, J. & Mesa, M. (2005). A comparison of the effects of D-003 and

- policosanol (5 and 10 mg/day) in patients with type II hypercholesterolemia: A randomized, double-blinded study. *Drugs Exp Clin Res* **31**(Suppl), 31–44.
37. Reiner, Z., Tedeschi-Reiner, E. & Romic, Z. (2005). Effects of rice policosanol on serum lipoproteins, homocysteine, fibrinogen, and C-reactive protein in hypercholesterolemic patients. *Clin Drug Invest* **25**, 701–707.
 38. Wright, C. M., Zielke, J. C. & Whayne, T. F. (2005). Policosanol, an aliphatic alcohol sugarcane derivative: Use in patients intolerant of or inadequately responsive to statin therapy. *Int J Angiology* **13**, 173–175.
 39. Berthold, H. K., Unverdorben, S., Degenhardt, R., Bulitta, M. & Gouni-Berthold, I. (2006). Effect of policosanol on lipid levels among patients with hypercholesterolemia or combined hyperlipidemia: A randomized controlled trial. *JAMA* **295**, 2262–2269.
 40. Castano, G., Arruzazabala, M. L., Fernandez, L., Mas, R., Carbajal, D., Molina, V., Illnait, J., Mendoza, S., Gamez, R., Mesa, M. & Fernandez, J. (2006). Effects of combination treatment with policosanol and omega-3 fatty acids on platelet aggregation: A randomized, double-blind clinical trial. *Curr Ther Res* **67**, 174–192.
 41. Cubeddu, L. X., Cubeddu, R. J., Heimowitz, T., Restrepo, B., Lamas, G. A. & Weinberg, G. B. (2006). Comparative lipid-lowering effects of policosanol and atorvastatin: A randomized, parallel, double-blind, placebo-controlled trial. *Am Heart J* **152**, 982e1–982e5.
 42. Dulin, M. F., Hatcher, L. F., Sasser, H. C. & Barringer, T. A. (2006). Policosanol is ineffective in the treatment of hypercholesterolemia: A randomized controlled trial. *Am J Clin Nutr* **84**, 1543–1548.
 43. Greyling, A., DeWitt, C., Oosthuizen, W. & Jerling, J. C. (2006). Effects of a policosanol supplement on serum lipid concentrations in hypercholesterolaemic and heterozygous familial hypercholesterolaemic subjects. *Br J Nutr* **95**, 968–975.
 44. Kassis, A. M. & Jones, P. J. H. (2006). Lack of cholesterol-lowering efficacy of Cuban sugar cane policosanols in hypercholesterolemic persons. *Am J Clin Nutr* **84**, 1003–1008.
 45. Cicero, A. F. G., Rovati, L. C. & Setnikar, I. (2007). Eulipidemic effects of berberine administered alone or in combination with other natural cholesterol-lowering agents: A single-blind clinical investigation. *Arzneimittel-Forschung* **57**, 26–30.
 46. Murota, K., Kawada, T., Matsui, N., Sakakibara, M., Takahashi, N. & Fushiki, T. (2000). Oleyl alcohol inhibits intestinal long-chain fatty acid absorption in rats. *J Nutr Sci Vitaminol* **2000**, 302–308.
 47. Castano, G., Canetti, M., Moreira, M., Tula, L., Mas, R., Illnait, J., Fernandez, L., Fernandez, J. C. & Diaz, E. (1995). Efficacy and tolerability of policosanol in elderly patients with type II hypercholesterolemia: A 12-month study. *Curr Ther Res* **56**, 819–828.
 48. Ortensi, G., Julio, G., Hector, V. & Pedro, A. T. (1997). A comparative study of policosanol versus simvastatin in elderly patients with hypercholesterolemia. *Curr Ther Res* **58**, 390–401.
 49. Castano, G., Mas, R., Arruzazabala, M. L., Noa, M., Illnait, J., Fernandez, J. C., Molina, V. & Menendez, A. (1999). Effects of policosanol and pravastatin on lipid profile, platelet aggregation and endothelium in older hypercholesterolemic patients. *Int J Clin Pharmacol Res* **19**, 105–116.

50. Castano, G., Mas, R., Fernandez, J. C., Illnait, J., Fernandez, L. & Alvarez, E. (2001). Effects of policosanol in older patients with type II hypercholesterolemia and high coronary risk. *J Gerontol A Biol Sci Med Sci* **56**, M186–M192.
51. Mas, R., Castano, G., Fernandez, L., Illnait, J., Fernandez, J. & Alvarez, E. (2001). Effects of policosanol on lipid profile and cardiac events in older hypercholesterolemic patients with coronary disease. *Clin Drug Invest* **21**, 485–497.
52. Castano, G., Mas, R., Fernandez, J. C., Fernandez, L., Illnait, J. & Lopez, E. (2002). Effects of policosanol on older patients with hypertension and type II hypercholesterolemia. *Drugs R D* **3**, 159–172.
53. Castano, G., Mas, R., Fernandez, L., Illnait, J., Mesa, M., Alvarez, E. & Lezcay, M. (2003). Comparison of the efficacy and tolerability of policosanol with atorvastatin in elderly patients with type II hypercholesterolemia. *Drugs Aging* **20**, 153–163.
54. Castano, G., Mas, R., Gamez, R., Fernandez, J., Illnait, J., Fernandez, L., Mendoza, S., Mesa, M., Gutierrez, J. A. & Lopez, E. (2004). Concomitant use of policosanol and beta-blockers in older patients. *Int J Clin Pharmacol Res* **24**, 65–77.
55. Fernandez, S., Mas, R., Gamez, R., Arquimedes, D., Fernandez, J., Orta, S. D., Illnait, J., Castano, G., Mendoza, S., Valdes, F. & Alvarez, E. (2004). A pharmacological surveillance study of the tolerability of policosanol in the elderly population. *Am J Geriatr Pharmacother* **2**, 219–229.
56. United States House of Representatives Committee on Government Reform (2005). New Medicare drug plans fail to provide meaningful drug discount prices.
57. Bellosta, S., Paoletti, R. & Corsini, A. (2004). Safety of statins: Focus on clinical pharmacokinetics and drug interactions. *Circulation* **109**(Suppl III), III-50–III-57.
58. Weiss, J., Dormann, S. M. G., Martin-Facklam, M., Kerpen, C. J., Ketabi-Kiyanvash, N. & Haefeli, W. E. (2003). Inhibition of P-glycoprotein by newer antidepressants. *J Pharmacol Exp Ther* **305**, 197–204.
59. Davignon, J. (2004). Beneficial cardiovascular pleiotropic effects of statins. *Circulation* **109**(Suppl III), III-39–III-43.
60. Vaughn, C. J. (2003). Prevention of stroke and dementia with statins: Effects beyond lipid lowering. *Am J Cardiol* **91**, 23B–29B.
61. Jick, H., Zornberg, G. L., Jick, S. S., Seshadri, S. & Drachman, D. A. (2000). Statins and the risk of dementia. *Lancet* **356**, 1627–1631.
62. Young-Xu, Y., Chan, K. A., Liao, J. K., Ravid, S. & Blatt, C. M. (2003). Long-term statin use and psychological well-being. *J Am Coll Cardiol* **42**, 690–697.
63. Alsheikh-Ali, A. A., Maddukuri, P. V., Han, H. & Karas, R. H. (2007). Effect of the magnitude of lipid lowering on risk of elevated liver enzymes, rhabdomyolysis, and cancer: Insights from large randomized statin trials. *J Am Coll Cardiol* **50**, 409–418.
64. Dale, K. M., Coleman, C. I., Henyan, N. N., Kluger, J. & White, C. M. (2006). Statins and cancer risk: A meta-analysis. *JAMA* **295**, 74–80.
65. Poynter, J. N., Gruber, S. B., Higgins, P. D., Almog, R., Bonner, J. D., Rennert, H. S., Low, M., Greenson, J. K. & Rennert, G. (2005). Statins and the risk of colorectal cancer. *N Engl J Med* **352**, 2184–2192.