Rev. CENIC Cienc. Biol.; Vol. 56. (publicación continua). 093-118. Año.2025. e-ISSN: 2221-2450.

REVIEW ARTICLE

# POLICOSANOL AND ITS POSSIBLE BENEFITS IN PATIENTS WITH CORONARY DISEASE

# POLICOSANOL Y SUS POSIBLES BENEFICIOS EN PACIENTES CON ENFERMEDAD CORONARIA

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Recibido: 24 de marzo de 2025; Aceptado: 15 de mayo de 2025;

## ABSTRACT

Coronary artery disease is the leading cause of death worldwide. It results from occlusion of the coronary arteries and causes an imbalance between oxygen supply and demand and usually involves the formation of plaques in the lumen of these arteries that impede blood flow. It is caused by a combination of modifiable and non-modifiable factors. Non-modifiable factors include gender, age, family history and genetics, while modifiable risk factors include smoking, obesity, lipid levels and psychosocial variables. Policosanol is a mixture of high molecular weight higher primary aliphatic alcohols purified from sugarcane wax with hypolipidemic effects demonstrated in preclinical and clinical studies, in addition to presenting other beneficial pleiotropic effects on the vascular tree such as its antiplatelet action accompanied by a reduction in plasma levels of thromboxane A2 and an increase in prostacyclin, antioxidant effects, decreased blood pressure values, improvement in the composition and stability of atherosclerotic plaque, antiproliferative effects and reduction of circulating endothelial cells in plasma.Taking into account this background, the objective of this review is to address coronary disease, its main risk factors, the treatment associated with risk factors, as well as to analyze the proposal for the use of policosanol in patients with coronary disease according to its demonstrated effects. It is concluded that although policosanol could constitute an option for the management of these patients, appropriate clinical studies are needed in this type of patients to corroborate the hypothesis presented.

**Keywords:** coronary disease; risk factors; policosanol; lipid-lowering; antiaggregant.

## RESUMEN

La enfermedad coronaria constituye la principal causa de muerte en todo el mundo. Resulta de la oclusión de las arterias coronarias y provoca un desajuste entre la oferta y la demanda de oxígeno y por lo general, implica la formación de placas en la luz de estas arterias que impiden el flujo sanguíneo. Es causada por una combinación de factores modificables y no modificables. Los factores no modificables incluyen el género, la edad, los antecedentes familiares y la genética, mientras que los factores de riesgo modificables incluyen el tabaquismo, la obesidad, los niveles de lípidos y las variables psicosociales. El policosanol es una mezcla de alcoholes alifáticos primarios superiores de alto peso molecular purificada de la cera de caña con efectos hipolipemiantes demostrados tanto en estudios preclínicos como clínicos, además de presentar otros efectos pleiotrópicos beneficiosos sobre el árbol vascular como su acción antiagregante plaquetaria acompañada de reducción de las cifras plasmáticas de tromboxano $A_2$ y aumento de prostaciclina, antioxidante, disminución de los valores de presión arterial, la mejoría de la composición y estabilidad de la placa aterosclerótica, efectos antiproliferativos, y reducción de células endoteliales circulantes en plasma. Teniendo en cuenta estos antecedentes, el objetivo de este esta reseña es abordar la enfermedad coronaria, sus principales factores de riesgo, el tratamiento asociado a los factores de riesgo, así como analizar la propuesta del uso del policosanol en pacientes con enfermedad coronaria de acuerdo a sus efectos demostrados. Se concluye que a pesar de que el policosanol pudiese constitur una opción para el manejo de estos pacientes, se necesitan realizar estudios clínicos apropiados en este tipo de pacientes para corroborar la hipótesis presentada.

**Palabras clave:** enfermedad coronaria; factores de riesgo; policosanol; hipolipemiante; antiagregante.

## INTRODUCTION

Coronary heart disease is a condition in which there is inadequate supply of blood and oxygen to the myocardium and constitutes the leading cause of death worldwide. It results from occlusion of the coronary arteries and causes a mismatch between oxygen supply and demand. It usually involves the formation of plaques in the lumen of the coronary arteries that impede blood flow (Ralapanawa *et al.*, 2021).

Coronary heart disease is a multifactorial phenomenon, etiological factors can be broadly classified into modifiable and non-modifiable factors. Non-modifiable factors include gender, age, family history and genetics, while modifiable risk factors include smoking, obesity, lipid levels and psychosocial variables (Duggan *et al.,* 2022).

The male gender is more predisposed than the female gender. Hypercholesterolemia remains an important modifiable risk factor for coronary heart disease. Increased low-density lipoprotein (LDL) increases the risk of coronary heart disease, and increased high-density lipoprotein (HDL) decreases the incidence of coronary heart disease. Inflammatory markers are also important risk factors for coronary artery disease. Some studies have suggested that high-sensitivity CRP (hsCRP) is the best predictor of coronary artery disease, although its use in a practical setting is controversial (Sarebanhassanabadi *et al.*, 2024).

The hallmark of the pathophysiology of coronary artery disease is the development of atherosclerotic plaque. Plaque is an accumulation of fatty material that narrows the lumen of the vessel and impedes blood flow. The first step in the process is the formation of a "fatty streak," which is formed by subendothelial deposition of lipid-laden macrophages, also called foam cells. When vascular injury occurs, the intimal layer is disrupted and monocytes migrate to the subendothelial space where they become macrophages. These macrophages take up oxidized LDL particles and foam cells are formed. T cells are activated, which release cytokines only to aid in the pathological process. The released growth factors activate smooth muscles, which also take up oxidized LDL particles and collagen and are deposited together with the activated macrophages and increase the foam cell population. This process leads to the formation of subendothelial plaque (Doenst *et al.*, 2022)

Over time, this plaque may increase in size or stabilize if no further damage to the endothelium occurs. If it stabilizes, a fibrous cap will form and the lesion will calcify over time. As time passes, the lesion may become hemodynamically significant enough that not enough blood will reach the myocardial tissue at the time of greatest demand and symptoms of angina will occur. However, symptoms will decrease at rest as oxygen needs decrease. For a lesion to cause angina at rest, it must be at least 90% stenosed. Some plaques may rupture and cause exposure of tissue factor, culminating in thrombosis. This thrombosis could cause subtotal or total occlusion of the lumen and could result in the development of acute coronary syndrome in the form of unstable angina, ST-segment elevation myocardial infarction, or non-ST-segment elevation myocardial infarction, depending on the level of insult (Doenst *et al.*, 2022; Sarebanhassanabadi *et al.*, 2024).

**Classification of coronary artery disease generally includes:**

-Stable ischemic heart disease
-Acute coronary syndrome:
◦ ST-segment elevation MI
◦ Non-ST-segment elevation MI
◦ Unstable angina

A thorough history and physical examination are very important before proceeding with further investigations. Coronary artery disease may present as stable ischemic heart disease or acute coronary syndrome. It may further progress to congestive heart failure if left uncontrolled. Patients should be asked about chest pain, its relationship to physical activity, and radiation of pain to the jaw, neck, left arm, or back. Dyspnea should be assessed at rest as well as with activity. The patient should also be asked about syncope, palpitations, tachypnea, lower extremity edema, orthopnea, and exercise capacity. A family history of ischemic heart disease should be obtained along with dietary, smoking, and lifestyle habits (Sulava & Johnson, 2022).

Physical examination should include inspection, palpation, and auscultation. Patients should be inspected for acute discomfort, jugular venous distention, and peripheral edema. Palpation should include palpation for thrill and fluid gagging. The extent of peripheral edema, if present, should be assessed. Jugular venous distention should be measured. Auscultation should include auscultation of the heart at all four sites and also the lungs, with particular focus on the lower areas (Jing *et al*., 2023).

There are several modalities to assess for coronary artery disease, including electrocardiogram, ultrasound, chest x-ray, stress testing, cardiac catheterization, and blood tests, to name the main ones. These tests are performed depending on the context in which patients present (Jing *et al*., 2023; Sulava & Johnson, 2022).

The electrocardiogram is a very basic but enormously useful test in the evaluation of coronary artery disease. It measures electrical activity in the cardiac conduction system and is measured by 10 leads attached to the skin at standardized locations. It provides information about the physiology and anatomy of the heart. It typically has 12 leads on the paper that is printed out once the test is performed and each lead correlates to the specific location of the heart. The important information to note on an electrocardiogram is the rate, rhythm, and axis of the heart. Information about acute and chronic pathological processes can then be obtained. In acute coronary syndrome, ST-segment changes and T wave changes can be seen. If an acute coronary syndrome has degenerated into arrhythmias, that can also be seen. In chronic settings, the electrocardiogram can show information such as axis deviation, bundle branch blocks, and ventricular hypertrophy. The electrocardiogram is also a cost-effective and readily available testing modality that is not user dependent (Jing *et al*., 2023; Sulava & Johnson, 2022).

Echocardiography is an ultrasound of the heart. It is a useful, noninvasive mode of testing performed in both acute and chronic settings, inpatient and outpatient settings. In acute situations, it could report on wall motion, valvular regurgitation and stenosis, infectious or autoimmune lesions, and chamber size. It is also useful in diagnosing acute lung pathologies such as pulmonary embolism. It also assesses the pericardial cavity. In chronic settings, it can be done to see the same information mentioned above and also a response to therapy. It is also used on an outpatient basis as part of stress testing. In addition to diagnosis, it also has a role

in therapeutics, for example, pericardiocentesis could be performed with echocardiography-guided needle. This test is user-dependent and could be expensive compared to electrocardiogram (Jing *et al.*, 2023).

Stress test is a relatively noninvasive test to evaluate coronary artery disease. It is used in case of suspected angina or angina equivalent and is useful in ruling in or ruling out coronary pathology when interpreted in an appropriate setting. During the test, the heart is artificially exposed to stress and if the patient exhibits certain abnormal echocardiogram changes in the ST segments or exhibits symptoms of angina, the test is cancelled at that time and coronary artery disease is diagnosed. Electrocardiographs are obtained before, during and after the procedure and the patient is continuously monitored for any symptoms. There are mainly two types of stress tests; stress test and pharmacological stress test. In stress tests, the patient has to run on a treadmill until he or she reaches 85% of the maximum heart rate predicted for his or her age. If a patient develops exertional hypotension, hypertension (>200/110 mmHg), ST segment elevations or depression, or ventricular or supraventricular arrhythmias (Jing *et al.*, 2023; Sulava & Johnson, 2022).

Chest radiography is an important component of the initial evaluation of cardiac disease. Standard imaging films include posteroanterior and left lateral decubitus positions. Sometimes, the anteroposterior projection is obtained especially in hospital settings with the patient lying down; however, this interpretation of anteroposterior films is significantly limited. Proper analysis of the posteroanterior and anteroposterior views provides useful and cost-effective information about the heart, lungs, and vasculature. Interpretation should be done step-by-step so as not to miss important information (Jing *et al.*, 2023).

Blood tests help establish the diagnosis and assess therapeutic responses. In acute settings, cardiac enzymes and B-type natriuretic peptides are often performed along with complete blood counts and metabolic panels. Cardiac enzymes such as creatine kinase and troponin provide information about an acute ischemic event. In chronic settings, the lipid panel provides important prognostic information. C-reactive protein (CRP) and erythrocyte sedimentation rate help evaluate conditions such as acute pericarditis. Liver function tests may be performed to evaluate an infiltrative process that can affect the liver and heart simultaneously, such as hemochromatosis. Liver tests are also performed to evaluate increased right heart pressure, especially in chronic settings (Onnis *et al.*, 2024).

Cardiac catheterization is the gold standard and most accurate modality for assessing ischemic coronary disease. However, it is an invasive procedure with associated complications. Not everyone is a candidate for the procedure. This procedure is performed in a cardiac catheterization laboratory, is experience dependent, and is performed under moderate sedation. There is contrast exposure during the procedure that could cause severe allergic reactions and kidney injury (Onnis *et al.*, 2024).

Coronary artery disease could present as stable ischemic heart disease or acute coronary syndrome. The former occurs in a chronic setting, while the latter occurs more in an acute setting. Treatment depends on the particular type of disease (Heidenreich *et al.*, 2022).

Stable ischemic heart disease presents as stable angina. Stable angina typically presents as substernal chest pain or pressure that worsens with exertion or emotional stress and is relieved by rest or nitroglycerin and lasts for two months. It is important to know that classic anginal symptoms may be absent and may present differently with atypical symptoms and dyspnea on exertion in certain demographic groups, including women, older people, and diabetics.

Treatment of stable ischemic heart disease includes pharmacologic and nonpharmacologic interventions. Lifestyle modifications include smoking cessation, regular exercise, weight loss, good control of diabetes and hypertension, and a healthy diet. Pharmacologic interventions include cardioprotective and antianginal medications (Heidenreich *et al.*, 2022).

All patients should receive guideline-directed medical therapy (GDMT), including low-dose aspirin, β-blockers, nitroglycerin as needed, and moderate- to high-intensity statins. If symptoms are not controlled with this, β-blocker therapy should be titrated to heart rates of 55 to 60 and the addition of calcium channel blockers and long-acting nitrates should be considered. Ranolazine could also be added to relieve symptoms of refractory angina. If maximal GDMT fails to relieve angina, cardiac catheterization should be performed to visualize coronary anatomy and a decision regarding percutaneous coronary intervention or coronary artery bypass grafting should be made based on the patient profile (Doenst *et al.*, 2022).

Acute coronary syndrome presents as sudden onset substernal chest pain or pressure that usually radiates to the neck and left arm and may be accompanied by dyspnea, palpitations, dizziness, syncope, cardiac arrest, or new-onset congestive heart failure (Doenst *et al.*, 2022; Heidenreich *et al.*, 2022).

Regular visits to cardiologists and family physicians are key to good long-term management of coronary artery disease. Medication adherence and lifestyle modification are important.9

Coronary artery disease has a wide range of differential diagnoses due to the proximity of the heart to adjacent organs, including the lungs, stomach, great vessels, and musculoskeletal organs. Acute anginal chest pain may mimic acute pericarditis, myocarditis, Prinzmetal's angina, pericardial effusion, acute bronchitis, pneumonia, pleuritis, pleural effusion, aortic dissection, gastroesophageal reflux disease (GERD), peptic ulcer, esophageal motility disorders, and costochondritis. Stable ischemic heart disease could also mimic GERD, peptic ulcer, costochondritis, and pleuritis. Careful history, physical examination, and diagnostic studies should be performed to narrow down the differential diagnosis and arrive at an accurate diagnosis (Doenst *et al.*, 2022; Heidenreich *et al.*, 2022).

Both medical and surgical treatment of ischemic heart disease are associated with their side effects and complications. These undesirable effects could be mitigated by careful selection, physician experience, and patient education. Aspirin treatment is associated with bleeding and idiosyncratic and allergic reactions to the drugs. Statin therapy may cause myalgia, diarrhea, and arthralgia among the side effects (Doenst *et al.*, 2022; Heidenreich *et al.*, 2022).

β-blockers may cause bradycardia and hypotension. Angiotensin-converting enzyme inhibitors (ACE inhibitors) may cause hypotension, dizziness, creatinine elevation, cough, and allergic reactions, including angioedema (Doenst *et al.,* 2022).

The prognosis of the disease depends on multiple factors some of which could be modified while others are not. Age, sex, family history and genetics, ethnicity, dietary and smoking habits of the patient, medication compliance, availability of medical care and financial status, and the number of arteries involved are some of the factors. Comorbid conditions including diabetes mellitus, hypertension, dyslipidemia, and chronic kidney disease also influence the overall outcome (Doenst *et al.*, 2022).

Arrhythmias, acute coronary syndrome, congestive heart failure, mitral regurgitation, ventricular free wall rupture, pericarditis, aneurysm formation, and mural thrombi are the main complications associated with coronary artery disease (Heidenreich *et al.*, 2022).

Coronary heart disease is caused by a combination of modifiable and non-modifiable factors. Primary care providers should focus on modifying modifiable risk factors at every routine visit. Close control of diabetes, hypertension, and lipid levels, as well as quitting smoking, losing weight, and exercising, can make a big difference. Because this is a global public health problem, more awareness needs to be raised in school curricula and through various media outlets (Sarebanhassanabadi *et al.*, 2024; Short *et al.*, 2021).

A significant group of clinical trials have been conducted in recent decades that have completely changed the way we care for patients with coronary heart disease (Short *et al.*, 2021).

## Relevance of risk factors

The concept of "risk factor" has traditionally been distinguished from "risk marker". The risk factor refers to a condition acquired by the subject, potentially modifiable, and the risk marker is a marker inherent to the subject that cannot be modified, such as sex, genetics or age. Most of the information on risk factors has been obtained from the prospective follow-up of different cohorts, among which the Framingham study stands out (Anderson *et al.*, 2021).

In this study, information was provided on 3969 men and 4522 women, with a follow-up that has even extended over several generations. It is perhaps the most famous cohort, but not the only one (Bavarsad *et al.*, 2020).

Coronary artery disease does not appear at a specific time, but rather develops continuously; atheromatous plaque appears long before clinical manifestations and develops progressively. The identification of preclinical stages or those individuals with a high burden of risk factors is crucial for the success of prevention strategies, since it is at these stages where action can be taken on the plaque and thus prevent its progression (Chrysant, 2011). The risk factors identified in classic studies are: high blood pressure, diabetes mellitus, hypercholesterolemia, sedentary lifestyle, obesity and smoking. Exposure to several risk factors in the same patient causes the risk to increase exponentially, not linearly (Doenst *et al.*, 2022).

## Risk assessment scales

The main current scientific societies recommend the evaluation of the patient's total risk, rather than the dichotomous identification of risk factors, which is considered to provide a more adequate view of the reality of the risk continuum (Visseren *et al.*, 2021) The first recommendations recommended the use of the Framingham risk scale. However, its use underestimates the risk in high-risk populations and overestimates it in low-risk populations, so it was not the most appropriate for use (Stewart *et al.*, 2020). Therefore, the SCORE system was developed based on 12 prospective studies from 11 different countries, based on the follow-up of a total of 117,098 men and 88,080 women and which estimates cardiovascular mortality at 10 years. The main characteristics of the SCORE that differentiate it from other risk calculation systems are:

1. It calculates the total risk, rather than the risk of coronary heart disease. This is intended to offer a more interdisciplinary and accurate assessment of the patient's risk.
2. It measures the probability of presenting fatal events. The data available from the registries are much more robust and reliable for fatal events, since the incidence of non-fatal events depends on the definition used, the accessibility of the population to the health system and its coding, among others. In addition, not all countries have population registries of coronary

heart disease, but almost all have specific mortality registries (Bavarsad *et al.*, 2020). The rate of non-fatal events is considered to be about 3 times higher in men and 4 times higher in women. Based on the risk of fatal events at 10 years, patients are classified into different categories based on their total risk, which will have implications for the treatment and intensity of the strategies adopted in each specific individual. In other sections of this same thematic unit, the use and utility of these risk scores will be explained (Wong, 2020).

## Classic risk factors

**Age and sex:** Age is one of the most important variables when calculating total risk. So much so that the paradox may arise that the calculated 10-year risk is low in young patients with a high burden of risk factors. In these patients, the potential benefit of an intervention is high, which is why current guidelines emphasize transmitting the importance of risk factor control to the patient. To do this, they recommend the use of relative risk (RR) tables or the concept of cardiovascular age (i.e., the age at which a person without risk factors would have the patient's risk). For a given age, women have a lower cardiovascular risk and it is considered that, in general, coronary disease is delayed by about 10 years in women. However, after menopause, the incidence of events increases abruptly, being approximately 3 times higher than in premenopausal women of the same age (Baena *et al.*, 2018; Berg *et al.,* 2017).

**High blood pressure:** High blood pressure is the leading risk factor, causing up to 9.4 million deaths in 2010 (Zheng *et al.*, 2022). It is the most prevalent risk factor, affecting up to 30%-40% of the adult population. According to the INTERHEART study, the attributable risk is up to 54% of strokes and 47% of ischemic heart disease. The risk increases progressively and linearly from values as low as systolic blood pressure of 115 mmHg (Deng *et al.*, 2024).

The absence of a physiological nocturnal decrease in blood pressure also presents a higher risk, with the same pressures during the rest of the day. Given these findings, the objectives of blood pressure treatment have been the subject of debate. In some studies, stricter target blood pressure values (120 mmHg versus less than 140 mmHg in the control group) showed a lower overall mortality and rate of major cardiovascular events, although frail and elderly patients were perhaps underrepresented in this study. A reduction of 10-12 mmHg of systolic blood pressure and 5-6 mmHg of diastolic blood pressure could reduce the risk of stroke and heart attack by 38% and 16%, respectively (Lewis *et al.*, 2021).

**Diabetes mellitus:** Patients with diabetes mellitus are at very high risk of cardiovascular events, especially those with long-standing diabetes. In fact, it is equivalent to high risk, the presence of which directly classifies the patient into high-risk categories (Dal Canto *et al.*, 2019; Marx *et al.*, 2023). In diabetes, there are a series of factors that explain the high risk that these patients suffer in the evolution:

1. Hyperglycemia.
2. The alteration of the lipid pattern as a consequence of hyperglycemia.
3. Presence of a greater degree of endothelial dysfunction, which implies greater metabolic and oxidative stress.
4. Global proinflammatory situation.
5. Direct alteration to the coagulation cascade.

Patients with type 1 diabetes mellitus are also at risk of presenting a higher rate of coronary artery disease, with a RR of events that ranges between 2 and 3 times that of the control group (Colom *et al.*, 2021). In patients with poor control, this increase in RR can reach more than 10

times the baseline risk according to some reports (Lacey *et al.*, 2018; Ruiz *et al.*, 2022). Diabetes is also associated with greater complications after having suffered an ischemic event such as coronary syndrome, with a higher incidence of heart failure, post-infarction angina, multivessel disease and recurrences of the disease. It is globally recognized that strict glycemic control reduces microvascular complications to a greater extent, and macrovascular complications to a lesser extent.

**Dyslipidemia:** Elevated plasma cholesterol levels, especially LDL cholesterol (LDL-C), cause atherosclerosis through known pathophysiological mechanisms. The relationship between LDL-C and coronary heart disease is continuous, with no clear threshold beyond which mortality increases. Furthermore, cholesterol reduction has been shown to achieve a decrease in the incidence and mortality from coronary heart disease in secondary prevention, with some studies even demonstrating reversibility of atheromatous plaque in individuals with excellent control. According to some studies, the attributable risk of LDL in acute myocardial infarction is up to 49% (Doenst *et al.*, 2022).

Both elevated LDL-C and low HDL-C levels act as risk factors; however, from the point of view of intervention, it is the reduction of LDL-C levels that has been shown to significantly reduce the number of events. By reducing LDL-C levels, risk is unequivocally reduced: each mmol/L reduction in LDL-C corresponds to a 25% reduction in cardiovascular mortality and morbidity in patients with intermediate risk (Doenst *et al.*, 2022).

**Calculated lipoprotein values:** In many laboratories, LDL-C levels are not measured directly, but are calculated using the Friedewald formula: (LDL-C = total cholesterol – HDL cholesterol – (0.2 x triglycerides); in mg/dl). In addition, other variables that are easy to obtain and interpret, such as non-HDL cholesterol, have recently gained importance. This is calculated by simply subtracting HDL-C from total cholesterol. It is a very good risk predictor, and the calculation is not affected by the presence of extreme triglyceride levels, as is the case with the Friedewald formula. It has several advantages: it does not require fasting, it is easy to calculate, and it may have value as a therapeutic target. On the negative side, it has not been evaluated as an objective in any of the large clinical trials for LDL-C reduction. However, it has been suggested that non-HDL cholesterol predicts risk even better than calculated LDL-C levels (Hu *et al.*, 2022).

A particular situation occurs in metabolic syndrome, especially prevalent in physically inactive individuals with abdominal obesity, insulin resistance and type 2 diabetes mellitus, which consists of elevated triglycerides, low HDL-C levels and the presence of small, dense lipoproteins with a high proatherogenic potential. In addition to HDL-C and LDL, there are other measurable molecules that provide information on the patient's lipid metabolism and indicate future risk:

1. Apolipoprotein B: This is the main atherogenic apolipoprotein present in LDL-C particles. Its levels can be measured and it appears to present a risk similar to that of LDL-C (Deng *et al.*, 2024).
2. Hypertriglyceridemia: This is an independent coronary risk factor. The intensity of its association, however, is weaker than with LDL-C levels. A triglyceride level greater than 1.7 mmol/l (150 mg/dl) is considered an established coronary risk factor.
3. HDL cholesterol: Low HDL-C, below 1 mmol/l (40 mg/dl) in men and 1.2 mmol/l (45 mg/dl) in women, is independently associated with increased risk (Xu *et al.*, 2024).

4. Lipoprotein a: It is a low-density lipoprotein that behaves as a risk factor, with a causal role in the process of atherosclerosis according to Mendelian randomization studies. It has not yet been established as a therapeutic target, and may be useful as a risk marker in young subjects with moderate risk (Vinci *et al.*, 2023).
5. Apo-B/apo-A1 ratio: Apolipoprotein A1 is the apoprotein of high-density lipoproteins. Therefore, the apo-B/apo-A1 ratio is one of the strongest risk markers (Kaneva *et al.*, 2015). However, current guidelines do not recommend its use, given its cost and the little differential information it provides with respect to the use of a conventional lipid profile.

**Obesity:** Both overweight and obesity are associated with an increased risk of cardiovascular morbidity and mortality, and a J-curve has been suggested, since the point of lowest risk has been observed in subjects with a body mass index between 20-25 kg/m$^2$. Despite the better control of risk factors that some developed societies have shown in recent years, the prevalence of obesity has increased significantly and worryingly in recent times, which may eclipse, in the near future, the gains in the field of public health achieved in other areas.

The most widely used obesity indicators, both for their reproducibility and for the evidence based on them, are the body mass index (BMI) and the waist-hip ratio. The presence of intra-abdominal fat is a more powerful risk marker than the presence of subcutaneous fat, and the gynoid obesity pattern is more benign than the android. Waist circumference limits are equal to or greater than 102 cm in men and equal to or greater than 88 cm in women. The concept of the "metabolically healthy obese" should be abandoned, since in overweight subjects without the presence of other risk factors, an increase in mortality from all causes has also been demonstrated, although to a lesser degree, compared to metabolically healthy individuals (Kim *et al.*, 2021).

**The obesity paradox:** Despite the undeniable evidence that a higher BMI is a risk factor and increases cardiovascular morbidity and mortality, in patients with established coronary disease the evidence is contradictory. The same occurs with patients with heart failure. A greater metabolic reserve probably confers a certain protection in stress situations (such as, for example, in a decompensation of heart failure) (Limpijankit *et al.*, 2022). However, physical exercise has been shown to have multiple benefits in this population subgroup, so physical exercise and not weight loss should be the primary objective of these patients.

**Vitamin D deficiency:** Deficiencies of vitamins A, E and D have been associated with a higher risk, and an increase in mortality has also been demonstrated in those lower tertiles of vitamin D levels (RR 1.35) (Gaksch *et al.,* 2017). However, some intervention studies have not shown clear benefits in the supplementation of these vitamins in the prevention of risk.

**Sedentary lifestyle:** Individuals who exercise only occasionally have a higher risk of acute coronary events and sudden death during or immediately after exercise than those who exercise regularly (Kunutsor & Laukkanen, 2024).

Regular exercise of moderate intensity is a vital component of a healthy lifestyle. Recently, there is some evidence that points to the possible existence of a tipping point (at very high levels of exercise) beyond which physical exercise does not provide benefits and may even result in increased cardiovascular morbidity such as the development of atrial fibrillation, adverse right ventricular remodeling, or even the risk of ischemic heart disease (Kunutsor & Laukkanen, 2024).

However, it should be remembered that any level of physical exercise is associated with a better prognosis than a sedentary lifestyle, and that these results are derived from the evaluation of people subjected to sustained strenuous efforts.

**Tobacco:** Tobacco use is a known risk factor. It not only increases the incidence of other risk factors, but also acts independently as a pro-atherogenic and pro-thrombotic factor, even in those people who are exposed to tobacco in a milder way (Oshunbade *et al.*, 2021). Tobacco affects endothelial function, oxidative processes, platelet function, fibrinolysis, inflammation, lipid oxidation and vasomotor function. Likewise, passive smoking is also a recognized risk factor. Living with a smoker has been documented to increase vascular risk by around 23% (Ghodeshwar *et al.*, 2023).

Cessation of tobacco use is considered beneficial from the moment it is achieved, being one of the most effective preventive measures available: a meta-analysis demonstrated a reduction in subsequent ischemic events and death of 0.57 and 0.74, respectively, in those patients who stopped smoking. At 15 years after quitting smoking, the risk is close to that of the population that has never smoked, although the risk curves never overlap (Ghodeshwar *et al.*, 2023).

**Influenza and coronavirus:** Acute infectious diseases have also been linked to a transient increase in cardiovascular events in the convalescence period. There are multiple studies that suggest an association between seasonal influenza and an increased risk of developing acute myocardial infarction. Recently, SARS-CoV-2 disease has also been associated with secondary myocardial damage and an increased risk of acute myocardial infarction (Guan *et al.*, 2020; Lorente *et al.* 2020).

## Preclinical vascular damage gauges

There are a number of situations that allow the identification of established coronary disease in a preclinical phase. Among the main preclinical vascular damage gauges are: the coronary calcium score, the detection of atheromatous plaques by carotid ultrasound and quantification of carotid intima-media thickness (IMT) and the ankle-brachial index (ABI).

**Coronary calcium score:** Coronary calcification represents a late phase of atherosclerotic coronary disease. The most widely used score in both studies and clinical practice is the Agatston score. A calcium score of more than 300 or greater than the 75th percentile of normal is considered to confer a high risk, and an Agatston score of 0 practically rules out the presence of significant atherosclerotic coronary disease (Haberl *et al.*, 2021).

The radiation dose administered is very limited (1 mSv); which is equivalent to about 10 chest X-rays. European guidelines consider the possibility of risk adjustment by quantifying coronary calcium in patients with intermediate risk between 5%-10% (Greenland *et al.*, 2018; Van Rosendael *et al.*, 2024).

**Carotid ultrasound:** The presence of significant atherosclerosis in any vascular territory is one of the most important predictors suggesting the presence of disease in other territories. Carotid ultrasound can detect the presence of coronary disease by:

1. The intima-media thickness ratio is a measure of early atherosclerosis, and a value greater than 0.9 mm is considered abnormal. Its measurement is not free of controversy and, given its high variability and poor reproducibility, it is not systematically recommended (Amato *et al.*, 2017).
2. The presence of plaques, which is an indicator of high risk and established coronary disease.

3. Arterial stiffness. Stiffness measured by pulsed Doppler at the aortic level, defined as a velocity greater than 12 m/s, has also been suggested as a risk reclassifier in people at moderate risk (Li *et al.*, 2010).
Ankle-brachial index: The ABI is a reproducible and easy-to-determine measure. An ABI less than 0.9 has a sensitivity of 70% and a specificity of 90% for presenting peripheral arterial disease (Fowkes *et al.*, 2018).

## Treatment of associated risk factors

To reduce risk, it is necessary to apply a comprehensive treatment plan that includes lifestyle modifications (He *et al.*, 2014), and treatments for associated risk factors.
However, prevention remains the most powerful weapon available to today's societies to reduce the morbidity and mortality caused by coronary disease. To do so, it is vitally important to determine the total individual risk, based on the presence of known risk factors. In addition, it is important to develop prevention strategies with interventions at both the population and individual level that contain the high prevalence of risk factors. The first requires the support of society and legislative measures and government impulses. The second is what directly affects health systems, and risk detection and prevention strategies must be implemented systematically, from the base of the system and Primary Care (Arnett *et al.*, 2019; Howard *et al.*, 2018; Mancia *et al.*, 2021).

## Policosanol

Considering the above, the proposal to use policosanol in patients with coronary artery disease is based not only on its proven lipid-lowering effects, but also on its beneficial pleiotropic effects, such as its antiplatelet action accompanied by a reduction in plasma levels of tromboxane $A_2$ and an increase in prostacyclin, its antioxidants, its decrease on blood pressure values, the improvement in the composition and stability of atherosclerotic plaque, its antiproliferative effects, and a reduction in circulating endothelial cells in plasma. It is logical to expect that policosanol will produce benefits in patients with coronary artery disease.
Below, we will address the main experimental and clinical evidence of policosanol, which supports its demonstrated beneficial effects both in the short and long term in a significant number of studies conducted both in Cuba and abroad in different types of patients, in which its excellent safety and tolerability profile was also demonstrated.

## Policosanol, experimental evidence

Policosanol, a mixture of 8 high molecular weight primary aliphatic alcohols purified from sugarcane wax (Mas, 2000), inhibits cholesterol synthesis (Menéndez *et al.*, 1994; Menendez *et al.*, 1996; Menendez *et al.*, 2001) by regulating the activity of hidroxy methyl glutaryl coenzyme A (HMGCoA) reductase, a key enzyme in cholesterol synthesis (Singh *et al.,* 2006), through activation of AMP kinase (Banerjee *et al.*, 2010; Oliaro *et al.*, 2009) due to an increase in the production of phosphorylated CaMKK, an effect that requires the metabolism of alcohols into their corresponding acids through peroxisomal β-oxidation (Menendez *et al.*, 2005), a fact consistent with our results on octacosanol metabolism (Menendez *et al.*, 1997). Furthermore, policosanol increases the number of receptors and the catabolic rate of LDL (Menéndez *et al.*, 1996), which contributes to its ability to reduce LDL-C levels. The lipid-

lowering effects of policosanol persist during long-term therapy (Mesa *et al.*, 1994; Ng *et al.*, 2005; Rodríguez *et al.*, 1994; Setnikar *et al.,* 2005).

Policosanol has pleiotropic effects: a) antiplatelet action accompanied by a reduction in plasma levels of thromboxane $A_2$ and an increase in prostacyclin (Arruzazabal *et al.*, 1992a; Arruzazabal *et al.*, 1992b; Arruzazabala *et al.*, 1993) b) antioxidant effects in vivo (Menendez *et al.*, 1999; Ohta *et al.*, 2008) c) improvement in the composition and stability of atherosclerotic plaque (Noa *et al.*, 2005), d) antiproliferative (Noa *et al.*, 1999; Noa *et a*l., 2001) and e) reduction of circulating endothelial cells in plasma (Noa *et al.*, 1997).

Policosanol has prevented the development of induced and spontaneous atherosclerotic lesions in rodents, rabbits, and monkeys (Arruzazabala *et al.*, 2000; Noa *et al.*, 1995; Noa *et al.*, 1996), as well as the symptomatology and mortality in induced cerebral ischemia in Mongolian gerbils (Arruzazabala *et al.*, 1993; Carbajal *et al.*, 1994).

On the other hand, hexacosanol, one of the three most abundant alcohols of policosanol, shows important neuroprotective effects, since it promotes the survival of cholinergic neurons of the septum after experimental axotomy and prevents the degeneration and death of hippocampal neurons induced by intracerebroventricular infusion of kainic acid in rats Borg *et al.*, 1987; Borg *et al.*, 1991).

In addition, another study supports the protective effects of octacosanol on 6-hydroxydopamine-induced parkinsonism in rats by preventing the reduction in the levels of pro-neuronal growth factor (pro NGF) and its receptors Taka and p-Akt that mediate the survival of striatal cells. Policosanol blocks the expression of the complex (proNGF-p75NTR-sortilin) and preserves the free radical scavenging capacity of the striatum (Wang *et al.*, 2010). These data support that, in addition to its beneficial effects on vascular function, policosanol has neuroprotective effects mediated by other mechanisms that contribute to post-stroke neurological recovery.

## Policosanol, clinical evidence

**Lipid-lowering effects** Short-term randomized, double-blind, placebo-controlled, comparative, and open-label clinical trials have demonstrated the lipid-lowering effects of policosanol in normocholesterolemic subjects, patients with type II hypercholesterolemia, postmenopausal women, with multiple risk factors, the elderly, in patients with hypercholesterolemia and liver dysfunction, and in type 2 diabetics (Alcocer *et al.*, 1999; Aneiros *et al.*, 1993; Aneiros *et al.,* 1995; Benitez *et al.,* 1997; Campilongo *et al.,* 1996; Castaño *et al.*, 1999; Castaño *et al.*, 2000a; Castaño *et al.*,2000b; Castaño *et al*, 2001; Castaño *et al.*, 2002a; Castaño *et al.*, 2002b; Castaño *et al.*, 2003a; Castaño *et al.*, 2003b; Crespo *et al.*, 1997; Crespo *et al.*, 1999; Chen *et al.*, 2005; Fernandez *et al.*, 2001; Figuera *et al.*, 2001; Mas *et al.*, 1999; Menendez *et al.,* 2000a; Menendez *et al.*, 2000b; Mirkin *et al.,* 2001; Musto *et al.*, 2010; Nikitin *et al.*, 2000, Ortensi *et al.*, 1997; Pella *et al.*, 2002; Pons *et al.*, 1994;; Prat *et al.*, 1999; Soltero *et al.*, 1993; Torres *et al.*, 1995; Wang *et al.*, 2008; Wright *et al.*, 2004; Zardoya *et al.*, 1996).

Long-term studies have demonstrated the persistence of these effects (Canetti *et al.*, 1995; Canetti *et al.*, 1997; Castaño *et al.*, 1995; Castaño *et al.*, 2002; Castaño *et al.*, 2004; Mas *et al.*, 2001; Pons *et al.*, 1994) and short-term studies have investigated the effects of policosanol + statins, fibrates, or Omega-3 fatty acids (Castaño *et al.*, 1998; Castaño *et al.,* 2005; Marcello *et al.*, 2000).

Policosanol (5-20 mg/d) reduces serum LDL-C and total cholesterol in a dose-dependent manner, with the maximum effect being reached at 20 mg/d. Short-term LDL-C reductions have ranged from 13.4% to 17.7% (5 mg/d), 20.2% to 23.2% (10 mg/d), and 26.1% to 37.8% (20 mg/d). Doses of 5, 10, and 20 mg/day have achieved HDL-C increases of 9%, 28.9%, and 36.4%, respectively, while their effects on triglycerides are modest. The effects are apparent after 8-12 weeks of therapy, and withdrawal does not cause a rebound effect (Aneiros *et al.*, 1993; Aneiros *et al.,* 1995; Campilongo *et al.,* 1996; Castaño *et al.*, 1999; Castaño *et al.*, 2000; Castaño *et al.*, 2001; Castaño *et al.*, 2003; Pons *et al.*, 1994; Zardoya *et al.*, 1996).

Short-term comparative studies have shown comparable reductions in LDL-C with policosanol 10 mg/d, lovastatin 20 mg/d, simvastatin 10 mg/d, pravastatin 10 mg/d, fluvastatin 20 mg/d, and lower than those with atorvastatin 10 mg/d. The effects on HDL-C have generally been superior to those of statins. (Benitez *et al.*, 1997; Castaño *et al.*, 1998; Castaño *et al.*, 2002; Fernández *et al.*, 2001)

On the other hand, policosanol (10 mg/d) produced greater reductions in LDL-C and total cholesterol, and increases in HDL-C than bezafibrate and gemfibrozil, although these were more effective in reducing triglycerides (Soltero *et al.*, 1993).

The hypolipidemic efficacy of policosanol is not only maintained, but is accentuated in the long term. Thus, while doses of 5 mg/d for 1 year reduced LDL-C levels by 23.7%, 10 mg/d produced greater reductions (24.8%-27.5%) (Castaño *et al.*, 1995).

A meta-analysis of policosanol studies (4596 patients) found that the mean LDL-C reduction (23.7%) with policosanol (5-40 mg/d, 1528 patients) (29 studies) was greater than that achieved with placebo (0.11%) (1406 patients) and with phytosterols and stanols (11%) (2-9 g/d) (23 studies) (893 cases) ($p<0.0001$), concluding that policosanol produced greater LDL-C reductions and better lipid profile changes (Chen *et al.*, 2005).

**Antiaggregant effects:** Studies in healthy volunteers, patients with type II hypercholesterolemia, and type 2 diabetes have demonstrated the antiaggregant effects of policosanol administered at effective doses as a lipid-lowering agent (10 and 20 mg/d) (Arruzazabala *et al.*, 1996; Arruzazabala *et al.*, 2002; Arruzazabala *et al.*, 1997; Arruzazabala *et al.*, 1998; Castaño *et al.*, 2006; Carbajal *et al.*, 1998; Scazziota *et al.*, 1996; Valdes *et al.*, 1996). Single doses (10-50 mg/d) significantly and modestly inhibited (<20%) platelet aggregation to epinephrine and adenosin difosfato (ADP), whereas 20 mg/d administered for the half-life of platelets (7 days) produced greater reductions in aggregation by epinephrine (22.5%) and ADP (21%), and modestly inhibited aggregation by collagen (11.6%) in healthy volunteers. A lower dose (10 mg/d) given for a longer period (14 days) inhibited aggregation to arachidonic acid (AA) (25.6%-25.8%), and produced modest reductions in aggregation to epinephrine (17.8%) and collagen (10.1%-16%). Increasing doses (10, 20, and 40 mg/d) in successive 7-day periods reduced aggregation to epinephrine and ADP by 34.7% and 27.8%, respectively, and modestly reduced aggregation to collagen (13.6%), whereas 20 and 40 mg/d for 30 days produced similar reductions in aggregation to AA (28.2% and 24.9%, respectively), collagen (21.1% and 20.2%), and ADP (30.9% and 29.1%), such that 20 mg/d produced the maximal antiplatelet effect (Arruzazabala *et al.*, 2002).

Policosanol (20 mg/d) for 7 days was more effective in inhibiting aggregation to epinephrine (32.6%) and ADP (37.3%) than aspirin (100 mg/d), whereas aspirin inhibited collagen aggregation more (61.4%), inhibited epinephrine aggregation (21.9%), and did not affect ADP-induced aggregation. Combination therapy showed advantages, as it markedly inhibited

aggregation to collagen (71.3%), epinephrine (57.5%), and ADP (31.0%). Studies in patients with Type II hypercholesterolemia and type 2 diabetes showed consistent results. Treatment with policosanol + Omega 3 fatty acids revealed a greater antiplatelet effect than Omega 3 + placebo (Castaño *et al.*, 2006). The antiplatelet effects of policosanol are accompanied by a reduction in serum thromboxane $A_2$ levels and a tendency towards an increase in prostacyclin levels.

**Antioxidant effects:** Some studies have shown the effect of policosanol on LDL oxidation. Doses of 5 and 10 mg/d administered for 8 weeks increased the latency (lag phase) (13.0% and 57%, respectively) and reduced the maximum rate of oxidation (Vmax) (11.4% and 37.7%) of LDL, and the generation of malondialdehyde (MDA) in macrophages (12.4% and 32.2%) (Menendez *et al.*, 2000). Doses of 5 mg/d administered for 12 weeks increased the lag phase (14.1%) without modifying Vmax (Arruzazabala *et al.*, 2000), and 10 mg/day for 8 weeks increased the lag phase (36.5%) and reduced Vmax (15.5%) of LDL oxidation, variables not modified by fluvastatin 20 mg/d in patients with hypercholesterolemia II. Policosanol (10 mg/d) and lovastatin (20 mg/d) administered for 8 weeks reduced Vmax (41.9% and 41.6%) of LDL oxidation in diabetics, but only policosanol increased the lag phase (20.9%) and total plasma antioxidant capacity (24.2%) (Castaño *et al.*, 2002).

## OTHER EFFECTS

**Effects in patients with peripheral arterial disease.** Policosanol (10 and 20 mg/d for 10-24 weeks) increased initial (DIC) and absolute (DAC) claudication distance in patients with intermittent claudication. The effects were marked (≥ 50%) with 20 mg/d, modest-moderate (>10%, <50%) with 10 mg/d, and persistent after long-term therapy. Furthermore, policosanol significantly improved lower limb symptoms (pain, coldness, paresthesia) and ankle/brachial systolic blood pressure index (ABI), a leading marker of peripheral atherosclerosis (Castaño *et al.*, 1999; Castaño *et al.*, 2001; Castaño *et al.*, 2003a; Castaño *et al.*, 2003b; Illnait *et al.*, 2008). Policosanol 10 mg/d and lovastatin 20 mg/d administered for 20 weeks reduced LDL-C in claudicant patients, but only policosanol improved DIC, DAC, ABI, and quality of life domains (health perception, impact on daily activities), suggesting that its pleiotropic effects, not LDL-C lowering, underlie such improvements (Castaño *et al.*, 2003).

Effects in middle-aged subjects. A 5-year cohort study (6611 patients: 3002 controls, 3609 treated) showed a lower frequency of all-cause hospitalizations in the policosanol group than in the control group (Mas *et al.*, 1999).

**Effects in patients with coronary artery disease.** Policosanol (10 mg/d) administered long-term (20 months), in addition to producing hypocholesterolemic effects, produced functional improvement and improvement of ischemic areas in patients with coronary artery disease (Batista *et al.*, 1996), and reduced the frequency of restenosis in obese patients undergoing coronary revascularization (Moreno *et al.*, 2005).

**Effects in populations with multiple risk factors.** Policosanol has reduced the frequency of severe vascular adverse events vs placebo in several studies in these populations.

**Effects in elderly with risk factors.** Doses of 5 and 10 mg/d administered for 24 weeks increased the ability to perform activities of increasing complexity without experiencing fatigue, dyspnea, tachycardia, sweating, and/or chest pain.

A study in 1470 elderly patients showed that policosanol (5-10 mg/d) administered for three years reduced the frequency of severe adverse events, vascular, coronary, cerebrovascular, and total mortality vs placebo (Mas *et al.*, 2002).

**Effects in patients with carotid stenosis and in patients with ischemic stroke.** One study showed that policosanol reduced the progression of carotid lesions vs placebo (Batista *et al.* 1995). On the other hand, two open studies in patients with ischemic stroke showed that policosanol (20 mg/d for 5 years), in addition to reducing total cholesterol, improved post-stroke recovery assessed with the Canadian Scale, none died and only one had recurrent stroke (Ortega *et al.*, 2006; Sanchez *et al.,* 2010). Two randomized, double-blind studies showed that patients with ischemic stroke treated with policosanol (20 mg/d) + aspirin (125 mg/d) for 6 months had better neurological recovery, assessed with the modified Rankin Scale, reduction of platelet aggregation, MDA and LDL-C, than with placebo + aspirin (125 mg/d) (Sanchez *et al.*, 2012; Sanchez *et al.*, 2013), while a comparative study with atorvastatin for three months of treatment showed similar efficacy in terms of neurological recovery of the included patients (Sanchez *et al.*, 2016).

Finally, two long-term studies (12 months) confirmed the effects of policosanol treatment on post-stroke neurological recovery and the benefits on the lipid profile of these patients (Gonzalez *et al.*, 2018; Sanchez *et al.*, 2017).

**Effects on blood pressure values.** Clinical studies conducted in the short, medium and long term in patients with type II hypercholesterolemia, postmenopausal women, with multiple risk factors, the elderly, in type 2 diabetics and in patients with ischemic stroke, in which as part of the safety analysis when evaluating the effect of policosanol on blood pressure values, it was observed that in patients treated with policosanol at its different approved doses, a significant reduction in systolic and diastolic blood pressure values occurred, when these were compared with baseline values, as well as when compared with the control group (placebo, statins or fibrates) (Batista *et al.*, 1995; Castaño *et al.*, 1999; Castaño *et al.*, 2000; Castaño *et al.*, 2002; Castaño *et al.*, 2004; Fernandez *et al.*, 2001; Mas *et al.*, 2001; Mas *et al.*, 2002; Ortega *et al.*, 2006; Ortensi *et al.*, 1997; Sanchez *et al.*, 2010; Sanchez *et al.*, 2012; Sanchez *et al.*, 2013; Sanchez *et al.*, 2017).

On the other hand, other clinical studies conducted have shown that treatment with policosanol reduces systolic and diastolic blood pressure values, when this is determined by different methods and at different treatment periods, both in subjects pre-hypertensive as well as hypertensive patients (Cho *et al.*, 2018; Kim *et al.*, 2017; Kim *et al.*, 2018), while a meta-analysis of several randomized controlled trials showed that treatment with policosanol significantly reduces systolic and diastolic blood pressure values (Askarpour *et al.*, 2019).

## Safety and tolerability

Single dose toxicity of policosanol is practically non-existent. Subchronic and chronic toxicity studies (rats, monkeys, dogs) did not reveal toxicity even at a dose 1724 times higher than the maximum therapeutic dose. Policosanol showed no evidence of genotoxicity (Ames assays, sister chromatid exchange, bone marrow micronuclei, and mouse spermatogenesis), fetal or reproductive toxicity, or long-term carcinogenic effects (Aleman *et al.*, 1994a; Aleman *et al.*, 1994b; Aleman *et al.*, 1995; Fernandez *et al.*, 2006a; Fernandez *et al.*, 2006b; Gamez *et al.*, 2001; Rodriguez *et al.*, 1994; Rodriguez *et al.*, 1997).

These results are consistent with clinical studies that have revealed an excellent short- and long-term safety profile of policosanol, even in vulnerable populations such as the elderly, patients with liver dysfunction, and diabetics. It has not produced any effects on the physical examination or laboratory parameters investigated, attributable to the treatment. Adverse events have not revealed significant differences vs placebo. A 4-year surveillance study in 27,874 patients confirmed the safety of policosanol, with a cumulative adverse event rate of only 0.3% (Fernandez *et al.*, 1998). A postmarketing study in the elderly followed for 3 years confirmed the excellent tolerability of the treatment (Fernandez *et al.*, 2004). The most common adverse events (≥ 0.05%) reported in postmarketing surveillance studies were weight loss (0.25%), polyuria (0.13%), polyphagia (0.08%), headache (0.07%), dizziness (0.06%), arthralgia (0.05%), and insomnia (0.05%). As can be seen, none of these were classified as common (≥ 1%) (Fernandez *et al.*, 1998; Fernandez *et al.*, 2004).

## CONCLUSSION

It is concluded that although policosanol could constitute an option for the management of patients with coronary disease, appropriate clinical studies are needed in this type of patients to corroborate the hypothesis presented.

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*Los autores declaran que no existen conflicto de intereses*