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CURRENT OPINION

Controversial role of plant sterol esters in the management of hypercholesterolaemia

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Introduction

Hypercholesterolaemia is a risk factor of cardiovascular diseases and is therefore a major target for primary and secondary prevention.[1,2] Maintaining a healthy diet and lifestyle reduces cardiovascular risk.[3] 'Functional foods' supplemented with phytosterols are advertised for the management of hypercholesterolaemia and have become a widely used non-prescription approach to lower plasma cholesterol levels. It is estimated that in 2005 worldwide 3 billion US-dollars were spent on various functional foods that have regulator-approved health claims for the management of elevated cholesterol levels.[4]

In September 2000, the *US Food and Drug Administration (FDA)* issued an interim final rule allowing a health claim for reducing the risk of coronary heart disease for foods that contain phytosterols and are low in saturated fat and cholesterol.[5] In fact, this was only the 12th time the FDA has authorized a health claim. The *National Cholesterol Education Program Expert Panel (NCEP ATP III)* recommends since 2001 phytosterol enriched functional foods as part of an optimal dietetic prevention strategy in primary and secondary prevention of cardiovascular diseases.[6] The *American Heart Association (AHA)* has followed and sees phytosterols 'as a therapeutic option . . . for individuals with elevated cholesterol levels'.[3] Since then other well-esteemed societies such as the *Spanish Cardiology Society*,[7] the *Association of Clinical and Public Health Nutritionists in Finland*,[8] and the *National Heart Foundation in Australia*,[9] to name only a few, have identified phytosterols as an important additional dietary option in the management of hypercholesterolaemia. However, recently released guidelines are more critical of food supplementation with phytosterols and draw attention to significant safety issues.[10,11]

Phytosterols and cholesterol absorption

'Phytosterols' are natural constituents of plants and are part of the broad group of isoprenoides. In plant cells, they contribute to the regulation of the fluidity and permeability of cell membranes, are substrates for the synthesis of numerous secondary plant metabolites and act as biogenic precursors of compounds involved in growth.[12] Phytosterols are structurally related to cholesterol. They are non-nutritive compounds whose chemical structure differs from that of cholesterol only by minor modifications. Sitosterol and campesterol are the most frequent plant sterols and constitute about 60% and 35%, respectively, of plant sterols in food. They differ from cholesterol in the structure of their side chain by a methyl or ethyl group at C-24. Plant stanols, on the other hand, are the saturated form of plant sterols, meaning they have no double bond in the sterol ring. Saturation of sitosterol, the most commonly occurring plant sterol, gives rise to sitostanol; saturation of campesterol gives rise to campestanol. See also *Figure 1*. Estimates for intestinal absorption range from 0.4 to 5% for plant sterols and from 0.02 to 0.3% for their saturated counterparts.[13,14] Consequently, plant stanol concentrations in serum are much lower than plant sterol concentrations. Phytosterols are abundant in fat-laden vegetables and vegetable products, such as vegetables oils and olive oil, but also in fruits and nuts. Although cholesterol and phytosterols are structurally similar, they are metabolized differently. In contrast to cholesterol, phytosterols are not synthesized in the body and are solely of dietary origin. The normal Western-type diet contains about 200–500 mg cholesterol, 200–400 mg plant sterols, and about 50 mg of plant stanols. In order to be absorbed, cholesterol and phytosterols are taken up

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in micelles. Sterol-laden micelles interact with the intestinal brush layer, enabling absorption in entrocytes. Phytosterols competitively inhibit intestinal absorption of cholesterol. The exact molecular mechanisms involved are not completely understood; however, it is clear that both cholesterol and phytosterols require the Niemann-Pick C1 Like 1 protein (NCP1L1) to obtain entry in enterocytes. In enterocytes, cholesterol is esterified via the enzyme acetyl-coenzyme A acetyltransferase 2 (ACAT2), packed into chylomycrons, and drained into the lymph system via the basolateral membrane. Non-esterified cholesterol and phytosterols are pumped back into the intestinal lumen via the ATP proteins ABCG5 and ABCG8. These complex mechanisms are responsible for the assimilation of about 50% of cholesterol, but less than 5% of plant sterols and even less than 0.5% of plant stanols. The major part of assimilated phytosterols is directly eliminated via the liver and the biliary system so that, in the end in healthy individuals, less than 1% is retained.[15]

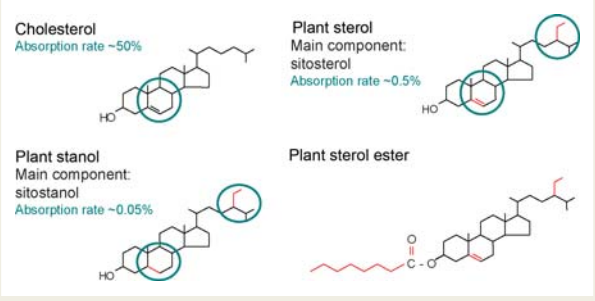

Figure 1 Chemical structure of cholesterol, sitosterol (plant sterol), and sitostanol (plant stanol). Both plant sterols and plant stanols differ from cholesterol only in the side chain attached to the sterol ring. Plant stanols are saturated plant sterols without a double bond in the sterol ring. Due to their saturation status, plant stanols are less effectively absorbed. Esterified plant sterols and plant stanols are supplemented in 'nutraceuticals' to reduce serum cholesterol levels (modified from ref. 14).

Phytosterols in nutraceuticals

The plant sterol sitosterol was first described as a therapeutic agent for hypercholesterolaemia in 1951.[16] In the late 1950s, Eli Lilly Company introduced the first plant sterol product, 'Cytellin', as a cholesterol-lowering pharmaceutical.[17] Due to its low water solubility and the resulting low bioavailability, a daily intake of 18 g of sitosterol was needed to achieve a reduction in serum cholesterol levels. The product was unmarketable as a pharmaceutical agent and production was stopped. A resurgence of interest in phytosterol effects came after it could be demonstrated that phytosterols were active when incorporated into the diet as spreads. In the beginning of the 90s, researchers succeeded by the esterification of phytosterols in developing a process which considerably improved the water solubility of phytosterols.[18] This process made it possible to greatly expand the market for phytosterols as dietary supplements, leading to a rapidly growing world-wide market for functional-foods.[19,20] At present in the EU, in addition to spreads, there are numerous other foods approved for the market to which phytosterols have been added, for example, salad dressing; milk, soy, yoghurt, cheesy products; soy and fruit drinks, even sausages and breads. Above all, combined consumption of these new types of products can lead to a cumulative intake of very high concentrations especially of plant sterols, which can affect the absorption of cartenoids and fat-soluble vitamin.[21] This can, for example, constitute a hazard to children, pregnant and breastfeeding women. A labelling, therefore, advises these individuals to avoid consuming these products. Furthermore, it has been suggested as a precaution that phytosterol intake should not exceed 3 g per day.[22]

Phytosterols and cardiovascular risk

Meta-analyses of more than 40 clinical studies indicate that phytosterols taken as dietary supplements can induce a reduction of LDL-cholesterol up to 15%[23,24] (*Figure 2*). However, ingestion of

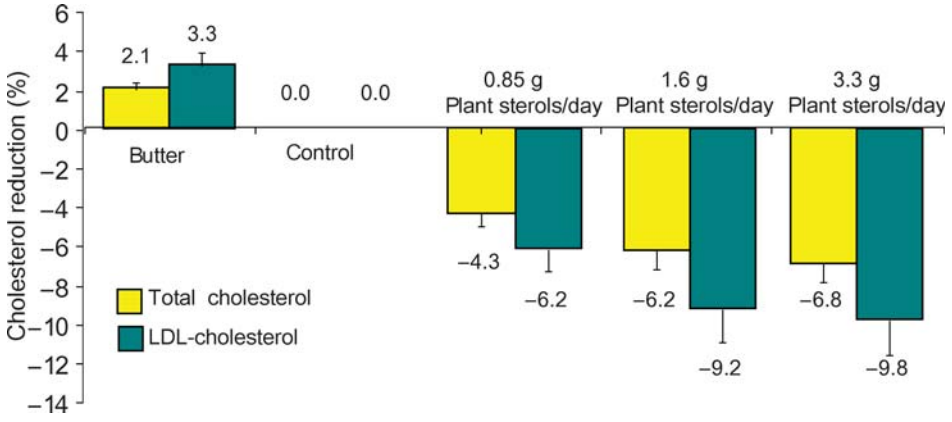

Figure 2 Plant sterols reduce serum cholesterol levels. Total cholesterol and LDL-cholesterol dependent on diet (modified from ref. 23).

more than 3 g/day does not lead to any further lowering of cholesterol levels. Of note, a diet supplementation with plant stanol esters reduces not only serum cholesterol levels, but also serum plant sterol concentrations.[25] The effectiveness of cholesterol-lowering products does not only depend on the amount of dietary phytosterols, but also on genetically determined differences in sterol metabolism. Thus, for example, Apo E-4 (apolipoprotein E-4) homozygote patients on a diet supplementation with phytosterols show a more significant reduction in LDL-cholesterol due to their increased cholesterol absorption capacity.[26] However, with this genotype lowered cholesterol levels are associated with markedly increased plant sterol serum concentrations. The significance of increased plant sterol levels, however, is not clear.

Speculations that plant sterols may represent a cardiovascular risk factor were first brought up after the understanding of the autosomal-recessively inherited disease of sitosterolaemia.[27] Elevated plant sterol concentrations, xanthomatosis, and premature, frequently lethal atherosclerosis in young subjects are the most striking features regarding patients with homozygous sitosterolaemia. Additional findings are thrombocytopenia, abnormally deformed erythrocytes with membranous incorporation of phytosterols, extending to haemolytic crisis, arthralgias, and increased liver enzyme levels. The reason for this are mutations of the gene locus of the ABCG5 and ABCG8 co-transporters, resulting in increased absorption and reduced biliary elimination of all sterols.[28] In contrast to healthy subjects who have a plant sterol plasma concentration lower than 1 mg/dL, patients who suffer from this rare autosomal-recessive, inherited disease, have plasma concentrations of between 12 and 50 mg/dL. On the other hand, cholesterol does not need to be excessively high. The fact that patients with this disease present with an aggressive vascular disease process despite nearly normal cholesterol levels brought up the question whether phytosterols have a particularly atherogenous potential. As sterol analyses of xanthomas of such patients indicate that phytosterols only contain a small portion of sterols and that the major portion consists of free and esterified cholesterol, it is currently suggested that plant sterols can promote the incorporation of cholesterol in tissue.[27–29] This speculation is in agreement with the findings of a recently published study in which the NPC1L1 inhibitor ezetimibe led to a regression in xanthomatosis in parallel to lowering of both cholesterol and plant sterol levels.[30]

Even though many different clinical trials have clearly demonstrated that phytosterols reduce LDL-cholesterol, it is unclear whether phytosterols have a positive effect on cardiovascular disease.[24] Until now, there are no data on the effect of phytosterol consumption on the development of cardiovascular diseases available.[32] In fact, there is evidence that elevated levels of plant sterols are associated with an increased cardiovascular risk. Glueck *et al.*[33] were the first to report that elevated plant sterols might be a risk factor for coronary heart disease. In a study with 595 hypercholesterolaemic patients, they found that slightly elevated plasma levels of plant sterols were a heritable marker for an increased cardiovascular risk. Salen *et al.*[31] reported that in homozygotes of sitosterolaemia cholesterol accounted for over 80% of plasma, tissue, and atheroma sterol. In seven subjects in a Glueck study, serum cholesterol was 7.09 mmol/L, whereas the concentration of campesterol, stigmasterol, and sitosterol combined was only 43.86 μmol/L.[34] Therefore, it can be speculated that a slight excess of serum plant sterol levels may increase sterol deposition in cardiovascular tissue. This hypothesis is supported by the study of Rajaratnam *et al.*[35] who found that in postmenopausal women, plant sterols were independently associated with coronary heart disease in a multivariate analysis. These findings were confirmed by Sutherland and his team in a study involving both sexes over all age groups.[36] Sudhop *et al.*[37] analysed the relation of a positive family history of coronary heart disease to serum plant sterol concentrations in CAD patients without lipid-modifying medications. There were no differences in levels of serum cholesterol, cholesterol precursors, and lipoproteins. The serum campesterol level in the control group was 0.38 mg/dL compared to 0.50 mg/dL in those patients with a positive family history. Given that the level of plant sterols was small compared with cholesterol (0.16 vs. 0.21%), the effect inducing a negative cardiovascular outcome in this study is indeed very potent. Similar findings have been reported for patients on statin treatment. The Scandinavian Simvastatin Survey Study (4S study) also identified a subpopulation of coronary artery disease patients with low endogenous synthesis of cholesterol and high absorption of cholesterol and plant sterols. The subjects of this subpopulation had the highest levels of plant sterols and the highest risk of recurrent coronary events despite lower levels of serum cholesterol due to simvastatin ingestion.[38] Larger epidemiological studies reported similar data. Results of the *PROCAM-study* showed that patients afflicted with myocardial infarction or sudden cardiac death had increased plant sterol concentrations.[39] Upper normal levels of plant sterols were associated with a three-fold increase of risk for coronary events among men in the highest tertile of coronary risk according to the *PROCAM-algorithm* (*Figure 3*). Similar data are available for the plant sterol campesterol from the *MONICA/KORA-study*. In this prospective study, campesterol correlated directly with the incidence of acute myocardial infarction.[40]

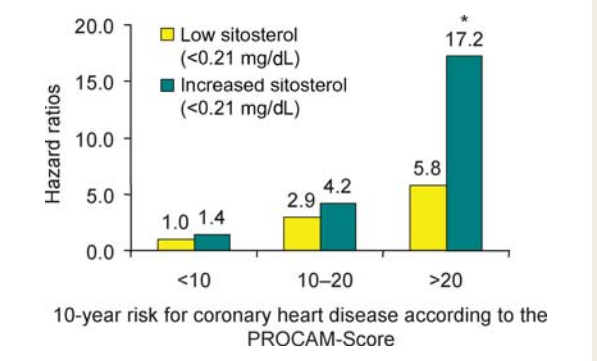

Figure 3 Plant sterols increase cardiac risk. PROCAM-score for the 10 year risk to develop coronary heart disease ($n = 477$) according to subgroups with increasing risk (PROCAM-score <10, 10–20, >20). Slightly elevated sitosterol levels are associated with increased cardiac risk. *$P < 0.05$ low sitosterol (<0.21 mg/dL) vs. elevated sitosterol (>0.21 mg/dL) (modified from ref. 39).

Current experimental findings from our own research group show that a diet supplementation with plant sterol esters that is equivalent to a commercially available spread induces endothelial dysfunction and leads to an increase of ischaemic stroke size in wild-type mice.[29] In atherosclerotic-prone apoE−/− mice, we compared the effects of a diet supplementation with plant sterol esters with equal cholesterol lowering by a second intervention in relation to atherosclerotic lesion formation. Ezetimibe was chosen as a comparator, because similar to plant sterols, this two-azetidione is an inhibitor of intestinal cholesterol absorption and lowers plasma cholesterol levels. As expected, the substantial lipid-lowering by both treatment principles reduced atherosclerotic lesion formation. However, despite equal plasma cholesterol levels, plant sterol ester supplementation was associated with twice the amount of plaque formation compared with ezetimibe. Thus, we found a positive correlation between sterol concentrations and the extent of atherosclerotic lesions.[29] Moreover, in a clinical study, we demonstrated that patients who were consuming plant sterol ester enriched margarine had increased concentrations of plant sterols in cardiovascular tissue.[29] Further mechanistic data suggest that vascular deposits of sterols, when compared with cholesterol, result in increased oxidation and release of oxygen radicals.[41] On the other hand, previous animal and *in vitro* experiments have shown that plant sterols have positive effects that directly inhibit tumour growth, including the slowing of cell cycle progression, the induction of apoptosis, and the inhibition of tumour metastasis, suggesting that these compounds have anticancer properties.[42] However, the induction of apoptosis is not limited to tumour cells, but extends also to vascular cells. Recent *in vitro* experiments demonstrated that the plant sterol sitosterol exerts a strong cytotoxic propensity inducing apoptosis in human endothelial cells, revealing detrimental effects on the vasculature.[43] In fact, the first experimental study reporting negative cardiovascular effects dates back to the year 2000. Ratnayake *et al.*[44] reported that increased serum levels of plant sterols increase rigidity of erythrocytes and shorten the life span of stroke-prone spontaneously hypertensive (SHRSP) rats. These findings were the reason for Health Canada, the federal department responsible for helping Canadians maintain and improve their health, to raise significant safety issues and not to allow functional foods enriched with plant sterol esters to be sold in Canada.[45]

Phytosterols as adjunct to over-the-counter drugs

Just recently, a plant sterol–aspirin combination product has been launched in the USA, despite the fact that the FDA has written warnings to companies marketing the combination of drugs with dietary supplements in the past.[46,47] This 'analgetic phytosterol supplement' combines 81 mg aspirin and 400 mg of plant sterols and carries both over-the-counter (OTC) drug and dietary supplement labelling and claims. The American Herbal Products Association (AHPA), however, took issue with this kind of marketing because it implied both active ingredients have been submitted to pharma-level testing when in fact only the OTC drug ingredients had been tested. According to the AHPA, this would be potentially deceptive for consumers and would constitute a change in FDA policies. At present, this issue highlights a legal grey area that requires further refinement.[48]

Do current guidelines for therapeutic lifestyle changes have to be reconsidered?

Since the introduction on the market of the first phytosterol enriched margarine, no cases with negative health effects have been reported. However, controlled studies are only available for an observational period of up to 1 year, for which the number of participants was low and the special effects of plant sterols were not studied separately, so that the possible pro-atherosclerotic effects due to long-term consumption could not be detected in these studies.[19,20,23,24,49] In contrast to functional foods enriched with saturated, less absorbable plant stanol esters (which reduce not only serum cholesterol, but also plant sterol levels), a diet supplementation with plant sterol esters has proven to lead to a significant increase in plant sterol levels.[20,50] Functional foods are marketed directly to consumers. In comparison to drugs, food supplements are subject to much 'weaker' authorization and control requirements, but this does not exclude the possibility that they might be hazardous.

Due to the lack of evidence regarding clinical events and the potential for negative side-effects, the 'health claim' of the *US Food and Drug Administration*, the *NCEP ATP III* guidelines, and the current diet and lifestyle recommendations of the *American Heart Association* should be re-evaluated. The German Drug Commission (Arzneimittelkommission der Deutschen Ärzteschaft) has stated in January 2004 that because of unclear safety data and lacking evidence of effectiveness, the general use of such products was not to be recommended.[10] Similarly, the recently revised guidelines for primary and secondary prevention of cardiovascular diseases of the *National Health System (NHS)* call for randomized controlled trials testing relevant clinical endpoints.[11] As long as results of such trials are pending, recommendation of functional foods or drugs supplemented with plant sterol esters to reduce serum cholesterol concentrations will be a matter of controversial debate.

Summary points

Currently there are no data available indicating that functional foods supplemented with plant sterol esters reduce cardiovascular events.

Findings in patients with the hereditary disease of sitosterolaemia, data from epidemiological studies, as well as recently published *in vitro* and *in vivo* data suggest that plant sterols potentially induce negative cardiovascular effects.

Prospective clinical studies testing relevant clinical endpoints are needed, before a diet supplementation with plant sterol esters can be recommended.

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CARDIOVASCULAR FLASHLIGHT

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Extrinsic compression of the right coronary artery

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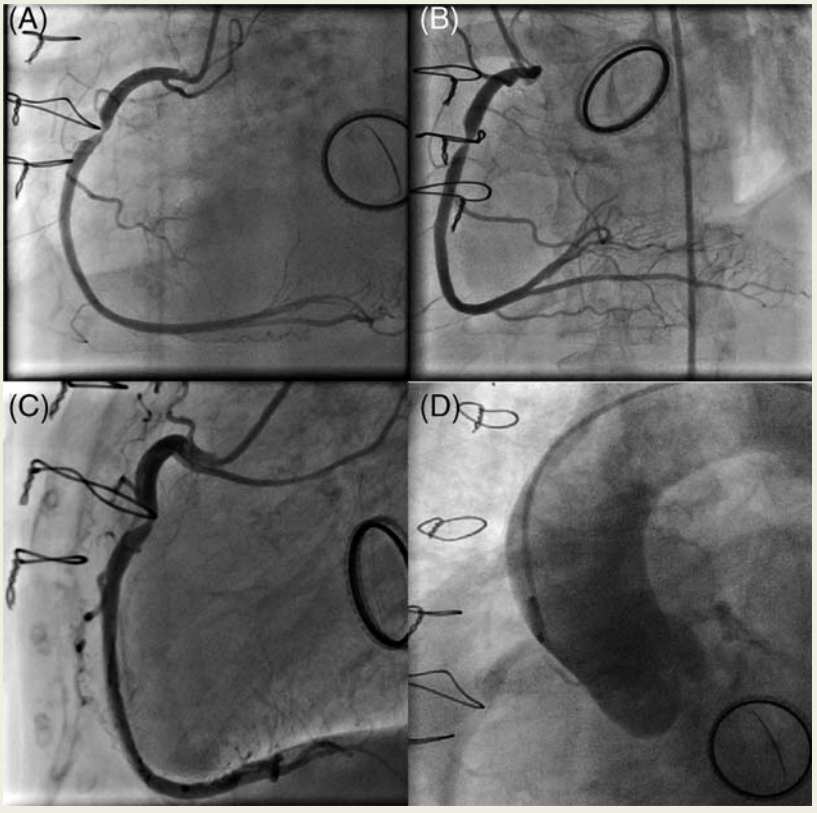
A 59-year-old woman was admitted to our department for cardiac catheterization due to aortic stenosis and atypical for angina symptoms. She had her mitral valve replaced in 1993 with a mechanical bileaflet St Jude valve, due to severe mitral stenosis. She was also in chronic atrial fibrillation and was taking oral anticoagulants. The electrocardiogram showed atrial fibrillation and ST depression in leads I, II, III, aVF, and V3–V6. Transthoracic and transoesophageal echocardiogram showed that the mechanical mitral valve was functioning well. The left ventricle dimensions were within normal limits and the systolic function was also normal. However, moderate to severe aortic valve stenosis and moderate to severe aortic regurgitation were noted. The right ventricle systolic pressure (RVSP) was 30 mmHg.



The left ventriculography revealed very good systolic performance of the left ventricle. No mitral regurgitation was noted and the systolic pull-back gradient across the aortic valve was 50 mmHg. The aortogram showed normal dimensions of ascending aorta and moderate to severe aortic regurgitation. The left coronary arteries were free of intraluminal disease and the right coronary artery (RCA) was a large dominant artery. However a significant focal stenosis in RCA was noted proximally due to extrinsic compression caused by a large surgical sternal metallic suture, used during the previous cardiac surgery.

The focal stenosis caused by the metallic suture was probably causing the atypical for angina symptoms. The RCA was not thrombosed throughout the years, probably because of the anticoagulation treatment that the patient is receiving for the mechanical mitral valve and the chronic AF. The patient was referred to the cardiac surgeons for removal of the metallic suture and aortic valve replacement.

See online supplementary movie available at *European Heart Journal* online.

Panel A. LAO 45°, CRA 0° view of the RCA.

Panel B. LAO 0°, CRA 20° view of the RCA.

Panel C. LAO 90°, CRA 0° view of the RCA.

Panel D. Aortogram in LAO 45°, CRA 0° view.