PLANT STANOL ESTER
CLINICAL SUMMARY

Plant stanol ester has been shown to lower cholesterol. High cholesterol is a risk factor in the development of coronary heart disease. A daily intake of 1.5–2.4 g plant stanols lowers cholesterol by 7–10% in 2 to 3 weeks. The beneficial effect is obtained with a daily intake of 1.5–3.0 g plant stanols.

Date of preparation: July 2022

Raisio Group
P.O. Box 101
FI-21201 Raisio
Finland
www.benecol.com

Contents

✍ Introduction

Maintaining a healthy blood cholesterol level is important to support heart wellbeing and reduce the risk of heart disease.

Functional foods with added plant stanol ester provide an effective way to lower 'bad' LDL cholesterol (LDL-C) as part of a healthy cholesterol-lowering diet.

This *Plant Stanol Ester Clinical Summary* outlines the clinical data around plant stanol ester, the active cholesterol-lowering ingredient in Benecol® functional foods.

✔ The relevance of lowering LDL cholesterol

More people die from cardiovascular disease (CVD) worldwide than from any other cause.[1] Of which, coronary heart disease (CHD) is the biggest culprit, due to the build-up of fatty deposits in the blood vessels (atherosclerosis) causing blockages and preventing blood supply to the heart or brain (heart attack or stroke).[2] The presence of CHD is attributable to a combination of risk factors including increasing age, male gender (at an earlier age), genetic factors, smoking, poor diet and physical inactivity. Some of these factors can be managed, while others are not modifiable. The good news is that 80% of premature heart attacks and strokes are preventable with careful management of modifiable risk factors.[3]

Elevated blood cholesterol, or hyperlipidaemia, is a major modifiable risk factor for CHD and widely studied. Low-density lipoproteins (LDL-C) in particular, have been directly implicated in the development of atherosclerotic CVD (ASCVD).[4] Millions of people around the world live with elevated cholesterol, and according to the World Health Organization a third of global CHD is attributable to high cholesterol alone.[5] It is estimated that raised cholesterol globally causes 2.6 million deaths and around 30 million disability-adjusted life years.[5]

It is well established that lowering LDL-C decreases the number and risk of coronary events.[6–8] A large number of epidemiological studies and clinical trials suggest that for every 10 mg/dL (0.26 mmol/L) decrease in LDL-C, the relative risk for CHD is reduced by approximately 10%.[4] Lowering LDL-C by 1 mmol/L leads to a reduction in the five-year risk of ASCVD events by 21-25%.[9,10] The reduced risk of coronary events is proportional to the reduction in LDL-C and thus used as a basis for preventive policies.[11] As a result, both primary prevention of heart attacks and strokes, as well as secondary prevention of recurrent events, involve lifestyle modification and drug therapies to manage dyslipidaemia and in particular to reduce LDL-C.[12]

LDL cholesterol: the earlier, the better; the lower, the better

Good evidence indicates the process of atherosclerosis can manifest before there are any apparent risk factors, progressing for decades before showing first symptoms. Intravascular ultrasound performed in 262 heart transplant recipients with no known coronary artery disease found that atherosclerotic lesion was present in 51.9% of the patients, including a large proportion of those from young age cohorts (Fig 1).[13]

ATHEROSCLEROSIS STARTS FROM EARLY LIFE

Coronary atherosclerosis begins at a young age with lesions present in 1 of 6 teenagers in this cohort, suggesting the need for increased efforts at coronary disease prevention in young adults.
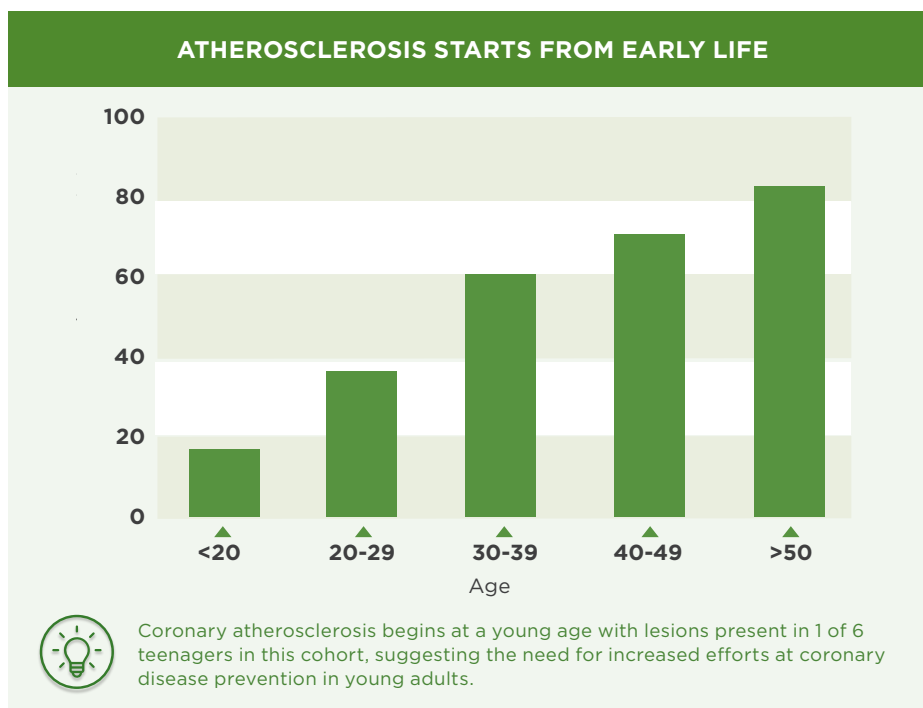
Fig 1. Prevalence of coronary atherosclerosis by age with 0.5- and 0.3-mm thresholds for defining atherosclerotic lesions. Adapted from Tuzcu et al. (2001)[13]

In 2017, Fernández-Friera *et al*. studied 1779 subjects who did not exhibit CVD risk factors and found that plaque or coronary artery calcification were present in 49.7% of these subjects.[14] The results demonstrate an independent and direct link between LDL-C levels and atherosclerotic burden (Fig 2). The findings suggest that many middle-aged individuals with an LDL-C concentration of greater than 50–60 mg/dL (1.3–1.6 mmol/L) are likely to have clinically manifested atherosclerosis.[15] These concentrations are currently considered as normal, according to clinical thresholds.

RELATIONSHIP BETWEEN LDL-C LEVELS AND ATHEROSCLEROSIS

As blood LDL-C levels rise, there is a linear and significant increase in the prevalence of atherosclerosis, ranging from 11% in the 60–70 mg/dL subgroup to 64% in the 150–160 mg/dL subgroup (P<0.001)
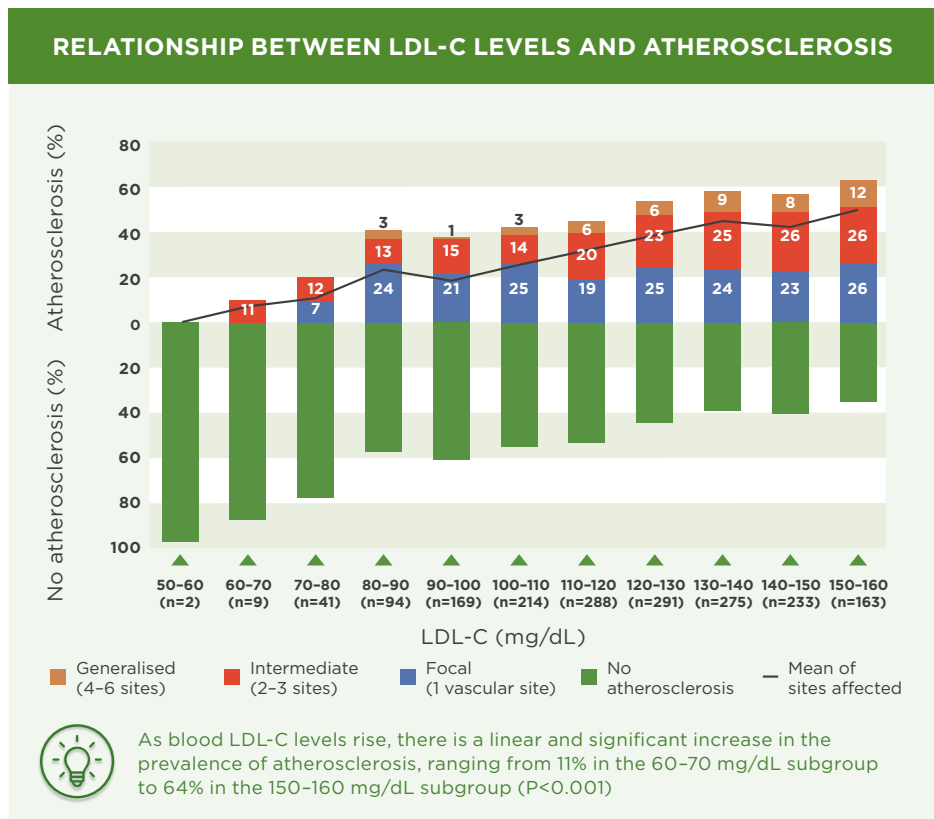
Fig 3 taken from Gylling *et al*. (2020)[15] summarises the evidence of subclinical atherosclerosis in two asymptomatic populations, in the absence of other conventional CVD risk factors.[14,16] Alarmingly, atherosclerotic plaques were present in 45% of subjects despite LDL-C concentrations being within the normal reference range (2.8 to 3.1 mmol/L). Based on the collective findings, there is a strong case for more effective LDL-C lowering, even in individuals without conventional CVD risk factors.

SUBCLINICAL ATHEROSCLEROSIS

Coronary and peripheral arteries PESA study

%

70
60
50
40
30
20
10
0

LDL-C (mmol/L): 1.3-1.5 · 1.6-1.8 · 2.3-2.6 · 2.8-3.1 · 2.9-4.1

Coronary arteries

%

30
20
10
0

<2.6 · 2.6-3.3 · 3.4-4.1

LDL-C (mmol/L)

💡 Increases in serum LDL-C have been associated with a greater prevalence of atherosclerotic calcification or plaques in subjects with no apparent cardiovascular disease risk factors.

Fig 3.
Serum LDL-C concentrations and the frequency of atherosclerotic changes in coronary and peripheral arteries in subjects without cardiovascular disease risk factors from Gylling et al. (2020)[15]

LDL-C=low density lipoprotein cholesterol.

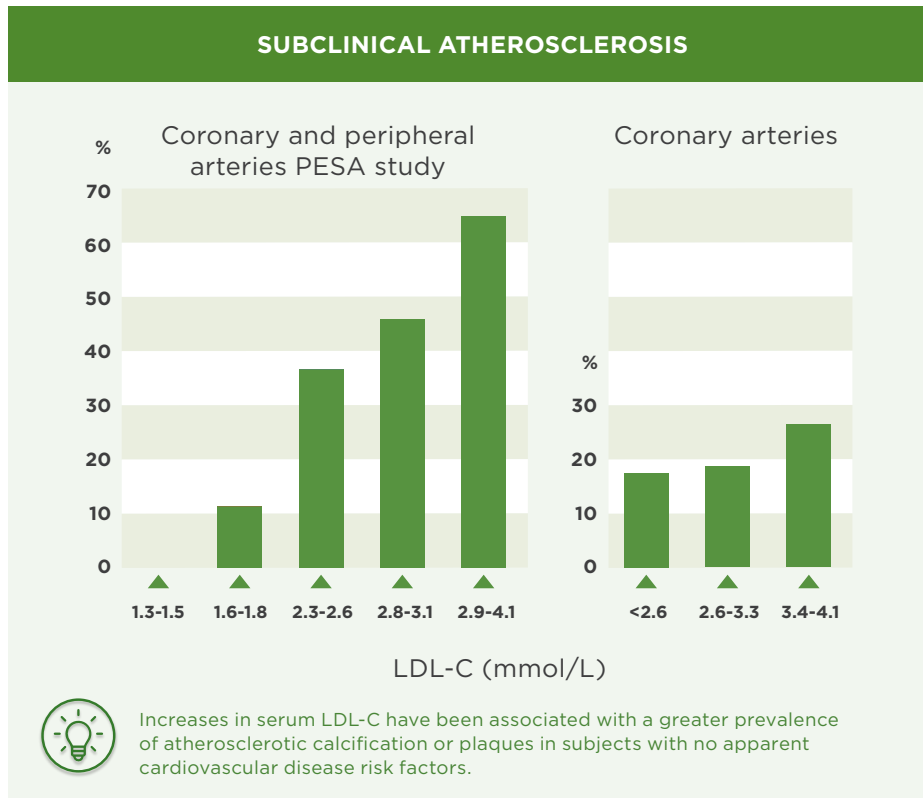A series of meta-analyses by Ference *et al.* have elegantly shown that a life-long low LDL-C level reduces the risk of CHD substantially more than lowering LDL-C later in life.[12] Long-term exposure to lower blood LDL-C was associated with a 54.5% reduction in the risk of CHD for each mmol/L lower LDL-C.[12] This represents a 3-fold greater reduction in the risk of CHD per unit lower LDL-C than that observed during treatment with a statin, which is started later in life. The authors conclude that a prolonged exposure to lower LDL-C beginning early in life is associated with a substantially greater reduction in the risk of CHD than the current practice of lowering LDL-C only later in life.[12] Although it has convincingly been shown that cholesterol lowering pays off in older age, this study provides strong evidence for a prophylactic approach to lower the risk of CHD by lowering LDL-C earlier in life, for example via lifestyle adjustment. The existing data therefore support the statement regarding *LDL-C: the earlier, the better; the lower, the better.*

During the 85th European Atherosclerosis Society (EAS) congress in Prague, the EAS published a consensus statement confirming the causal role of LDL-C in the development of ASCVD.[4] The consensus statement is based on a meta-analysis of more than 200 prospective cohort studies, Mendelian randomisation studies and randomised controlled trials, including in total over 2 million participants, more than 20 million person-years of follow-up, and over 150 000 cardiovascular events. The main conclusion presented in the consensus statement is: "Consistent evidence from numerous and multiple different types of clinical and genetic studies unequivocally establishes that LDL causes ASCVD."[4]

The EAS consensus statement discusses compelling evidence that the causal effect of LDL-C on ASCVD is largely independent of the mechanism by which LDL-C is 'lowered'. It therefore confirms that LDL-C is not only a biomarker, but a causal factor for ASCVD. The consensus statement also states that the effect of LDL-C is cumulative, meaning that the higher the LDL-C is and the longer a person has elevated LDL-C, the higher the risk of ASCVD.[4] Thus, lowering LDL-C early in life provides a major opportunity to reduce the lifetime risk of a cardiovascular event.

Even small LDL cholesterol reductions are beneficial

The well established linear relationship between LDL-C and relative risk of CHD has been consistently supported by clinical, epidemiological and genetic studies (Fig 4).[4,11,18] The relationship suggests that even small LDL-C reductions are worthwhile to minimise risk of disease and that an additional reduction in CHD risk is obtained when LDL-C is reduced below the typically recommended upper LDL-C concentration of 110 mg/dL (3.0 mmol/L).
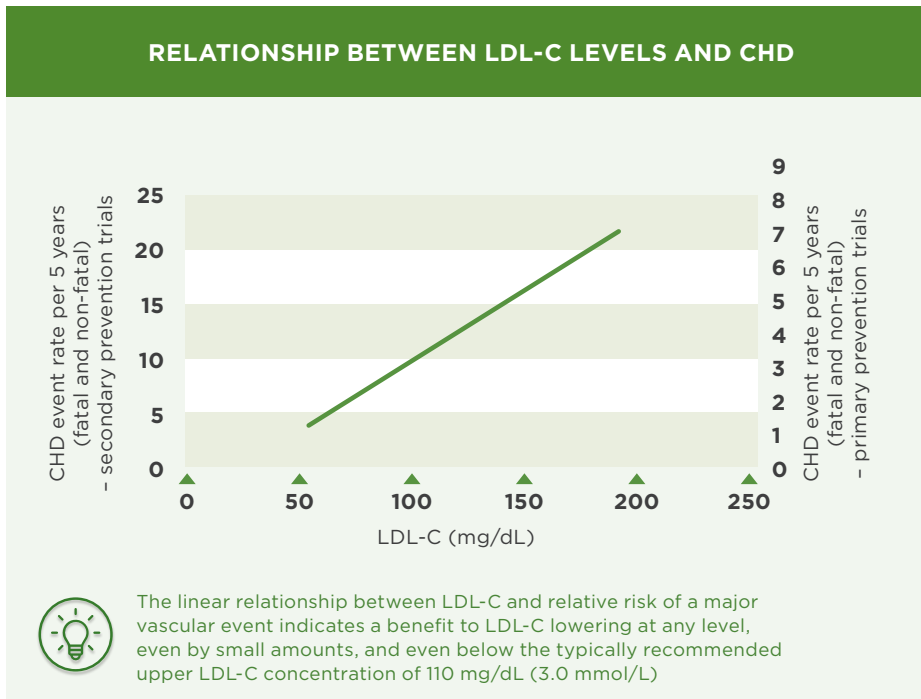
RELATIONSHIP BETWEEN LDL-C LEVELS AND CHD

CHD event rate per 5 years (fatal and non-fatal) – secondary prevention trials

CHD event rate per 5 years (fatal and non-fatal) – primary prevention trials

LDL-C (mg/dL)

The linear relationship between LDL-C and relative risk of a major vascular event indicates a benefit to LDL-C lowering at any level, even by small amounts, and even below the typically recommended upper LDL-C concentration of 110 mg/dL (3.0 mmol/L)

Fig 4.
Linear association between LDL-C level and absolute CHD event rate based on the extensive clinical evidence. Trendlines for primary and secondary prevention associations are virtually superimposable. Adapted from Ference et al. 2018.[4]

CHD=coronary heart disease; LDL-C=low-density lipoprotein cholesterol.

Findings from the Oslo Diet-Heart Study further support the benefit of moderate LDL-C lowering by dietary means.[19] Survivors of a myocardial infarction were randomly assigned to either a cholesterol-lowering dietary intervention or control group. After 5 years of follow-up the intervention group had a mean decrease in total cholesterol of 17.6%, compared with only 3.7% in the control group.

With a starting mean total cholesterol in both groups of 296 mg/dL (7.65 mmol/L), the mean total cholesterol concentration at the end of the 5-year period was 244 mg/dL (6.31 mmol/L) in the intervention group and 285 mg/dL (7.37 mmol/L) in the control group, both higher than the normal upper level of total cholesterol officially recommended (200 mg/dL [5.17 mmol/L]). After 11 years, incidence of myocardial infarction mortality was significantly reduced in the diet group compared with the control group (32 vs 57; P=0.004) and there were also fewer coronary deaths (fatal myocardial infarction and sudden death): 79 in the diet group vs 94 in the control group (P=0.097).[19] Thus, the Oslo Diet-Heart Study clearly shows that you do not need to

reach cholesterol concentrations below the upper recommended levels to obtain the benefit from cholesterol lowering.

A panel of the International Atherosclerosis Society (IAS) highlight the importance of lifestyle changes and urges lifestyle changes to be implemented as part of the primary prevention.[11] The IAS panel favoured the use of lifestyle intervention to reverse unhealthy life habits and stated that drugs should be reserved for patients at greater risk.[11]

The Myocardial Infarction Genetics Consortium Investigators found that gene mutations causing loss of function to a dietary cholesterol transporter in the gut were associated with both reduced LDL-C levels and a reduced risk of CHD.[15] Carriers of these loss-of-function mutations had significantly lower levels of total cholesterol and LDL-C (mean adjusted difference, −12 mg/dL [0.31 mmol/L]; P=0.04), which in turn was associated with a 53% reduction in the risk of CHD.[20] The lower level of cholesterol observed in carriers of these mutations correspond to cholesterol reductions that can be achieved using dietary modifications in a non-carrier, meaning the findings of this study strongly indicate that this level of LDL-C lowering is large enough to result in risk reduction of CHD, the extent of which is dependent on how early in life the LDL-C lowering is achieved.
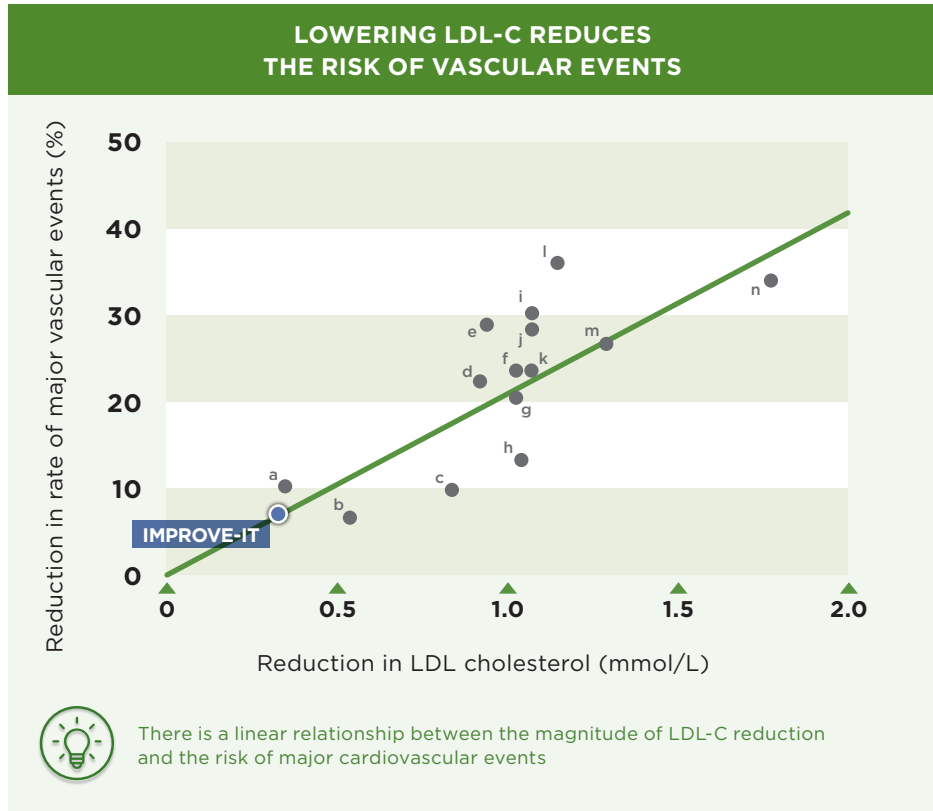
Reducing LDL cholesterol can have a clinically relevant treatment effect

To determine the clinical benefit of reducing LDL-C, investigators have measured the impact of LDL-C level on rate of vascular events. The Cholesterol Treatment Trialists' (CCT) Collaborators conducted a meta-analysis of individual data from 27 randomised trials studying the effects of lowering LDL-C with statin therapy in people at low risk of vascular disease.[18] The findings concluded a reduction of LDL-C with a statin reduced the risk of major vascular events (rate ratio 0.79, 95% CI 0.77–0.81, per 1.0 mmol/L reduction), largely irrespective of age, sex, baseline LDL-C or previous vascular disease, and of vascular and all-cause mortality.[18]

More recently, the IMPROVE-IT study investigated the effect of adding ezetimibe to statin therapy on the rate of cardiovascular events.[8] Ezetimibe is a drug that lowers blood LDL-C by reducing cholesterol absorption, with 10 mg/day reducing LDL-C on average by 18%. As with plant stanol ester, ezetimibe reduces LDL-C by partly blocking the absorption of dietary and biliary cholesterol from the digestive tract. When added to statin therapy, ezetimibe resulted in incremental lowering of LDL-C and improved cardiovascular outcomes.[8]

The IMPROVE-IT study provides strong evidence that lowering LDL-C through the reduction of cholesterol absorption from the digestive tract results in an expected reduction in the risk of major vascular events.[8] It indicates that the linear relationship between the reduction in absolute concentrations of LDL-C and the reduction in fatal and non-fatal vascular events, as established by the CTT Collaborators,[13] can be used to estimate the expected reduction in the rate of major vascular events due to LDL-C lowering, in the case of the IMPROVE-IT study, by reduction of cholesterol absorption (Fig 5).

LOWERING LDL-C REDUCES THE RISK OF VASCULAR EVENTS

There is a linear relationship between the magnitude of LDL-C reduction and the risk of major cardiovascular events

Silverman *et al.* further established that LDL-lowering regimes that work primarily via upregulation of LDL receptor expression, e.g., ezetimibe treatment, reduce the risk of ASCVD events to a similar degree as statin treatment per 1 mmol/L LDL-C lowering.[10]

*a: Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico (GISSI Prevenzione);
b: Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial–Lipid Lowering Trial (ALLHAT-LLT); c: Assessment of Lescol in Renal Transplantation (ALERT); d: Lescol Intervention Prevention Study (LIPS); e: Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TexCAPS); f: Cholesterol and Recurrent Events (CARE); g: Long-term Intervention with Pravastatin in Ischaemic Disease (LIPID); h: Prospective Study of Pravastatin in the Elderly at Risk (PROSPER); i: Anglo-Scandinavian Cardiac Outcomes Trial–Lipid Lowering Arm (ASCOT-LLA); j: West of Scotland Coronary Prevention Study (WOSCOPS); k: Post–Coronary Artery Bypass Graft (Post CABG); l: Collaborative Atorvastatin Diabetes Study (CARDS); m: Heart Protection Study (HPS); n: Scandinavian Simvastatin Survival Study (4S). Adapted from Cannon et al. 2015.[8]*

Summary

- High blood cholesterol, or hyperlipidaemia, is a major modifiable risk factor for CHD; one of the major causes of death globally

- Experts agree that elevated plasma LDL-C is causal in the development of ASCVD

- It has been estimated that for every 10 mg/dL (0.26 mmol/L) decrease in LDL-C, the relative risk for CHD is reduced by approximately 10%

- Strong evidence indicates that lowering LDL cholesterol through the reduction of cholesterol absorption from the digestive tract results in an expected reduction in the risk of major vascular events

⊘ Plant stanol ester: what it is and how it lowers LDL cholesterol

Plant stanols and plant sterols are plant-based compounds that lower blood cholesterol. Their benefit was discovered in the 1950s,[21] but it was not until several decades later when researcher Ingmar Wester developed a method for incorporating plant stanols (in the form of plant stanol esters) into food products. This innovation allowed for plant stanols to be clinically studied, and during the early 1990s the cholesterol-lowering effect of plant stanol ester was verified.

Plant stanols are structural components of plant cells and naturally found in foods. The most common dietary sources of plant stanols are cereals, mainly wheat and rye.[22,23] Daily intake of plant stanols from a normal diet is about 20–30 mg/d.[24,25] Plant stanols structurally resemble cholesterol (Fig 4), which is why they can interfere with cholesterol absorption in the small intestine. Reduced absorption of cholesterol results in reduced serum total cholesterol and LDL-C levels, yet the average diet does not contain enough plant stanols to effectively lower serum cholesterol.

There are technical limitations related to the use of plant stanols in free form in foods, as they tend to form crystals that will not lower cholesterol optimally, and feel granular in the mouth. To ensure an adequate intake of plant stanols in a palatable form, a process to esterify plant stanols with vegetable oil fatty acids was developed. Adding esterified plant stanols to a food product does not affect its taste or mouthfeel, and most importantly, esterified plant stanols lower cholesterol effectively.[26,27]

Plant stanol ester cholesterol-lowering efficacy

Plant stanol ester lowers blood cholesterol by partly inhibiting the absorption of cholesterol in the small intestine. As soon as the plant stanol ester reaches the small intestine it is rapidly hydrolysed to free plant stanols and fatty acids.[28] Free plant stanols can then interfere with the solubilisation of cholesterol, i.e. the incorporation of cholesterol into mixed micelles (Fig 6).[29] This happens because of the structural similarity of plant stanols and cholesterol (Fig 7). Solubilisation of cholesterol into mixed micelles is a necessary part of cholesterol uptake; the less cholesterol is solubilised into mixed micelles, the more cholesterol is excreted from the body.

Fig 6. Simplified cross section of small intestine. Mixed micelles carry cholesterol and other fat-soluble substances to the intestinal wall to be absorbed. Due to structural similarity, plant stanols can partly replace cholesterol from the micelles, disturbing its absorption. Adapted from Gylling et al. 2014.[29]

WITHOUT PLANT STANOL

WITH PLANT STANOL

50% OF CHOLESTEROL IS ABSORBED

20% OF CHOLESTEROL IS ABSORBED

● Micelle   ● Cholesterol   ● Plant stanol

With sufficient plant stanols present, only 20% of cholesterol is absorbed in the small intestine

THE MOLECULAR STRUCTURES OF CHOLESTEROL AND PLANT STANOL ESTER

Cholesterol

OH

Plant stanol ester
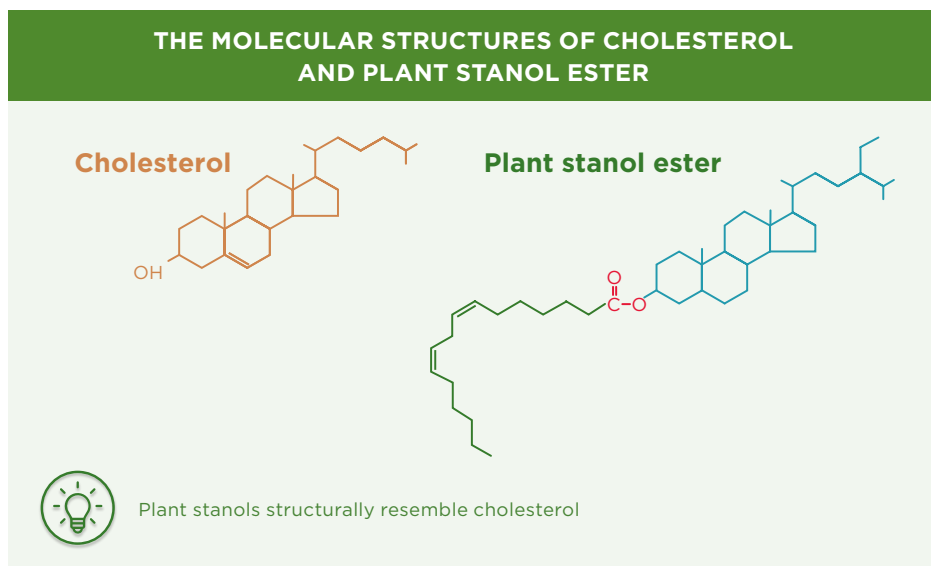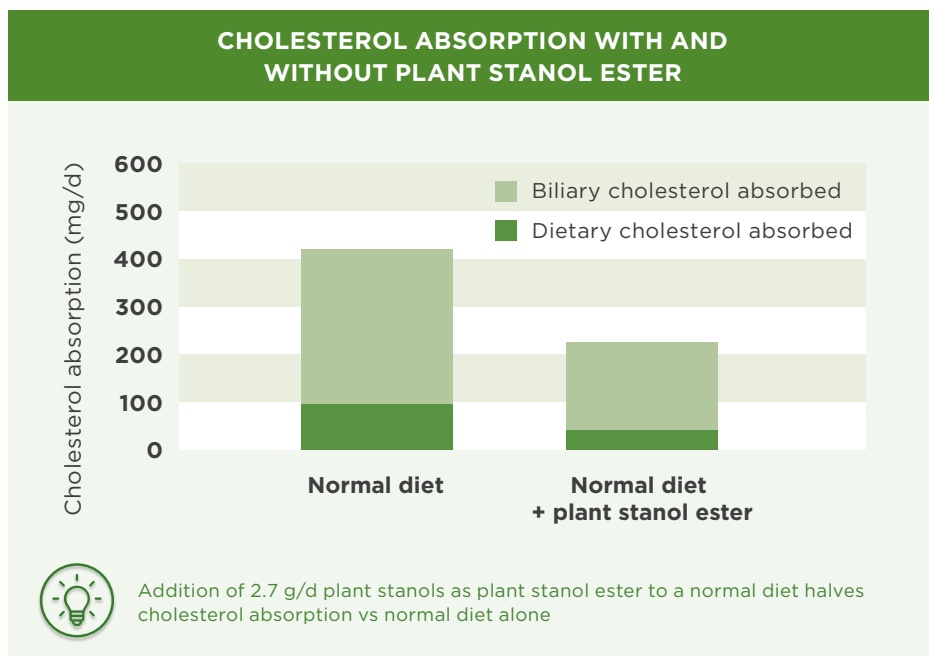
Plant stanols structurally resemble cholesterol

Fig 7.
Plant stanol ester is formed when a plant stanol molecule (blue) is joined to a vegetable oil fatty acid (green) by an ester bond (red). Plant stanol molecule closely resembles cholesterol (orange).

Plant stanols may also influence cholesterol absorption in the enterocyte, or in the brush border membrane of the enterocyte, but these mechanisms are yet to be fully understood.[30,31]

Consuming plant stanol ester inhibits the absorption of both dietary cholesterol (the cholesterol coming to the digestive tract via food) and biliary cholesterol (the cholesterol coming to the digestive tract with the bile solution).[32] Cholesterol absorption efficiency is reduced by about 50% with 2 g/d plant stanols (Fig 8).[32,33] Consuming plant stanols with a meal ensures optimal reduction of cholesterol absorption, because bile is excreted into the digestive tract following a meal. Plant stanol ester does not have to be consumed with every meal, however, and consumption once a day is enough for full effect.[34] This finding supports the notion that the cholesterol-lowering effect of plant stanols is not only limited to changes in micellar composition; plant stanols may also affect cholesterol trafficking in enterocytes through a currently unknown mechanism.[30,31]

Fig 8.
Plant stanols reduce
the absorption of both
dietary and biliary
cholesterol.
Adapted from
Gylling et al. 1997.[32]

CHOLESTEROL ABSORPTION WITH AND WITHOUT PLANT STANOL ESTER

Cholesterol absorption (mg/d)

- Biliary cholesterol absorbed
- Dietary cholesterol absorbed

600
500
400
300
200
100
0

Normal diet

Normal diet + plant stanol ester

Addition of 2.7 g/d plant stanols as plant stanol ester to a normal diet halves cholesterol absorption vs normal diet alone

The reduced cholesterol absorption achieved with plant stanol ester leads to significantly reduced levels of serum total cholesterol and LDL-C, with no effect on HDL cholesterol.[e.g.27,29,32,35,36] Lowering LDL-C with plant stanols does not affect the mean size of the LDL particles.[37]

Plant stanol ester is safe and well tolerated

Plant stanols are effectively eliminated from the body in an unchanged form: when foods with added plant stanols are consumed, only about 0.05–0.2% of plant stanols are absorbed.[38,39] On a normal diet, serum plant stanol concentration is approximately 10–15 µg/dL.[40] A daily intake of 2 g plant stanols (as plant stanol ester) increases serum plant stanol concentrations to 20–30 µg/dL.[35] Even if daily intake is higher (up to 9 g/d), serum levels of plant stanols remain at low levels.[41,42]

Clinical safety markers and adverse effects have been monitored in all plant stanol ester intervention studies and no safety issues have been detected, even in long-term use.[43-45] Plant stanol ester consumption has also shown to be safe and well tolerated for mothers and their babies during pregnancy and breastfeeding.[46]

Fat-soluble vitamins are also absorbed via micelles, so one question has been raised as to whether plant stanol ester consumption disturbs their uptake – but plasma levels of fat-soluble vitamins A and D are not affected by consumption of plant stanol ester.[35,40,41,47] A small decrease in plasma ß-carotene concentration has been noted in some,[34, 35, 47, 48] but not all studies.[49] However, the dose of plant stanols (up to 9 g/d) or the duration of the intervention did not account for the observed differences, and plasma ß-carotene concentrations remained within reference values.[34,41,42,50-52]This suggests that other factors, such as diet and seasonal changes, may be more important in explaining the variation in plasma ß-carotene levels.[50] The moderate decrease in plasma ß-carotene levels related to plant stanol ester consumption can be prevented by consuming fruit and vegetables according to dietary guidelines.[53]

Summary

- Plant stanols are plant-based compounds found naturally in foods, which when added in the form of plant stanol esters to cholesterol-lowering functional foods can provide a solution to help manage blood lipids

- Plant stanols structurally resemble cholesterol, causing them to interfere with cholesterol absorption in the small intestine resulting in reduced absorption of cholesterol and reduced serum total cholesterol and LDL-C levels

- Consuming sufficient quantities of plant stanol ester with a meal ensures optimal reduction of cholesterol absorption

(↓10%) Robust and sustainable cholesterol reduction

To date, over 80 clinical studies have been published exploring the efficacy of plant stanol ester in different usage situations. The main finding is that whatever the circumstances are, a daily intake of 1.5–3.0 g of plant stanols (as plant stanol ester) reduces serum total cholesterol and LDL-C dose-dependently from 7 to 12.5%, on average, with no effect on HDL cholesterol (Fig 9).[54-57]

Reducing cholesterol with plant stanol ester is fast. There is a measurable reduction in serum LDL-C within the first week of continuous plant stanol ester use,[58,59] and full reduction is typically achieved within 2–3 weeks.[52,53,60]

THE TYPICAL CHOLESTEROL-LOWERING EFFECT OF PLANT STANOL ESTER

Change in serum LDL-C (%)

0

-5

-10

10%

-15

Week 0   Week 1   Week 2   Week 3   Week 4

Plant stanol ester lowers cholesterol fast, and with daily consumption the effect is sustained long term
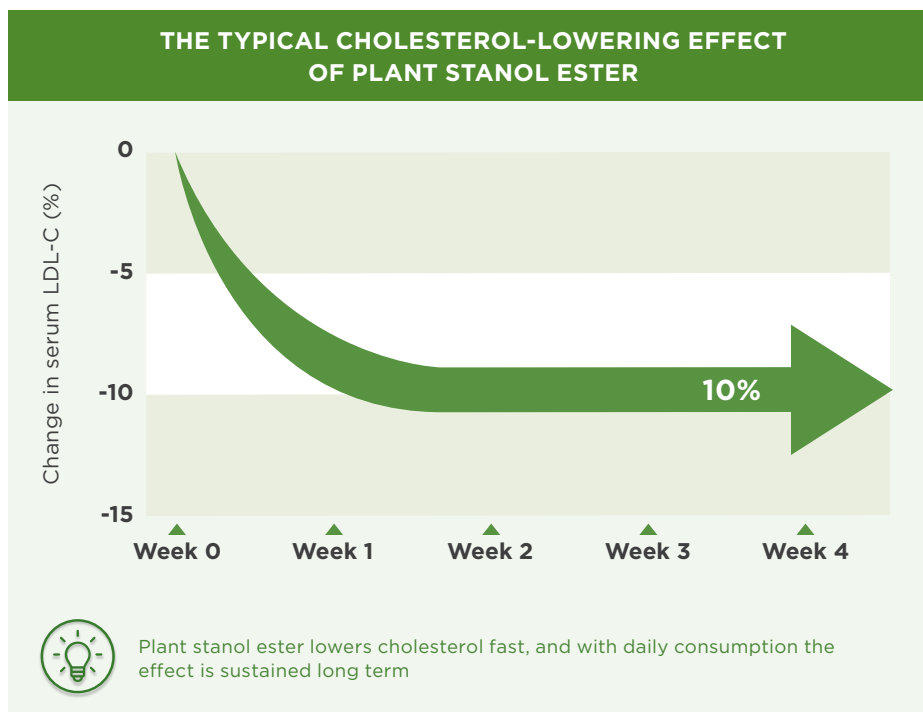
Fig 9.
The cholesterol-lowering effect of plant stanol ester is fast, and the effect is sustained with sufficient daily consumption. Magnitude of reduction depends on the daily plant stanol dose. Adapted from EFSA Panel on Dietetic Products, Nutrition and Allergies. 2012.[57]

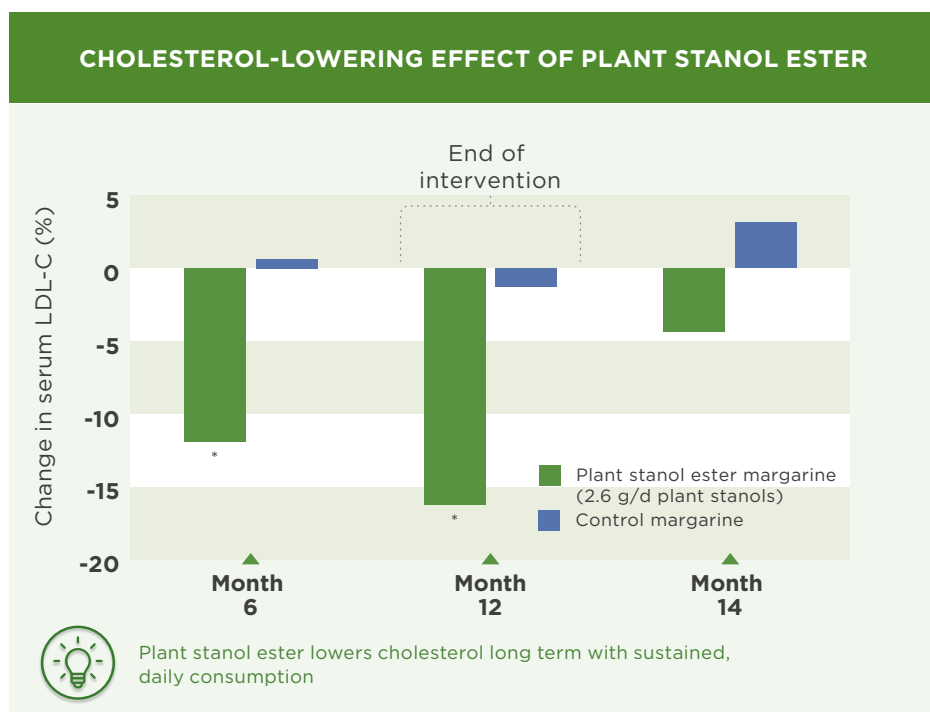*LDL-C=low-density lipoprotein cholesterol.*

Cholesterol reduction with plant stanol ester can also be sustained with daily intake. The landmark study by Miettinen *et al.* in 1995 showed that the cholesterol-lowering effect of plant stanol ester was sustained throughout the 12-month intervention period.[27] After the intervention period ended and plant stanol ester consumption was ceased, however, LDL-C quickly rose back to starting levels, suggesting that plant stanol ester needs to be consumed on a daily basis to gain long-term benefits (Fig 10).

The sustained cholesterol-lowering effect of plant stanol ester has been confirmed in other long-term studies (12–18 months duration).[61-63] The sustained effect has also been shown in conjunction with statin treatment,[57] both plant stanol ester containing margarine,[22,56,57] and single-serving yogurt drinks.[63]

It is not necessary to consume plant stanol ester at every meal to lower cholesterol efficiently.[34] As long as plant stanol ester consumption is sufficient and daily, the efficacy is consistent – independent of whether the daily dose is consumed at one occasion or divided over several meals.[34]

Fig 10. Cholesterol-lowering effect of plant stanol ester enriched margarine. Reduction in LDL-C was sustained throughout the study, but as the use of the margarine was ceased after 12 months, the levels rose again close to the starting values. *P<0.001 vs. control. Adapted from Miettinen et al. 1995.[27]

LDL-C=low-density lipoprotein cholesterol.

CHOLESTEROL-LOWERING EFFECT OF PLANT STANOL ESTER

End of intervention

Change in serum LDL-C (%)

5
0
-5
-10
-15
-20

Plant stanol ester margarine (2.6 g/d plant stanols)
Control margarine

Month 6   Month 12   Month 14

Plant stanol ester lowers cholesterol long term with sustained, daily consumption

How much plant stanol ester is enough?

The effect of plant stanol ester is dose dependent. Studies from the 1990s confirmed that a dose of around 1.5–3 g/d plant stanols as plant stanol ester was optimal to achieve most of the cholesterol-lowering potential of plant stanols (Fig 10).[27,64,65] As higher doses were studied, however, efficacy was shown to improve gradually by increasing the dose up to an intake of 9 g/d.[41,42,56] For a clinical benefit, ensuring an adequate daily intake of plant stanols is important: if the daily intake is low, optimal cholesterol-lowering effect will not be achieved.
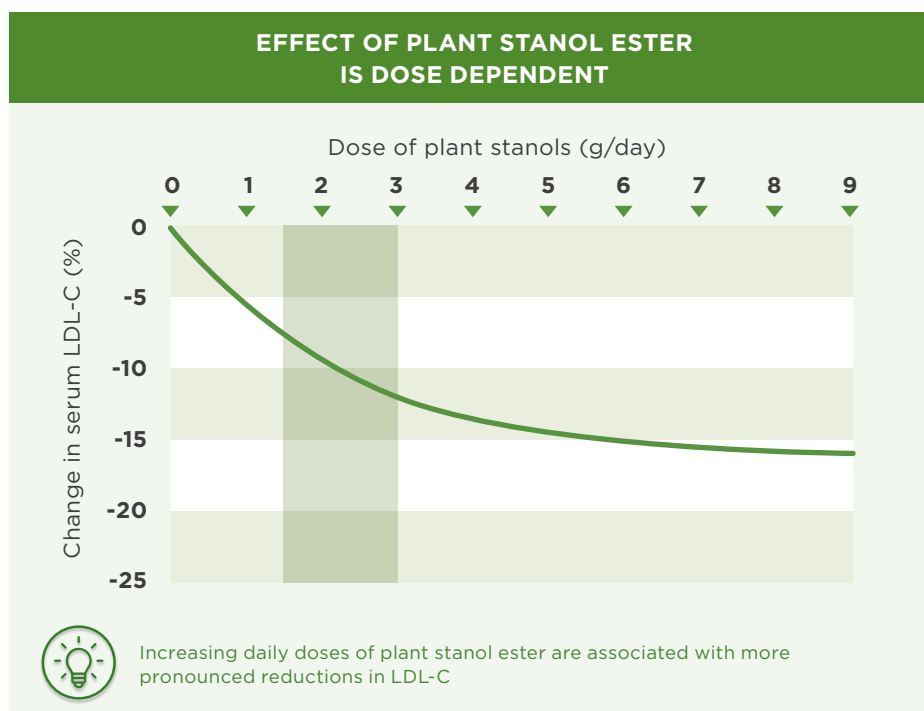
EFFECT OF PLANT STANOL ESTER IS DOSE DEPENDENT

Dose of plant stanols (g/day)

Change in serum LDL-C (%)

Increasing daily doses of plant stanol ester are associated with more pronounced reductions in LDL-C

Fig 11.
For best benefit an intake of around 1.5–3 g plant stanols as plant stanol ester per day is recommendable. If intake is low or irregular the cholesterol-lowering benefit may not be achieved. Higher daily dose gives a better result. Adapted from Musa-Veloso et al. 2011.[56]

LDL-C=low-density lipoprotein cholesterol.

Effective in any type of food

Plant stanol ester needs to be consumed with a meal.[56] This is because lipid-digesting enzymes excreted when a meal is consumed are needed to cleave the plant stanol from the fatty acid, which happens rapidly and allows the plant stanols to work. All plant stanol ester-containing foods therefore need to be consumed with a meal to work, with the exception of cereal bars which are considered a meal themselves.

It is easiest to add plant stanol ester into the fat-phase of a food. In the first clinical studies on plant stanol ester, the ingredient was added to mayonnaise.[64-67] However, margarine was better suited to Finnish eating habits, which is why the first Benecol product launched in Finland in 1995 was a margarine. As a result, the vast majority of the clinical studies have assessed plant stanol ester incorporated into spreads.[26,27,32-36,40-42,48,58-62,68-101]

To date, several product formats have been shown to be suitable matrices for plant stanol ester. Food matrices studied include dairy products like butter,[102] low-fat hard cheese,[103] yogurt,[52,104-108] yogurt drinks,[63,105,109-112] and milk;[105] non-dairy soy-based drinks[113,114] soy-based yogurts;[42] instant coffee mix;[115] cereal products such as biscuits,[116] cereal bars,[90] cakes and cookies,[34] muesli,[117] and pasta.[110] Also the convenience food format has been tested with a meat-based ready-made low-fat meal.[110] Outside the traditional food category the efficacy of plant stanol ester in food supplement form has been tested with capsules[118,119] and chewy pastilles.[120,121]

Plant stanol ester has been shown to lower cholesterol. High cholesterol is a risk factor in the development of coronary heart disease. A daily intake of 1.5–2.4 g plant stanols lowers cholesterol by 7–10% in 2 to 3 weeks. The beneficial effect is obtained with a daily intake of 1.5–3.0 g plant stanols.

Summary

- Functional foods with added plant stanol ester provide a safe and effective way to lower cholesterol as part of a cholesterol-lowering diet

- The cholesterol-lowering effect of the plant stanols in Benecol have been demonstrated in over 80 published clinical studies

- Research has shown that in just 2–3 weeks, a daily intake of 2 grams of plant stanols lowers LDL-C by an average of 10%

- This effect is sustained provided plant stanols are consumed in the recommended quantities as part of daily main meals

Plant stanol ester and risk of ASCVD events

Though well established that plant stanol ester consumption lowers serum LDL-C concentrations safely and effectively, no ASCVD endpoint studies are available for feasibility reasons. The impact on ASCVD risk can be postulated using the extensive evidence supporting LDL-C lowering with regard to the number and risk of coronary events.

It is recognised by clinical experts that there is a lack of practical feasibility to carrying out an outcomes study pertaining specifically to the impact of foods with added plant stanols on CVD prevention. The European Atherosclerosis Society Consensus Panel on Phytosterols concluded that such an intervention would require an extremely large number of subjects (>50,000) and the benefit LDL-C lowering from consumption of foods with added plant stanols,would be difficult to demonstrate definitively in a clinical trial of optimally treated patients at high risk of ASCVD.[29] The Joint British Societies stated in their consensus recommendations for the prevention of cardiovascular disease that "although there is no ASCVD outcome data for such products (and never likely to be), it is reasonable to postulate a beneficial effect on CVD outcomes based on the LDL lowering hypothesis".[122]

LDL-cholesterol has been directly implicated in the development of ASCVD; the well-established linear relationship between lowered LDL-C concentrations and the reduced risk of atherosclerotic CVD events suggests a benefit to morbidity and mortality regardless of the means of LDL-lowering.

An estimation of the reduced risk of ASCVD due to plant stanol ester use is warranted in light of the Silverman *et al.* publication since plant stanols upregulate LDL receptor expression.[10] LDL-lowering regimes that work primarily via upregulation of LDL receptor expression were shown to reduce the risk of ASCVD events to a similar degree as statin treatment.[10] Ezetimibe and plant stanols have similarities

in terms of cholesterol metabolism as both reduce cholesterol absorption and upregulate LDL receptor expression.

Gylling *et al*. (2020) elegantly presented new estimates of the effect of plant stanol ester consumption on LDL-C levels and the risk of ASCVD events.[15] The estimates are based on published data concerning the effect of ezetimibe in reducing the risk of ASCVD events in the IMPROVE-IT study which were matched to the CTT Collaborators' regression line.[8,9]

Gylling *et al.* were interested in determining whether the regression equation presented by the CTT Collaborators could be used to estimate the risk of ASCVD events in relation to plant stanol ester consumption. LDL-C concentrations changes were based on the results of a large published plant stanol meta-analysis and the correlating changes in the risk of ASCVD events were estimated using the CTT Collaborators' regression equation.[9,15,56]

The resulting novel estimations demonstrated that plant stanol consumption of 2 g/d reduced LDL-C concentrations by 0.33 mmol/L, which was expected to reduce the risk of ASCVD events by 6.9%. For plant stanol consumption of 3 g/day, the respective estimates were −0.42 mmol/L and −8.8% (Fig 12). Authors concluded that given the difficulty of investigating the actual clinical outcomes, using the LDL-C reduction data as a surrogate outcome is justified and that plant stanol esters as part of a heart-healthy diet plausibly offer a means to reduce the risk of ASCVD events at a population level.[15]
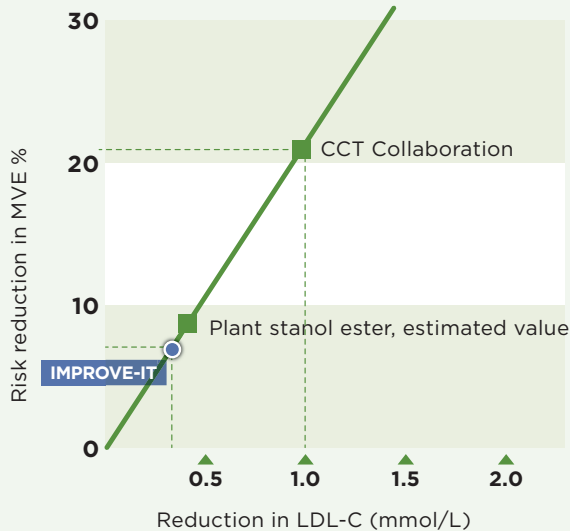
Silverman *et al*.[10] established that lowering LDL-C by non-statin interventions that work primarily via upregulation of LDL receptor expression reduce the risk of ASCVD to a similar extent as statin when standardised to a LDL-C reduction of 1 mmol/L. Plant stanol ester (X) similarly to Ezetimibe[8] reduce cholesterol absorption and upregulate LDL receptor expression and can based on the Silverman *et al*. findings be expected to also reduce the ASCVD risk.

📄 **Summary**

- Though well established that plant stanol ester consumption lowers serum LDL-C concentrations safely and effectively, no ASCVD endpoint studies are available for feasibility reasons

- The impact on ASCVD risk can be postulated using the well-established linear relationship between lowered LDL-C concentrations and the reduced risk of atherosclerotic CVD events

- A novel estimation demonstrated that plant stanol consumption of 2 g/d reduced LDL-C concentrations by 0.33 mmol/L, which was expected to reduce the risk of ASCVD events by 6.9%

- Plant stanol esters as part of a heart-healthy diet plausibly offer a means to reduce the risk of ASCVD events at a population level

ESTIMATED BENEFIT AND REDUCTION OF LDL-C BY PLANT STANOL ESTER CONSUMPTION

Fig 12. Estimated clinical benefit and reduction of LDL-C by plant stanol ester consumption (3 g plant stanols/day) depicted on the regression line published by the Cholesterol Treatment Trialists' Collaboration, and on which the IMPROVE-IT study results were plotted. From Gylling et al. (2020)[15]

MVE = Major Vascular Events; LDL-C=low density lipoprotein cholesterol.

💡 It is possible to estimate the changes in the risk of ASCVD events using existing data investigating plant stanols and LDL-C reduction, and separately LDL-C reduction and risk of ASCVD events. The estimation suggests that plant stanol consumption of 2 g/day may reduce LDL-C concentrations by 0.33 mmol/L, which was expected to reduce the risk of ASCVD events by 6.9%. For plant stanol consumption of 3 g/day, the respective estimates were −0.42 mmol/L and –8.8%.[15]

Effective cholesterol reduction in different subject groups

Approximately half of the adult population in developed countries have elevated cholesterol values.[5] Plant stanol ester has been shown to be equally effective in all different population and patient groups, regardless of age, sex, genetics or dietary preferences.

The efficacy of plant stanol ester has been studied in hypercholesterolaemic individuals with different genetic backgrounds all over the world. Studies have been made in different cultures, each with unique food preferences and dietary patterns. The cholesterol-lowering efficacy of plant stanol ester is proven to be universal in all populations studied, ranging from Finland,[e.g.27,41] Sweden,[97,113] the United Kingdom,[90] the Netherlands,[e.g42,52] Germany,[110] Spain,[63,111] Greece,[91] Turkey,[104] the United States,[35] Canada,[119] Colombia,[112] Japan,[95] Korea,[106] Thailand,[114-116] Australia,[108] to Indonesia.[123]

The relative cholesterol-lowering effect of plant stanol ester is independent of baseline cholesterol values. Subjects with normal or only mildly elevated LDL-C show similar relative LDL-C reduction (of approximately 7–10%)[79,84,106] as hypercholesterolaemic subjects.

Maintaining low cholesterol levels throughout life is the most effective way to prevent coronary events,[17] so cholesterol-lowering dietary tools should be utilised as early as possible; in childhood if needed.[124] Plant stanol ester is an effective and safe tool for cholesterol lowering in both hypercholesterolaemic,[76,88,125] and healthy children,[84,89] shown in children from age 2 years upwards.

Clinical studies have shown that the individual response to plant stanol ester varies. It is not clear whether this is a real phenomenon or a chance finding caused, for example, by normal cholesterol fluctuation or insufficient use of the products. It has been suggested that the serum cholesterol-lowering effect of plant stanol ester might be stronger in people with effective cholesterol absorption, rather than effective synthesis of cholesterol within the body.[126]
Yet, not even studies where the efficacy of cholesterol absorption has been measured at baseline have given any clear answers to this question.[32,73,86]

Primary prevention

Diabetes and metabolic syndrome

Diabetes is an independent risk factor for CVD; thus, managing other CVD risk factors, including serum total cholesterol and LDL-C, is considered essential in both type 1 and type 2 diabetes. Plant stanol ester is a useful strategy for LDL-C reduction in people with type 1 diabetes,[89] also after statin medication has been initiated,[92] as well as in people with type 2 diabetes.[26,33,127]

Metabolic syndrome is a state characterised by an accumulation of risk factors that may lead to development of type 2 diabetes or CVD. Plant stanol ester alone or combined with a low-dose statin, lowered serum non-HDL cholesterol and triacylglycerol in people with metabolic syndrome.[109]

Familial hypercholesterolaemia

Individuals with familial hypercholesterolemia (FH) suffer from genetically elevated LDL-C levels from birth. If left untreated, the risk of premature CVD and mortality is significantly increased in these individuals. A good response to plant stanol ester has been noted in adults both with and without statin medication,[88,96,99] as well as in children with FH.[77,88]

A recent review of the literature concluded that FH patients who use dietary plant stanols from 6 years onwards and a combination of statin and dietary stanol from 10 years onwards, will benefit from a 21% lower LDL-C burden compared with non-treated FH patients.[128]

Secondary prevention

Arterial disease

Once arterial disease is diagnosed, a strict medical plan is initiated to treat risk factors and to prevent future cardiovascular events. In addition to medication, following a heart-healthy diet lowers the risk of any further cardiovascular events.[129] Plant stanol ester offers an effective and recommended means[130] to lower total cholesterol and LDL-C, also in secondary prevention.[32,131]

Summary

- Plant stanol ester has been shown to be equally effective in different population and patient groups, regardless of age, sex, genetics or dietary preferences

- The relative cholesterol-lowering effect of plant stanol ester is independent of baseline cholesterol values

- Maintaining low cholesterol levels throughout life is the most effective way to prevent coronary events, so cholesterol-lowering dietary tools should be utilised as early as possible – in childhood if needed

- Plant stanol ester is an effective and safe tool for cholesterol lowering in all patient groups

⊕ Plant stanol ester complements other lifestyle changes and cholesterol medication

The main principles of a cholesterol-lowering diet are a) replacing saturated fat with unsaturated fat, b) increasing the intake of soluble fibre, and c) using foods with added plant stanol ester.[e.g.126] Adapting any of these changes to a daily diet is beneficial, but together they deliver the best results.

Plant stanol ester is effective in any kind of diet

The reduction in LDL-C achieved with plant stanol ester is independent of the background diet. Plant stanol ester works just as well in a typical 'Western-type' diet with a relatively high content of saturated fat and cholesterol,[e.g.27] as in heart-healthy diets low in saturated fat and cholesterol.[77,78,91,97]
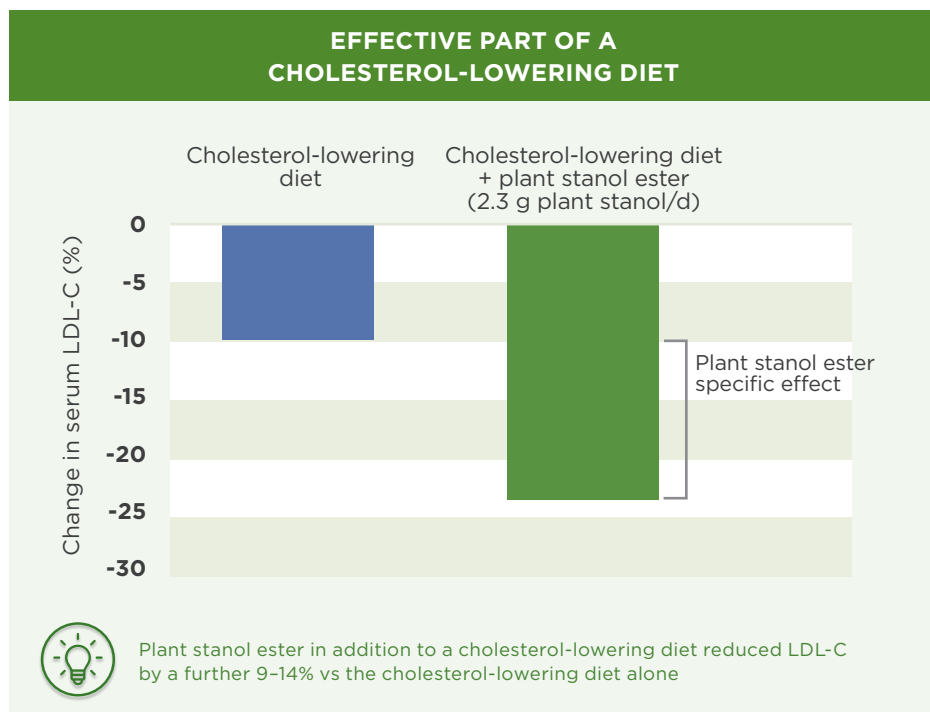
Diets already low in cholesterol do not diminish the cholesterol-lowering effect of plant stanol ester. Dietary cholesterol is only about 30% of cholesterol entering the intestine with the majority of cholesterol deriving from the bile solution secreted by the liver. Therefore, plant stanol ester works effectively also when a low-cholesterol diet is consumed,[78,84,97] reducing the absorption of mainly biliary cholesterol.[32]

The combined cholesterol-lowering effect of plant stanol ester and different types of heart-healthy diets has been examined in several studies. The studies have shown that plant stanol ester is an effective cholesterol-lowering agent as part of a diet that is already healthy and lipid-lowering. Compared to the low-fat diet alone, the low-fat diet with plant stanol ester reduced LDL-C by an additional 9–14% (Fig 13).[78] Similar results have been shown with a strictly controlled lipid-lowering diet[77,97] and in children consuming low-fat, low-cholesterol diets.[84]

**EFFECTIVE PART OF A
CHOLESTEROL-LOWERING DIET**

Cholesterol-lowering
diet

Cholesterol-lowering diet
+ plant stanol ester
(2.3 g plant stanol/d)

Change in serum LDL-C (%)

0, -5, -10, -15, -20, -25, -30

Plant stanol ester
specific effect

Plant stanol ester in addition to a cholesterol-lowering diet reduced LDL-C
by a further 9–14% vs the cholesterol-lowering diet alone

With increasing research data, the perception of a heart-healthy diet has shifted from the strictly low-fat, low-cholesterol diet, to a diet that is not necessarily low in fat, but has a healthy fat composition. One example of this is the traditional Mediterranean diet. Athyros *et al.*[91] compared the effects of plant stanol ester and the Mediterranean diet on blood lipid levels, and estimated the CVD risk in mildly hypercholesterolaemic individuals. Both lipid-lowering strategies were effective in lowering the estimated risk of CVD. With plant stanol ester, the reduction in estimated risk was mainly due to a significant and steady reduction in LDL-C concentration. The Mediterranean diet gradually reduced several of the CVD risk factors, and by 4 months its effects became comparable to those seen in the plant stanol ester group (Fig 14). Although combining plant stanol ester with the Mediterranean diet has not been studied, it can be assumed that this combination would be the most beneficial dietary approach, allowing individuals to benefit from the changes induced by the total diet quality and from the more precise LDL-C reduction achieved with plant stanol ester.
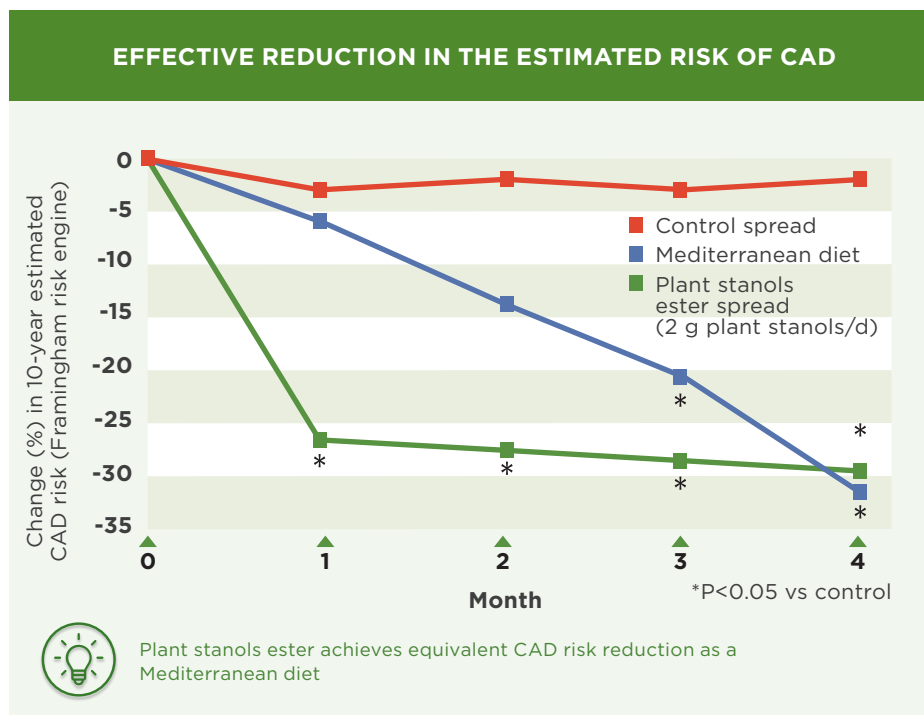
EFFECTIVE REDUCTION IN THE ESTIMATED RISK OF CAD

Fig 14.
A Plant stanols ester is as effective at lowering the estimated risk of CAD as a Mediterranean diet. Adapted from Athyros et al. 2011.[86]

CAD=coronary artery disease.

Plant stanols ester achieves equivalent CAD risk reduction as a Mediterranean diet
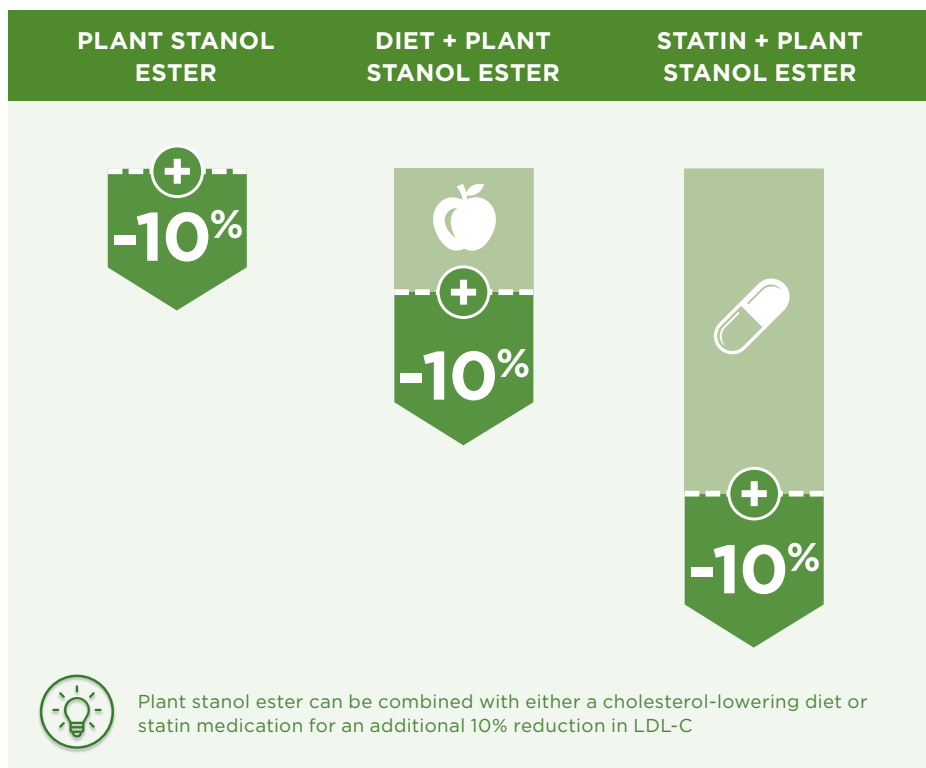
An additive cholesterol-lowering effect to statins

While plant stanol ester partially blocks the absorption of cholesterol in the digestive tract, the most widely used cholesterol-lowering drugs – HMG-CoA reductase inhibitors, or more commonly statins – inhibit the synthesis of cholesterol. Owing to the different mechanisms of action, the cholesterol-lowering effects of statins and plant stanol ester are additive.

Plant stanol ester can be combined with cholesterol-lowering statin medication for additional LDL-C reduction (Fig 15).[e.g. 62,70,92] In clinical studies, dietary plant stanols have been shown to induce an average incremental decrease in plasma LDL-C levels of 10% when added on top of statin therapy. This reduction is superior to that obtained by doubling the statin dose (6–7%).[29,133] Moreover, evidence suggests that 25% of statin-treated patients exhibit inadequate LDL-C lowering as a result of low endogenous cholesterol synthesis, and may benefit more from approaches that target cholesterol absorption.[134]

*Fig 15.
Plant stanol ester
(1.5–3 g of plant
stanols a day) lowers
cholesterol as part of
any kind of lifestyle by
7–12.5% on average.
Best total results are
achieved when other
dietary alterations
are implemented as
well. Combining plant
stanol ester with statin
medication may help
to postpone the need
to increase the statin
dose or help reach
further reduction
when maximal statin
dose is already in use.
Adapted from Gylling
et al. 2014;[29] De Jong
et al. 2008;[62] Blair
et al. 2000.[70]*

*LDL-C=low-
density lipoprotein
cholesterol.*

PLANT STANOL ESTER	DIET + PLANT STANOL ESTER	STATIN + PLANT STANOL ESTER
+
-10%	+
-10%	+
-10%

Plant stanol ester can be combined with either a cholesterol-lowering diet or statin medication for an additional 10% reduction in LDL-C

Plant stanol ester consumption has been studied in various patient groups and populations using statins: hypercholesterolaemic but otherwise healthy individuals,[62,70,71,74,98] adults and children with FH,[88,135] coronary patients,[32,75] cardiac transplant recipients,[87] and people with type 1[92] or type 2 diabetes.[33]

Adherence to statin treatment varies widely,[136] and has been reported to be poor in both the short and long term. Studies indicate that adherence to statin therapy could be improved in those consuming functional cholesterol-lowering foods.[136]

Summary

- The reduction in LDL-C achieved with plant stanol ester is independent of background diet

- Plant stanol ester is an effective cholesterol-lowering agent as part of a diet that is already healthy and lipid lowering

- The distinct mechanism of action of plant stanols for reducing cholesterol absorption in the intestine also enables an additive effect to statins

- Plant stanols can provide an additional 10% improvement in cholesterol lowering compared with statin medication alone

Prevention and treatment guidelines recommending plant stanol ester

The role of plant stanol ester as part of a cholesterol-lowering diet has been acknowledged in prevention and treatment guidelines and position papers issued by international bodies such as the International Atherosclerosis Society,[132] the European Society of Cardiology,[131,132] the European Atherosclerosis Society,[e.g.137, 138] and the World Health Organization.[139]

Clinically proven efficacy and safety have ensured that plant stanol ester has become an integral part of the dietary treatment of high cholesterol in primordial and primary prevention, as well as in different patient groups (table 1, pages 38–39). The European Atherosclerosis Society consensus panel from 2014 defines the target groups for plant stanol ester as:[29]

• Individuals who have elevated serum cholesterol levels and are at low or intermediate global cardiovascular risk but who do not need cholesterol-lowering medication

• High and very high risk patients, such as patients with diabetes, who fail to achieve LDL-C targets on statins alone, or are statin intolerant

• Adults and children (from the age of 6 years) with FH

Patient group	Guideline
Primordial and primary prevention	The Task Force for cardiovascular disease prevention in clinical practice with representatives of the European Society of Cardiology (ESC) and 12 medical societies Visseren FLJ, Mach F, Smulders YM, *et al*. 2021 ESC Guidelines on cardiovascular disease prevention in clinical practice. *Eur Heart J 2021; 42(34): 3227-3337.* The Task Force for the management of dyslipidemias of the European Society of Cardiology (ESC) and the European Atherosclerosis Society (EAS) Mach F, Baigent C, Catapano AL *et al*. ESC/EAS Guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk. *Eur Heart J 2020; 41(1): 111-188.* National Lipid Association Jacobson TA, Ito MK, Maki KC *et al.* National Lipid Association recommendations for patient-centered management of dyslipidemia: part 1 – full report. *J Clin Lipidol 2015; 9(2): 129–169.* Joint British Societies JBS 3 board: Joint British Societies' consensus recommendations for the prevention of cardiovascular disease. *Heart 2014; 100: ii1–ii67.* International Atherosclerosis Society An International Atherosclerosis Society Position Paper: Global recommendations for the management of dyslipidemia. *J Clin Lipidol 2014; 8(1): 29–60.* Joint WHO/FAO Expert Consultation Report of a Joint WHO/FAO Expert Consultation: Diet, nutrition, and the prevention of chronic diseases. *WHO Technical Report Series, No.797 – TRS 797, 2003.*
Familial hypercholesterolaemia	European Atherosclerosis Society • Wiegman A, Gidding SS, Watts GF *et al.* Familial hypercholesterolaemia in children and adolescents: gaining decades of life by optimizing detection and treatment. *Eur Heart J 2015; 36(36): 2425–2437.* • Nordestgaard BG, Chapman MJ, Humphries SE *et al.* Familial hypercholesterolaemia is underdiagnosed and undertreated in the general population: guidance for clinicians to prevent coronary heart disease. Consensus statement of the European Atherosclerosis Society. *Eur Heart J 2013; 34: 3478–3490*.

Patient group	Guideline
Diabetes	American Diabetes Association • Standards of Medical Care in Diabetes. Cardiovascular Disease and Risk Management. *Diabetes Care 2015; 38: S49–S57.* • Evert AB, Boucher JL, Cypress M *et al.* Nutrition therapy recommendations for the management of adults with diabetes. A position statement of American Diabetes Association. *Diabetes Care 2013; 36: 3821–3842.*
Children	National Heart, Lung, and Blood Institute Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents. *Pediatrics 2011; 128: Suppl 5: S1–S44.* American Academy of Pediatrics Stephen R. Daniels, Frank R. Greer and the Committee on Nutrition. Lipid Screening and Cardiovascular Health in Childhood. *Pediatrics 2008; 122: 198–208.* Canadian Cardiovascular Society and Canadian Pediatric Cardiology Association The Detection, Evaluation, and Management of Dyslipidemia in Children and Adolescents *Can J Cardiol 2022; 38(8): 1168-1179.*
Secondary prevention	American Diabetes Association & American College of Cardiology Foundation Brunzell JD, Davidson M, Furberg CD *et al.* Lipoprotein Management in Patients With Cardiometabolic Risk: Consensus Conference Report From the American Diabetes Association and the American College of Cardiology Foundation. *J Am Coll Cardiol 2008; 51: 1512–24.*

⬇ Beyond cholesterol reduction

Effects of plant stanol ester on triglycerides

The effect of plant stanol ester on serum triglyceride concentration seems to be dependent on the baseline values. Plant stanol ester does not have a significant effect on serum triglyceride concentrations in individuals with normal levels.[e.g.27] Plant stanol ester has been shown, however, to lower the concentrations in individuals with elevated baseline serum triglyceride levels.[85,109,140] The higher the baseline value, the larger the reduction, both absolute and relative (Fig 16). Plat and Mensink[141] hypothesised that the effect of plant stanol ester on serum triglyceride concentrations originates from a lowered hepatic production of large triglyceride-rich very low density lipoprotein-1 (VLDL-1) particles, but the exact mechanism is unknown.

PREDICTED RELATIVE CHANGE IN SERUM TRIGLYCERIDES AND LDL-C

Daily intake of plant stenols

Baseline triglycerides 1.0 mmol/L, %reduction in trigly

Baseline triglycerides 2.0 mmol/L, %reduction in trigly

Baseline triglycerides 3.0 mmol/L, %reduction in trigly

Baseline LDL-C 3.0 mmol/L, %reduction in LDL-C

Baseline LDL-C 4.0 mml/L, %reduction in LDL-C

Baseline LDL-C 5.0 mml/L, %reduction in LDL-C

The higher the baseline serum triglyceride level, the greater the reduction in LDL-C achieved with plant stanol ester
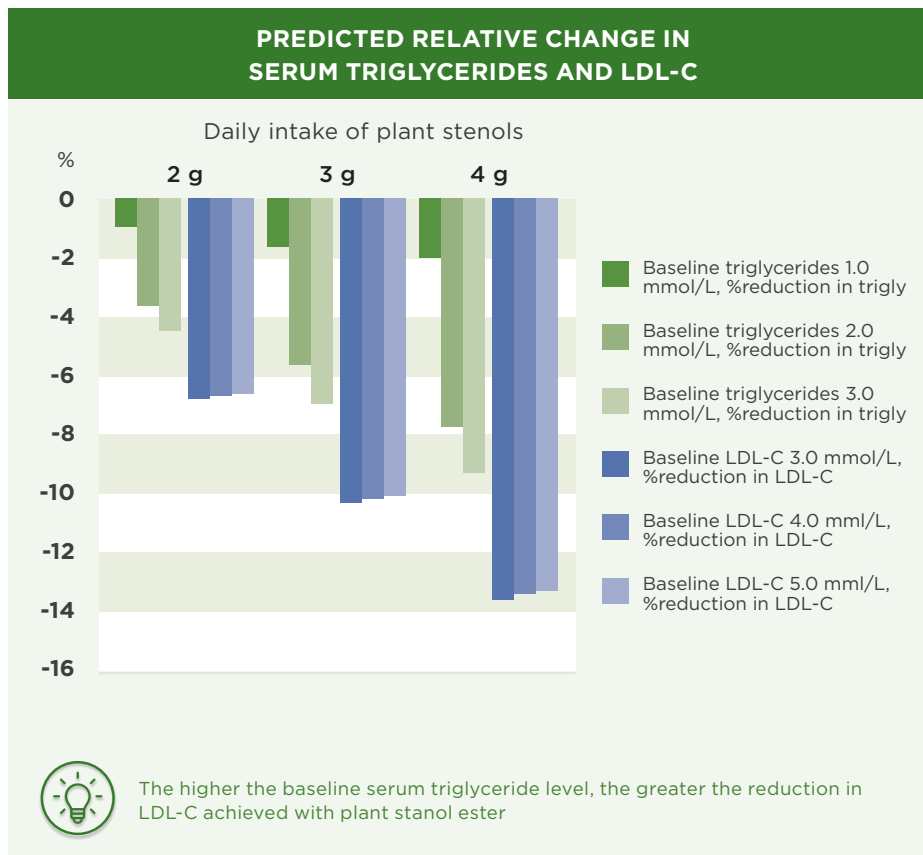
Fig 16. Predicted relative changes in serum triglyceride and LDL-C concentrations at different plant stanol intakes and baseline concentrations. Percentage reductions in LDL-C are dose dependent but of similar magnitude at all baseline concentrations (the blue series). However, percentage reductions in serum triglycerides are also dose dependent but significant reductions are only seen when the baseline concentration is elevated (≥2.0 mmol/L; the green series). Adapted from Naumann et al. 2008.[140]

LDL-C=low-density lipoprotein cholesterol.

Effects of plant stanol ester on arterial health and endothelial function

At population level, even modest reductions in LDL-C level have been shown to significantly decrease the incidence of CHD, and lower LDL-C levels sustained for decades result in lower CHD risk also at individual level.[128,142,143] Despite the well established LDL-C-lowering benefit, however, the endpoint benefit of plant stanol ester on coronary health has not been confirmed in a clinical intervention study.

Endothelial dysfunction is an early indicator of atherosclerotic changes in the vascular wall, preceding the formation of atherosclerotic plaque. This surrogate marker for atherosclerosis development has been used to evaluate the possible health benefit of lowering cholesterol with plant stanol ester. Most intervention studies with plant stanol ester where blood vessel functions have been measured have been conducted in individuals without impaired blood vessel function.[61,72,82,93,94,98,107] Unfortunately, to date, no clinical studies have been conducted using impaired endothelial function as inclusion criteria. Raitakari *et al.*[82] suggested that in individuals with impaired baseline endothelial function, the consumption of plant stanol ester might be associated with beneficial changes in arterial elasticity and endothelial function. There is also indication from a 6-month intervention study that plant stanol ester may counteract the impairment of arterial stiffness in men.[72] Furthermore, in a case-control study by Raitakari *et al.*[81] the arterial elasticity of long-time regular plant stanol ester margarine users was better compared with non-users.

Most of the above mentioned studies were of short dutation (4–16 weeks), the longest intervention lasting for 1 year.[61] As atherosclerosis development is a life-long process, it is likely that a modest LDL-C reduction comparable to that achieved with plant stanol ester consumption will not produce measurable changes in the vascular wall in such a short time. Endothelial function may not be ideal for showing benefit from dietary interventions, as a recent study with improvement in dietary fat quality also failed to show any change in endothelial function despite significant LDL-C reduction.[144] To show clinical benefits from cholesterol lowering with plant stanol ester, other methods may need to be considered.

Accumulation of LCL-C in the arterial wall is known to cause ASCVD. While high plasma concentrations of LDL drive this, LDL quality may also contribute. Ruuth *et al.*[145] examined whether differences in LDL quality were linked with LDL composition and CAD death, identifying the susceptibility of LDL to aggregate as a novel measurable and modifiable factor in the progression of ASCVD. Excess consumption of saturated fats increases LDL-C aggregation susceptibility, while consumption of spread with added plant stanol ester decreases it. Thus, these dietary changes appear to influence, in addition to LDL-C levels, also LDL-C quality and potentially the future risk of ASCVD.[145]

Possible new indications

Current plant stanol ester research looks beyond the cholesterol-lowering effect of this ingredient – the interest is now in possible effects on immunity and inflammation. Initial results from *in vitro* studies indicate that plant stanols may have beneficial immunomodulatory effects in the cells of asthma patients.[146,147] Promising results have also emerged showing that plant stanol ester inhibited hepatic inflammation in mice, suggesting that plant stanol ester could also have a protective effect on non-alcoholic liver inflammation in humans.[148]

In 2016, Brüll *et al.* published the findings of a randomised, double-blind, placebo-controlled intervention investigating the effect of plant stanol esters on immune response in asthma patients. Asthma patients in the plant stanol ester group showed higher antibody levels after vaccination and a substantial reduction in plasma total immunoglobulin E, interleukin-1b, and tumour necrosis factor compared with the control group.[149]

Ongoing research is being undertaken at the Maastricht University Medical Center with a long-term study (follow-up 1 year) involving patients with proven mild asthma who will consume 3 g/d of plant stanols. In addition to evaluating changes in asthma symptoms, changes in lipoprotein metabolism and cardiovascular risk will be explored.[150]

Summary

- Emerging research has explored the benefits of plant stanols further than just LDL-C lowering

- Plant stanol ester has been shown to lower triglyceride concentrations in individuals with elevated baseline serum triglyceride levels

- In individuals with impaired baseline endothelial function, the consumption of plant stanol ester might be associated with beneficial changes in arterial elasticity and endothelial function

- There are possible effects of plant stanols on immunity and inflammation, for example in the immunomodulatory activity in the cells of asthma patients or hepatic inflammation with respect to non-alcoholic liver inflammation

References

1. World Health Organization. Cardiovascular diseases (CVDs) fact sheet. WHO 2021 [online] available at: https://www.who.int/en/news-room/fact-sheets/detail/cardiovascular-diseases-(cvds) (accessed July 2022).

2. World Health Organization. Cardiovascular Diseases. WHO 2022 [online] available at: https://www.who.int/health-topics/cardiovascular-diseases (accessed July 2022).

3. World Health Organization. Cardiovascular diseases: Avoiding heart attacks and strokes. WHO 2015 [online]available at: https://www.who.int/news-room/questions-and-answers/item/cardiovascular-diseases-avoiding-heart-attacks-and-strokes (accessed July 2022)

4. Ference BA, Ginsberg HN, Graham I *et al*. Low-density lipoproteins cause atherosclerotic cardiovascular disease. 1. Evidence from genetic, epidemiologic, and clinical studies. A consensus statement from the European Atherosclerosis Society Consensus Panel. Eur Heart J 2017; 38: 2459–2472.

5. World Health Organization. Raised cholesterol. WHO 2022 [online] available at: https://www.who.int/data/gho/indicator-metadata-registry/imr-details/3236 (accessed July 2022).

6. Baigent C, Blackwell L, Emberson J *et al*. Efficacy and safety of more intensive lowering of LDL cholesterol: a meta-analysis of data from 170,000 participants in 26 randomised trials. Lancet 2010; 376: 1670–1681.

7. Mills EJ, Chong G, Ghement I *et al*. Efficacy and safety of statin treatment for cardiovascular disease: a network meta-analysis of 170,255 patients from 76 randomized trials. QJM 2011; 104: 109–124.

8. Cannon CP, Blazing MA, Giugliano RP *et al*. Ezetimibe added to statin therapy after acute coronary syndromes. N Engl J Med 2015; 18; 372(25): 2387–2397.

9. Cholesterol Treatment Trialists' (CTT) Collaborators. Efficacy and safety of cholesterol-lowering treatment: Prospective meta-analysis of data from 90 056 participants in 14 randomized trials of statins. Lancet 2005; 366: 1267–1278.

10. Silverman MG, Ference BA, Im K, et al. Association between lowering LDL-C and cardiovascular risk reduction among different therapeutic interventions. A systematic review and meta-analysis. JAMA 2016; 316: 1289–1297.

11. Grundy SM, Arai H, Barter P *et al*. Expert Dyslipidemia Panel of the International Atherosclerosis Society Panel members. An International Atherosclerosis Society Position Paper: Global recommendations for the management of dyslipidemia – full report. J Clin Lipidol 2014; 8(1): 29–60.

12. Mach F, Baigent C, Catapano AL *et al*. 2019 ESC/EAS Guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk. Eur Heart J 2020; 41(1): 111-188.

13. Tuzcu EM, Kapadia SR, Tutar E, et al. High prevalence of coronary atherosclerosis in asymptomatic teenagers and young adults: evidence from intravascular ultrasound. Circulation 2001; 103(22): 2705-10.

14. Fernández-Friera L, Fuster V, López-Melgar B *et al*. Normal LDL-cholesterol levels are associated with subclinical atherosclerosis in the absence of risk factors. J Am Coll Cardiol 2017; 70(24): 2979–2991.

15. Gylling H, Strandberg TE, Kovanen PT, et al. Lowering Low-Density Lipoprotein Cholesterol Concentration with Plant Stanol Esters to Reduce the Risk of Atherosclerotic Cardiovascular Disease Events at a Population Level: A Critical Discussion. Nutrients 2020; 12(8): 2346.

16. Won KB et al. Independent role of low-density lipoprotein cholesterol in subclinical coronary atherosclerosis in the absence of traditional cardiovascular risk factors. Eur Heart J Cardiovasc Imaging 2019; 20: 866–872.

17. Ference BA, Yoo W, Alesh I *et al*. Effect of long-term exposure to lower low-density lipoprotein cholesterol beginning early in life on the risk of coronary heart disease: a mendelian randomization analysis. J Am Coll Cardiol 2012; 60: 2631–2639.

18. Cholesterol Treatment Trialists' (CTT) Collaborators. The effects of lowering LDL cholesterol with statin therapy in people at low risk of vascular disease: meta-analysis of individual data from 27 randomised trials. Lancet 2012; 380(9841): 581–590.

19. Leren P. The Oslo Diet-Heart study. Eleven-year report. Circulation 1970; 42(5): 935–942.

20. Myocardial Infarction Genetics Consortium Investigators. Inactivating mutations in NPC1L1 and protection from coronary heart disease. N Engl J Med 2014; 371: 2072–2082.

21. Peterson DW. Effect of soybean sterols in the diet on plasma and liver cholesterol in chicks. Proc Soc Exp Biol Med 1951; 78: 143–147.

22. Piironen V, Toivo J, Lampi A. Natural sources of dietary plant sterols. J Food Compos Anal 2000; 13: 619–624.

23. Piironen V, Toivo J, Lampi AM. Plant sterols in cereals and cereal products. Cereal Chem 2002; 79(1): 148–154.

24. Phillips KM, Tarrago-Trani MT, Stewart KK. Phytosterol content of experimental diets differing in fatty acid composition. Food Chem 1999; 64: 415–422.

25. Valsta LM, Lemstr.m A, Ovaskainen M-L *et al*. Estimation of plant sterol and cholesterol intake in Finland: quality of new values and their effect on intake. Br J Nutr 2004; 92: 671–678.

26. Gylling H, Miettinen TA. Serum cholesterol and cholesterol and lipoprotein metabolism in hypercholesterolaemic NIDDM patients before and during sitostanol ester-margarine treatment. Diabetologia 1994; 37: 773–780.

27. Miettinen TA, Puska P, Gylling H *et al*. Reduction of serum cholesterol with sitostanol-ester margarine in a mildly hypercholesterolemic population. N Engl J Med 1995; 333: 1308–1312.

28. Nissinen M, Gylling H, Vuoristo M *et al*. Micellar distribution of cholesterol and phytosterols after duodenal plant stanol ester infusion. Am J Physiol Gastrointest Liver Physiol 2002; 282: G1009–G1015.

29. Gylling H, Plat J, Turley S *et al*; European Atherosclerosis Society Consensus Panel on Phytosterols. Plant sterols and plant stanols in the management of dyslipidaemia and prevention of cardiovascular disease. Atherosclerosis 2014; 232(2): 346–360.

30. De Smet E, Mensink RP, Plat J. Effects of plant sterols and stanols on intestinal cholesterol metabolism: suggested mechanisms from past to present. Mol Nutr Food Res 2012; 56: 1058–1072.

31. Nakano T, Inoue I, Murakoshi T. A newly integrated model for intestinal cholesterol absorption and efflux reappraises how plant sterol intake reduces circulating cholesterol levels. Nutrients 2019; 11(2): E310.

32. Gylling H, Radhakrishnan R, Miettinen TA. Reduction of serum cholesterol in postmenopausal women with previous myocardial infarction and cholesterol malabsorption induced by dietary sitostanol ester margarine: women and dietary sitostanol. Circulation 1997; 96: 4226–4231.

33. Gylling H, Miettinen TA. Effects of inhibiting cholesterol absorption and synthesis on cholesterol and lipoprotein metabolism in hypercholesterolemic non-insulin-dependent diabetic men. J Lipid Res 1996; 37: 1776–1785.

34. Plat J, van Onselen EN, van Heugten MM *et al*. Effects on serum lipids, lipoproteins and fat soluble antioxidant concentrations of consumption frequency of margarines and shortenings enriched with plant stanol esters. Eur J Clin Nutr 2000; 54: 671–677.

35. Nguyen TT, Dale LC, von Bergmann K *et al*. Cholesterol-lowering effect of stanol ester in a US population of mildly hypercholesterolemic men and women: a randomized controlled trial. Mayo Clinic Proc 1999; 74: 1198–1206.

36. Cater NB, Garcia-Garcia AB, Vega GL *et al*. Responsiveness of plasma lipids and lipoproteins to plant stanols esters. Am J Cardiol 2005; 96(1A): 23D–28D.

37. Blomqvist SM, Jauhiainen M, van Tol A *et al*. Effect of sitostanol ester on composition and size distribution of low- and high-density lipoprotein. Nutr Metab Cardiovasc Dis 1993; 3: 158–164.

38. Ostlund RE Jr, McGill JB, Zeng C-M *et al*. Gastrointestinal absorption and plasma kinetics of soy Δ(5)-phytosterols and phytostanols in humans. Am J Physiol Endocrinol Metab 2002; 282: E911–E916.

39. Lütjohann D, Meese CO, Crouse JR *et al*. Evaluation of deuterated cholesterol and deuterated sitostanol for measurement of cholesterol absorption in humans. J Lipid Res 1993; 34: 1039–1046.

40. Hallikainen MA, Sarkkinen ES, Gylling H *et al*. Comparison of the effects of plant sterol ester and plant stanols ester-enriched margarines in lowering serum cholesterol concentrations in hypercholesterolaemic subjects on a low-fat diet. Eur J Clin Nutr 2000; 54: 715–725.

41. Gylling H, Hallikainen M, Nissinen MJ *et al*. The effect of very high daily plant stanol ester intake on serum lipids, carotenoids, and fat-soluble vitamins. Clin Nutr 2010; 29: 112–118.

42. Mensink RP, de Jong A, Lütjohann D *et al*. Plant stanols dose-dependently decrease LDL-cholesterol concentrations, but not cholesterol-standardized fat-soluble antioxidant concentrations, at intakes up to 9 g/d. Am J Clin Nutr 2010; 92: 24–33.

43. Schiepers OJ, de Groot RHM, van Boxtel MPJ *et al*. Consuming functional foods enriched with plant sterol or stanol esters for 85 weeks does not affect neurocognitive functioning or mood in statin-treated hypercholesterolemic individuals. J Nutr 2009; 139: 1368–1373.

44. Berendschot TT, Plat J, de Jong A *et al*. Long-term plant stanol and sterol ester-enriched functional food consumption, serum lutein/zeaxanthin concentration and macular pigment optical density. Br J Nutr 2009; 101: 1607–1610.

45. Kelly ER, Plat J, Mensink RP *et al*. Effects of long term plant sterol and -stanol consumption on the retinal vasculature: A randomized controlled trial in statin users. Atherosclerosis 2011; 214: 225–230.

46. Laitinen K, Isolauri E, Kaipiainen L *et al.* Plant stanol ester spreads as components of a balanced diet for pregnant and breast-feeding women: evaluation of clinical safety. Br J Nutr 2008; 101: 1979–1804.

47. Gylling H, Puska P, Vartiainen E *et al.* Retinol, vitamin D, carotenes and alfa-tocopherol in a serum of a moderately hypercholesterolemic population consuming sitostanol ester margarine. Atherosclerosis 1999; 145: 279–285.

48. Weststrate JA, Meijer GW. Plant sterol-enriched margarines and reduction of plasma total- and LDL-cholesterol concentrations in normocholesterolaemic and mildly hypercholesterolaemic subjects. Eur J Clin Nutr 1998; 52: 334–343.

49. Raeini-Sarjaz M, Ntanios FY, Vanstone CA *et al.* No changes in serum fat-soluble vitamin and carotenoid concentrations with the intake of plant sterol/stanol esters in the context of a controlled diet. Metabolism 2002; 51: 652–656.

50. Hallikainen MA, Sarkkinen ES, Uusitupa MIJ. Effects of low-fat stanol ester enriched margarines on concentrations of serum carotenoids in subjects with elevated serum cholesterol concentrations. Eur J Clin Nutr 1999; 53: 966–969.

51. Plat J, Mensink RP. Effects of diets enriched with two different plant stanol ester mixtures on plasma ubiquinol-10 and fat-soluble antioxidant concentrations. Metabolism 2001; 50: 520–529.

52. Mensink RP, Ebbing S, Lindhout M *et al.* Effects of plant stanol esters supplied in low-fat yoghurt on serum lipids and lipoproteins, non-cholesterol sterols and fat soluble antioxidant concentrations. Atherosclerosis 2002; 160: 205–213.

53. Noakes M, Clifton P, Ntanios F *et al.* An increase in dietary carotenoids when consuming plant sterols or stanols in effective in maintaining plasma carotenoid concentrations. Am J Clin Nutr 2002; 75: 79–86.

54. Scientific Opinion of the Panel on Dietetic Products, Nutrition and Allergies on a request from McNeil Nutritionals Ltd. related to the scientific substantiation of a health claim on plant stanol esters and lower/reduced blood cholesterol and reduced risk of (coronary) heart disease. EFSA Journal 2008; 825: 1–13.

55. EFSA Panel on Dietetic Products, Nutrition and Allergies (NDA). Scientific Opinion on the substantiation of a health claim related to 3 g/day plant stanols as plant stanol esters and lowering blood LDL-cholesterol and reduced risk of (coronary) heart disease pursuant to Article 14 of Regulation (EC) No 1924/2006. EFSA Journal 2012; 10(5): 2692.

56. Musa-Veloso K, Poon TH, Elliot JA *et al.* A comparison of the LDL-cholesterol lowering efficacy of plant stanols and plant sterols over a continuous dose range: Results of a meta-analysis of randomized, placebo-controlled trials. Prostaglandins Leukot Essent Fatty Acids 2011; 85: 9–28.

57. EFSA Panel on Dietetic Products, Nutrition and Allergies (NDA). Scientific Opinion on the substantiation of a health claim related to 3 g/day plant stanols as plant stanol esters and lowering blood LDL-cholesterol and reduced risk of (coronary) heart disease pursuant to Article 14 of Regulation (EC) No 1924/2006. EFSA Journal 2012; 10(5): 2693.

58. Miettinen TA, Vuoristo M, Nissinen M *et al.* Serum, biliary, and fecal cholesterol and plant sterols in colectomized patients before and during consumption of stanol ester margarine. Am J Clin Nutr 2000; 71: 1095–1102.

59. Hallikainen M, Sarkkinen E, Wester I *et al.* Short-term LDL cholesterol-lowering efficacy of plant stanol esters. BMC Cardiovasc Disord 2002; 2: 14.

60. Jones PJ, Raeini-Sarjaz M, Ntanios FY *et al.* Modulation of plasma lipid levels and cholesterol kinetics by phytosterol versus phytostanol esters. J Lipid Res 2000; 41: 697–705.

61. Gylling H, Hallikainen M, Raitakari OT *et al.* Long-term consumption of plant stanol and sterol esters, vascular function and genetic regulation. Br J Nutr 2008; 101: 1688–95.

62. De Jong A, Plat J, Lütjohann D *et al.* Effects of long-term plant sterol or stanol ester consumption on lipid and lipoprotein metabolism in subjects on statin treatment. Br J Nutr 2008; 100: 937–941.

63. Párraga-Martínez I, López-Torres-Hidalgo JD, Del Campo-Del Campo JM *et al.* Long-term effects of plant stanols on the lipid profile of patients with hypercholesterolemia. A randomized clinical trial. Rev Esp Cardiol (Engl Ed) 2015; 68(8): 665–671.

64. Miettinen TA, Vanhanen H. Dietary sitostanol related to absorption, synthesis and serum level of cholesterol in different apolipoprotein E phenotypes. Atherosclerosis 1994; 105: 217–226.

65. Vanhanen HT, Kajander J, Lehtovirta H *et al.* Serum levels, absorption efficiency, faecal elimination and synthesis of cholesterol during increasing doses of dietary sitostanol esters in hypercholesterolaemic subjects. Clin Sci 1994; 87: 61–67.

66. Vanhanen H. Cholesterol malabsorption caused by sitostanol ester feeding and neomycin in pravastatin treated hypercholesterolaemic patients. Eur J Clin Pharmacol 1994; 47: 169–176.

67. Vanhanen HT, Blomqvist S, Ehnholm C *et al.* Serum cholesterol, cholesterol precursors, and plant sterols in hypercholesterolemic subjects with different apoE phenotypes during dietary sitostanol ester treatment. J Lipid Res 1993; 34: 1535–1544.

68. Alhassan S, Reese KA, Mahurin J *et al*. Blood lipid responses to plant stanol ester supplementation and aerobic exercise training. Metabolism 2006; 55: 541–549.

69. Baumgartner S, Mensink RP, Husche C *et al*. Effects of plant sterol- or stanol-enriched margarines on fasting plasma oxyphytosterol concentrations in healthy subjects. Atherosclerosis 2013; 227: 414–419.

70. Blair SN, Capuzzi DM, Gottlieb SO *et al*. Incremental reduction of serum total cholesterol and low-density lipoprotein cholesterol with the addition of plant stanol ester-containing spread to statin therapy. Am J Cardiol 2000; 86: 46–52.

71. Castro Cabezas M, de Vries JH, van Oostrom AJ *et al*. Effects of a stanol-enriched diet on plasma cholesterol and triglycerides in patients treated with statins. J Am Diet Assoc 2006; 106: 1564–1569.

72. Gylling H, Halonen J, Lindholm H *et al*. The effects of plant stanol ester consumption on arterial stiffness and endothelial function in adults: a randomised controlled clinical trial. BMC Cardiovasc Disord 2013; 13: 50.

73. Gylling H, Miettinen TA. The effect of cholesterol absorption inhibition on low density lipoprotein cholesterol level. Atherosclerosis 1995; 117: 305–308.

74. Gylling H, Miettinen TA. Baseline intestinal absorption and synthesis of cholesterol regulate its response to hypolipidaemic treatments in coronary patients. Atherosclerosis 2002; 160: 477–481.

75. Gylling H, Miettinen TA. LDL cholesterol lowering by bile acid malabsorption during inhibited synthesis and absorption of cholesterol in hypercholesterolemic coronary subjects. Nutr Metab Cardiovasc Dis 2002; 12: 19–23.

76. Gylling H, Siimes MA, Miettinen TA. Sitostanol ester margarine in dietary treatment of children with familial hypercholesterolemia. J Lipid Res 1995; 36: 1807–1812.

77. Hallikainen MA, Sarkkinen ES, Uusitupa MIJ. Plant stanol esters affect serum cholesterol concentrations of hypercholesterolemic men and women in a dose-dependent manner. J Nutr 2000; 130: 767–776.

78. Hallikainen MA, Uusitupa MI. Effects of 2 low-fat stanol ester-containing margarines on serum cholesterol concentrations as part of a low-fat diet in hypercholesterolemic subjects. Am J Clin Nutr 1999; 69: 403–410.

79. Niinikoski H, Viikari J, Palmu T. Cholesterol-lowering effect and sensory properties of sitostanol ester margarine in normocholesterolemic adults. Scand J Nutr 1997; 41: 9–12.

80. Normén L, Dutta P, Lia A *et al*. Soy sterol esters and beta-sitostanol ester as inhibitors of cholesterol absorption in human small bowel. Am J Clin Nutr 2000; 71: 908–913.

81. Raitakari OT, Salo P, Ahotupa M. Carotid artery compliance in users of plant stanol ester margarine. Eur J Clin Nutr 2008; 62: 218–224.

82. Raitakari OT, Salo P, Gylling H *et al*. Plant stanol ester consumption and arterial elasticity and endothelial function. Br J Nutr 2008; 100: 603–608.

83. Relas H, Gylling H, Miettinen TA. Effect of stanol ester on postabsorptive squalene and retinyl palmitate. Metabolism 2000; 49: 473–478.

84. Tammi A, Rönnemaa T, Gylling H *et al*. Plant stanol ester margarine lowers serum total and low-density lipoprotein cholesterol concentrations of healthy children: the STRIP project. Special Turku Coronary Risk Factors Intervention Project. J Pediatr 2000; 136: 503–510.

85. Theuwissen E, Plat J, van der Kallen CJ *et al*. Plant stanol supplementation decreases serum triacylglycerols in subjects with overt hypertriglyceridemia. Lipids 2009; 44(12): 1131–1140.

86. Thuluva SC, Igel M, Giesa U *et al*. Ratio of lathosterol to campesterol in serum predicts the cholesterol-lowering effect of sitostanol-supplemented margarine. Int J Clin Pharmacol Ther 2005; 43: 305–310.

87. Vorlat A, Conraads VM, Vrints CJ. Regular use of margarine-containing stanol/sterol esters reduces total and low-density lipoprotein (LDL) cholesterol and allows reduction of statin therapy after cardiac transplantation: preliminary observations. J Heart Lung Transplant 2003; 22: 1059–1062.

88. Vuorio AF, Gylling H, Turtola H *et al*. Stanol ester margarine alone and with simvastatin lowers serum cholesterol in families with familial hypercholesterolemia caused by the FH-North Karelia mutation. Arterioscler Thromb Vasc Biol 2000; 20: 500–506.

89. Williams CL, Bollella MC, Strobino BA *et al*. Plant stanol ester and bran fiber in childhood: effects on lipids, stool weight and stool frequency in preschool children. J Am Coll Nutr 1999; 18: 572–581.

90. O'Neill FH, Brynes A, Mandeno R *et al*. Comparison of the effects of dietary plant sterol and stanol esters on lipid metabolism. Nutr Metab Cardiovasc Dis 2004; 14: 133–142.

91. Athyros VG, Kakafika AI, Papageorgiou AA *et al.* Effect of a plant stanol ester-containing spread, placebo spread, or Mediterranean diet on estimated cardiovascular risk and lipid, inflammatory and haemostatic factors. Nutr Metab Cardiovasc Dis 2011; 21: 213–221.

92. Hallikainen M, Kurl S, Laakso M *et al.* Plant stanol esters lower LDL cholesterol level in statin-treated subjects with type 1 diabetes by interfering the absorption and synthesis of cholesterol. Atherosclerosis 2011; 217: 473–478.

93. Hallikainen M, Lyyra LT, Laitinen T *et al.* Endothelial function in hypercholesterolemic subjects: effects of plant stanol and sterol esters. Atherosclerosis 2006; 188: 425–432.

94. Hallikainen M, Lyyra-Laitinen T, Laitinen T *et al.* Effects of plant stanol esters on serum cholesterol concentrations, relative markers of cholesterol metabolism and endothelial function in type 1 diabetes. Atherosclerosis 2008; 199: 432–439.

95. Homma Y, Ikeda I, Ishikawa T *et al.* Decrease in plasma low-density lipoprotein cholesterol, apolipoprotein B, cholesteryl ester transfer protein, and oxidized low-density lipoprotein by plant stanol ester-containing spread: a randomized, placebo-controlled trial. Nutrition 2003; 19: 369–374.

96. Ketomäki A, Gylling H, Miettinen TA. Removal of intravenous Intralipid in patients with familial hypercholesterolemia during inhibition of cholesterol absorption and synthesis. Clin Chim Acta 2004; 344: 83–93.

97. Andersson A, Karlstrom B, Mohsen R *et al.* Cholesterol-lowering effects of a stanol ester-containing low-fat margarine used in conjunction with a strict lipid-lowering diet. Eur Heart J Suppl 1999; 1: S80–S90.

98. De Jong A, Plat J, Bast A *et al.* Effects of plant sterol and stanol ester consumption on lipid metabolism, antioxidant status and markers of oxidative stress, endothelial function and low-grade inflammation in patients on current statin treatment. Eur J Clin Nutr 2008; 62: 263–273.

99. Ketomäki A, Gylling H, Miettinen TA. Non-cholesterol sterols in serum, lipoproteins, and red cells in statin-treated FH subjects off and on plant stanol and sterol ester spreads. Clin Chim Acta 2005; 353: 75–86.

100. Kratz M, Kannenberg F, Gramenz E *et al.* Similar serum plant sterol responses of human subjects heterozygous for a mutation causing sitiosterolemia and controls to diets enriched in plant sterols or stanols. Eur J Clin Nutr 2007; 61: 896–905.

101. Ketomäki AM, Gylling H, Antikainen M *et al.* Red cell and plasma plant sterols are related during consumption of plant stanol and sterol ester spreads in children with hypercholesterolemia. J Pediatr 2003; 142: 524–531.

102. Gylling H, Miettinen TA. Cholesterol reduction by different plant stanol mixtures and with variable fat intake. Metabolism 1999; 48: 575–580.

103. Jauhiainen T, Salo P, Niittynen L *et al.* Effects of low-fat hard cheese enriched with plant stanol esters on serum lipids and apolipoprotein B in mildly hypercholesterolaemic subjects. Eur J Clin Nutr 2006; 60: 1253–1257.

104. Buyuktuncer Z, Fisunoglu M, Guven GS *et al.* The cholesterol lowering efficacy of plant stanol ester yoghurt in a Turkish population: a double-blind, placebo-controlled trial. Lipids Health Dis 2013; 12: 91.

105. Seppo L, Jauhiainen T, Nevala R *et al.* Plant stanol esters in low-fat milk products lower serum total and LDL cholesterol. Eur J Nutr 2007; 46: 111–117.

106. Hyun JY, Oh YK, Joo BK *et al.* Plant stanol esters in low-fat yogurt reduces total and low-density lipoprotein cholesterol and low-density lipoprotein oxidation in normocholesterolemic and mildly hypercholesterolemic subjects. Nutr Res 2005; 25: 743–753.

107. Jakulj L, Vissers MN, Rodenburg J *et al.* Plant stanols do not restore endothelial function in prepubertal children with familial hypercholesterolemia despite reduction of low-density lipoprotein cholesterol levels. J Pediatr 2006; 148: 495–500.

108. Noakes M, Clifton PM, Doornbos AM *et al.* Plant sterol ester-enriched milk and yoghurt effectively reduce serum cholesterol in modestly hypercholesterolemic subjects. Eur J Nutr 2005; 44: 214–222.

109. Plat J, Brufau G, Dallinga-Thie GM *et al.* A plant stanol yoghurt drink alone or combined with a low-dose statin lowers serum triacylglycerol and non-HDL-cholesterol in metabolic syndrome patients. J Nutr 2009; 139: 1143–1149.

110. Salo P, Wester I. Low-fat formulations of plant stanols and sterols. Am J Cardiol 2005; 96: 51D–54D.

111. Algorta Pineda J, Chinchetru MJ, Aguirre J *et al.* [Hypocholesteremic effectiveness of a yogurt containing plant stanol esters]. In Spanish. Rev Clin Esp 2005; 205: 63–66.

112. Vásquez-Trespalacios EM, Romero-Palacio J. Efficacy of yogurt drink with added plant stanol esters (Benecol®, Colanta) in reducing total and LDL cholesterol in subjects with moderate hypercholesterolemia: a randomized placebo-controlled crossover trial NCT01461798. Lipids Health Dis 2014; 13: 125.

113. Hallikainen M, Olsson J, Gylling H. Low-fat nondairy minidrink containing plant stanol ester effectively reduces LDL cholesterol in subjects with mild to moderate hypercholesterolemia as part of a western diet. Cholesterol 2013; Article ID 192325: 1–8.

114. Kriengsinyos W, Sumriddetatchajorn K, Yamborisut U. Reduction of LDL-cholesterol in mildly hypercholesterolemic Thais with plant stanol ester-fortified soy milk. J Med Assoc Thai 2011; 94: 1327–1336.

115. Chaiyodsilp S, Chaiyodsilp P, Pureekul T *et al.* A prospective randomized trial for reduction of serum low density lipoprotein (LDL) with plant stanol ester mixed in coffee in a hypercholesterolemic Thai population. Bangkok Med J 2013; 5: 9–12.

116. Kriengsinyos W, Wangtong A, Komindr S. Serum cholesterol reduction efficacy of biscuits with added plant stanol ester. Cholesterol 2015; 2015: 353164.

117. Theuwissen E, Mensink RP. Simultaneous intake of beta-glucan and plant stanol esters affects lipid metabolism in slightly hypercholesterolemic subjects. J Nutr 2007; 137: 583–588.

118. Lagström H, Helenius H, Salo P. Serum cholesterol-lowering efficacy of stanol ester incorporated in gelatin capsules. Scand J Food Nutr 2006; 50: 124–130.

119. Woodgate D, Chan CHM, Conquer JA. Cholesterol-lowering ability of a phytostanol softgel supplement in adults with mild to moderate hypercholesterolemia. Lipids 2006; 41: 127–132.

120. Nissinen MJ, Gylling H, Miettinen TA. Effects of plant stanol esters supplied in a fat free milieu by pastilles on cholesterol metabolism in colectomized human subjects. Nutr Metab Cardiovasc Dis 2006; 16: 426–435.

121. Laitinen K, Simonen P, Ollus A *et al.* Cholesterol lowering efficacy of plant stanol ester chewable food supplement. Poster session presented at: ISA2015 International Symposium on Atherosclerosis; 2015 May 23–26; Amsterdam, The Netherlands.

122. Joint British Societies (JBS) 3 board. Joint British Societies' consensus recommendations for the prevention of cardiovascular disease. Heart 2014; 100: ii1–ii67.

123. Lestiani L, Chandra DN, Laitinen K *et al.* Double-blind randomized placebo controlled trial demonstrating serum cholesterol lowering efficacy of a smoothie drink with added plant stanols ester in an Indonesian population. Cholesterol 2018; 2018: 4857473.

124. National Heart, Lung, and Blood Institute. Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents. Pediatrics 2011; 128(Suppl 5): S1–S44.

125. Ketomäki A, Gylling H, Miettinen TA. Effects of plant stanol and sterol esters on serum phytosterols in a family with familial hypercholesterolemia including a homozygous subject. J Lab Clin Med 2004; 143: 255–262.

126. Plat J, Mackay D, Baumgartner S *et al.* Progress and prospective of plant sterol and plant stanol research: Report of the Maastricht meeting. Atherosclerosis 2012; 22: 521–533.

127. Vuorio A, Kovanen PT. Decreasing the cholesterol burden in heterozygous familial hypercholesterolemia children by dietary plant stanol esters. Nutrients 2018; 10(2): E1842.

128. De Jong. Plant sterols and stanols: effects on lipid metabolism, vascular function and immunity in patients with hypercholesterolemia and type 2 diabetes. Maastricht University 2007.

129. Dehghan M, Mente A, Teo KK *et al*; Ongoing Telmisartan Alone and in Combination With Ramipril Global End Point Trial (ONTARGET)/Telmisartan Randomized Assessment Study in ACEI Intolerant Subjects With Cardiovascular Disease (TRANSCEND) Trial Investigators. Relationship between healthy diet and risk of cardiovascular disease among patients on drug therapies for secondary prevention: a prospective cohort study of 31 546 high-risk individuals from 40 countries. Circulation 2012; 126: 2705–2712.

130. Brunzell JD, Davidson M, Furberg CD *et al.* Lipoprotein management in patients with cardiometabolic risk: consensus conference report from the American Diabetes Association and the American College of Cardiology Foundation. J Am Coll Cardiol 2008; 51: 1512–1524.

131. Gylling H, Rajaratnam R, Vartiainen E *et al.* Changes in serum level and metabolism of cholesterol with plant stanol esters in postmenopausal women with and without coronary artery disease. Menopause 2006; 13: 286–293.

132. Expert Dyslipidemia Panel of the International Atherosclerosis Society Panel members. An International Atherosclerosis Society Position Paper: Global recommendations for the management of dyslipidemia. J Clin Lipidol 2014; 8(1): 29–60.

133. National Institute for Health and Care Excellence. Cardiovascular disease: risk assessment and reduction, including lipid modification. NICE 2016 [online] available at: https://www.nice.org.uk/guidance/cg181/chapter/Appendix-A-Grouping-of-statins (accessed September 2019).

134. Lütjohann D, Stellaard F, Mulder MT *et al*. The emerging concept of "individualized cholesterol-lowering therapy": A change in paradigm. Pharmacol Ther 2019; 199: 111–116.

135. Hedman M, Miettinen TA, Gylling H *et al*. Serum noncholesterol sterols in children with heterozygous familial hypercholesterolemia undergoing pravastatin therapy. J Pediatr 2006; 148: 241–246.

136. Ofori-Asenso R, Jakhu A, Zomer E *et al*. Adherence and persistence among statin users aged 65 years and over: a systematic review and meta-analysis. J Gerontol A Biol Sci Med Sci 2018; 73(6): 813–819.

137. The Task Force for the management of dyslipidemias of the European Society of cardiology (ESC) and the European Atherosclerosis Society (EAS). ESC/EAS Guidelines for the management of dyslipidemias. Eur Heart J 2011; 32: 1769–1818.

138. Piepoli MF, Hoes AW, Agewall S *et al*. 2016 European Guidelines on cardiovascular disease prevention in clinical practice: The Sixth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of 10 societies and by invited experts) Developed with the special contribution of the European Association for Cardiovascular Prevention & Rehabilitation (EACPR). Atherosclerosis 2016; 252: 207–274.

139. Report of a Joint WHO/FAO Expert Consultation. Diet, nutrition, and the prevention of chronic diseases. WHO Technical Report Series, No. 797 – TRS 797, 2003.

140. Naumann E, Plat J, Kester AD *et al*. The baseline serum lipoprotein profile is related to plant stanol induced changes in serum lipoprotein cholesterol and triacylglycerol concentrations. J Am Coll Nutr 2008; 27: 117–126.

141. Plat J, Mensink RP. Plant stanol esters lower serum triacylglycerol concentrations via a reduced hepatic VLDL-1 production. Lipids 2009; 44: 1149–1153.

142. Vartiainen E, Laatikainen T, Peltonen M *et al*. Thirty-five-year trends in cardiovascular risk factors in Finland. Int J Epidemiol 2010; 39: 504–518.

143. Björck L, Capewell S, O'Flaherty M *et al*. Decline in coronary mortality in Sweden between 1986 and 2002: comparing contributions from primary and secondary prevention. PLoS ONE 2015; 10(5): e0124769.

144. Vafeiadou K, Weech M, Altowaijri H *et al*. Replacement of saturated with unsaturated fats had no impact on vascular function but beneficial effects on lipid biomarkers, E-selectin, and blood pressure: results from the randomized, controlled Dietary Intervention and VAScular function (DIVAS) study. Am J Clin Nutr 2015; pii: ajcn097089.

145. Ruuth M, Nguyen SD, Vihervaara T *et al*. Susceptibility of low-density lipoprotein particles to aggregate depends on particle lipidome, is modifiable, and associates with future cardiovascular deaths. Eur Heart J 2018; 39(27): 2562–2573.

146. Brüll F, Mensink RP, Steinbusch MF *et al*. Beneficial effects of sitostanol on the attenuated immune function in asthma patients: results of an In Vitro approach. PLoS ONE 2012; 7: e46895.

147. Brüll F, Mensink RP, van den Hurk K *et al*. TLR2 activation is essential to induce a Th1 shift in human pheripheral blood mononuclear cells by plant stanols and plant sterols. J Biol Chem 2010; 285(5): 2951–2958.

148. Plat J, Hendrikx T, Bieghs V *et al*. Protective role of plant sterol and stanol esters in liver inflammation: insights from mice and humans. PLoS One 2014; 9: e110758.

149. Brüll F, De Smet E, Mensink RP *et al*. Dietary plant stanol ester consumption improves immune function in asthma patients: results of a randomized, double-blind clinical trial. Am J Clin Nutr 2016; 103(2): 444–453.

150. ClinicalTrials.gov. Plant stanol esters and preventing asthma symptoms (PLANTASTIC). ClinicalTrials.gov 2019 [online] available at: https://clinicaltrials.gov/ct2/show/study/NCT03983603?term=plant+stanol&cond=Asthma&rank=1 (accessed September 2019).

151. Plat, J.; Mensink, R.P. Effects of plant stanol esters on LDL receptor protein expression and on LDL receptor and HMG-CoA reductase mRNA expression in mononuclear blood cells of healthy men and women. FASEB J. 2002, 16, 258–260.