Plant sterols and plant stanols in the management of dyslipidaemia and prevention of cardiovascular disease

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Review

Plant sterols and plant stanols in the management of dyslipidaemia and prevention of cardiovascular disease

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This European Atherosclerosis Society (EAS) Consensus Panel dedicates this Position paper to the memory of Professor Tatu Miettinen, a pioneer in the study of the impact of plant sterols/stanols on cholesterol absorption and homeostasis.

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Safety

Intestinal cholesterol absorption
Phytosterols

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Abstract

Objective: This EAS Consensus Panel critically appraised evidence relevant to the benefit to risk relationship of functional foods with added plant sterols and/or plant stanols, as components of a healthy lifestyle, to reduce plasma low-density lipoprotein-cholesterol (LDL-C) levels, and thereby lower cardiovascular risk.

Methods and results: Plant sterols/stanols (when taken at 2 g/day) cause significant inhibition of cholesterol absorption and lower LDL-C levels by between 8 and 10%. The relative proportions of cholesterol versus sterol/stanol levels are similar in both plasma and tissue, with levels of sterols/stanols being 500-10,000-fold lower than those of cholesterol, suggesting they are handled similarly to cholesterol in most cells. Despite possible atherogenicity of marked elevations in circulating levels of plant sterols/stanols, protective effects have been observed in some animal models of atherosclerosis. Higher plasma levels of plant sterols/stanols associated with intakes of 2 g/day in man have not been linked to adverse effects on health in long-term human studies. Importantly, at this dose, plant sterol/stanol-mediated LDL-C lowering is additive to that of statins in dyslipidaemic subjects, equivalent to doubling the dose of statin. The reported 6–9% lowering of plasma triglyceride by 2 g/day in hypertriglyceridaemic patients warrants further evaluation.

Conclusion: Based on LDL-C lowering and the absence of adverse signals, this EAS Consensus Panel concludes that functional foods with plant sterols/stanols may be considered 1) in individuals with high cholesterol levels at intermediate or low global cardiovascular risk who do not qualify for pharmacotherapy, 2) as an adjunct to pharmacologic therapy in high and very high risk patients who fail to achieve LDL-C targets on statins or are statin-intolerant, 3) and in adults and children (>6 years) with familial hypercholesterolaemia, in line with current guidance. However, it must be acknowledged that there are no randomised, controlled clinical trial data with hard end-points to establish clinical benefit from the use of plant sterols or plant stanols.

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1. Introduction and rationale

The on-going pandemic of obesity, metabolic syndrome and diabetes is directly associated with an ever-increasing worldwide incidence of premature atherosclerosis and cardiovascular disease (CVD). Indeed, the European Union budget for CVD is currently estimated at €196 billion a year, with about one-half of this attributed to direct healthcare costs [1]. However, limiting the expenditure for CVD to the healthcare systems of the European Union grossly underestimates its true cost. Most public health expenses are linked to treatment, a notion which strongly argues for urgent investment in CVD prevention to improve health in European populations and to stem the socioeconomic consequences.

Recent studies of the relationship of lifetime risk of CVD to risk factor burden clearly indicate that individuals with an optimal risk factor profile, (including well-controlled blood pressure and cholesterol, non-smoking and non-diabetic), display substantially lower risk of CV events over their lifetime than those with two or more of these major risk factors [2]. Ranking of nine CV risk factors in the INTERHEART cross-sectional study in 52 countries revealed that dyslipidaemia alone accounted for most of the population-attributable risk for myocardial infarction; here, dyslipidaemia was defined as an excess of cholesterol transported in atherogenic apolipoprotein (apo)B-containing lipoproteins (among which low-density lipoproteins [LDL] predominate), relative to that in non-atherogenic apoA-I-containing, high-density lipoproteins (HDL) [3].

Robust data attest to the causal role of LDL-cholesterol (LDL-C) in coronary atherosclerosis. Reductions in LDL-C levels achieved by treatment with diet, statins or bile acid sequestrants, or by ileal bypass surgery, in prospective clinical trials of 3 or more years duration, have been demonstrated in meta-regression analyses to significantly reduce CV morbidity and mortality [4,5].

As atherosclerosis is a chronic, progressive disease typically initiated during the first three decades of life, it follows that lowering LDL-C early may substantially delay or even prevent the onset of atherosclerosis, particularly in the coronary circulation. Indeed, evidence that prolonged exposure to low plasma LDL-C levels is associated with markedly greater reduction in CV risk compared with current strategies aimed at lowering LDL-C in middle age, has been provided by a meta-analysis of Mendelian randomisation studies, involving polymorphisms in six distinct genes of cholesterol metabolism [6].

These findings prompt a key question: How can LDL-C be maintained at low levels throughout life without imposing additional burden on the healthcare system? Clearly, lifestyle, which encompasses dietary habits, must be seriously considered, particularly as extensive nutritional and behavioural changes may lower LDL-C levels by up to 20% [7].

The liver is the principal regulator of circulating LDL-C levels. Not only is it the site of formation of very low-density lipoproteins (VLDL), the precursors of most LDL particles in the circulation, but it is also the site of most receptor-mediated clearance of LDL [8]. Both the liver and intestine are central to body cholesterol homeostasis. Indeed, after lipolysis-mediated removal of dietary triglycerides from chylomicrons, the liver rapidly clears circulating chylomicron remnants, which carry cholesterol that was absorbed in the small intestine [9]. The resultant increase in hepatic cholesterol stimulates VLDL secretion and hence LDL formation, and down-regulates hepatic LDL receptor activity. Such events potentially lead to elevations in plasma LDL-C levels. Both chylomicron remnants and VLDL remnants, in addition to LDL, can deliver cholesterol to the artery wall, initiating or exacerbating atherosclerosis. When cholesterol absorption in the small intestine was inhibited by ezetimibe in apoE deficient mice, atherosclerosis was dramatically reduced [10].

In humans, inhibition of cholesterol absorption by ezetimibe results in lowering of plasma LDL-C levels because of increased fractional removal of LDL from the circulation, consistent with less dietary cholesterol arriving at the liver via chylomicron remnants with subsequent upregulation of LDL receptors [11,12]. Inhibition of cholesterol absorption by ezetimibe was also associated with reduced chylomicron secretion into plasma as determined by reduced production of apoB48 (Fig. 1) [12].

Thus it follows that the cholesterol absorption pathway represents an attractive target in the management of dyslipidaemia, with a specific focus on both reducing the cholesterol content of chylomicron and VLDL remnants and lowering LDL-C levels. This pathway presents clinical opportunities for dietary supplementation with agents that attenuate intestinal cholesterol absorption, among which plant sterols and plant stanols are prominent.

The European Atherosclerosis Society (EAS) convened an international Consensus Panel of basic scientists and clinical investigators with expertise in cholesterol metabolism, plant sterol and plant stanol biology, and CVD. Our goals were (i) to critically appraise state-of-the-art knowledge pertaining to the potential of plant sterols and plant stanols (hereafter referred to as plant sterols/stanols) for lowering LDL-C, with a view to prevents premature atherosclerosis and CVD, and (ii) to propose recommendations for optimal integration of foods with added plant sterols/stanols, as part of a healthy lifestyle, for attenuation of CV risk. These recommendations can provide guidance and support for clinicians and health professionals in the prevention of CVD across the spectrum of CV risk.

2. Biology and mode of action of plant sterols/stanols

2.1. Origins

Plant sterols/stanols are bioactive components with similar functions as that of cholesterol in mammals. Plant sterols are steroid alkaloids which differ from cholesterol in the structure of their

![Fig. 1. Scheme illustrating the potential impact of cholesterol absorption from the small intestine on plasma levels of chylomicron remnants and LDL, with detrimental effects on the vascular wall. Cholesterol (Chol, C) entering the intestinal lumen primarily from the bile and the diet is absorbed to varying degrees and packaged in chylomicrons (CM-C) for transport via the lymph into the circulation. Therein, hydrolysis of much of the triacylglycerol present in the nascent CM results in the formation of cholesterol-rich remnant particles (CMr-C) that are ordinarily rapidly cleared from the circulation by the liver. Delivery of excess intestinal cholesterol to the liver can result in suppression of low density lipoprotein-receptor (LDL-R) activity and endogenous cholesterol synthesis, or acceleration of hepatic very low density lipoprotein-cholesterol (VLDL-C) secretion, or both. Such events will potentially raise plasma LDL-cholesterol (LDL-C) concentration. If hepatic clearance of CMs is delayed, then these particles may contribute directly to plaque formation. Together, these various pathways illustrate how agents that limit cholesterol absorption may elicit favourable changes in atherogenic plasma lipoproteins that culminate in attenuating plaque formation.](image-url)
side chain, while plant stanols are 5α-saturated derivatives of plant sterols (Fig. 2).

The main food sources of plant sterols are vegetable oils, spreads and margarines, breads, cereals, and vegetables (Table 1); these contribute 50–80% of the daily plant sterol intake, with fruits adding a further 12% [13–15]. In the typical Western diet, the mean daily intake of plant sterols is about 300 mg [13,14], but can be as high as 600 mg in vegetarians [16]. The most abundant are sitosterol and campesterol, which contribute 60% and 20%, respectively, of plant sterol intake [13,14]. By comparison, the amounts of plant stanols in the diet are much lower, with only about 17–24 mg per day (predominantly sitostanol and campestanol) [14]. Cereals, especially wheat and rye, are the richest source of plant stanols.

2.2. Transport and circulating levels

These dietary components undergo low fractional absorption in the intestine, of the order of 0.5–2% for plant sterols and 0.04–0.2% for plant stanols [17]. As a result of low absorption and efficient excretion into bile after uptake by the liver, circulating levels are low, varying from 7 to 24 μmol/L (0.3–1.0 mg/dL) for plant sterols, and from 0.05 to 0.3 μmol/L (0.002–0.012 mg/dL) for plant stanols [18]; these levels are of the order of 500-fold and 10,000-fold lower, respectively, than those of cholesterol.

Long-term consumption of foods with added plant sterols (mean intake ± standard deviation [SD] 1.1 ± 0.6 g/day) increases their circulating levels (from 19 to 30 μmol/L [0.8–1.2 mg/dL] with plant sterol consumption), and a decrease in circulating plant sterols (from 16 to 23%), were observed [19]. The quantitative distribution of plant sterols/stanols across the major lipoprotein classes is similar to that of cholesterol, and thus they circulate primarily in LDL particles (65–70%).

### Table 1
Plant sterol and plant stanol contents in different foods. Data are given as mg/100 g (dry weight, either range or mean value).

<table>
<thead>
<tr>
<th>Food item</th>
<th>Plant sterols</th>
<th>Plant stanols</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vegetable oils</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Corn oil</td>
<td>686–952</td>
<td>23–33</td>
</tr>
<tr>
<td>Rapeseed oil (canola oil)</td>
<td>250–767</td>
<td>2–12</td>
</tr>
<tr>
<td>Soybean oil</td>
<td>221–328</td>
<td>7</td>
</tr>
<tr>
<td>Sunflower oil</td>
<td>263–376</td>
<td>4</td>
</tr>
<tr>
<td>Olive oil</td>
<td>144–193</td>
<td>0.3–4</td>
</tr>
<tr>
<td>Palm oil</td>
<td>60–78</td>
<td>Traces</td>
</tr>
<tr>
<td>Cereals</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Corn</td>
<td>66–178</td>
<td>–</td>
</tr>
<tr>
<td>Rye</td>
<td>71–113</td>
<td>12–22</td>
</tr>
<tr>
<td>Wheat</td>
<td>45–83</td>
<td>17</td>
</tr>
<tr>
<td>Barley</td>
<td>80</td>
<td>2</td>
</tr>
<tr>
<td>Millet</td>
<td>77</td>
<td>–</td>
</tr>
<tr>
<td>Rice</td>
<td>72</td>
<td>3</td>
</tr>
<tr>
<td>Oats</td>
<td>35–61</td>
<td>1</td>
</tr>
<tr>
<td>Nuts</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peanuts</td>
<td>320</td>
<td>–</td>
</tr>
<tr>
<td>Almond</td>
<td>143</td>
<td>–</td>
</tr>
<tr>
<td>Vegetables</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Broccoli</td>
<td>39</td>
<td>2</td>
</tr>
<tr>
<td>Cauliflower</td>
<td>18–40</td>
<td>Traces</td>
</tr>
<tr>
<td>Carrot</td>
<td>12–16</td>
<td>Traces</td>
</tr>
<tr>
<td>Lettuce</td>
<td>9–17</td>
<td>0.5</td>
</tr>
<tr>
<td>Potato</td>
<td>7</td>
<td>0.6</td>
</tr>
<tr>
<td>Tomato</td>
<td>7</td>
<td>1</td>
</tr>
<tr>
<td>Fruits and berries</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Avocado</td>
<td>75</td>
<td>0.5</td>
</tr>
<tr>
<td>Passion fruit</td>
<td>44</td>
<td>Not detected</td>
</tr>
<tr>
<td>Raspberry</td>
<td>27</td>
<td>0.2</td>
</tr>
<tr>
<td>Orange</td>
<td>24</td>
<td>Not detected</td>
</tr>
<tr>
<td>Apple</td>
<td>12–18</td>
<td>0.8</td>
</tr>
<tr>
<td>Banana</td>
<td>12–16</td>
<td>Not detected</td>
</tr>
</tbody>
</table>

*Not reported.*

Source: Adapted from Piironen V & Lampi AM (2004) [15].

![Fig. 2. Chemical structure of plant stanols and plant sterols.](image)
The ATP-binding cassette co-transporters G5 and G8 (ABCG5/ABCG8) play a crucial role in controlling the absorption of plant sterols/stanols by secreting absorbed molecules back into the intestinal lumen [20,21]. In phytosterolaemia, severe loss of function mutations in genes coding for the ABCG5/ABCG8 transporters result in dramatic elevation in plasma plant sterol/stanol levels, which are more than 50-fold higher than those in normal individuals after consumption of plant sterols, and many of these individuals develop premature atherosclerosis (Box 1) [20–22]. Further consideration of this rare genetic disease is, however, beyond the scope of the present paper, which is focussed on plant sterol/stanol consumption as part of a healthy diet for prevention of CVD.

2.3. Tissue levels

There are limited data available for tissue levels in subjects receiving foods with added plant sterols/stanols. In healthy human subjects, plant sterols/stanols are taken up into tissues in similar proportions relative to cholesterol, and the ratio of cholesterol to plant sterols/stanols, which displays a wide range (0.001–0.01 × 10^−6), is similar to or less than that in plasma, consistent with the absence of preferential accumulation or retention in tissues (see Supplementary Table 1). Similar findings have been reported for cerebrospinal fluid and brain tissue in healthy control subjects, and also in phytosterolaemia [23,24]. In healthy volunteers, data on tissue plant sterol/stanol levels are available for the carotid artery wall and for non-stenotic and stenotic aortic valve cusps [25–28]. In these tissues, cholesterol content is 20 μg/mg of tissue, while total plant sterol and plant stanol concentrations are ~0.04 μg/mg and ~0.001 μg/mg of tissue, respectively. Plant sterol concentrations vary widely between tissues (see Supplementary Table 1) [25–30].

During consumption of plant sterol-enriched foods, there was a 5-fold elevation in campesterol in stenotic aortic valve cusps [28]. However, in another study, the concentration of plant stanols in the arterial wall was not modified during consumption of foods enriched with plant stanols [27]. Clearly, there is a need for large, long-term clinical studies to exclude the possibility that consumption of dietary plant sterols/stanols might result in accumulation in arterial tissues, and evaluation of these agents as modulators of plaque formation or regression is equally of interest. Such studies present multiple methodological challenges, not least of which is access to plaque tissue for analysis of sterol composition, and for determination of the expression profile of key genes of cholesterol and plant sterol metabolism.

2.4. Markers of intestinal cholesterol absorption and synthesis

Serum cholesterol precursors and plant sterols, especially when expressed as ratios relative to cholesterol, can constitute markers of the rates of synthesis and absorption of cholesterol in nondyslipidaemic subjects, as well as in several clinical conditions including primary and familial hypercholesterolaemia (FH), obesity and type 2 diabetes, and during some interventions including plant stanol consumption [31,32]. Overall, such markers have good validity, but there are exceptions (see Supplementary Appendix) [31–33], and full validation in multiple conditions is essential. Moreover, there are a number of methodological issues relating to standardisation of these markers. An on-going survey is investigating the degree of variability in sterol/stanol analytical data across different laboratories (see Supplementary Appendix).

2.5. Intestinal handling of cholesterol and non-cholesterol sterols: mechanism by which plant sterols/stanols added to the diet inhibit the absorption of cholesterol

The handling of sterols and stanols entering the intestinal lumen from the diet and bile is essentially a triphasic process (Fig. 3) [34–37]. The first phase is largely physicochemical in nature, occurs intraluminally, and culminates in the incorporation of cholesterol and other sterols and stanols into mixed micelles that serve as vehicles to carry these poorly water-soluble substances up to the surface of the brush border membrane on the enterocyte. This solubilisation step is essential for the subsequent entry of any type of sterol into the absorptive cell, from where it may potentially reach the circulation.

The second major phase is the uptake of cholesterol and other sterols or stanols into the enterocyte, a process that is facilitated by a plasma membrane-localised, general sterol transporter protein, Niemann-Pick C1-like 1 (NPC1L1). Within the absorptive cells, sterols undergo different fates, depending mainly on their chemical structure. Collectively, these events within the enterocyte broadly constitute the third major phase of intestinal handling. The bulk of the cholesterol is esterified by acyl CoA: cholesterol acyltransferase-2 (ACAT2) and incorporated into nascent chylomicrons, which initially enter the lymph before joining the circulation via the thoracic duct [38,39]. The absolute content of plant sterols/stanols in chylomicrons is markedly lower than that of cholesterol, with up to 50% in esterified form [39]. Importantly, the bulk of plant sterols/stanols is pumped back into the gut lumen via the ABCG5/ABCG8 transporter, resulting in minimal entry of these plant-derived molecules into the circulation [34,40,41]. Finally, foods with added gram quantities of plant sterols/stanols cause a significant inhibition of cholesterol absorption, most likely through disruption of the intraluminal solubilisation step [37], although other possible mechanistic explanations have been proposed [42].
As discussed above, the ABCG5/G8 genes play a crucial role in regulating circulating levels of plant sterols [20,21]. In the KORA study, common variants of rs41360247 and rs4245791 in the ABCG8 gene accounted for 8% of the variance in circulating levels of plant sterols [43]. The relationships of these and other variants in high linkage disequilibrium with circulating plant sterol levels have been confirmed in the CARLA, LURIC, and YFS cohorts [43,44].

3. Lipid modifying effects of plant sterols/stanols

3.1. LDL cholesterol lowering

Epidemiological studies in the UK (n = 22,256), Sweden (n = 77,652) and China (n = 3940) observed that naturally-occurring dietary plant sterol intake is inversely related to plasma total- and LDL-C levels [45–47]. However, in a well-controlled study in healthy subjects, low (126 mg plant sterols/2000 kilocalories) or high intake of plant sterols (449 mg plant sterols/2000 kilocalories) did not affect plasma LDL-C concentrations in spite of modulating cholesterol metabolism [48]. Furthermore, even at the highest levels of dietary intake, plant sterols/stanols occurring naturally in the diet have a modest hypocholesterolaemic effect. On the other hand, when natural plant sterols were omitted from the diet, serum LDL-C concentrations increased [49].

In contrast to the minimal effects of variation in consumption of naturally-occurring plant sterols/stanols in the diet, early studies such as that by Farquhar et al. (1956) demonstrated that beta-sitosterol supplementation lowered both total serum cholesterol and LDL-C (as beta-lipoprotein lipid) in young men with atherosclerotic heart disease [50]. Subsequently, Miettinen et al. (1995) demonstrated for the first time that foods (such as margarine, see Box 2) enriched with sitostanol ester lowered both total serum cholesterol and LDL-C in mildly hypercholesterolaemic subjects [51].

Subsequent data show consistent support for the LDL-C lowering effects of foods with added plant sterols/stanols [52–54]. In the most recent meta-analysis, consumption of foods with added plant sterols/stanols (2 g/day) lowered LDL-C to a similar extent (8.2% and 9.3%, respectively) [54]. Regrettably, there is a paucity of data relating to the potential of higher plant sterol/stanol doses to further lower LDL-C levels, and thus CV risk [6,54,55]. It has been suggested that maximal LDL-C lowering may be greater with plant stanols (up to 16%) and plant stanol esters (17%), but this conclusion relies on limited studies using doses of 4–9 g/day, none of which involved direct head-to-head comparisons with plant sterols. Whether there is a position for plant sterol and/or plant stanol intakes to be raised higher than those currently recommended (2–3 g/day) in prevention strategies for the general population remains open. The fact that there is consistent, robust evidence indicating that lowering of LDL-C by different mechanisms (statins, diet, partial ileal bypass, bile acid sequestrants) results in reduction in CV risk, underlies the rationale for inclusion of plant sterols/stanols in international clinical guidelines for the management of dyslipidaemia [5,56]. In this context, it must be recognised that the use of functional foods enriched with plant sterols/stanols is currently not advised for children under 6 years. There is, however, a substantial database showing consistent LDL-C lowering efficacy in children. In controlled clinical trials in children

Box 2

Types of foods with added plant sterols or plant stanols

| Low-fat spread/margarine |
| Yoghurt drinks |
| Dairy-free drinks |
| Low- or reduced-fat milk |
| Soft cheese |
| Orange juice |
| Muesli |
| Bread |
| Biscuits |
and adolescents aged 4–15 years, consumption of foods supple-
mented with plant sterols/stanols (1.5–3 g/day) resulted in
consistent LDL-C reduction (by 5–15%) in normolipaemic children
(n = 98), and equally in children with FH (n = 224; by 9–19%) (see
Supplementary Table 2) [57–66]. The magnitude of such reductions
is comparable to that observed in adults. On this basis, the Panel
proposes that dietary supplementation with plant sterols/stanols
may be considered in children (from the age of 6 years) with FH
who require lipid lowering treatment as an adjunct to lifestyle
advice and potential pharmacotherapy, although long term safety
studies are clearly needed.

3.2. Additional effects on the plasma lipid profile

Most studies with plant sterols/stanols were conducted in in-
dividuals with isolated hypercholesterolaemia. The available data
suggest that triglyceride levels are reduced by 6–20% at intakes of
1.5–2 g/day of plant sterol/stanol, with essentially no effect on
HDL-C [67–69]. Pooled analyses showed a modest reduction in
plasma triglycerides of 6% and 4% for recommended intakes of plant
sterols (1.6–2.5 g/day) or plant stanols (2 g/day), respectively
[69,70]. Indeed, evidence suggests a relationship between baseline
triglyceride levels and the magnitude of this effect, with 9% reduction
when baseline triglycerides were 19 mmol/L (170 mg/dL), but no effect at baseline levels of 1.0 mmol/L (90 mg/dL) [69]. In
subjects with metabolic syndrome and moderate hyper-
triglyceridaemia, plant stanols lowered hepatic production of both
large (>60 nm) and medium size (35–60 nm) VLDL particles [67].
Other studies documented a reduction in small, dense LDL particles
in patients with type 2 diabetes or metabolic syndrome after con-
sumption of plant stanols/sterols [68,71]. Based on one study, it
appears that plant sterols/stanols do not influence lipoprotein(a)
levels [72].

Finally, it is of considerable interest that LDL-C reduction, sub-
sequent to consumption of a plant stanol ester-enriched diet in a
population of metabolic syndrome subjects, was without effect on
plasma levels of proprotein convertase subtilisin/kexin type 9
(PCSK9) (J Plat, unpublished data), a potential contrast to the
elevation in PCSK9 levels induced upon statin-mediated LDL-C
lowering [73].

Future studies of the potential effects of foods with added plant
sterols/stanols in attenuating the atherogenicity of the postprandial
period in well-phenotyped cohorts of subjects with metabolic
syndrome or type 2 diabetes would be of special interest. Such
investigations should focus on normalisation of both the qualitative
and quantitative features of atherogenic triglyceride-rich lipopro-
teins and their remnants during this phase.

4. Effects on atherosclerosis

4.1. Studies in animal and cell-based models

Because plant sterols/stanols effectively reduce plasma LDL-C
concentrations, their use could constitute a potential protective
strategy against the initiation and progression of atherosclerosis.
Most of the available supportive data relate to studies in animal-
and cell-based models, however, these have inherent limitations.
Thus, investigations in animal models have been of short duration,
while very high (pharmacological) doses have been typically
applied in both animal and cell models, thereby highlighting the
need for cautious interpretation of the experimental findings.

4.1.1. Animal models

To date, more than 30 studies have investigated the effect of
plant sterol/stanol supplementation on experimental
atherosclerosis in various animal models (see Supplementary
Table 3 and reviewed by Kritchevsky and Chen [2005]) [74].
In genetically-modified mouse models of atherosclerosis, protective
effects were observed despite increases (up to 10-fold) in plasma
plant sterol/stanol concentrations [28,75,76]. Such effects included
reduction in arterial lipid accumulation, and inhibition of lesion
formation and progression. Moreover, regression of existing lesions
correlated with the cholesterol-lowering action of plant sterols/
stanols.

4.1.2. Cell-based models

4.1.2.1. Cellular metabolism of plant sterols/stanols and potential
impact on cholesterol metabolism. The proportions of plant sterols/
stanols relative to cholesterol found in plasma are maintained in
tissue sterols [24,28], suggesting that they are handled similarly to
cholesterol in most cells. While direct studies of cellular plant sterol
metabolism are relatively limited in scope, they support this view.
For example, the rates of uptake and accumulation of sitosterol and
cholesterol by macrophages are similar [77], and substantial
esterification of beta-sitosterol (=sitosterol) and other plant sterols
can be measured in many tissues and cells [26,78,79]. On the basis
of limited data, efflux of sitosterol and sitostanol to HDL from hu-
man macrophages appears to be more efficient than that of
cholesterol [77].

Cholesterol homeostasis is tightly controlled at the transcription-
al level via Sterol Regulatory Element-Binding Protein-2 and
liver X receptor (LXR)-dependent regulation, and also by post-
translational control of the turnover of a number of key enzymes,
receptors and transporters. Plant sterols appear to have little or no
impact on these processes. Their ability to activate LXR-dependent
genesis is negligible or very low [80–84]. A plant sterol-enriched diet
had no effect on mouse intestinal LXR target gene expression [85].
In future studies, more comprehensive evaluation of the effects of
‘physiological’ concentrations of plant sterols/stanols on the he-
patic and intestinal gene expression profile would be of consider-
able interest.

4.1.2.2. Influence of plant sterols/stanols on inflammatory pathways.

In macrophages, recent studies have shown that lipid accumulation
and inflammatory responses are co-ordinated through LXR-
mediated transrepression of inflammatory genes by desmosterol,
an intermediate in cholesterol synthesis and an endogenous LXR
ligand [86,87]. Interestingly, as plant sterol/stanol consumption
results in a compensatory increase in endogenous cholesterol
synthesis [31], the corresponding increase in intracellular des-
mosterol concentrations could result in plant sterol/stanol-induced
anti-inflammatory effects. Indeed, a number of in vitro studies
indicate that some plant sterols exert anti-inflammatory effects on
activated macrophages. However, these studies have significant
limitations, as they involved addition of plant sterols and/or stanols
under conditions, which (although seldom directly measured),
almost certainly significantly increase the plant sterol:cholesterol
ratio to values well in excess of the normal 1:500 to 1:1000 ratio
that exists in vivo. This is likely even when plant sterols are added at
‘physiological’ concentrations. Future studies must include direct
measurement of the cellular levels of cholesterol and plant sterols
and should aim to mimic those found in vivo.

There are conflicting findings with respect to the effects of
sitosterol and campesterol on production of proinflammatory fac-
tors by macrophages [88–92]. Interestingly, sitosterol stimulated
anti-oxidant pathways and inhibited either phorbol ester- or
lipo polysaccharide-stimulated prostaglandin synthesis in mouse
macrophages [93–96]. The potential relevance of these findings to
the atherosclerotic process is unclear at present, but warrants
further research. In addition to macrophages, substantial evidence
4.2. Studies in humans

4.2.1. Relationship of plant sterol/stanol consumption and vascular health

Human studies evaluating the effect of dietary plant sterols/stanols on measures of arterial structure or function using carotid intima media thickness, brachial artery size, flow-mediated dilation (FMD), and arterial stiffness have not shown any major, consistent effects on vascular or endothelial function during short and mid-term plant sterol or plant stanol intake [64,66,98–103]. All studies were small and mostly of short duration, and importantly, several studies were in subjects with low CV risk exhibiting normal vascular function at baseline. Despite significant reductions in LDL-C levels, no consistent changes in measures of inflammation, oxidative stress or endothelial function were observed. In a study of apparently healthy non-smokers, daily use of plant stanol margarine for ≥2 years did not improve carotid artery compliance [103], and in a shorter (3 months) study, failed to impact FMD [98]. Similarly, in two studies in pre-pubertal children with FH, dietary plant sterol/stanol consumption did not improve endothelial function despite significant LDL-C lowering [64,66].

Recent research has focused on the characteristics of the microcirculation as markers of early arterial disease [104]. In one trial [105], intake of foods enriched with plant sterols/stanols (2.5 g/day) for 85 weeks by statin-treated subjects showed an association between the increase in serum campesterol concentrations and changes in both retinal arteriolar and venular diameters. Retinal venular diameters increased (by 2.3 ± 3.1 μm) and arteriolar diameter decreased (by 0.7 ± 4.7 μm) in the group receiving added plant sterols, although these effects did not reach significance. However, the change in cholesterol-standardised campesterol concentrations correlated positively with the change in venular diameter independent of changes in LDL-C concentration. Other studies with endpoints including coagulation [72], platelet aggregation measures [106], oxidant stress [107], inflammation [108] or other biomarkers did not demonstrate convincing benefit. It is possible, however, that the reduction of LDL-C by 10%, as typically mediated by intake of foods with added plant sterols/stanols, may not attain the threshold required for impact on these parameters. Adequately powered, controlled studies of the effects of plant sterols/stanols on morphological, functional and biochemical surrogate markers of atherosclerosis are needed. Based on present evidence, there is no indication that dietary supplementation with plant sterols/stanols are associated with either benefit or harm to vascular function.

4.2.2. Relationship of circulating plant sterols/stanols and CV risk: Cohort studies

Several observational studies have investigated the association between circulating plant sterols and atherosclerosis in the general population. Some early reports found moderately elevated plant sterol levels to be positively associated with vascular disease [109,110], although others suggested an inverse or lack of relationship between circulating plant sterols and CV risk [111–113]. A recent meta-analysis including 17 studies (n = 11,832) [114], showed no significant associations of circulating campesterol and sitosterol with vascular disease over a range of circulating plant sterol concentrations (average concentrations for first and third tertiles, 0.17 and 0.47 mg/dL [4 and 12 μmol/L] for campesterol, and 0.13 and 0.38 mg/dL [3 and 10 μmol/L] for sitosterol). Two studies showed inverse relationships between plant sterols and CV risk, one study did not find any association, and a further study reported a positive association between plant sterols and CV risk [115–118].

Since these retrospective/case-control and prospective/cohort studies do not provide the highest level of evidence in defining causality, and as placebo-controlled trials with these endpoints are lacking, Mendelian randomisation studies may be informative. Moderate elevations of circulating plant sterols, which are associated with plant sterol-raising variants in the ABCG8 gene, showed a positive association with prevalent coronary artery disease [43,119–122]. Such an increase in risk can, however, be entirely explained by the association of ABCG8 variants with intestinal cholesterol absorption, as reflected by circulating cholestanol levels, and with LDL-C plasma concentration, rather than circulating levels of plant sterols [44,123–126]. The ABO gene has also been associated with elevated circulating sterol levels and CV risk [43]. However, the ABO locus exhibits even greater pleiotropy than the ABCG5/G8 locus, as it regulates von Willebrand factor, coagulation factor VIII, intercellular adhesion molecule–1, P-selectin, and E-selectin levels [127–129]. In the largest report to date (n = 12,425), circulating levels of plant sterols were lower in the group with coronary artery disease (CAD), and concentrations of the plant stanols, campestanol and sitostanol, which are much lower than those of plant sterols, were not different between the groups with and without CAD [130]. Thus, the available Mendelian randomisation studies do not provide a scientific basis to discourage the use of plant sterol- or plant stanol-containing functional foods.

A healthy diet is the cornerstone of CVD prevention. In this respect, it is of critical importance that indisputable evidence supports the contention that lowering of plasma LDL-C levels confers clinical benefit, irrespective of mechanism, and that such mechanisms include dietary intervention [4–7,131–133]. Indeed, robust data show that there is no qualitative difference between statin- and non-statin-mediated reduction in LDL-C when comparing their estimated effects on myocardial infarction or CHD death on the basis of the Bayes factor [5]. Thus, the regression lines for all individual diet (n = 5), bile acid sequestrant (n = 3), surgery (n = 1), and statin (n = 10) trials were similar and consistent with a one-to-one relationship between LDL-C lowering and reduction in
CHD and stroke over 5 years of treatment [5]. In this context, and as discussed above, it is of immediate relevance that consumption of 2 g/day of plant sterols/stanols, as part of a healthy diet, lowers LDL-C plasma levels by approximately 10% [52–54].

The EAS Consensus Panel on Phytosterols, however, recognises that there is a lack of randomised data pertaining specifically to the impact of foods with added plant sterols/stanols on CVD prevention. Large-scale outcome trials of food products with added plant sterols/stanols for CVD prevention in the setting of low to intermediate risk are not practically feasible, given the very large number of subjects (>50,000) required for adequate power (see Supplementary Appendix 2. Feasibility of an outcomes study for food products with added plant sterols/stanols). Furthermore, the benefit of consistent, but relatively small, additional LDL-C lowering from consumption of foods with added plant sterols/stanols, as part of a healthy diet, would be difficult to demonstrate definitively in a clinical trial of optimally treated patients at high CV risk, even if 25–30,000 individuals were enrolled. The absence of randomised, controlled trial data with hard end-points to establish clinical benefit from the use of plant sterols or plant stanols must be considered when health professionals choose to advise their use as supplements to a healthy diet.

5. Safety

In the context of benefit-risk considerations, substantial interest has focused on the safety aspects of plant sterols/stanols when used as cholesterol-lowering agents. Given that the level of plant sterol/stanol intake required for cholesterol lowering ranges from 1 to 3 g/day, well above typical consumption patterns which rarely exceed 400–600 mg/day, a considerable literature has amassed exploring possible deleterious effects of prolonged plant sterol/stanol consumption. Indeed, for some individuals zealously consuming multiple foods with added plant sterols/stanols, it is feasible that intakes could rise considerably above the 3 g/day level considered to represent the ceiling at which the dose-response curve for cholesterol-lowering with plant sterols begins to plateau. However, evidence from clinical studies and post-launch monitoring indicates that overconsumption of foods with added plant sterols/stanols is not an issue [19,134].

Specific areas of concern surrounding plant sterol/stanol consumption include (i) possible negative effects on fat-soluble vitamin status, and (ii) and cancer risk. Overall, longer-term post-launch monitoring efforts have failed to answer the question whether foods with added plant sterols/stanols cause any unexpected negative health effects [135,136]. Several longer-term feeding trials have similarly failed to identify any negative action of plant sterol/stanol consumption on clinical chemistry, haematology or clinical symptomology [52–54,137,138].

A repeated observation in some, but not all, plant sterol feeding trials is modest suppression of plasma carotenoid concentrations (by 10%), especially for the highly lipophilic hydrocarbon carotenoids (beta-carotene, alpha-carotene and lycopene) [139,140]. It has been suggested that this may arise from suppression of intestinal absorption [141]. Increasing consumption of fruits and vegetables offsets any decline in fat-soluble vitamin levels induced by plant sterol/stanol intakes in the range that lowers cholesterol [139].

Considerable controversy has occurred over the past decade regarding a possible atherogenic role of high circulatory levels of plant sterols/stanols. Reports are conflicting, although the most recent work seems to indicate that plasma levels of plant sterols associated with recommended intakes (2 g/day) do not pose a health risk. Mendelian randomisation studies have claimed to show that increased circulatory levels of plant sterols increase CVD risk, but since the ABCG5/G8 polymorphisms examined have pleiotropic effects, the results of these studies can readily be explained by an increased cholesterol absorption rate (see above).

Lastly, considerable evidence from animal and cell studies suggests, if anything, a protective role of sitosterol against certain cancers [142–145]. Thus, there is no increase in cancer risk with recommended daily intakes of functional foods containing 2–3 g/day of plant sterols/stanols. In fact, surveillance data associate reduced risk of certain cancers with plant sterol/stanol intakes [146,147]. Possible mechanisms based on animal and cell work suggest direct actions on apoptosis or indirect actions through the intracellular cholesterol-lowering ability of these agents [145].

Overall, evidence from longer-term monitoring trials, as well as experimental models, indicates that plant sterols/stanols present a favourable safety profile, thereby supporting their use in cholesterol lowering, either alone or adjunctive to pharmacotherapy. Based on the epidemiology, the genetics, and the wealth of current clinical trial evidence demonstrating LDL-C lowering with plant sterols/stanols and lack of significant safety concerns, the use of plant sterols/stanols in treating hypercholesterolaemia can be encouraged [56]. The question remains how best to optimise their use in lipid management.

6. Optimising the use of plant sterols/stanols in lipid lowering

6.1. Combination therapy

In addition to a role in primary prevention in the general population, foods with added plant sterols/stanols may provide additional LDL-C lowering in dyslipidaemic patients at high CV risk treated with lipid-lowering drugs. Thus, it is important to define the lipid-modifying effects of dietary plant sterols/stanols (2–3 g/day) in combination with pharmacotherapies so as to optimise their clinical use.

6.1.1. Statins

Statins are inhibitors of the rate-limiting enzyme of cholesterol biosynthesis, HMG-CoA reductase. As such, their action directly decreases intracellular levels of cholesterol and its precursors, enhances the catabolism of apoB-containing lipoproteins (mainly LDL) via upregulation of hepatic LDL receptors, and reduces de novo hepatic (and potentially intestinal) lipoprotein production. Since plant sterols/stanols act via a distinct mechanism, i.e. by lowering plasma cholesterol through downregulation of intestinal cholesterol uptake, it can be speculated that plant sterols/stanols may exert an additive effect when combined with a statin. In clinical studies, dietary plant sterols/stanols induce an incremental decrease in LDL-C levels of 10–15% when added on top of statin therapy, which is superior to that (6%) obtained by doubling the statin dose [148–151]. In vivo studies of LDL-apoB kinetics in patients with type 2 diabetes mellitus indicated that the additive effects on LDL-C reduction when stanols were added to statins resulted from decreased production of LDL [152]. Thus, the generally accepted efficacy of plant sterol/stanol consumption (2–3 g/day) is maintained on top of statin therapy.

6.1.2. Ezetimibe

As the lipid-lowering mechanism of ezetimibe is mediated by inhibition of intestinal cholesterol absorption, ezetimibe could be considered a competitor of dietary plant sterols/stanols at the molecular level. Importantly, however, the targets differ; ezetimibe blocks the NPC1L1 transporter, while plant sterols/stanols displace cholesterol from intestinal micelles. Moreover, as NPC1L1 is also the entry gate for dietary plant sterols/stanols into the body, ezetimibe-mediated inhibition of this mechanism should both enhance their effects in the lumen of the intestine, and also reduce their plasma...
levels. However, clinical data are limited, and in the largest study to date, there was a significant incremental reduction in intestinal cholesterol absorption during administration of ezetimibe plus plant sterols/stanols (2 g/day) associated with a significant 8% reduction in LDL-C levels when foods enriched with plant sterols/stanols are consumed with a fish oil for one month resulted in lower postprandial triglyceride levels than fish oils alone [160]. Overall, the limited data examining the potential lowering of postprandial triglyceride excursions do not show significant effects, which might relate to low levels of baseline triglycerides in subjects in these studies.

6.2. Postprandial lipaemia

Since foods with added plant sterols/stanols reduce cholesterol absorption, they might also reduce the production of intestinally-derived chylomicrons and chylomicron remnants. The few studies that have been conducted, using either a single standardised meal or day-long measures of plasma triglycerides, have not shown any effect of either acute or chronic plant sterol/stanol intake on postprandial triglycerides [150,158,159]. Where measured, levels of postprandial plant sterols/stanols were variable [158,159]. Interestingly, consumption of plant sterols esterified with fish oil for one month resulted in lower postprandial triglyceride levels than fish oils alone [160]. Overall, the limited data examining the potential lowering of postprandial triglyceride excursions do not show significant effects, which might relate to low levels of baseline triglycerides in subjects in these studies.

7. EAS consensus panel recommendations

Currently, foods with added plant sterols/stanols may be considered in individuals with high cholesterol levels but equally in those with intermediate or low global CV risk who do not qualify for pharmacotherapy [56]. On the basis of critical appraisal of the evidence base above, this EAS Consensus Panel therefore considers that there is a place for these products, in conjunction with other components of a healthy diet for prevention of CVD [56,156]. Currently there are insufficient data regarding the lipid-lowering efficacy of a combination of bile acid sequestrants and dietary plant sterols/stanols. However, as bile acid sequestrants interact with lipophilic substances, it is likely that such a combination will interfere with intestinal sterol/stanol absorption. Additionally, dietary plant sterols, but not plant stanols, suppressed bile acid synthesis, probably altering bile acid sequestrant-mediated cholesterol-lowering efficacy [157]. In conclusion, the 10% reduction in serum LDL-C concentrations typical of consumption of foods with added plant sterols/stanols at doses of approximately 2 g/day, persists on top of the effect of statins. Limited data suggest an additive effect of plant sterols/stanols with ezetimibe and fibrates.

Box 4

Consensus panel recommendations

- Daily consumption of foods with added plant sterols and/or plant stanols in amounts of up to 2 g/day is equally effective in lowering plasma atherogenic LDL-C levels by up to 10%, and thus may be considered as an adjunct to lifestyle in subjects at all levels of CV risk. At higher daily intakes (9 g/day), the effects of plant stanols appear more pronounced, but additional studies are needed to confirm these results and examine safety at higher doses.
- Plant sterols and plant stanols can be efficaciously combined with statins. Very limited data suggest plant sterols/stanols may also lower LDL-C levels in combination with a fibrate or ezetimibe. In this way, the potential for attainment of LDL-C goals as a function of overall CV risk can be enhanced.
- Enhanced consumption of plant sterols and plant stanols may be considered as an adjunct to lifestyle and dietary approaches for moderately reducing elevated plasma triglyceride levels, especially when levels are elevated before treatment. This needs further study in appropriate populations with elevated triglycerides.

Fig. 4. Addition of functional foods with plant sterols/stanols, as a component of lifestyle intervention, may have potential value in individuals with high LDL-C levels at intermediate or low global cardiovascular risk who do not qualify for pharmacotherapy (as indicated by pink shading), in line with the joint ESC/EAS Guidelines for Management of Dyslipidaemia [56]. Equally, foods with added plant sterols/stanols may be considered in the context of lifestyle intervention in subjects at high or very high cardiovascular risk (as indicated by blue shading). Adapted from Reiner et al. (2011) [56].
lifestyle interventions, in patients receiving lipid-lowering therapy with statins or other agents who do not achieve LDL-C targets, or in those with statin intolerance (see Box 4 and Fig. 4). Finally, given the increasing importance of early preventive strategies in hypercholesterolaemia [6], the potential for inclusion of plant sterol- or plant stanol -enriched foods in the diet of adults and children (>6 years) with FH, as an adjunct to lifestyle and pharmacotherapy, may be considered. We base these recommendations on the proven ability of plant sterols/stanols to lower plasma LDL-C levels in the absence or presence of concomitant statin therapy, and equally on evidence that they reduce plaque size in atherosclerosis-prone animal models. We understand that, in the absence of CVD outcome data from randomised clinical trials, the evidence for use of plant sterols/stanols is incomplete.

Healthcare professionals should take into account the level of overall CV risk of patients, and their preferences. In addition, the

**Box 5**

Unresolved questions

- Does inter-individual variability occur in the cholesterol-lowering efficacy of plant sterols/stanols, i.e. is it possible to identify hyper- versus hypo-responders? If so, is it also possible to overcome lack of or poor responsiveness with higher plant sterol/stanol intake?
- Do plant sterols/stanols affect lipoproteins beyond LDL-C, i.e. atherogenic triglyceride-rich lipoproteins and their remnants, LDL and HDL subfractions, and lipoprotein(a)?
- Do plant sterols/stanols reduce the potential atherogenicity of postprandial lipid and lipoproteins, especially in subjects with cardiometabolic disease such as type 2 diabetes?
- How do plant sterols/stanols affect lipoprotein metabolism in specific populations, for instance in patients with the metabolic syndrome or type 2 diabetes mellitus who exhibit an atherogenic lipoprotein phenotype?
- How do plant sterols affect cellular lipid homeostasis?
- How do plant sterols affect the function of cells involved in the development of atherosclerosis, such as endothelial cells, monocytes and macrophages under resting and ‘activated’ conditions in vitro, ex vivo and in vivo?
- Do plant sterols/stanols have significant effects on biochemical surrogate markers of atherosclerosis including coagulation, platelet aggregation, oxidant stress, and subclinical inflammation?
- Is consumption of foods with added plant sterols/stanols (2 g/day), as part of a healthy diet, associated with clinical outcomes benefits? Given that large randomised outcomes studies in low to moderate risk subjects are not practically feasible, can sufficiently powered, randomised controlled studies show significant effects of plant sterols and/or stanols on morphological and functional (e.g. endothelial function) surrogate markers of arterial phenotype and/or atherosclerosis?

<table>
<thead>
<tr>
<th>Product type</th>
<th>Cost per kg (UK sterling)</th>
<th>Incremental cost ratio*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spreads</td>
<td>2.10</td>
<td>3.14</td>
</tr>
<tr>
<td>Health drinks</td>
<td>2.25</td>
<td>3.68</td>
</tr>
<tr>
<td>Yoghurt</td>
<td>1.33</td>
<td>1.90</td>
</tr>
</tbody>
</table>

* Ratio of cost of foods with added plant sterols to cost of foods without plant sterols.

**Table 2**


**Box 6**

Health economic evaluation of consumption of foods with added plant sterols and/or plant stanols

Nutrition economics follows a 4-step process in order to compute the health and economic impact of penetration of the market place of foods with added plant sterols/stanols.

To adopt the 4-step cost-of-illness approach:

- Determine a success rate for adoption of foods with added plant sterols/stanols across the target population
- Evaluate the extent of LDL-C reduction due to consumption of foods with added plant sterols/stanols
- Assess the decrease in coronary heart disease (CHD) prevalence due to the estimated reduction in plasma LDL-C levels
- Estimate the healthcare savings resulting from the reduction in CHD prevalence

This multistep approach can be applied with a range of inputted values for the 4 steps above, ranging from optimistic to pessimistic.

Further studies are needed to address unresolved questions highlighted in this appraisal (see Box 5). Key priorities include (i) evaluation of the effects of plant sterols/stanols in patients with metabolic syndrome; (ii) Mendelian randomisation studies to investigate the effects of plant sterols/stanols on clinical outcomes; and (iii) evaluation of long-term safety and effects on clinical outcomes in registries. Finally, although this EAS Consensus Panel did not find evidence for any health risk associated with consumption of these functional foods, the Panel recognises the lack of outcomes data showing clinical benefit. Given practical constraints, and the inability to differentiate LDL-C lowering effects of concomitant pharmacotherapeutic and dietary approaches in polymedicated patients, health economic modelling (see Box 6) may offer a feasible approach to investigate whether wider use of these functional foods has the potential for healthcare savings due to reduction in CVD prevalence. On the other hand, the EAS Consensus Panel would clearly welcome, and applaud, efforts by the food industry to plan and conduct a well-designed and adequately powered study of the effects of plant sterol/stanol-supplemented foods on CVD outcomes.

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Conflict of interest

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Appendix A. Supplementary material

Supplementary data related to this article can be found online at http://dx.doi.org/10.1016/j.atherosclerosis.2013.11.043.

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