It’s time to personalize and optimize lipid-lowering therapy

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This editorial refers to ‘Genetic variability in the absorption of dietary sterols affects the risk of coronary artery disease’, by A. Helgadottir et al., on page 2618.

As early as 1929, Schoenheimer reported that mammals not only synthesize cholesterol de novo, but also selectively absorb dietary cholesterol from the intestine while excluding plant sterols and other non-cholesterol sterols (xenosterols). This work has been the cornerstone for subsequent studies, demonstrating that cholesterol homeostasis is a complex interplay between endogenous cholesterol synthesis, absorption of dietary cholesterol, and excretion of excess cholesterol via the hepatobiliary and intestinal systems. Although endogenous cholesterol synthesis and breakdown pathways are now well defined, the pathway for dietary sterol absorption (cholesterol and xenosterols) is not completely understood. Plant sterols are essential components of the membranes in plants and perform many functions which cholesterol does in mammalian systems. Their chemical structures differ from that of cholesterol, primarily in the R’ structure of their side chain (typically an extra methyl- or an ethyl-group at C-24). However, these structural differences are sufficient to lead to mammals developing a sophisticated mechanism to exclude these xenosterols. Plant sterols are abundant in fat-laden vegetables and vegetable products. A western diet contains almost equal amounts of plant sterols and cholesterol. Although structurally similar, these sterols are metabolized differently. Both plant sterols and cholesterol are incorporated into micelles (though plant sterols can compete with cholesterol for entry into micelles); entry into micelles is necessary for intestinal absorption. Indeed, the ability of plant sterols to compete with cholesterol for entry into micelles and lower plasma cholesterol modestly was one of the first therapies used as a treatment for hyperlipidaemia—an effect now touted in many functional foods for lipid lowering.

The exact molecular mechanism(s) by which micellar sterols gain entry into the enterocyte remain obscure, though it is clear that all sterols require the Niemann–Pick C1-like 1 protein (NPC1L1) to enter the enterocyte. In the enterocyte, cholesterol (but not plant sterols) is esterified via acyl-CoA cholesterol transferase 2 (ACAT2), packed into chylomicrons, and exported into the lymph system via the basolateral membrane. Non-esterified plant sterols and ‘excess’ cholesterol, however, are pumped back into the intestinal lumen via the ATP-binding cassette transporter (ABCG5/G8) heterodimer. As a result, we typically absorb 50% of dietary cholesterol, but <5% of plant sterols; the small amounts of these xenosterols are preferentially excreted by the ABCG5/G8 heterodimer in the liver into the hepatobiliary system, resulting in a very efficient system to maintain a low level of exposure to these xenosterols. These complex ‘defence mechanisms’ against plant sterols lead to 1000-fold lower plasma concentrations of plant sterols (~0.200 mg/dl or 4.83 mmol/L for both sitosterol and campesterol) compared with cholesterol (~200 mg/dl or 5.18 mmol/L). In patients with a rare autosomal-recessive disease, sistorsteraemia (phytosterolaemia), caused by mutations in ABCG5 or ABCG8, up to 40-fold elevated plasma concentrations of plant sterols are present. There is increased incidence and prevalence of early atherosclerosis, and early cardiovascular death. These transporters therefore regulate dietary sterol absorption and xenosterol exclusion. The understanding of this disease has led to speculations that plant sterols per se are atherogenic.

In the current issue of the European Heart Journal, Helgadottir et al. report a genetic analysis of cohorts of healthy individuals in Iceland, Denmark, and the UK, segregating subjects based upon genetic variants in ABCG5 or ABCG8 (105 490 cases vs. 844 025 controls) to explore whether variability in dietary cholesterol and plant sterol absorption impact the risk of coronary artery disease (CAD).
use genetic risk scores (GRSs) for non-HDL cholesterol to determine whether ABCG5/8 variants confer greater risk of CAD than predicted by their effect solely on non-HDL cholesterol. They identified nine rare ABCG5/8-coding variants with substantial impact on plasma non-HDL cholesterol and phytosterols. A GRS of ABCG5/8 variants which predicted a 1 mmol/L increase in non-HDL cholesterol was associated with a two-fold increase in CAD risk. GRSs for other genes that regulate non-HDL cholesterol (such as APOB, HMG-reductase, PCSK9, and LDL receptor) but which do not regulate plant sterol levels, predicted that a 1 mmol/L increase in non-HDL cholesterol increased the CAD risk by 1.5-fold. Helgadottir and colleagues concluded that variants in ABCG5/8 accounted for ~62% of CAD risk by regulating non-HDL cholesterol, but that the remaining 38% was due to changes in plant sterols, concluding that plant sterols may therefore play a role in the pathogenesis of atherosclerosis. If true, this will be the strongest evidence so far that ‘normal’ variable exposure to xenosterols may have pathological consequences in humans.

We have previously demonstrated that a diet supplemented with plant sterols impaired endothelium-dependent vasodilation, increased lesion size following cerebral ischaemia, and led to a more pronounced atherosclerotic lesion formation in mice. Comparing cholesterol absorption inhibition using ezetimibe with a diet supplemented with plant sterols, both of which lowered plasma cholesterol to a comparable level, we observed that mice fed the plant sterol diet had several-fold increased plasma levels of plant sterols and exhibited two- to four-fold larger atherosclerotic lesions. Moreover, plasma plant sterol levels correlated strongly with atherosclerotic lesions. In a clinical study, we found that patients consuming plant sterol-enriched margarines were characterized by increased plasma concentrations of plant sterols and, importantly, increased tissue deposition. In patients undergoing coronary angiography, markers of cholesterol metabolism were associated with future cardiovascular events, and Ceglarek and colleagues have verified only recently that plant sterols in atherosclerotic plaques of the carotid arteries were associated with symptomatic advanced carotid artery stenosis. The data reported by Helgadottir et al. reiterate our earlier concerns in regard to dietary supplementation with large amounts of plant sterols, beyond what is our natural diet. The authors rightly point out that clinical trials with hard cardiovascular outcomes are needed to determine whether phytosterol-supplemented foods lower cardiovascular risk, or whether they may be ‘casting out devils through Beelzebub’.

There is a wide interindividual variation in cholesterol absorption, and the data reported by Helgadottir et al. have to be put into a broader perspective; subjects who are genetic high (chole-)sterol absorbers are characterized by low endogenous cholesterol synthesis, and vice versa. Ezetimibe, which inhibits the absorption of

![Take home figure](https://academic.oup.com/eurheartj/article-abstract/41/28/2629/5875674) From diet to plaques: transport of cholesterol and plant sterols. Bile acids (BAs) are synthesized from cholesterol (C) and are essential for C and plant sterol (PS) absorption for incorporation into micelles. Free C and PS are transported through the unstirred water layer to the enterocyte mucosa. The sterol transporter Niemann–Pick C1-like 1 protein (NPC1L1) transfers sterols into the enterocyte mucosa. Most of the free PS and a minor part of free C are re-secreted into the intestinal lumen by the ABCG5/8 heterodimer into the intestinal lumen. Newly formed chylomicrons, containing C and PS, are secreted into the lymph (major pathway), while small portions of C and PS can leave the enterocyte via apoA-containing HDL (minor pathway). Chylomicrons are converted into chylomicron remnants and enter the hepatocyte via the LDL receptor to deliver the dietary sterols to the intrahepatic sterol pool. C synthesis also contributes to this pool, C, but not PS, can be broken down into BAs. The hepatocyte can pump sterols (C and PS) into bile. In the hepatocyte, free C and PS are transported into the biliary tract by ABCG5/G8, and part of C and PS can be retransported into the hepatic cells by NPC1L1 (note, in humans ezetimibe, can therefore prevent sterol entry at both the enterocyte and hepatocyte level). Finally C, PS, and BAs are collected in the gallbladder and secreted into the intestine. However, most importantly, in VLDL, IDL, and LDL, both C and PS can be transported in the bloodstream and finally accumulate in the arterial wall.
cholesterol and plant sterols by blocking NPC1L1, has a more pronounced LDL-cholesterol-lowering effect in these high-absorber patients, an effect also seen in type 1 diabetes compared with statin therapy in type 2 diabetes. Statins, which are inhibitors of endogenous cholesterol synthesis, on the other hand, work better in subjects with high endogenous cholesterol synthesis. Early results from the landmark Scandinavian Simvastatin Survival Study (4S) demonstrated that patients with high baseline cholesterol absorption (indirectly judged) did not benefit as much from statin treatment as low absorbers. In fact, patients with high cholesterol absorption were characterized by a 16.6% increase in cardiovascular events on statin monotherapy. Tatu Miettinen, who was the principal investigator of the Finish cohort of the 4S study concluded that patients with high baseline cholesterol synthesis are responders to statin therapy, whereas patients with high cholesterol absorption are non- or ‘adverse’ responders. Moreover, Miettinen and colleagues speculated that the increase in cardiovascular events in simvastatin-treated patients was due to increased absorption of ‘atherogenic’ plant sterols, and they concluded that patients characterized as high cholesterol absorbers should be treated with an additional cholesterol absorption inhibitor to prevent an increase in the levels of plant sterols. The recently published HII-PROPER trial can be regarded as a ‘proof of concept’. In that study, only patients with high (chol-)sterol absorption demonstrated a significant reduction in cardiovascular events by the addition of ezetimibe to pitavastatin. Patients with lower plasma levels of sitosterol—low (chol-)sterol absorbers—did not benefit from an additional cholesterol absorption inhibitor. Therefore, Yamaguchi and colleagues concluded that ‘sitosterol measurement in acute coronary syndrome patients with dyslipidemia might contribute to a personalized lipid-lowering approach’.

In line with this evidence, we suggested earlier that proxies of cholesterol absorption (indirectly judged) did not benefit from an additional cholesterol absorption inhibitor to prevent an increase in the levels of plant sterols. The recently published HII-PROPER trial can be regarded as a ‘proof of concept’. In that study, only patients with high (chol-)sterol absorption demonstrated a significant reduction in cardiovascular events by the addition of ezetimibe to pitavastatin. Patients with lower plasma levels of sitosterol—low (chol-)sterol absorbers—did not benefit from an additional cholesterol absorption inhibitor. Therefore, Yamaguchi and colleagues concluded that ‘sitosterol measurement in acute coronary syndrome patients with dyslipidemia might contribute to a personalized lipid-lowering approach’.

There are also a couple of interesting points raised by Helgadottir and her colleagues. First, variants in ABCG5/ABCG8 were shown to affect platelet volumes and, although the changes in platelet volumes are small, these are statistically highly significant. While platelet dysfunction in subjects with sitosterolaemia, who manifest very high plasma plant sterol elevations, has been well characterized and animal studies show a direct effect on platelet function by plant sterols, the clinical relevance of these very small changes is not easy to decipher. Secondly, at least three subjects with sitosterolaemia (and maybe up to 6) were identified in Iceland and that would indicate a prevalence of at least 1:100 000 of this very rare disease. This is much higher than the rest of the world where this is ‘guessimated’ to be ≥1:3 000 000 and suggests that the prevalence is high in Iceland from a restricted gene pool, but may also highlight that we are missing many undiagnosed cases in the rest of the world.

The study by Helgadottir et al. is not only the best study so far to support the hypothesis that variations at the ABCG5/ABCG8 locus is mechanistically involved in atherosclerotic heart disease, but it also lends a strong impetus to study the role of xenosterols in this process too.

Conflict of interest: none declared.

References