excluded that such differences may be due to different methods of sterol measurements. In contrast to cholesterol, sterol measurements in different laboratories are not standardized and validated, as has been shown previously (6). In addition, the data entered in the meta-analysis were mean or median data rather than individual patient data. In fact, the authors themselves suggested in their previous analysis that the next level of evidence should be a meta-analysis of individual patient data (7).

Our group has previously shown that patients on hemodialysis are characterized as "high cholesterol absorbers" (8). On longitudinal analysis, higher levels of cholestanol were associated with increased mortality. Interestingly, in our cohort, higher levels of cholestanol were associated with lower rather than higher levels of total cholesterol. These data could explain the findings in the SHARP (Study of Heart and Renal Protection) study (9) but are not in line with the currently reported findings (1).

The cholesterol absorption rate is dependent on the presence of bile acids favoring the formation and uptake into micelles before transport by NPC1L1 from the intestinal lumen into the enterocyte. The production of bile acids is mainly regulated by the cholesterol 7-alpha-hydroxylase (CYP7A1), the rate-limiting enzyme in normal bile acid synthesis. From this point of view, the polymorphism of CYP7A1 may be more interesting than the polymorphism of CYP27A1. A marked loss of CYP27A1, as in cerebrotendineous xanthomatosis, leads to increased production of cholestanol. This production is secondary to the marked induction of CYP7A1 with increased formation of 7α-hydroxy-4-cholesten-3-one and its further conversion into cholestanol (10,11). The origin of cholestanol in cerebrotendineous xanthomatosis is thus clearly different from the normal situation.

Finally, in the online ahead of print version of the manuscript, which differs from the printed version in this regard, Silbernagel et al. (1) claim that the European Society of Cardiology (ESC)/European Atherosclerosis Society (EAS) recommend plant sterol–enriched functional foods. However, the current ESC/EAS guidelines for the management of dyslipidemias state that "currently there are no data available indicating that cholesterol lowering through plant sterol ingestion results in prevention of CVD. Long-term surveillance is also needed to guarantee the safety of the regular use of phytosterol-enriched products" (12). In our opinion, both the ESC and the EAS draw attention to significant safety issues, and thus this is not a clear recommendation.

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REFERENCES

1. Silbernagel G, Chapman MJ, Genser B, et al. High intestinal cholesterol absorption is associated with cardiovascular disease and risk alleles in ABCG8 and ABO: evidence from the LURIC and YFS cohorts and from a meta-analysis. J Am Coll Cardiol 2013;62:291–9, E-pub ahead of print May 22, 2013.
2. Weingärtner O, Lütjohann D, Ji S, et al. Vascular effects of diet supplementation with plant sterols. J Am Coll Cardiol 2008;51:1553–61.
3. Weingärtner O, Böhm M, Laufs U. Controversial role of plant sterol esters in the management of hypercholesterolaemia. Eur Heart J 2009;30:404–9.
4. Weingärtner O, Böhm M, Laufs U. Cholesterol-lowering foods and reduction in serum cholesterol levels. JAMA 2011;306:2217–8.
5. Silbernagel G, Genser B, Nestel P, et al. Plant sterols and atherosclerosis. Curr Opin Lipidol 2013;24:12–7.
6. Chan YM, Varady KA, Trautwein E, et al. Plasma concentrations of plant sterols: physiology and relationship with coronary heart disease. Nutr Rev 2006;64:385–402.
7. Genser B, Silbernagel G, De Backer G, et al. Plant sterols and cardiovascular disease: a systematic review and meta-analysis. Eur Heart J 2012;33:444–51.
8. Rogacev KS, Pinsdorf T, Weingärtner O, et al. Cholesterol synthesis, cholesterol absorption, and mortality in hemodialysis patients. Clin J Am Soc Nephrol 2012;7:943–8.
9. Baigent C, Landray MJ, Reith C, et al. The effects of lowering LDL cholesterol with simvastatin plus ezetimibe in patients with chronic kidney disease (Study of Heart and Renal Protection): a randomized placebo-controlled trial. Lancet 2011;377:2181–92.
10. Skrede S, Björkhem I, Buchmann MS, et al. A novel pathway for biosynthesis of cholestanol with 7 alpha-hydroxylated C27-steroids as intermediates, and its importance for the accumulation of cholestanol in cerebrotendinous xanthomatosis. J Clin Invest 1985;75:448–55.
11. Björkhem I. Cerebrotendinous xanthomatosis. Curr Opin Lipidol 2013;24:283–7.
12. Reiner Z, Catapano AL, De Backer G, et al. ESC/EAS guidelines for the management of dyslipidaemias. Eur Heart J 2011;32:1769–818.

Reply

Intestinal Cholesterol Absorption and Cardiovascular Risk

We thank Weingärtner et al. for their thoughtful comments on our report (1).

The current guidelines for the management of dyslipidemia endorsed by the European Atherosclerosis Society (EAS) and the European Society of Cardiology (ESC) do not include a clear recommendation for the use of plant sterols or stanols as cholesterol-lowering agents (2). For this reason, we did not make an explicit statement on this matter (1).

It is correct that plant sterol levels in the LURIC (LUdwigshafen RIsk and Cardiovascular health) study were lower than those in the YFS (Young Finns Study) (1). This observation may be accounted for by several factors (3,4). For example, a healthy diet rich in fruits and vegetables is associated with high circulating plant sterols (3). By contrast, old age, high body mass index, type 2 diabetes, and inflammation are associated with low plant sterol concentrations (3,4). The participants in the LURIC study were markedly older and had a higher body mass index than the participants in the YFS. Moreover, the LURIC cohort had a high prevalence of diabetes and displayed increased markers of inflammation. On the other hand, the participants in the YFS may have maintained a more healthy diet than a typical patient with coronary artery disease. Differences in analytical methods may also have caused some of the discrepancy. Therefore, we have joined a worldwide harmonization initiative headed by Dr. Lütjohann.

Regarding the meta-analysis, it may be preferable to use individual patient data compared with data extracted from various publications with different models of adjustment. However, an individual patient meta-analysis would not be expected to reveal a different outcome because the studies included were consistent and the overall results were highly significant ($p < 0.001$) (1).

Cholesterol homeostasis in patients with chronic kidney disease is indeed an interesting area of research because combination therapy with simvastatin and the cholesterol absorption inhibitor ezetimibe significantly reduced cardiovascular events in these patients (5). It is still indeterminate, however, as to whether cholesterol absorption predicts the effectiveness of statin use to prevent cardiovascular complications in patients on chronic hemodialysis.

Finally, we have analyzed the associations of 12 single nucleotide polymorphisms (rs11786580, rs6997473, rs4738687, rs1457042, rs1457043, rs2162459, rs8192870, rs8192871, rs8192877, rs8192879, rs3808607, rs3824260) within the *CYP7A1* gene with circulating cholestanol and the cholestanol/cholesterol ratio in both the LURIC study and the YFS. None of these single nucleotide polymorphisms were significantly related to cholestanol or to the cholestanol ratio (all $p > 0.05$).

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REFERENCES

1. Silbernagel G, Chapman MJ, Genser B, et al. High intestinal cholesterol absorption is associated with cardiovascular disease and risk alleles in ABCG8 and ABO: evidence from the LURIC and YFS cohorts and from a meta-analysis. J Am Coll Cardiol 2013;62:291–9.
2. European Association for Cardiovascular Prevention & Rehabilitation, Reiner Z, Catapano AL, De Backer G, et al., ESC Committee for Practice guidelines (CPG) 2008-2010 and 2010-2012 Committees. ESC/EAS Guidelines for the management of dyslipidaemias: the Task Force for the Management of Dyslipidaemias of the European Society of Cardiology (ESC) and the European Atherosclerosis Society (EAS). Eur Heart J 2011;32:1769–818.
3. Silbernagel G, Genser B, Nestel P, März W. Plant sterols and atherosclerosis. Curr Opin Lipidol 2013;24:12–7.
4. Silbernagel G, Fauler G, Renner W, et al. The relationships of cholesterol metabolism and plasma plant sterols with the severity of coronary artery disease. J Lipid Res 2009;50:334–41.
5. Baigent C, Landray MJ, Reith C, et al., SHARP Investigators. The effects of lowering LDL cholesterol with simvastatin plus ezetimibe in patients with chronic kidney disease (Study of Heart and Renal Protection): a randomised placebo-controlled trial. Lancet 2011;377:2181–92.