

between lower thresholds for glycosylated hemoglobin (as well as albuminuria and possibly other variables of interest) and adverse cardiovascular events were beyond the scope of our study, we agree that such investigations would be valuable and should be pursued in future studies.

In response to Magliano et al.: we agree that the proportion of deaths due to cardiovascular disease in our study is likely to be an underestimation and that cardiovascular disease probably contributed to a fair share of the deaths categorized as having diabetes as the underlying cause. However, because many of the deaths due to diabetes had multiple or unspecified complications (including cardiovascular disease), and furthermore, because we were not able to validate the final chain of events leading to death from the

data in the register, we used a conservative approach.

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Mutations in *NPC1L1* and Coronary Heart Disease

TO THE EDITOR: The Myocardial Infarction Genetics Consortium Investigators (Nov. 27 issue)¹ reported an association between reduced frequency of coronary artery disease and modestly lower levels of total cholesterol and low-density lipoprotein (LDL) cholesterol in carriers of inactivating variants of *NPC1L1* as compared with noncarriers. In the Geisinger MyCode cohort, we found seven heterozygous carriers of an inactivating variant in *NPC1L1* (R406X) in persons of European ancestry. Using a validated definition for coronary artery disease from the database of Genotypes and Phenotypes (dbGaP), we found no carrier of an inactivating variant of *NPC1L1* with coronary artery disease as compared with 1001 cases of disease in 15,886 noncarriers. In persons for whom data on lipid levels were available before or without lipid-lowering therapy, there was no significant difference in mean plasma levels of LDL cholesterol between *NPC1L1* inactivating carriers and noncarriers (126 mg per deciliter vs. 125 mg per deciliter), and mean total cholesterol was lower in *NPC1L1* inactivating carriers than in noncarriers (206 mg per deciliter vs. 210 mg per deciliter). Our data are consistent with the suggestion of the Consortium that the modest change in plasma lipid levels alone does not explain the apparent protective effect of the *NPC1L1* stop variants against coronary artery disease.

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1. The Myocardial Infarction Genetics Consortium Investigators. Inactivating mutations in *NPC1L1* and protection from coronary heart disease. *N Engl J Med* 2014;371:2072-82.

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TO THE EDITOR: The Myocardial Infarction Genetics Consortium Investigators tested the association between inactivating mutations in *NPC1L1* and the risk of coronary heart disease. Heterozygous carriers of *NPC1L1* inactivating mutations had a mean LDL cholesterol level that was only 12 mg per deciliter lower than in noncarriers, but resulted in a dramatic relative risk reduction of 53%. This finding validates the concept that lifelong LDL cholesterol reduction has a greater impact on risk¹ than pharmacologic interventions, such as statin therapy, initiated later in life.²

We have previously hypothesized that increased dietary sterol (cholesterol and xenosterol) absorption via *NPC1L1* is associated with increased cardiovascular risk.^{3,4} We further posit that there are sterol species in our diets (such as oxysterols, oxysterols, etc.) that may be mechanistically linked to atherosclerosis development. We

recommend plant sterol levels be determined in this study population to further assess cardiovascular risk in relation to non-cholesterol sterol absorption via NPC1L1. More attention should now be focused on these pathways and concepts to prevent atherosclerotic disease. The study by Kathiresan and colleagues suggests that dietary sterol exposure deserves increased scrutiny and investigation.

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TO THE EDITOR: The findings reported by the Myocardial Infarction Genetics Consortium Investigators are very much in agreement with the observation that common variants within ABCG5/G8, which are associated with increased cholesterol absorption and LDL cholesterol, are correlated with higher cardiovascular risk.^{1,2} Although the beneficial effect of inactivating mutations within the *NPC1L1* gene with regard to cardiovascular outcomes is plausible, the effect size seems relatively large. The authors offered several possible explanations for the higher than expected effect size including the suggestion that lower concen-

trations of plant sterols may contribute to reduction of cardiovascular risk. Stender et al. have demonstrated in two Danish cohorts that the increase in cardiovascular risk associated with variants in ABCG5/G8, which are also associated with increased plant sterols, can be entirely explained by the increase in LDL cholesterol.³ Moreover, alterations of plant sterols were not associated with cardiovascular risk in patients without sitosterolemia.⁴ Finally, patients with sitosterolemia do not necessarily have normal LDL cholesterol.⁵ Therefore, sample size issues rather than low plant sterols may explain the relatively large effect size.

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Drs. Silbernagel and März report receiving a research grant from Unilever R&D, Vlaardingen, the Netherlands, and Dr. März reports receiving a research grant from Danone Research, Palaiseau, France; both companies market plant sterols. Dr. März also reports being an employee of and holding equity in Synlab Services GmbH, Mannheim, Germany, a company that offers laboratory testing, including measurement of LDL cholesterol.

No other potential conflict of interest relevant to this letter was reported.

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TO THE EDITOR: The Myocardial Infarction Genetics Consortium Investigators assess the protective role of inactivating mutations in *NPC1L1* on cor-

onary heart disease, finding a greater benefit than expected on the basis of the reduction in LDL cholesterol levels. Another contributing factor may be the involvement of NPC1L1 and its inhibitor ezetimibe on insulin resistance pathways. Ezetimibe has been reported to have an inhibitory effect on hepatic synthesis of LDL and progression to steatosis, as well as on the induced augmentation of adiponectin production.¹ However, studies have also demonstrated an action of ezetimibe in the reduction of blood insulin and HbA1C levels.² Possible mechanisms include an increase in glucagon-like peptide-1 activity and in pancreatic beta cell mass, which have been observed in animal models.³ This is consistent with the finding of increased insulin sensitivity in *NPC1L1* knock out mice, or in mice treated with ezetimibe, when exposed to a diabetic diet.⁴ The role of these pathways and *NPC1L1* mutations on glucose metabolism merits further *in vivo* investigation.

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The Concept of Risk in Comparative Effectiveness Research

TO THE EDITOR: Lantos and Spertus (Nov. 27 issue)¹ highlight a problem with the latest draft of the Office for Human Research Protections (OHRP) policy: the assumption that participation in a study inherently poses a risk, regardless of the treatment provided.² The results of two large systematic reviews refute this assumption.^{3,4}

Vist et al.³ assessed trial participation by comparing similar patients receiving similar treatment inside and outside trials. They concluded that trial participants fared no worse or no better than their nontrial counterparts.

Fernandes et al.⁴ took a broader approach and included studies that provided the same treatment inside and outside the trial and studies in which a treatment was provided within the trial that was unavailable outside the trial. Regardless of the study type, there was no evidence to suggest that trial participants were worse off than nonparticipants. In fact, within one subgroup, trial participants even fared better than nonparticipants, possibly because they were given a more effective treatment. The OHRP should reconsider its overgeneralized policy, which mis-

informs patients by portraying their doctor's preference as consistently safer than any study treatment.

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