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Cholesterol Gene Polymorphisms and Cardiovascular Events

TO THE EDITOR: Kathiresan and coworkers (March 20 issue)¹ find that a genotype score of nine, which was crafted from a combination of four single-nucleotide polymorphisms (SNPs) affecting high-density lipoprotein (HDL) cholesterol and five SNPs influencing low-density lipoprotein (LDL) cholesterol, is an independent risk factor for incident cardiovascular disease. Similarly, Willer et al. recently showed that 11 SNPs associated with elevated LDL levels (most of which overlap with the genes included in the article by Kathiresan et al.) increase the risk of coronary artery disease.² In contrast, the HDL-modulating SNPs reported by Willer et al. were not associated with the risk of coronary artery disease, although the HDL genes (cholesterol ester transfer protein [CETP], hepatic lipase [LIPC], lipoprotein lipase [LPL], and ATP-binding cassette subfamily A member 1 [ABCA1]) were similar to those in the article by Kathiresan et al. By presenting a combined genotype score comprising distinct risk factors (i.e., HDL cholesterol and LDL cholesterol), Kathiresan et al. imply a predictive value of all of these SNPs; this is in clear contrast to the findings of Willer et al. Therefore, it would have been much more informative if the genotype scores for LDL and HDL genes had been reported separately, thereby allowing closer comparison with related studies.

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TO THE EDITOR: Genotype scores for risk prediction are becoming increasingly popular; for instance, the use of these scores has recently been proposed to predict cardiovascular disease and prostate cancer.¹ The concept relies on two major assumptions. First, polymorphisms act independently and additively on the risk of disease. Second, their effects are approximately interchangeable. The first assumption may be true, especially with regard to polymorphisms belonging to different biologic systems, but in practice it cannot be verified because current studies are underpowered to do so. The second assumption is very questionable. For example, in the study reported by Kathiresan et al., the difference in the LDL cholesterol level between homozygote genotypes was 72 mg per deciliter for the proprotein convertase subtilisin/kexin type 9 (PCSK9) polymorphism and 3 mg per deciliter for the LDL receptor (LDLR) polymorphism. Similarly, in terms of risk, the score assumed that it is equivalent to carry HDL-lowering or LDL-increasing alleles, despite the fact that a score based only on HDL-related genotypes led to a hazard ratio of 1.22, as compared with 1.11 for a score based on LDL-related genotypes. Paradoxically, such scores take us away from the goal of individualized medicine.

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THE AUTHORS REPLY: Vergeer et al. request separate reporting of scores composed of data based on LDL cholesterol polymorphisms and HDL cholesterol polymorphisms. We provided this information in the Supplementary Appendix of our article. Specifically, we evaluated the relative contributions of SNPs related to LDL cholesterol and those related to HDL cholesterol by constructing separate genotype scores based on LDL or HDL cholesterol. Both the genotype score of five SNPs that are associated with modulation in levels of LDL cholesterol (score range, 0 to 10) and the genotype score of four SNPs that are associated with modulation in levels of HDL cholesterol (score range, 0 to 8) were independently related to incident cardiovascular events in fully adjusted models (hazard ratio, 1.11, 95% confidence interval [CI], 1.01 to 1.23; $P=0.03$ for the genotype score related to LDL cholesterol; hazard ratio, 1.22, 95% CI, 1.08 to 1.37; $P=0.001$ for the geno-

type score related to HDL cholesterol). We agree that there is mixed evidence regarding whether HDL-related polymorphisms affect the risk of coronary artery disease, and further work is needed to clarify this important question.

Tiret et al. object to our use of a genotype score in which each allele is given equal weight because the contribution of each allele to the cholesterol level varies. As we noted in the Discussion section of our article, in the interest of simplicity, we assigned an equal weight in our genotype score to each unfavorable allele. Weighting the genotype score on the basis of the SNP effect on lipid level may improve the estimation of the relationship between SNPs and cardiovascular disease; however, such weighting makes another simplifying assumption — that the effect of each SNP on the risk of cardiovascular disease relates to its effect on cholesterol in a linear fashion. We submit that further methodologic study is required to define the optimal approach for combining risk variants to predict disease.

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Imiquimod for Vulvar Intraepithelial Neoplasia

TO THE EDITOR: Van Seters et al. (April 3 issue)¹ report that regression of vulvar intraepithelial neoplasia was significantly greater in the imiquimod group than in the placebo group. However, the small number of patients treated with imiquimod (26), the low complete response rate, and the short follow-up period (1 year) do not provide support for the conclusion that imiquimod should be the first-choice treatment for vulvar intraepithelial neoplasia. Only 9 of 26 patients had complete regression of lesions at 5 months, which is not a good result as compared with surgery (either excision or vulvectomy) or laser ablation.^{2,3} More-

over, invasive carcinoma developed in three patients (one in the imiquimod group and two in the placebo group), whereas surgical treatment would have allowed a complete excision of lesions and histologic examination would have detected invasive disease.⁴

Nevertheless, imiquimod seems to reduce the prevalence of recurrent human papillomavirus (HPV). Therefore, it could be a complementary treatment to surgery to prevent recurrence, rather than an isolated treatment of severe vulvar intraepithelial neoplasia that could evolve into carcinoma.