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momentum, driven by the extensive datasets on better radial access outcomes to encourage the next generation of interventionalists to step to the front of the world's stage in patient care.

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Phenotypes, Genotypes, and the 9p21 Locus for Prediction of Cardiovascular Events

I would like to commend Hoppmann et al. (1) for their thorough and well-executed paper. In this regard, I agree with the editorial by Horne and Anderson (2) that discusses the importance of the Hoppmann et al. (1) study. Thoughtfully executed prospective studies that attempt to clinically examine genomic data first identified in genome-wide association studies are at a premium.

Other remarks in the editorial by Horne and Anderson (2) are a source of disagreement. First, the authors make the argument that because replications of the 9p21 single nucleotide polymorphisms (SNPs) have been done in populations that suffer from both documented coronary artery disease (CAD) and myocardial infarction (MI), these individual phenotypes—when grouped together—confound the type of risk (phenotype) that can be attributed to these genetic factors. Although their argument is understood, it is important to point out that on the basis of experience, these genetic markers are statistically significant in both subpopulations to sometimes nearly equal extent. These data are sometimes not shown in final reports and are only rarely shown in supplemental data. The authors then attempt to differentiate the pathogenesis of CAD and that of MI as 2 distinct entities, which further precludes attribution of genetic risk to either of those 2 phenotypes individually. It is difficult to assume that the well-known progression of CAD to MI (barring less usual suspects such as spasm or dissection) can be so thoroughly extricated from each other as to invalidate the dozens of studies that have replicated the 9p21 locus as a risk marker for CAD and MI.

The authors then make the argument that because the study by Hoppmann et al. (1) finds there to be a negative association between restenosis and these genomic markers, restenosis must be a distinct pathophysiologic entity from CAD because it is not "driven" by genetic factors at 9p21.3. Though this might be the case as evidenced by much work in cell biology and immunology, an assumption based on 1 prospective clinical study that examined 4 SNPs is difficult to accept. Additionally, it should be noted that the 4 SNPs tested by Hoppmann et al. (1) are not the most frequently validated SNPs for 9p21 but rather an amalgam of SNPs from different studies that first identified the variants. This is possibly due to the initiation of the 3-year prospective study before replications of the more popular variants in better-characterized populations.

It is certainly necessary to temper our enthusiasm for direct-to-consumer genetic testing until these markers can be better understood, a point of agreement with Horne and Anderson (2). In the interim, we should encourage more studies such as the one presented by Hoppmann et al. (1) and continue our emphasis on preventative cardiovascular medicine.

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Reply

We would like to thank Dr. Abdullah for the remarks regarding our editorial (1). We appreciate the subtleties of our assertions and acknowledge that the important biological distinctions among myocardial infarction (MI), coronary artery disease (CAD), and restenosis might be unfamiliar. We appreciate the opportunity to clarify our arguments.

It was not our intent to claim that prior studies associating 9p21.3 with MI risk are invalid but to say that some erroneous conclusions about pathophysiological implications for coronary heart disease were drawn from those landmark studies. Because restenosis is a different process than CAD (2), our intent also was to note that 9p21.3 is not involved in its distinctive pathophysiology (1).

A major component of our argument is, in fact, that 9p21.3 single nucleotide polymorphisms "are statistically significant in both subpopulations to sometimes nearly the same extent." To illustrate, consider 1 European study that showed a similar effect