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CORRESPONDENCE

Letters to the Editor

Quotations From Anticipated Coronary Heart Disease Mortality Trends

In a recent editorial published in the *Journal*, Greenland and Lloyd-Jones (1) commented on coronary heart disease mortality trends in the U.S. (2). They quoted an editorial by Brown and Goldstein (3) by stating that these authors were "proclaiming the 'end of heart attacks by the century.' " The original editorial by Brown and Goldstein (3) precisely stated that "recent breakthroughs . . . may well end coronary disease as a major public health problem early in the next century." Brown and Goldstein were also said to predict "that current knowledge, if fully applied, could end heart attacks within a short time" (1). Brown and Goldstein (3) did not proclaim the end of heart attacks and used vague language ("may") to stress the speculative nature of their beliefs. The eye-catching title of Brown and Goldstein's editorial "Heart Attacks: Gone With the Century?" (3) is formulated as a question only. Furthermore, if the incidence, mortality, adverse quality of life, and high costs of coronary heart disease were markedly diminished and no longer a major public health problem, this would not necessarily imply that heart attacks would no longer occur.

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Genomics of Aortic Valve Disease

I read with great interest the recent article by Bossé et al. (1) that summarized the molecular mechanisms underlying calcific aortic valve disease, the genetic epidemiology of calcific aortic valve disease, and advances in genomic approaches and their applications to elucidating calcific aortic valve disease. Indeed, recent studies have indicated that calcific aortic valve disease is influenced by genetic factors, and the article provided a succinct review of the literature. However, the authors may have "overstated" their assertion that there are no other heritability or inheritance studies that have reported on calcific aortic valve disease other than those reporting on the bicuspid aortic valve. Using an affected sibpair design, we performed genome-wide linkage analysis in African-American and white hypertensive sibships participating in the Hypertension Genetic Epidemiology Network Study and found strong evidence of linkage of aortic valve sclerosis to chromosome 16q22.1–q22.3 (logarithm of odds [LOD] score = 3.1) (2). There was also suggestive evidence of linkage of aortic valve sclerosis to chromosome 19p13.11–p11 (LOD score = 2.88), another position in chromosome 16q22.1–q22.3 (LOD score = 2.63), chromosome 1q42 (LOD score = 2.12), and chromosome 2q37 (LOD score = 2.03). The presence of multiple peaks in several chromosomal regions suggests pleiotropy in susceptibility genes predisposing to aortic valve sclerosis. The study extended the report from Probst et al. (3) that showed clusters of families affected by aortic valve stenosis and that also indicated that offspring of affected individuals had aortic valve sclerosis, suggesting that aortic valve sclerosis may be an early manifestation of familial aortic valve stenosis. Further studies are underway to identify the specific genes contained in these novel chromosomal regions we found in the study that are responsible for the observed linkage results. Although the identification of genes influencing calcific aortic valve disease is challenging, it offers much promise in defining novel mechanistic paradigms and developing therapeutic strategies in the prevention and treatment of calcific aortic valve disease.

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Reply

We appreciate the precision comments by Dr. Bella concerning our recent review on the genetics/genomics of calcific aortic valve

stenosis (1). The Hypertension Genetic Epidemiology Network (HyperGEN) Study Group conducted a genome-wide linkage scan on aortic valve sclerosis (2) that deserves to be discussed. This HyperGEN cohort was a substudy of a larger National Heart, Lung, and Blood Institute program, the Family Blood Pressure Program, designed to search for hypertension/blood pressure genes. The authors reported familial aggregation of aortic valve sclerosis with a sibling recurrence risk ratio of 2.3 and identified many linkage signals throughout the genome, suggesting the multilocus nature of aortic valve sclerosis. However, their results also highlighted the challenge of collecting samples of a sufficient size to study this disease. Major research resources were invested in the HyperGEN cohort to phenotype and genotype 1,871 patients. However, in the end, only 41 patients with isolated aortic valve sclerosis from families with at least 2 affected siblings were informative for the genetic linkage analyses. The authors also recognized the limitation of their ascertainment scheme that was based on hypertension to identify genetic loci influencing aortic valve sclerosis. Accordingly, recycling data from larger studies conducted on related traits provided a cost-effective way to identify new leads. However, studies specifically designed to study calcific aortic valve disease are likely to be more powerful and are clearly warranted.

By addressing study design and focusing on genomic approaches that are likely to be more successful, we should re-emphasize the need for genome-wide *association* scans on case-control studies. The identification of genes of complex diseases by this approach was considered one of the scientific breakthroughs of the year in 2007 (3). In contrast, genome-wide *linkage* studies have been used extensively in the past and have proven to be very productive to identify genes for monogenic traits. However, limited success has been reported for complex diseases (4), and a good example is the results from the Family Blood Pressure Program (5). Even in studies in which strong linkage peaks were originally identified, positional cloning attempts to find the causal genes responsible for the linkage signals have often been disappointing (4). Hence, the article by Bella et al. (2) is certainly worth mentioning, but the results of this study also provide an impetus for the design and realization of future genomic studies with a population and methodology that are more suitable for a complex disease such as calcific aortic valve stenosis.

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Plaque Rupture: Plaque Stress, Shear Stress, and Pressure Drop

We read with interest the article by Fukumoto et al. (1) in a previous issue of the *Journal*. They used 3-dimensional intravascular ultrasound and computational fluid dynamics (CFD) to study wall shear stress (WSS) distribution in arteries with ruptured plaques. Their results showed that there are local elevations of WSS concentrations at proximal sites in the plaques and that these correspond to the rupture sites.

We want to emphasize that WSS is calculated as blood viscosity multiplied by the derivative of flow velocity with respect to the distance from the vessel wall ($\tau = \eta \times \partial u/\partial y$). Flow velocity varies along the stenotic artery across the plaque as the lumen narrows. Generally the maximum WSS should be at the location of the maximum stenosis, where the velocity is the highest and the lumen diameter is the smallest. There should not be any local elevation of WSS concentration if the lumen surface is smooth and there are no bad mesh elements. The use of image-based CFD can often cause problems with the geometry reconstruction and mesh generation. WSS is largely dependent on the geometry. Therefore, any effort to improve the model reconstruction and mesh generation is useful to improve the accuracy of the WSS calculation.

Pressure distribution across the stenosis is not shown in the article (1); it is not clear how pressure boundary condition was given in this study, but it is thought to be more important for plaque vulnerability. There is a pressure drop across the plaque because of the stenosis. According to the Bernoulli principle, this increased blood velocity produces a lower lateral blood pressure acting on the plaque. Thus, a pressure gradient build-up is created across the plaque that could rupture it. Any increase in systemic pressure or increase in the narrowing of the lumen would further increase the velocity through the narrowed lumen and increase the pressure drop. Furthermore, the magnitude of the pressure drop is much higher than the WSS. It can be tens to hundreds of times the magnitude of WSS for different degrees of stenosis.

Plaque stress (stress within the plaque) may be a more important factor when the mechanism of plaque rupture is considered. The arterial wall continuously interacts with hemodynamic forces, which include WSS and blood pressure. Plaque stress is the result of external hemodynamic forces. Plaque rupture itself represents structural failure of a component of the diseased vessel, and it is therefore reasonable to propose that the biomechanical properties of atheromatous lesions may influence their vulnerability to rupture. Recognizing which features contribute to this increased vulnerability may improve risk stratification and allow aggressive interventions to be targeted at patients with plaques that are prone