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EDITORIAL COMMENT

Aortic Stenosis

Moving From Treatment to Prevention*

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Calcific aortic valve disease (CAVD), including both aortic sclerosis and stenosis, often leads to severe valve obstruction, for which the only treatment is aortic valve replacement (1). Recently, significant attention has focused on less invasive ways to replace the valve by using transcatheter approaches, which has expanded our treatment of patients with clinically significant disease. Less attention, however, has been directed at what causes CAVD and how it might be prevented. Certainly, progress has been made in this regard. Although previously viewed as simply the result of longstanding wear and tear, it is now well-established that active biological processes underlie the development and progression of CAVD (2). Intriguing studies more than a decade ago linking hyperlipidemia to CAVD led to several trials testing the use of statins to slow the progression of CAVD. With the failure of that intervention, there has been far less activity centered on medical therapies to prevent or slow the progression of CAVD. We remain in need of a better understanding of what causes CAVD to effectively prevent it.

To date, there have been a few epidemiological studies that have examined the risk factors associated with CAVD. The Cardiovascular Health Study is most commonly cited, but these relationships have also been examined in the Multi-Ethnic Study of Atherosclerosis and Framingham studies (3–5). Together, these studies have demonstrated an association between hypertension, smoking, low-density lipoprotein, lipoprotein (a), metabolic syndrome, diabetes, and CAVD. However, these studies were significantly limited by their cross-sectional design.

SEE PAGE 1523

In this issue of the *Journal*, Yan et al. (6) extend and strengthen these prior observations, providing novel insights on the association between common cardiovascular risk factors and the development of clinically significant aortic stenosis (AS). Using a confluence of multiple, linked databases, they examined a very large unselected population of 1.12 million individuals in Canada age 65 years or older followed longitudinally over a median of 13 years. Unlike prior studies that used an imaging endpoint (echocardiogram or computed tomography) for CAVD, their main outcome was incident severe AS, defined as hospitalization for AS and/or aortic valve interventions including surgical or transcatheter aortic valve replacement. This likely minimized ascertainment bias. They appropriately excluded patients with prior cardiac conditions, including a history of valvular disease, although these exclusions were based on prior hospitalization records, which could have underreported the actual presence of these conditions.

The authors found an independent association between each of the cardiac risk factors evaluated and incident AS: hypertension (adjusted hazard ratio [HR]: 1.71), diabetes (adjusted HR: 1.49), and dyslipidemia (adjusted HR: 1.17). Insofar as chronic obstructive pulmonary disease was used as a surrogate for smoking, there was a relationship between smoking and incident AS. A graded hazard for those with diabetes based on intensity of medical management (none to oral medications to insulin) was observed, as was a positive dose-response

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relationship between the number and duration of cardiac risk factors and incident AS. The authors then provided helpful context for their findings by reporting the population-attributable risk for each of these risk factors. In this regard, hypertension was dominant at 23.4%, whereas diabetes and dyslipidemia were more modest at 5.6% and 4.4%, respectively. The population-attributable risk associated with all 3 risk factors was 34.4%.

What are the implications of these findings? The authors rightly point out that "these data raise the intriguing hypothesis that aggressive risk factor modification may retard the progression of aortic sclerosis and stenosis." However, it is uncertain whether *control* of these factors, once identified, would mitigate the risk of incident or progressive CAVD—that is an important unanswered question for future research. This question is unlikely to be examined in randomized clinical trials, but data could come from other detailed large databases documenting the degree of control of these risk factors and subsequent risk of AS. Moreover, and this is where the primary endpoint of the study matters, this article provides data on factors attributable to the development of significant enough AS that hospitalization or valve replacement is required. It will be helpful to know the factors attributable to the *development or initiation* of CAVD (i.e., aortic sclerosis) on the one hand and the *progression* of CAVD to clinically significant valve obstruction (i.e., severe AS) on the other. There is undoubtedly overlap between these factors, but it will be important to elucidate to guide appropriately timed and targeted prevention efforts. Adding nuance to this, targeting a risk factor with the intent to decrease the incidence or progression of CAVD may have the unintended consequence of worsening clinical outcomes. For example, although hypertension has been associated with an increased risk of incident and progressive CAVD, the blood pressure level associated with optimal clinical outcomes in patients with established AS is not clear; lower blood pressure may decrease the progression of established CAVD, but too low of a target may not be optimal in patients with established AS who often have left ventricular hypertrophic remodeling (7,8). These granular details need to be understood to guide clinical practice.

This study also raises interesting questions about disease mechanisms. Hypertension accounts for one-quarter of the population-attributable risk for incident AS, but what predisposes some hypertensive patients to develop AS, whereas most do not? How, precisely, does hypertension predispose to CAVD? Do other properties of the vasculature, such as vascular stiffness or ascending aortic anatomy or size, act synergistically with an elevated blood pressure to influence the development and progression of CAVD, perhaps by influencing shear stress or closing forces on the valve?

A challenge and opportunity to address an unmet need is also implicit in these results. Although these risk factors accounted for a relatively large percentage of the population-attributable risk for AS, they leave two-thirds of that risk unexplained. By comparison, as pointed out by the authors, traditional risk factors account for approximately three-quarters of the population-attributable risk for peripheral arterial disease and acute myocardial infarction, although smoking and obesity were included in the estimates for these other diseases (9,10). Accordingly, a large knowledge gap exists, which has important implications for our ability to develop strategies to prevent CAVD. Effectively targeting these known risk factors to prevent cardiovascular disease is difficult enough, but it is impossible to target the factors—valvular, hemodynamic, circulating—that we do not know about in order to prevent CAVD. To make the most "efficient" preventive leaps forward, it will be optimal to identify factors to target that represent a relatively large percentage of the population-attributable risk for incident or progressive CAVD.

Since the first successful surgical aortic valve replacement occurred more than a half-century ago, our focus has been on fixing the severely calcified valve, a mechanical problem that has been viewed as requiring a mechanical solution. There has been a steady reduction in the risk of this procedure and the introduction of less invasive transcatheter options, which together have allowed us to treat more patients earlier and with better outcomes. However, as we have shifted from thinking of the disease as a passive degenerative process to one characterized by an active biology, we still have yet to identify interventions that are effective at preventing the initiation or progression of CAVD. This study provides a helpful stimulus to turn our attention to the *prevention* of CAVD even as we continue our efforts to improve options and therapies for those with clinically significant disease.

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