In the developed world, aortic stenosis (AS) is the most prevalent valvular heart disease and, after hypertension and coronary artery disease, the most common heart disease overall in Europe and North America (1). In the elderly, the prevalence of AS has been reported to be between 2% and 9% (2,3). Aortic sclerosis, the precursor of AS, has been found in 29% of subjects older than 65 years (4). Since AS is a degenerative disease, the availability of echocardiography and the increasing mean age of the population will ensure a steady stream of these patients.

Although there is no question that symptomatic AS mandates surgery, management of many other AS patients is not as clearcut, either because symptoms are vague or the patient is considered too old or frail to survive aortic valve replacement. It is also important to realize that many patients with AS will experience cardiovascular events not strictly due to AS itself (5,6). Although its rate of progression is variable, calcific AS generally worsens over time. At present, there is no proven therapy to retard the progression of milder forms of the disease, which are usually the ones found by echocardiography. Because we can now follow AS progression by echocardiography/Doppler, much recent work has focused on better refining the natural history of the disease (1,7) and developing medical treatment to delay or even arrest its progression (1,8). In fact, since AS is often found in an asymptomatic phase, or even incidentally, there is a unique opportunity for secondary or even primary prevention of non-AS events. This is the context for the provocative study of Nadir et al. (9), published in this issue of the Journal.

These investigators performed a retrospective study of the population of Tayside, Scotland, which included data concerning echocardiography, comprising more than 110,000 scans performed on patients with a diagnosis of AS from 1993 to 2008. Cox regression model (adjusted for confounding variables) and propensity score analysis were used to assess the impact of treatment with angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin receptor blockers (ARBs)—renin-angiotensin system (RAS) inhibition—on all-cause mortality and on cardiovascular events. Of the total of 2,117 patients with AS (mean age 73 ± 12 years), approximately one-third were being treated with either ACEIs or ARBs. Over a mean follow-up of 4.2 years, patients so treated experienced one-fourth fewer cardiovascular events than those not so treated, and this group had a similarly lower rate of all-cause mortality (9).

This study suggests an important benefit of RAS inhibition in patients with AS, which might seem like heresy. However, we should better understand the patients being studied, the nature of the study, and the possible biological mechanisms to decide whether treatment options for asymptomatic patients with moderate or more severe AS should now include RAS inhibition. Based on the registry nature of the study, there are important things that we cannot know. Symptom status cannot be ascertained, although because symptomatic AS is a class I indication for aortic valve replacement (10), it is likely that most patients were asymptomatic. Second, we are not certain exactly why patients were treated with RAS inhibition. The population comprised people in their 70s with, on average, moderate to severe AS by a mean Doppler gradient. The prevalence of diabetes and left ventricular dysfunction was significantly higher in the RAS group, as was the prevalence of treatment with beta-blockers and statins, which was more than 3 times higher in the non-RAS group, suggesting a higher burden of atherosclerotic disease. Because the 2 groups varied significantly, the authors used propensity score matching as a means of accounting for nonrandom assignment to the 2 groups (11). However, in this subset, the observed effect of ACEI/ARB assignment persisted, suggesting a true effect of the treatment rather than confounding. Although comforting, the use of propensity score matching does not rule out confounding, particularly from variables that were not measured in the cohort. In particular, there is a significant chance that patients denied RAS inhibition might have been deemed to be at too high a risk because of renal insufficiency or other comorbid conditions to tolerate the drugs (12).

Are the findings plausible biologically? To answer this question, we should recall the important change in thinking about the pathogenesis of AS that has occurred over the past 2 decades, namely, the recognition that...
calcific AS and atherosclerosis have similar predisposing risk factors and share pathophysiological features (5,6). Thus, as the authors speculate, AS patients who have coexistent coronary artery disease and myocardial ischemia could benefit from the cardioprotective effects of ACEI therapy, as was shown in the HOPE (Heart
Outcomes Protection Evaluation) study (13). It is possible, as the authors speculate, that the atherosclerotic plaque–stabilizing effects and consequent reduction in cardiovascular events conferred by ACEIs could possibly explain the early divergence of survival curves observed in the current study. This contention is supported by abundant data that activation of the renin–angiotensin–aldosterone axis is known to impair vascular homeostasis. Indeed, endothelial dysfunction, inflammation, and thrombosis are all known consequences of RAS activation (14).

Do the results make sense clinically? The answer, in our opinion, is “yes.” First, it is clear that this was a high-risk population (Fig. 1), perhaps more easily permitting the detection of a signal of benefit of RAS inhibition. As the Figure 1 shows, the mortality in the study group was similar to that found in the Pellikka et al. (7) long-term follow-up study of asymptomatic patients with severe AS. The event rate was slightly worse than that in the placebo group of HOPE and patients slightly younger in mean age but with proven atherosclerotic disease (or diabetes plus 1 or more risk factors) (13). Interestingly, the outcome of the present study is reminiscent of HOPE, in which RAS inhibition with ramipril was associated with a relative risk reduction of 26% for cardiovascular death (24% in the current study) and an all-cause mortality relative risk reduction of 16% (13) (23% in the current study). Thus, the results of Nadir et al., in our opinion, are plausible in view the beneficial effect of RAS inhibition in patients with atherosclerotic disease.

It is also important to not overlook the potential antihypertensive effects of RAS inhibition in explaining the findings reported by Nadir at al. (9). Blood pressure data were available for only 16% of the entire population and the details of blood pressure acquisition were not controlled. Given that many agents inhibiting the RAS axis are available in once-daily preparations, it is possible that real changes in blood pressure (either ambulatory or nocturnal) could have been missed in this study. Thus, it is possible that the ACEI/ARB population could have had a small, but significant effect on blood pressure that contributed to the findings (15).

Other speculative mechanisms for which no data are provided include reduction in fibrosis in response to pressure overload (16) and the possibility that RAS inhibition may also attenuate the progression of hypertrophy in this pressure load situation, as has been shown in hypertension (17) and in the HOPE study (18). Hypertrophy regression or even lack of progression is of proven benefit (18). Finally, the study does not permit the delineation of whether RAS inhibition was associated with less progression of the hemodynamic valvular lesion, although other studies on this topic indicate that this was unlikely (1).

There has been a long-standing concern that vasodilation in the face of fixed left ventricular outflow obstruction is contraindicated and life threatening, and discussion of the role of vasodilator therapy does not find its way into the valve disease guidelines for AS (10). Perhaps the importance of the current data is that they make us rethink this notion. O’Brien et al. (19) demonstrated that ACEIs are safe and well tolerated in patients with mild to moderate AS with preserved left ventricular function. Chockalingam et al. (20) studied the use of ACEIs in symptomatic patients with severe AS who were not candidates for surgery. Given the atherosclerotic “substrate” of calcific AS, many patients will already be treated with these agents, as the physicians in Tayside, Scotland, show us.

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Key Words: angiotensin-converting enzyme inhibitors ▪ angiotensin receptor blockers ▪ aortic stenosis.