Can We Predict or Prevent Progression of Aortic Stenosis?
Masao Daimon, MD, PhD

There is no disputing that aortic stenosis (AS) is a progressive disease and its progression is closely associated with poor outcome. In the current era, with the aging of societies and consequent increase in the prevalence of atherosclerosis, a degenerative, calcified aortic valve (AV) has become the most common cause of AS. Surgical AV replacement (AVR) is an established standard therapy for patients with AS, but transcatheter AVR is a new therapeutic option. However, undesirable perioperative mortality still accompanies these invasive interventions, and unnecessary interventions are to be avoided from the socioeconomic point of perspective. We need to predict the progression of disease as accurately as possible for deciding the optimal timing of an invasive intervention. Thereby, it is a critical issue to unveil the pathophysiology underlying the progression of AS. Furthermore, identification of AS pathophysiology can lead to preventive strategies for AS. To date, a number of studies have reported on resolving this issue, but the correlation of pathophysiology and progressing factors of AS remains controversial.

In this issue of the Journal, Yamamoto et al report a prospective multicenter study that investigated the risk factors for progression of degenerative AV in Japan. Despite the fact that ethnic difference in the risk of developing AS is speculated, there is a paucity of prospective Japanese studies regarding this issue. One of the significant findings in Yamamoto’s report is that none of the traditional risk factors for atherosclerosis were related to progression of degenerative AV. It is an established fact that there is overlap of the clinical factors traditionally associated with degenerative AV and with atherosclerosis. Major risk factors for degenerative AV reported in population-based studies are: male sex, older age, smoking, renal failure, hypertension, diabetes, and lipid disorders such as elevated low-density lipoprotein cholesterol and lipoprotein (a). However, the pathophysiology of progressing AS is more complicated than we had expected (Figure), and none of the clinical studies has ever shown that controlling these clinical factors can prevent the progression of AS. Progression of AS from degenerative AV involves valve calcification, aside from valve thickening, and factors associated with disease progression differ from those associated with initiation of degenerative valve. Interestingly, osteoblast-like cells derived from bone marrow...
are postulated to play a role in the complex process of valve calcification.\textsuperscript{9} In addition, a growing number of studies are also reporting a genetic predisposition to AS.\textsuperscript{9,10}

The other notable finding\textsuperscript{4} is that progression of degenerative AV to AS was unpredictable, which implies the need for careful periodic follow-up of patients with a degenerative AV, regardless of clinical characteristics. The progression of degenerative AV to severe AS often accompanies the development of symptoms in some form. However, the clinical symptoms of AS are sometimes elusive, particularly in the elderly. The current guideline\textsuperscript{11} recommends follow-up with echocardiography every 3–5 years in asymptomatic patients with mild AS. Simultaneously, degenerative AV is significantly increasing with an aging society. Thus, a periodic follow-up strategy using echocardiography for every patient with degenerative AV may not meet health economics, which Yamamoto et al discuss.\textsuperscript{4}

At least, however, periodic follow-up with routine auscultation should be recommended in order not to miss the development of significant AS.

I was also intrigued with the finding that even patients without severe AS had a high prevalence of symptoms. Table 1 shows that 42.0\% of patients with degenerative AV, and 46.5\% of patients with mild AS had NYHA functional class II/III.\textsuperscript{11} Today, the risk factors for AS are analogous not only with those of atherosclerosis, but also for those with left ventricular (LV) diastolic dysfunction.\textsuperscript{15} Namely, development of AS symptoms may be not only associated with valve narrowing, but also with comorbidities of LV diastolic dysfunction and reduced vascular compliance by traditional risk factors.\textsuperscript{12} Currently, the development of symptoms is the most important trigger for invasive intervention in AS. However, the multiple causes of AS symptoms should be taken into consideration in devising the therapeutic strategy for AS.

Next, Yamamoto et al conclude that the administration of angiotensin-receptor blocker (ARB) for patients with a degenerative AV before the development of AS, or an angiotensin-converting enzyme inhibitor (ACEI) early after the development of AS, may be beneficial.\textsuperscript{4} However, careful attention is required in interpreting their results. The renin-angiotensin system (RAS) is involved in a pathway that promotes calcification of AV, and some retrospective or small-scale prospective studies\textsuperscript{11,13} have shown that blocking the RAS may slow the progression of AS. Nevertheless, most of the prospective randomized controlled trials have failed to show any significant effects in preventing progression of AS. The current study was a non-randomized trial and there is a strong indication of selection bias in medications among the study population. Nearly half of the patients with AS had NYHA II/III symptoms, and some of these patients may have been administered ACEI/ARB for symptoms related to heart failure. Baseline characteristics were not similar between patients with and without ARB. Furthermore, the number of patients in the degenerative AV group who had been administered ARB was only 69 and those who had been administered ACEI in the mild AS group was only 27, and these limited numbers of study subjects did not allow definitive conclusions to be reached. Additional randomized prospective controlled trials are warranted to confirm the findings. To date, medications other than ARB/ACEI, such as statins\textsuperscript{14} and bisphosphonates,\textsuperscript{15} have been administered in attempts to prevent progression of AS. However, none of those trials could prove any significant effects.

Further accumulation of clinical and experimental evidence is required to disclose and document the complexity of the process of developing AS, so that we can predict progression of AS and establish a preventive strategy for AS. The current prospective multicenter observational study is expected to provide further evidence for a therapeutic strategy for AS.

References