An Ideal Time to Solve a Clinical Dilemma in the Golden Age of Aortic Stenosis Therapy
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Aortic stenosis (AS) has become one of the most important diseases in this era of progressively aging societies. With the emergence of transcatheter aortic valve implantation (TAVI), AS is now in the limelight. In general, severe AS is defined as a peak aortic valve velocity (Vp) ≥4 m/s, which corresponds to a mean aortic valve gradient ≥40 mmHg and an aortic valve area (AVA) <1.0 cm². However, because the Vp is flow-dependent, an AVA <1.0 cm² has been used as the standard to define severe AS. Current AHA/ACC guidelines list the indications for aortic valve replacement (AVR) in patients with severe AS and define the stages of AS ranging from patients at risk of AS (stage A) or with progressive hemodynamic obstruction (stage B) to the severe asymptomatic (stage C) and symptomatic AS (stage D). In the clinical setting, patients with asymptomatic severe AS (stage C) remain a dilemma for the physician because these patients need to be carefully followed while waiting for their AS to meet the indication for AVR except in cases of asymptomatic very severe AS with a peak aortic valve velocity ≥5.0 m/s or reduced left ventricular ejection fraction (LVEF; <50%) (Figure).

However, it is quite difficult to identify whether a patient with severe AS who declares no symptoms is truly asymptomatic. The current guidelines recommend exercise stress testing to assess physiological changes with exercise and to confirm...
the absence of symptoms in asymptomatic severe AS patients. The guidelines add a comment that exercise stress tests are relatively safe in asymptomatic severe AS, even though the test may cause alterations in the patient’s vital signs. Therefore, an experienced physician is needed to safely perform the stress test, which means that the stress test is special and lacks versatility in the clinical setting.

Conversely, it is also important to assess AS as a progressive disease. In stage C, repeat transthoracic echocardiography (TEE) is recommended at intervals of 6–12 months when Vp is ≥4.0 m/s because the rate of progression of symptoms is high; the event-free survival rate is only 30–50% at 2 years in asymptomatic AS patients with Vp ≥4.0 m/s. More importantly, the rate of progression varies among patients with asymptomatic severe AS because various comorbidities are associated with progression and mortality. In the guidelines, AVR may be considered for the asymptomatic AS patient with an aortic velocity ≥4.0 m/s or a mean pressure gradient ≥40 mm Hg if the patient is at low surgical risk and serial testing shows an increase in Vp ≥0.3 m · s−1 · year−1. Thus, rapid progression is a useful surrogate for determining the timing of AVR in asymptomatic severe AS patients. Unlike stress testing for severe AS, repeat TTE examinations are more feasible in clinical practice. However, the rate of progression is calculated as an average rate over several years, and it is not clear which period should be used as the surrogate to determine rapid progression. However, in this issue of the Journal, Nishimura and colleagues show that the first-year rate of progression of the Vp is a significant predictor of cardiac events in patients with asymptomatic severe AS. In addition, they show that it is safe to follow up patients with asymptomatic severe AS during the first year of the follow-up period. In contrast, as a noteworthy point from this study, there is discordance in the definition of severe AS between this study and the guidelines. The current guidelines define very severe AS as a Vp ≥5 m/s. In contrast, Nishimura et al used an AVA <0.75 cm² as their definition of very severe AS, which might classify some severe AS as very severe AS. Indeed, the average Vp in the enrolled patients was 3.685 m/s, which means that the majority of the participants were classified as having low-gradient severe AS. However, the discrepancy between the definitions in the guidelines and this study rather provides an advantage for the definition used in the study because quite a number of elderly patients with severe AS in Japan may be classified as having so-called paradoxical low-gradient severe AS, which is characterized by a low pressure gradient and low aortic valve velocity despite having a preserved LVEF. The clinical outcomes of paradoxical AS have been controversial in previous studies. Recently, a Japanese multicenter cohort study showed diversity of cardiac function and clinical outcomes in paradoxical AS. Therefore, the rate of progression in the first year may provide additional information to help stratify the risk, in particular, among asymptomatic patients with paradoxical AS.

Doppler echocardiography is the established modality to comprehensively assess AS. However, there are several issues with the assessment of AS severity by Doppler echocardiography. Nishimura et al used a first-year rate of progression of Vp of 0.22 m · s−1 · year−1 as their cut-off value to predict cardiac events, but the reproducibility of Doppler measurements has not been assessed, which is a concern in the clinical use of the first-year rate of progression of Vp. Accurate determination of the peak aortic valve velocity depends on various factors (Table). Therefore, the rate of progression of Vp should be interpreted with caution. To improve reproducibility, physicians and sonographers must increase the quality of examinations on a regular basis.

Calcification of the aortic valve is the determinant of rapid progression, and the first-year rate of progression of AS is also related to this factor. However, echocardiography might have drawbacks in accurately quantifying the severity of aortic valve calcification related to limitations of ultrasound when assessing calcified lesions. Recently, cardiac computed tomography (CT) imaging has been widely used to evaluate aortic valve morphology, including quantification of valve calcification, in the TAVI era. A recent study revealed that the amount of aortic valve calcification provided an accurate assessment of the severity of AS. Thus, cardiac CT imaging may be helpful in interpreting the rate of progression of AS. In particular, multimodality assessments should be considered to stratify the risk of cardiac events in patients with a Vp ≥4.0 m/s, for whom the physician feels that the patient is vulnerable despite a lack of symptoms.

On the basis of the findings from a previous study, we seem to have enough time to assess patients with asymptomatic severe AS through the first year of follow-up after the diagnosis of severe AS. The dilemma in a patient with asymptomatic severe AS may be solved during this important period with repeat TTE examinations, in which most attention should be paid to reproducibility, and the use of cardiac CT imaging should also be considered in some cases.

**Table. Influential Factors for Measurements of Peak Velocity of Aortic Valve**

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<td>Heart rate variability: arrhythmia</td>
<td>Pressure recovery</td>
<td>Image quality</td>
<td>Quality of Doppler signal</td>
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<tr>
<td>Blood pressure: uncontrolled hypertension</td>
<td></td>
<td>Knowledge of anatomy and ultrasound windows</td>
<td>Severe calcification</td>
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<td>Stroke volume: low flow</td>
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<td>Incidence angle of the Doppler signal</td>
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None.

**Disclosures**

None.

**References**


3. Otto CM, Burwash IG, Legget ME, Munt BI, Fujikawa M, Healy NL,


