Exercise echocardiography in aortic stenosis with preserved ejection fraction

Adriana Postolache[1], Mai-Linh Nguyen Trung[1], Julien Tridetti[1], Simona Sperlongano[2], Alexandra Maria Chitroceanu[3], Raluca Dulgheru[1], Patrizio Lancellotti[1,4]

[1]Department of Cardiology and Cardiovascular Surgery, GIGA Cardiovascular Sciences, CHU SartTilman, University of Liège Hospital; Liège-*Belgium*
[2]Unit of Cardiology, Department of Translational Medical Sciences, University of Campania "Luigi Vanvitelli", Monaldi Hospital; Naples-*Italy*
[3]Unit of Cardiovascular Research, University and Emergency Hospital, University of Medicine and Pharmacy Carol Davila; Bucharest-*Romania*
[4]Gruppo Villa Maria Care and Research, Maria Cecilia Hospital, Cotignola, and Anthea Hospital; Bari-*Italy*

Abstract

The appropriate timing of intervention and follow-up in asymptomatic patients with aortic stenosis remains controversial. Risk stratification is a key, especially with the use of a multimodality imaging approach, including exercise stress echocardiography. This review focuses on the use of exercise echocardiography in asymptomatic patients with moderate and severe aortic stenosis with preserved left ventricular ejection fraction. It describes the exercise echocardiography protocol, parameters to be evaluated, and its role in guiding the timing of intervention and follow-up in these patients. *(Anatol J Cardiol 2020; 23: 312-7)*

Keywords: exercise echocardiography, aortic stenosis, outcome

Introduction

Aortic stenosis (AS) is the most frequent valvular heart disease in Western countries (1). In both European and American guidelines, surgical (SAVR) or transcatheter aortic valve replacement/intervention (TAVI) is indicated in patients with severe AS with symptoms of left ventricular dysfunction defined as a left ventricular ejection fraction (LVEF) <50% (2, 3). The appropriate timing for intervention in asymptomatic patients with severe AS remains controversial, especially considering the important advances in transcatheter therapies recently. In contrast, more recent studies have shown that patients with moderate AS are also at increased risk of death (4). In the era of multimodality imaging, exercise echocardiography holds a relevant place in the management of asymptomatic patients with moderate and severe AS, by providing important information for defining the optimal timing of intervention and selecting patients at risk, in need of a more frequent follow-up.

Exercise echocardiography protocol

Both treadmill and bicycle exercise echocardiography can be performed, but semi-supine bicycle exercise on the tilted table is the preferred method in Europe as it allows for continuous two-dimensional (2D) and Doppler echocardiographic evaluation of the valve, ventricle, and its hemodynamic consequences during exercise (5). A symptom-limited graded exercise test is recommended. Classically, the initial workload of 25 W is maintained for 2 min, and the workload is increased every 2 min by 25 W, but an increase by 10 W can be more appropriate in elderly patients. The total exercise time, maximum workload, reason for stopping the test, peak heart rate, and blood pressure are recorded. Complete resting echocardiography is performed at rest, prior to exercise, with the aim of evaluating the severity of AS and its consequences (extravalvular cardiac damage or stage of AS). With each stage of AS (stage 0 no damage, stage 1 left ventricular damage, stage 2 left atrium and mitral valve damage, stage 3 pulmonary circulation and tricuspid valve damage,

Address for correspondence: Patrizio Lancellotti, MD, Department of Cardiology and Cardiovascular Surgery, GIGA Cardiovascular Sciences, CHU SartTilman, University of Liège Hospital; Liège-*Belgium*
E-mail: plancellotti@chuliege.be
Accepted Date: 17.04.2020 **Available Online Date:** 22.05.2020

DOI:10.14744/AnatolJCardiol.2020.76500

stage 4 right ventricle damage or subclinical heart failure), there is a progressive increase in mortality rate in both symptomatic and asymptomatic patients (6). Thus, evaluating the stage of the disease could be helpful in further risk stratification of asymptomatic patients with AS (7). As aforementioned, an LVEF <50% represents an indication for intervention in patients with severe AS (2,3), but this value is questioned by the results of more recent studies, suggesting that intervention should be considered at an earlier stage in these patients. In the HAVEC registry, patients with an LVEF between 50% and 60% had a less favorable outcome and had more heart-failure-related deaths than those with an LVEF >60% (8).

Global longitudinal strain (GLS) can detect subclinical LV systolic dysfunction, before a decrease in LVEF has occurred. The inclusion in the rest protocol of LV-GLS and valvuloarterial impedance (Zva) (defined as systolic arterial pressure + mean aortic valve gradient/LV stroke volume index) has been shown to have incremental prognostic value. In a recent study on 504 patients with asymptomatic severe AS and preserved LVEF, a LV-GLS value <-17% and Zva >4.5 mm Hg/mL/m^2 were associated with an increased risk of death at 5 years (9). The echocardiographic parameters that should be evaluated at each stage of exercise stress echocardiography are presented in Figure 1. Ideally, continuous wave Doppler of the aortic valve at exercise should be performed from the window from which the maximum velocity was obtained at rest (5).

1. Exercise echocardiography in asymptomatic patients with severe aortic stenosis

SAVR or TAVI is indicated in symptomatic patients with severe AS (2, 3). However, due to the advanced age of patients and slow disease progression, with patients unintentionally limiting their activities, it is often difficult to identify the apparently "asymptomatic" patients based on clinical history alone. This is why both European and American guidelines recommend exercise testing in asymptomatic patients with severe AS (2, 3). Exercise testing is contraindicated in patients with severe AS with definite or probable cardiac symptoms (2, 3), but it is safe in asymptomatic patients and provides better risk stratification than conventional echocardiography (10, 11). Simple exercise testing is often difficult to interpret in physically inactive or older patients and patients with confounding diseases (lung disease, comorbidities), and it is particularly in these patients that exercise echocardiography, cardiopulmonary exercise testing (CPET), and biomarkers should be considered. Compared to simple exercise testing, exercise echocardiography can evaluate both the symptomatic status and hemodynamic consequences of AS and provides additional prognostic information (12-14). An abnormal exercise stress echocardiography is associated with an eightfold higher risk of major adverse cardiac events, including a 5.5-fold higher risk of sudden death and increased long-term mortality risk, while a normal test provides reassurance with an excellent 1-year prognosis without the need for surgical intervention (10, 15).

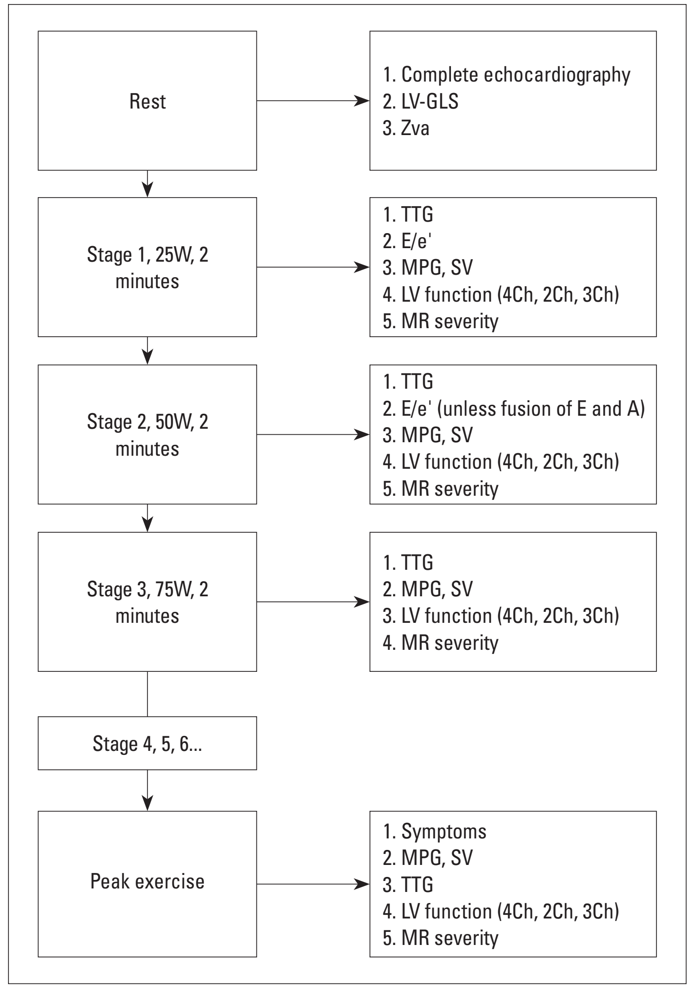

Figure 1. Parameters that can be evaluated during exercise stress echocardiography in patients with aortic stenosis, adapted from Lancellotti et al. (24) with permission

AS - aortic stenosis; Ch - chamber; E - early diastolic wave velocity; LV - left ventricle; LV-GLS - left ventricular global longitudinal strain; MG - mean pressure gradient; MR - mitral regurgitation; SV - stroke volume; TTG - transtricuspid pressure gradient; Zva - valvuloarterial impedance

Exercise ECG parameters

In patients with asymptomatic severe AS, approximately two-thirds of exercise echocardiographic results are abnormal. Exercise-induced limiting symptoms (dyspnea at low workload, angina, dizziness, and syncope) occur in approximately 30–40% of apparently asymptomatic patients with AS (10). The occurrence of exercise-limiting symptoms predicts the rapid development of symptoms in daily life, cardiac death (including sudden death), and need for AVR (10, 16), particularly in young physically active patients (<70 years) (16). In a study on 533 asymptomatic patients with severe AS and preserved LVEF, patients who achieved <85% predicted METs had a more than twofold increase in the risk of death, whereas a slower heart rate recovery at 1-min post-exercise was associated with an almost doubling of the risk of adverse events during follow-up (15). The occurrence of rapidly reversible dyspnea at high workloads (close to the age-sex predicted maximum workload) is on the contrary considered normal

Anatol J Cardiol 2020; 23: 312-7
DOI:10.14744/AnatolJCardiol.2020.76500

(11). According to the International Guidelines on Valvular Heart Disease, an abnormal exercise test showing symptoms clearly related to AS [class I, level of evidence C in the European Society of Cardiology (ESC) guidelines and class I, level of evidence B in the American College of Cardiology/American Heart Association (ACC/AHA) guidelines], decrease in systolic blood pressure below baseline by 20 mm Hg (class IIa, level of evidence C in the ESC guidelines, and IIa, level of evidence B in the ACC/AHA guidelines), and decrease in exercise tolerance (class IIa, level of evidence B in the ACC/AHA guidelines) are potential indicators for intervention in "apparently" asymptomatic patients with severe AS and preserved LVEF (2, 3).

Echocardiographic parameters

Regardless of the resting echocardiographic data and exercise ECG results, exercise-induced changes in indices of AS severity and cardiac function are independent determinants of poor prognosis in patients with asymptomatic severe AS (11). An increase in mean transaortic pressure gradient by ≥18–20 mm Hg during exercise is associated with an increased risk of cardiac death, development of spontaneous symptoms, and need for AVR (12-14, 17-19). Such an increase in pressure gradient reflects the presence of either a more severe AS (the more severe the stenosis at rest, the higher the increase in gradient for a given flow rate during exercise) or noncompliant and rigid aortic valve (no or minimal enlargement of aortic valve orifice area during test) or both. The exercise-induced changes in mean transaortic pressure gradient should be interpreted considering the exercise-induced changes in LV stroke volume and function. The absence of LV contractile reserve with exercise (absence of an exercise-induced increase in EF) may reflect more advanced disease with LV afterload mismatch and/or exhaustion of coronary flow reserve with exercise. These patients are more likely to exhibit an abnormal response to exercise and have an increase in cardiac events during follow-up (14, 17, 19).

Several rather small studies have shown that longitudinal LV strain seems to be a good parameter in predicting the occurrence of symptoms and cardiac events in asymptomatic patients with AS with preserved LVEF. It has been suggested that an exercise increase in GLS by >-1.4% using 2D speckle tracking analysis might indicate the presence of LV contractile reserve (18). In a recent study, resting and, more significantly, exercise basal longitudinal strain, defined as the average of the six basal segments at peak heat rate, were associated with the risk of cardiac events in patients with asymptomatic moderate and severe AS and preserved LVEF (20). As all these studies were small scale, further studies are needed to determine the best cutoff value of exercise-induced change in GLS to identify patients at increased risk of developing LV systolic dysfunction or cardiac events during follow-up (5).

Pulmonary hypertension (PHT) is a strong predictor of reduced exercise capacity and poor outcome in patients with severe AS (21). In asymptomatic patients, the prevalence of PHT at

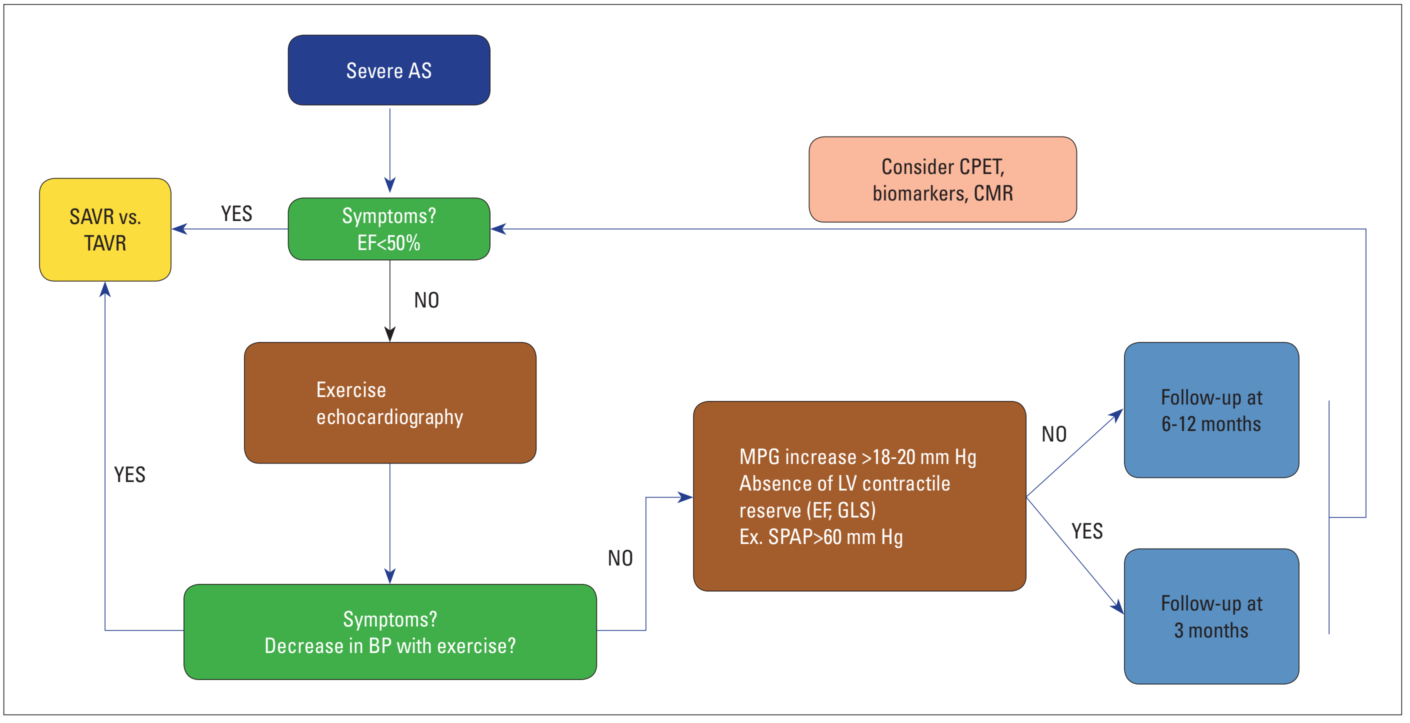

Figure 2. Proposed algorithm for treatment and follow-up of patients with severe aortic stenosis and preserved left ventricular ejection fraction based on stress echocardiography

AS - aortic stenosis; BP - blood pressure; CPET - cardiopulmonary exercise testing; CMR - cardiac magnetic resonance imaging; EF - ejection fraction; Ex. PAPS - exercise systolic pulmonary artery pressure; GLS - global longitudinal strain of the left ventricle; LV - left ventricle; MPG - mean pressure gradient; SAVR - surgical aortic valve replacement; TAVR - transcatheter aortic valve replacement rest is relatively low, while the reported prevalence at exercise [systolic pulmonary artery pressure (PAP) > 60 mm Hg] was 55%, and its presence was independently associated with a twofold increased risk of cardiac events at a 3-year follow-up (22).

The evaluation of LV diastolic parameters, mitral regurgitation (MR), and presence of ischemia are part of the stress echocardiography protocol, although their prognostic values have not been evaluated so far (11, 12, 17). Exertional dyspnea could also be explained by diastolic dysfunction and increase in LV filling pressure (estimated by E/e') and an increase in MR severity with exercise, whereas ischemia could also be the cause of chest pain in patients with AS.

Therefore, due to the lack of large-scale prospective randomized studies, none of these echocardiographic parameters currently represents an indication for intervention in asymptomatic patients with severe AS. Exercise echocardiography could help identify a subset of patients with early and subtle but harmful consequences of AS, who may require AVR earlier and might benefit from a more frequent follow-up. Patients with asymptomatic severe AS and preserved LVEF, who on exercise echocardiography develop a >18–20 mm Hg increase in mean gradient and signs of impaired contractile reserve as assessed by EF and GLS or exercise-induced PHT (exercise systolic PAP >60 mm Hg), should be closely followed (3 months), including careful and objective evaluation of symptoms, serial brain natriuretic peptide assessment, and repeated exercise stress echocardiography. In contrast, patients with appropriate exercise echocardiographic adaptation (i.e. increase by <20 mm Hg in mean aortic pressure gradient, good LV contractile reserve, no exercise PHT) may be safely followed every 6–12 months (Fig. 2 and 3).

2. Exercise echocardiography in patients with moderate aortic stenosis

More recent studies have shown that moderate AS is also associated with poor survival rates, with a marked increased risk of death from all causes and cardiovascular diseases seen once the mean aortic valve gradient is >20 mm Hg (4). There are a few studies on stress echocardiography in patients with moderate AS, suggesting that exercise echocardiography could help in guiding the appropriate clinical follow-up in these patients. Basically, the same echocardiographic parameters described for patients with severe AS can be used in patients with moder-

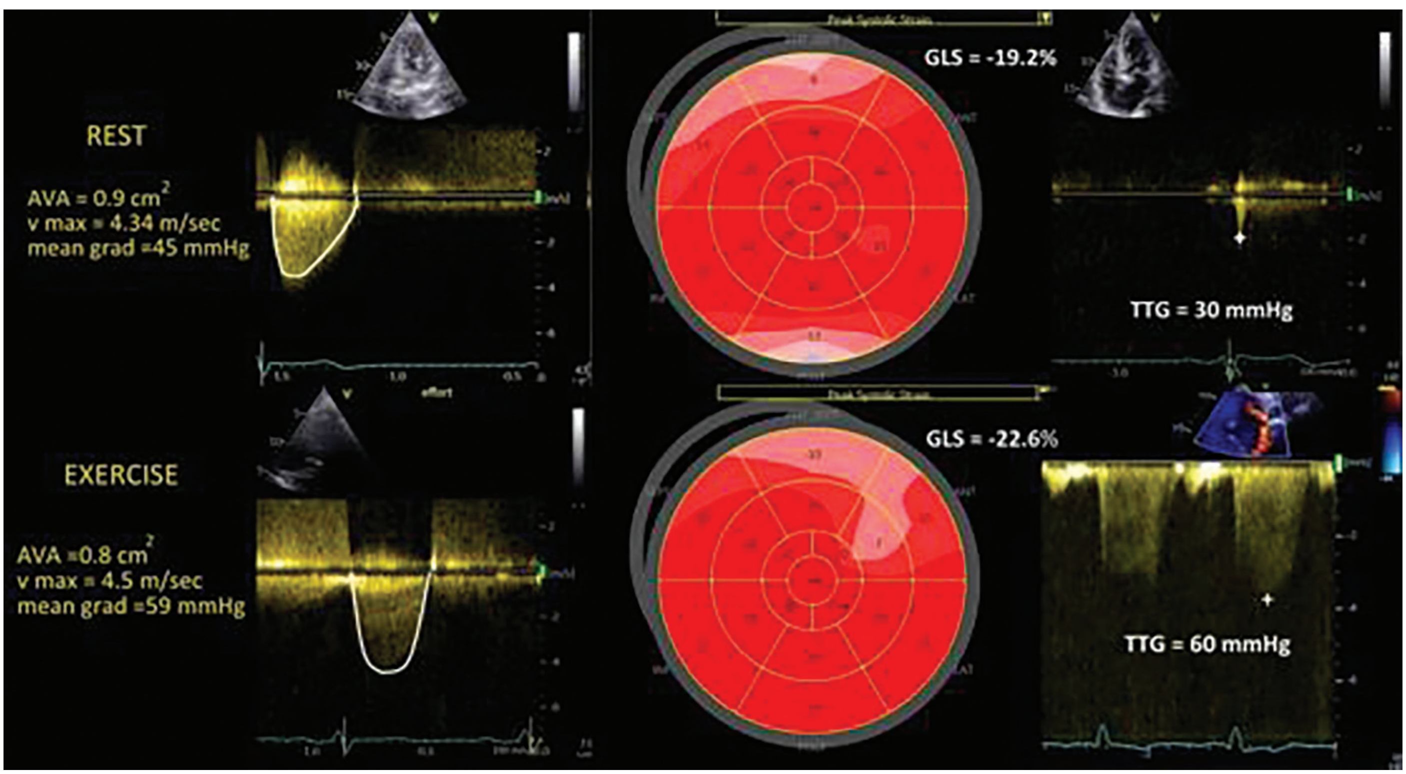

Figure 3. Exercise stress echocardiography in an asymptomatic patient with severe aortic stenosis (AS). Rest echocardiographic evaluation (upper panel) confirms the presence of high-gradient severe AS with preserved left ventricular ejection fraction (rest EF estimated at 60%, not shown), preserved LV-GLS, and transtricuspid pressure gradient (TTG) at rest measured at 30 mm Hg. The patient stopped the test prematurely (maximum heart rate, 99 bpm, representing 65% of the maximum predicted heart rate) because of severe dyspnea, which persisted for a long time in the recovery period. There was neither a decrease in systolic blood pressure nor other symptoms. At exercise echocardiography (lower panel), the mean aortic pressure gradient increase was 14 mm Hg, EF reached 67%, and LV-GLS was 22.6%, indicating the presence of contractile reserve. At exercise, the TTG also markedly increase but at an early stage indicated significant pulmonary hypertension. The case of the patient was discussed in the heart team meeting, and surgical aortic valve replacement was scheduled

V max - peak transaortic velocity; mean grad - mean transaortic pressure gradient; AVA - aortic valve area; GLS - global longitudinal strain, TTG - transtricuspid pressure gradient

Anatol J Cardiol 2020; 23: 312-7
DOI:10.14744/AnatolJCardiol.2020.76500

ate AS (5). In a small scale study on patients with at least moderate asymptomatic AS and preserved LVEF, an exercise increase in mean pressure gradient >20 mm Hg was associated with a faster progression of AS during the follow-up (23). In another study, patients with a resting mean AV gradient >35 mm Hg and exercise-induced increase in mean gradient >20 mm Hg had a significantly higher risk of death or surgical AVR during a mean follow-up duration of 20 months (19). These patients could represent a higher risk group for disease progression and should be followed more closely (every 6–12 months) (19).

Conclusion

The optimal management and time for intervention in patients with asymptomatic severe AS is still unknown. A multimodality and multiparametric assessment of these patients should be conducted, including exercise testing, especially with echocardiography, CPET, biomarkers, and cardiac magnetic resonance imaging. Exercise echocardiography can identify “apparently” asymptomatic patients who develop exercise abnormalities and in whom intervention can be indicated. This tool can also help in identifying a subset of asymptomatic patients who are at increased risk of further cardiac events and in whom a more frequent follow-up is recommended.

Conflict of interest: None declared.

Peer-review: Internally peer-reviewed.

Authorship contributions: Concept – A.P., M.N.T., J.T., S.S., A.M.C., R.D., P.L.; Design – A.P., M.N.T., J.T., S.S., A.M.C., R.D., P.L.; Supervision – A.P., M.N.T., J.T., S.S., A.M.C., R.D., P.L.; Funding – None; Materials – None; Data collection and/or processing – None; Analysis and/or interpretation – A.P., M.N.T., J.T., S.S., A.M.C., R.D., P.L.; Literature search – A.P., M.N.T., J.T., S.S., A.M.C., R.D., P.L.; Writing – A.P., M.N.T., J.T., S.S., A.M.C., R.D., P.L.; Critical review – A.P., M.N.T., J.T., S.S., A.M.C., R.D., P.L.

References

1. Iung B, Baron G, Butchart EG, Delahaye F, Gohlke-Bärwolf C, Levang OW, et al. A prospective survey of patients with valvular heart disease in Europe: The Euro Heart Survey on Valvular Heart Disease. Eur Heart J 2003; 24: 1231-43.
2. Baumgartner H, Falk V, Bax JJ, De Bonis M, Hamm C, Holm PJ, et al.; ESC Scientific Document Group. 2017 ESC/EACTS Guidelines for the management of valvular heart disease. Eur Heart J 2017; 38: 2739-91.
3. American College of Cardiology/American Heart Association Task Force on Practice Guidelines; Society of Cardiovascular Anesthesiologists; Society for Cardiovascular Angiography and Interventions; Society of Thoracic Surgeons, Bonow RO, Carabello BA, Kanu C, de Leon AC Jr, Faxon DP, Freed MD, et al. ACC/AHA 2006 guidelines for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (writing committee to revise the 1998 Guidelines for the Management of Patients With Valvular Heart Disease): developed in collaboration with the Society of Cardiovascular Anesthesiologists: endorsed by the Society for Cardiovascular Angiography and Interventions and the Society of Thoracic Surgeons. Circulation 2006; 114: e84-231.
4. Strange G, Stewart S, Celermajer D, Prior D, Scalia GM, Marwick T, et al.; National Echocardiography Database of Australia contributing sites. Poor Long-Term Survival in Patients With Moderate Aortic Stenosis. J Am Coll Cardiol 2019; 74: 1851-63.
5. Lancellotti P, Pellikka P, Budts W, Chaudhry FA, Donal E, Dulgheru R et al. The clinical use of stress echocardiography in non-ischaemic heart disease: recommendations from the European Association of Cardiovascular Imaging and the American Society of Echocardiography. Eur Heart J Cardiovasc Imaging 2016; 17: 1191-229.
6. Tastet L, Tribouilloy C, Maréchaux S, Vollema EM, Delgado V, Salaun E, et al. Staging Cardiac Damage in Patients With Asymptomatic Aortic Valve Stenosis. J Am Coll Cardiol 2019; 74: 550-63.
7. Lancellotti P, Vannan MA. Timing of intervention in aortic stenosis. N Engl J Med 2020; 382: 191-3.
8. Lancellotti P, Magne J, Dulgheru R, Clavel MA, Donal E, Vannan MA et al. Outcomes of Patients With Asymptomatic Aortic Stenosis Followed Up in Heart Valve Clinics. JAMA Cardiol 2018; 3: 1060-8.
9. Huded CP, Masri A, Kusunose K, Goodman AL, Grimm RA, Gillinov AM, et al. Outcomes in Asymptomatic Severe Aortic Stenosis With Preserved Ejection Fraction Undergoing Rest and Treadmill Stress Echocardiography. J Am Heart Assoc 2018; 7: pii: e007880.
10. Rafique AM, Biner S, Ray I, Forrester JS, Tolstrup K, Siegel RJ. Meta-analysis of prognostic value of stress testing in patients with asymptomatic severe aortic stenosis. Am J Cardiol 2009; 104: 972-7.
11. Lancellotti P, Magne J, Piérard LA. The role of stress testing in evaluation of asymptomatic patients with aortic stenosis. Curr Opin Cardiol 2013; 28: 531-9.
12. Picano E, Pibarot P, Lancellotti P, Monin JL, Bonow RO. The emerging role of exercise testing and stress echocardiography in valvular heart disease. J Am Coll Cardiol 2009; 54: 2251-60.
13. Lancellotti P, Lebois F, Simon M, Tombeux C, Chauvel C, Pierard LA. Prognostic importance of quantitative exercise Doppler echocardiography in asymptomatic valvular aortic stenosis. Circulation 2005; 112 (9 Suppl): I377-82.
14. Maréchaux S, Ennezat PV, LeJemtel TH, Polge AS, de Groote P, Asseman P, et al. Left ventricular response to exercise in aortic stenosis: an exercise echocardiographic study. Echocardiography 2007; 24: 955-9.
15. Masri A, Goodman AL, Barr T, Grimm RA, Sabik JF, Gillinov AM, et al. Predictors of Long-Term Outcomes in Asymptomatic Patients With Severe Aortic Stenosis and Preserved Left Ventricular Systolic Function Undergoing Exercise Echocardiography. Circ Cardiovasc Imaging 2016; 9: pii: e004689.
16. Das P, Rimington H, Chambers J. Exercise testing to stratify risk in aortic stenosis. Eur Heart J 2005; 26: 1309-13.
17. Lancellotti P, Karsera D, Tumminello G, Lebois F, Pierard LA. Determinants of an abnormal response to exercise in patients with asymptomatic valvular aortic stenosis. Eur J Echocardiogr 2008; 9: 338-43.
18. Donal E, Thebault C, O'Connor K, Veillard D, Rosca M, Pierard L, et al. Impact of aortic stenosis on longitudinal myocardial deformation during exercise. Eur J Echocardiogr 2011; 12: 235-41.

19. Maréchaux S, Hachicha Z, Bellouin A, Dumesnil JG, Meimoun P, Pasquet A, et al. Usefulness of exercise-stress echocardiography for risk stratification of true asymptomatic patients with aortic valve stenosis. Eur Heart J 2010; 31: 1390-7.
20. Levy-Neuman S, Meledin V, Gandelman G, Goland S, Zilberman L, Edri O, et al. The Association Between Longitudinal Strain at Rest and Stress and Outcome in Asymptomatic Patients With Moderate and Severe Aortic Stenosis. J Am Soc Echocardiogr 2019; 32: 722-9.
21. Lewis GD, Bossone E, Naeije R, Grünig E, Saggar R, Lancellotti P, et al. Pulmonary vascular hemodynamic response to exercise in cardiopulmonary diseases. Circulation 2013; 128: 1470-9.
22. Lancellotti P, Magne J, Donal E, O'Connor K, Dulgheru R, Rosca M, et al. Determinants and prognostic significance of exercise pulmonary hypertension in asymptomatic severe aortic stenosis. Circulation 2012; 126: 851-9.
23. Ringle A, Levy F, Ennezat PV, Le Goffic C, Castel AL, Delelis F, et al. Relationship between exercise pressure gradient and haemodynamic progression of aortic stenosis. Arch Cardiovasc Dis 2017; 110: 466-74.
24. Lancellotti P, Dulgheru R, Go YY, Sugimoto T, Marchetta S, Oury C, et al. Stress echocardiography in patients with native valvular heart disease. Heart 2018; 104: 807-13.