# ENERGY LOSS INDEX – IMPLICATIONS FOR THE ASSESSMENT OF AORTIC STENOSIS SEVERITY

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*In aortic stenosis (AS) therapeutic decisions are based on presence of symptoms and echocardiographic assessment of hemodynamic severity. Accurate echocardiographic assessment of AS severity is therefore of major clinical importance. It is well-known that pressure recovery in the aortic root influences the accuracy of assessment of AS severity from the continuity equation. Overestimation of AS severity by unadjusted aortic valve area index (AVAI) is largest in patients with small aortic roots or low peak aortic jet velocity. Clinically important pressure recovery is particularly present in these patients groups. In asymptomatic mild AS, the percentage of reclassification from severe AS to non-severe AS by pressure recovery adjustment of AVAI (Energy loss index [ELI]) may be up to 45.7%. It was recently demonstrated from the Simvastatin and Ezetimibe in Aortic Stenosis (SEAS) study that ELI in such patients provides better risk classification than conventional measures of AS severity, including peak aortic jet velocity and mean aortic gradient. In particular ELI improved prediction of combined mortality and hospitalization for heart failure in AS patients with small aortic roots. These novel findings suggest that calculation of ELI should be included in routine assessment of AS severity.*

## Epidemiology and pathogenesis of aortic stenosis

Aortic stenosis (AS) is the most frequent heart valve disease in Europe and North America and one of the most common cardiovascular disease besides hypertension and coronary artery disease[1, 2]. Every 4th person over the age of 65 and 50% of subjects over the age of 75 years has evidence of aortic sclerosis and 2 to 9% of the population aged 75 years and older has AS in population based reports using echocardiography analysed in core laboratories[1, 3, 4]. The age-related increase in prevalence of AS is more predominant among men [1, 3]. The increased prevalence of degenerative calcific AS is mainly a consequence of aging of the population, and more elderly patients with degenerated tricuspid aortic valve[1-4], while congenital (bicuspid) AS is the main cause of AS in younger age, present in 5 to 28% of AS patients[5, 6]. Calcific AS is described as an active disorder. Similar to the pathogenesis of atherosclerosis, atherogenic lipid deposition[7, 8], chronic inflammation with T-lymphocytes[9-12] and macrophage[7] infiltration, ossification and bone formation[10, 13 14] and production of osteopontin and other proteins[15-16] are involved in the development of aortic valve leaflet calcification with thickening, immobility and outflow tract obstruction. Identified risk factors for calcific AS, besides age, include male gender, smoking, hypertension, hyperlipidemia, height, body mass index and diabetes[3, 8, 17- 22]. Calcium metabolism is also of importance for the development of AS in the elderly, as demonstrated by Lindroos et al[22].

Clinical factors associated with aortic sclerosis and stenosis in these smaller studies and in the large prospective *Cardiovascular Health Study*, including more than 5000 subjects 65 years or older, are also similar to risk factors for atherosclerosis[3]. Furthermore it is shown in a large population based prospective study, including more than 5500 subjects[23] and in smaller studies [24, 25], that AS is associated with clinical atherosclerotic disease. In addition, presence of angiotensin converting enzyme (ACE) and angiotensin II have been demonstrated in sclerotic aortic valves[26] as well as in atherosclerotic lesions[27, 28]. In patients with bicuspid valves, significant AS develops 2 decades younger than those with tricuspid valves due to higher mechanical stress[29, 30].

From these observations, medical therapies with statins and ACE inhibitors which have been shown to delay the progression of atherosclerosis[31-33]and improve outcome in patients with atherosclerosis[34, 35] were tested to affect the progression of AS. In animal models[36] and several retrospective studies and small case-control studies[37-39] it is reported that statins could slow the progression of AS. In contrast, prospective studies, including the *SEAS* [5] and *ASTRONOMER*[40] trial, could not find any beneficial effect of lipid-lowering therapy on the progression of AS. In addition, no beneficial effect of ACE inhibitors on the progression of AS could be demonstrated in a retrospective large cohort of 211 patients[41].

## Natural history of aortic stenosis

The progression of AS is estimated between 0.14 and 0.45 m/s/year by peak aortic jet velocity, 2.7 and 7 mmHg by mean aortic gradient and by reduction of aortic valve area (AVA) between 0.03 and 0.12 $cm^2$/year[5, 6, 42, 43]. An asymptomatic period over several decades is followed by development of one or more cardinal symptoms: angina pectoris, syncope or heart failure[44]. At the time of diagnosis 30 to 50% of patients with severe AS are still asymptomatic[45], and 1/3 of these patients will become symptomatic within 2 years[46]. Within 4 to 5 years, 2/3 of patients with initially asymptomatic severe AS will have either an aortic valve replacement due to development of symptoms or experience cardiac death[6, 43, 46]. The survival rate in the asymptomatic period is comparable to that observed in general population[47]. Prospective studies demonstrate that in asymptomatic period sudden cardiac death occurs in 3-5%/year[44], but is very rare in patients with normal exercise capacity (<1%/year)[6, 43, 46, 48].

With onset of symptoms prognosis worsens markedly in patients with severe AS[44, 46], and the treatment of choice is aortic valve replacement surgically or catheter based[49]. Average survival without aortic valve replacement after the onset of symptoms has been reported to be less than 2-3 years[50]. In patients with severe AS following development of angina and syncope expected survival is 3 years, in patients with dyspnea 2 years and in patients with heart failure 1.5 to 2 years[44].

In AS therapeutic decisions are based on hemodynamic severity, left ventricular (LV) function, size and wall thickness, degree of valve calcification, blood pressure response during exercise as well as functional status[43, 43, 51, 52]. It is often difficult, especially in older patients and in patients with co-morbidities to accurately detect and interpret associated symptoms. Operative treatment of pseudosevere AS exposes the patients for unnecessary perioperative risk and does not relief symptoms. Risk of sudden death without preceding symptoms and the potential risk of irreversible myocardial damage argue for early elective valve replacement[44]. Otto et al. described that 79% of initially asymptomatic AS patients with peak aortic jet velocity >4m/s required aortic valve replacement within 2 years[6]. Rosenhek et al. reported that survival also in mild and moderate AS was significantly worse than assumed, with a 80% higher mortality rate compared to normal population, which was particularly attributed to severe valve calcification, presence of coronary artery disease and AS severity[42]. The identification of high risk patients with asymptomatic severe AS who would benefit from an early valve replacement may be difficult. Correct and reliable quantification of the degree of severity and knowledge of the hemodynamic progression is of particular importance in this context.

## Quantitative diagnosis of aortic stenosis

Risk assessment in asymptomatic patients with AS is based on transthoracic echocardiography[49, 51, 53]. Currently recommended measures for assessing the severity of AS include AVA calculated by the continuity equation, AVA indexed for body surface area (AVAI), peak aortic jet velocity and mean aortic gradient, calculated by the simplified Bernoulli-equation (Table 1)[49, 51-53]. Recommended cut-off values for severe AS are AVA <1.0cm² and AVAI ≤0.6cm²/m², respectively, and for crude, non-flow-corrected parameters mean aortic gradient >40mmHg or peak aortic jet velocity >4.0m/sec is recommended[49, 51]. Defining severe AS by the measures mean aortic gradient and peak aortic jet velocity is recommended only in patients with normal cardiac output/transvalvular flow (stroke volume index >35ml/m²)[51]. Of note, flow can be reduced also when LV ejection fraction (EF) is normal, an entity recently described as paradoxical low flow (stroke volume index <35ml/m²) AS [55].

As stated in the current guidelines, an AVAI ≤0.6cm²/m² should not be used alone for diagnosis of severe AS in clinical decision making, but should be considered in combination with pressure gradients, LV function, size and wall thickness, degree of valve calcification and patient functional status[51]. Although the above recommended cut-off values are expected to give a consistent classification of AS severity in patients with normal LV function, inconsistent severity grading by these cut-off values is quite common and has been reported in up to 30% of patients[56-57]. Recently, it was demonstrated that asymptomatic patients with inconsistently graded severe AS (mean aortic gradient<40 mmHg but AVAI<0.6 cm²/m²) and preserved LV EF (≥55%) had a less impaired prognosis than patients with consistently graded severe AS, more comparable to that seen in patients with moderate AS[58].

Inconsistently graded AS can arise from several causes including measurement errors, small aortic root, reduced EF or paradoxically low flow [53, 55, 59-61]. The entity of paradoxically low flow severe AS, defined as inconsistently graded severe AS despite normal EF and the presence of low flow, probably is related to high arterial load or myocardial fibrosis with reduced myocardial function despite a normal EF[55, 60].

*Table 1. Equations for measures of AS severity*

| Measures | Equation |
|---|---|
| Aortic valve area (cm²) | (CSALVOTxVTILVOT)/VTIAS |
| Aortic valve area index (cm²/m²) | AVA/BSA |
| Aortic gradient (mmHg) | 4v² |
| Pressure recovery (mmHg) | 4v²x2AVA/Aa[1-(AVA/Aa)] |
| Energy loss index (cm²/m²) | (AVAxAa)/(Aa-AVA)/BSA |

*CSA= cross-sectional area; LVOT= left ventricular outflow tract; VTI= velocity time integral; AS= aortic stenosis; BSA= body surface area; v=velocity; Aa= aortic area.*

## Pressure recovery in aortic stenosis

Downstream pressure recovery in the aorta affects transvalvular pressure gradient measurement and estimation of AVA by continuity equation in patients with AS[62]. The total energy of flow consists of pressure energy and kinetic energy. Convergence of flow through the stenotic aortic valve to the vena contracta converts pressure energy to kinetic energy with a resulting reduction in pressure at the vena contracta, which was first demonstrated by Clark in experimental fluid mechanic studies of AS[63-65]. When the blood velocity decreases distal to the stenosis, some of the energy is transformed back to pressure energy, resulting in a net pressure gradient lower than the maximal pressure gradient (Figure 1)[66, 67]. The difference between maximal pressure gradient and net pressure gradient is called pressure recovery. Pressure recovery therefore reduces the work load imposed on the left ventricle. The actual amount of pressure recovery will depend on how much energy has been lost at the stenosis due to viscous and turbulent energy losses. As expected from experimental data[62, 63, 68] and confirmed in small[67, 69, 70] and large[61] clinical studies, the absolute magnitude of pressure recovery was greater in subjects with higher

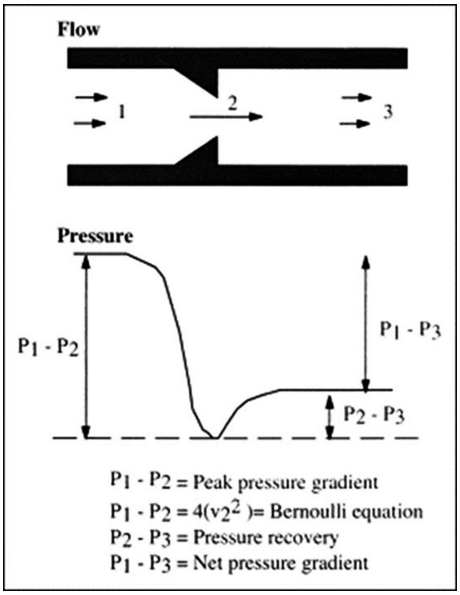


*Figure 1. Upper picture: schematic representation of flow in a stenosis. Lower picture: pullback pressure recording[36].*

aortic jet velocities and smaller aortic root size.

The amount of pressure recovery can be calculated from the dynamic pressure (simplified Bernoulli equation), the AVA and the cross-sectional area of the ascending aorta (Table 1)[62, 71]. Pressure recovery in the ascending aorta is recommended to be calculated at its maximum[62] and this is found at the smallest aortic root diameter, which corresponds to the sinotubular junction in most patients (Figure 2)[61, 72].

However, although the amount of pressure recovery increases with the severity of the stenosis, the proportion of pressure recovery in relation to the peak aortic gradient decreases with increasing AS severity[68]. Confirming these previous findings in experimental studies as well as in invasive studies in small patient populations[69], the

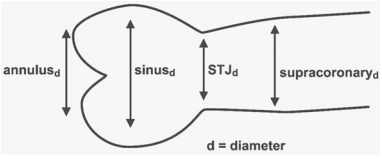


*Figure 2. Schematic representation of the aortic root at different levels. STJ= sinotubular junction*

functional significance of pressure recovery in patients with normal LV function is proportionately larger in patients with lower peak aortic jet velocities, presenting milder degree of AS[61, 62, 73, 74]. Clinically important pressure recovery, defined as >20% of the peak aortic pressure gradient, is present in 16.8% of patients, shown in a large multicentre study of initially asymptomatic AS patients[61]. As women have smaller aortic roots, the amount of pressure recovery is greater and its proportion to peak aortic gradient significantly higher compared to men[61].

The clinical implication of pressure recovery is that AVA calculated by Doppler-based methods underestimate valve area compared to catheter-based methods, where aortic pressure is routinely measured in the aortic root several centimeters distal to the aortic valve[62, 69-71, 73]. Physiologically, it is the recovered pressure, i.e. the net pressure drop, the gradient between the LV outflow tract and the aortic root distal to the vena contracta, that reflects the work load imposed on the LV in AS rather than the maximal pressure drop at the vena contracta measured by Doppler echocardiography[75]. The influence of pressure recovery for accurate grading of AS is of particular relevance in patients with mild to moderate AS defined by unadjusted AVA and in patients with small aortic diameters (aortic sinotubular junction diameter <3.0cm)[61,69].

To overcome these limitations, Garcia et al.[44] derived an equation to estimate the pressure recovery adjusted effective AVA, called energy loss index (ELI) (Table 1). It has been suggested that ELI may more accurately reflect the severity of AS and therefore may be a superior measure of AS severity[75-77]. Of note, the currently recommended cut-off values for definition of severe AS are based on invasive studies, where the AVA is calculated by the Gorlin formula[78, 79]. It therefore is of importance to mention that the present guidelines make no distinction between invasive and non-invasive derived estimates of AS severity[49, 51]. From a large population of patients with mild to moderate asymptomatic AS, it was demonstrated that ELI was on average 30% larger than AVAI and the difference between AVAI and ELI and therewith overesti-

mation of AS severity by AVAI compared to ELI increased with lower peak aortic jet velocity and smaller aortic root dimension[61]. Similarly, with increasing peak aortic jet velocity the difference between AVAI and ELI diminishes[61, 69, 80]. For ELI, the recommended cut-off value for definition of severe AS is identical to invasively derived cut-off value for AVAI with ≤0.6cm²/m²[49, 61, 81]. By using ELI instead of AVAI, the percentage of patients reclassified from severe to non-severe AS was reported to be up to 45.7% among asymptomatic AS patients[61,69, 73,74].

## Energy loss index as predictor of outcome in aortic stenosis patients

Only limited data existed on the prognostic value of ELI when we started out the present work. Garcia et al. had reported in a small retrospective study in moderate to severe AS, that ELI was superior to AVAI in prediction of combined death or aortic valve replacement within 8 months after the echocardiographic evaluation[76]. We tested this in a prospectively planned analysis within the large *SEAS* study which included 1563 initially asymptomatic AS patients followed for 4.3 years with serial echocardiograms. As recently published, 1 cm/m² lower baseline ELI predicted a 2-fold higher rate of combined aortic valve replacement, hospitalization for heart failure and cardiovascular death as well as combined total mortality and hospitalization for heart failure due to progression of AS independent of the conventional measures of AS like mean aortic gradient and peak aortic jet velocity[82]. In reclassification analysis, using ELI resulted in improved risk classification[82]. In particular, ELI was superior in risk prediction among patients with small aortic roots, a subgroup of AS patients where clinical significant pressure recovery is often found[61, 62, 76]. Of note, this included improved prediction not only of need for aortic valve replacement, which may be influenced by doctor's preference, but also for hospitalization for heart failure and death from any cause. In contrast, no improvement in risk prediction from using ELI was found in the groups of patients with inconsistently graded AS (mean gradient <40mmHg combined with AVAI≤0.6cm²/m²)[82]. The latter finding that ELI did not improve risk prediction among patients with inconsistently graded AS, probably reflects the inhomogeneity of this patient group, and the many different causes for inconsistently grading, as pointed out above. Our finding that ELI improves risk prediction from mean aortic gradient and peak aortic jet velocity in asymptomatic AS patients also adds to a previous report by Bermejo et al. who reported peak aortic jet velocity and mean aortic gradient to be superior to AVA in predicting risk for all-cause mortality in 307 symptomatic patients with moderate to severe AS[82].

## Conclusion

Calculation of ELI is recommended for more accurate assessment of AS severity. First, using ELI in mild to moderate AS prevents the common overestimation of AS severity by unadjusted AVAI in such patients. Second, ELI provides independent and superior risk classification to that derived from conventional measures of AS severity including peak jet velocity, mean gradient and AVAI in patients with asymptomatic mild to moderate AS. In particular, use of ELI is important for evaluation of AS patients with small aortic roots.

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## References

1. Nkomo VT, Gardin JM, Skelton TN, Gottdiener JS, Scott CG, Enriquez-Sarano M. Burden of valvular heart diseases: a population-based study. *Lancet.* 2006;368:1005-1011.
2. Iung B, Baron G, Butchart EG, Delahaye F, Gohlke-Bärwolf C, Levang OW, Tornos P, Vanoverschelde JL, Vermeer F, Boersma E, Ravaud P, Vahanian A. A prospective survey of patients with valvular heart disease in Europe: The Euro Heart Survey

on Valvular Heart Disease. *Eur Heart J.* 2003;24:1231-1243.

3. Stewart BF, Siscovick D, Lind BK, Gardin JM, Gottdiener JS, Smith VE, Kitzman DW, Otto CM. Clinical factors associated with calcific aortic valve disease. Cardiovascular Health Study. *J Am Coll Cardiol.* 1997;29:630-634.
4. Lindroos M, Kupari M, Heikkilä J, Tilvis R. Prevalence of aortic valve abnormalities in the elderly: an echocardiographic study of a random population sample. *J Am Coll Cardiol.* 1993;21:1220-1225.
5. Rossebø AB, Pedersen TR, Boman K, Brudi Ph, Chambers J, Egstrup K, Gerdts E, Gohlke-Baerwolf Ch, Holme I, Kesäniemi YA, Malbecq W, Nienaber CA, Ray S, Skjaerpe T, Wachtell K, Willenheimer R. Intensive lipid lowering with Simvastatin and Ezetimibe in aortic stenosis. *N Engl J Med.* 2008;359:1-14.
6. Otto CM, Burwash IG, Legget ME, Munt BI, Fujioka M, Healy NL, Kraft CD, Miyake-Hull CY, Schwaegler RG. Prospective study of asymptomatic valvular aortic stenosis: clinical, echocardiographic and exercise predictors of outcome. *Circulation.* 1997;95:2262-2270.
7. Otto CM, Kuusisto J, Reichenbach DD, Gown AM, O`Brian KD. Characterization of the early lesion of `degenerative` valvular aortic stenosis: histologic and immunhistochemical studies. *Circulation.* 1994;90:844-853.
8. Olsson M, Rosenqvist M, Nilsson J. Expression of HLA-DR antigen and smooth muscle cell differentiation markers by valvular fibroblasts in degenerative aortic stenosis. *J Am Coll Cardiol.* 1994;24:1664-1671.
9. Olsson M, Dalsgaard CJ, Haegerstrand A, Rosenqvist M, Rydén L, Nilsson J. Accumulation of T lymphocytes and expression of interleukin-2 receptors in nonrheumatic stenotic aortic valves. *J Am Coll Cardiol.* 1994;23:1162-1170.
10. O'Brien KD, Reichenbach DD, Marcovina SM, Kuusisto J, Alpers CE, Otto CM. Apolipoproteins B, (a), and E accumulate in the morphologically early lesion of 'degenerative' valvular aortic stenosis. *Arterioscler Thromb Vasc Biol.* 1996;16:523-532.
11. Olsson M, Thyberg J, Nilsson J. Presence of oxidized low density lipoprotein in nonrheumatic stenotic aortic valves. *Arterioscler Thromb Vasc Biol.* 1999;19:1218-1222.
12. Wallby L, Janerot-Sjöberg B, Steffensen T, Broqvist M. T lymphocyte infiltration in non-rheumatic aortic stenosis: a comparative descriptive study between tricuspid and bicuspid aortic valves. *Heart.* 2002;88:348-351.
13. Mohler ER 3rd, Gannon F, Reynolds C, Zimmerman R, Keane MG, Kaplan FS. Bone formation and inflammation in cardiac valves. *Circulation.* 2001;103.
14. Caira FC, Stock SR, Gleason TG, McGee EC, Huang J, Bonow RO, Spelsberg TC, McCarthy PM, Rahimtoola SH, Rajamannan NM. Human degenerative valve disease is associated with up-regulation of low-density lipoprotein receptor-related protein 5 receptor-mediated bone formation. *J Am Coll Cardiol.* 2006;47:1707-1712.
15. Rajamannan NM, Subramamaniam M, Rickard D, Stock SR, Donovan J, Springett M, Orszulak T, Fullerton DA, Tajik AJ, Bonow RO, Spelsberg T. Human aortic valve calcification is associated with an osteoblast phenotype. *Circulation.* 2003;107:2181-2184.
16. O`Brian KD, Kuusisto J, Reichenbach DD, Ferguson M, Giachelli C, Alpers CE, Otto CM. Osteopontin is expressed in human aortic valvular lesions. *Circulation.* 1995;92:2163-2168.
17. Gotoh T, Kuroda T, Yamasawa M, Nishinaga M, Mitsuhashi T, Seino Y, Nagoh N, Kayaba K, Yamada S, Matsuo H, et al. Correlation between lipoprotein(a) and aortic valve sclerosis assessed by echocardiography (the JMS Cardiac Echo and Cohort Study). *J Am Coll Cardiol.* 1995;76:928-932.
18. Mohler ER, Sheridan MJ, Nichols R, Harvey WP, Waller BF. Development and progression of aortic valve stenosis: atherosclerosis risk factors--a causal relationship? A clinical morphologic study. *Clin Cardiol.* 1991;14:995-999.
19. Aronow WS, Schwartz KS, Koenigsberg M. Correlation of serum lipids, calcium, and phosphorus, diabetes mellitus and history of systemic hypertension with presence or absence of calcified or thickened aortic cusps or root in elderly patients. *Am J Cardiol.* 1987;59:998-999.
20. Hoagland PM, Cook EF, Flatley M, Walker C, Goldman L. Case-control analysis of risk factors for presence of aortic stenosis in adults (age 50 years or older). *Am J Cardiol.* 1985;55:744-747.
21. Deutscher S, Rockette HE, Krishnaswami V. Diabetes and hypercholesterolemia among patients with calcific aortic stenosis. *J Chronic Dis.* 1984;37:407-415.
22. Lindroos M, Kupari M, Valvanne J, Strandberg T, Heikkilä J, Tilvis R. Factors associated with calcific aortic valve degeneration in the elderly. *Eur Heart J.* 1994;15:865-870.
23. Otto CM, Lind BK, Kitzman DW, Gersh BJ, Siscovick DS. Association of aortic-valve sclerosis with cardiovascular mortality and morbidity in the elderly. *N Engl J Med.* 1999;341:142-147.
24. Olsen MH, Wachtell K, Bella JN, Gerdts E, Palmieri V, Nieminen MS, Smith G, Ibsen H, Devereux RB. Aortic valve sclerosis relates to cardiovascular events in patients with hypertension (a LIFE substudy). *Am J Cardiol.* 2005;95:132-136.

25. Agmon Y, Khandheria BK, Meissner I, Sicks JR, O'Fallon WM, Wiebers DO, Whisnant JP, Seward JB, Tajik AJ. Aortic valve sclerosis and aortic atherosclerosis: different manifestations of the same disease? Insights from a population-based study. *J Am Coll Cardiol.* 2001;28:827-834.
26. O'Brien KD, Shavelle DM, Caulfield MT, McDonald TO, Olin-Lewis K, Otto CM, Probstfield JL. Association of angiotensin-converting enzyme with low-density lipoprotein in aortic valvular lesions and in human plasma. *Circulation.* 2002;106:2224-2230.
27. Schieffer B, Schieffer E, Hilfiker-Kleiner D, Hilfiker A, Kovanen PT, Kaartinen M, Nussberger J, Harringer W, Drexler H Expression of angiotensin II and interleukin 6 in human coronary atherosclerotic plaques: potential implications for inflammation and plaque instability. *Circulation.* 2000;101:1372-1378.
28. Tummala PE, Chen XL, Sundell CL, Laursen JB, Hammes CP, Alexander RW, Harrison DG, Medford RM. Angiotensin II induces vascular cell adhesion molecule-1 expression in rat vasculature: A potential link between the renin-angiotensin system and atherosclerosis. *Circulation.* 1999;100:1223-1229.
29. Beppu S, Suzuki S, Matsuda H, Ohmori F, Nagata S, Miyatake K. Rapidity of progression of aortic stenosis in patients with congenital bicuspid aortic valves. *Am J Cardiol.* 1993;71:322-327.
30. Pachulski RT, Chan KL. Progression of aortic valve dysfunction in 51 adult patients with congenital bicuspid aortic valve: assessment and follow up by Doppler echocardiography. *Br Heart J.* 1993;69:237-240.
31. Pitt B, Mancini GB, Ellis SG, Rosman HS, Park JS, McGovern ME. Pravastatin limitation of atherosclerosis in the coronary arteries (PLAC I): reduction in atherosclerosis progression and clinical events. PLAC I investigation. *J Am Coll Cardiol.* 1995;26:1133-1139.
32. Jukema JW, Bruschke AV, van Boven AJ, Reiber JH, Bal ET, Zwinderman AH, Jansen H, Boerma GJ, van Rappard FM, Lie KI, et al. Effects of lipid lowering by pravastatin on progression and regression of coronary artery disease in symptomatic men with normal to moderately elevated serum cholesterol levels. The Regression Growth Evaluation Statin Study (REGRESS). *Circulation.* 1995;91.
33. Hayek T, Attias J, Coleman R, Brodsky S, Smith J, Breslow JL, Keidar S. The angiotensin-converting enzyme inhibitor, fosinopril, and the angiotensin II receptor antagonist, losartan, inhibit LDL oxidation and attenuate atherosclerosis independent of lowering blood pressure in apolipoprotein E deficient mice. *Cardiovasc Res.* 1999;44:579-587.
34. Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Study (4S). *Lancet.* 1994;344:1383-1389.
35. Prevention of cardiovascular events and death with pravastatin in patients with coronary heart disease and a broad range of initial cholesterol levels. The Long-Term Intervention with Pravastatin in Ischaemic Disease (LIPID) Study Group. *N Engl J Med.* 1998;339:1349-1357.
36. Rajamannan NM, Subramaniam M, Springett M, Sebo TC, Niekrasz M, McConnell JP, Singh RJ, Stone NJ, Bonow RO, Spelsberg TC. Atorvastatin inhibits hypercholesterolemia-induced cellular proliferation and bone matrix production in the rabbit aortic valve. *Circulation.* 2002;105:2660-2665.
37. Aronow WS, Ahn C, Kronzon I, Goldman ME Association of coronary risk factors and use of statins with progression of mild valvular aortic stenosis in older persons. *Am J Cardiol.* 2001;88:693-695.
38. Bellamy MF, Pellikka PA, Klarich KW, Tajik AJ, Enriquez-Sarano M. Association of cholesterol levels, hydroxymethylglutaryl coenzyme-A reductase inhibitor treatment and progression of aortic stenosis in the community. *J Am Coll Cardiol.* 2002;40:1723-1730.
39. Novaro GM, Tiong IY, Pearce GL, Lauer MS, Sprecher DL, Griffin BP. Effect of hydroxymethylglutaryl coenzyme a reductase inhibitors on the progression of calcific aortic stenosis. *Circulation.* 2001;104:2205-2209.
40. Chan LC, Teo K, Dumesnil JG, Ni A, Tam J; for the ASTRONOMER Investigators. Effect of lipid lowering with Resuvastatin on progression of aortic stenosis. Results of the aortic progression observation: measuring effects of Rosuvastatin (ASTRONOMER) trial. *Circulation.* 2010;121:306-314.
41. Rosenhek R, Raer F, Loho N, Gabriel H, Heger M, Klaar U, Schemper M, Binder T, Maurer G, Baumgartner H. Statins but not angiotensin-converting enzyme inhibitors delay progression of aortic stenosis. *Circulation.* 2004;110:1291-1295.
42. Rosenhek R, Klaar U, Schemper M, Scholten C, Heger M, Gabriel H, Binder T, Maurer G, Baumgartner H. Mild and moderate aortic stenosis. Natural history and risk stratification by echocardiography. *Eur Heart J.* 2004;25:199-205.
43. Rosenhek R, Binder T, Porenta G, Lang I, Christ G, Schemper M, Maurer G, Baumgartner H. Predictors of outcome in severe, asymptomatic aortic stenosis. *N Engl J Med.* 2000;343:611-617.
44. Ross J, Braunwald E. Aortic stenosis. *Circulation.* 1968;38:61-67.
45. Baumgartner H. Aortic stenosis: medical and surgical management. *Heart.* 2005;91:1483-1488.

46. Pellikka PA, Sarano ME, Nishimura RA, Malouf JF, Bailey KR, Scott CG, Barnes ME, Tajik AJ. Outcome of 622 adults with asymptomatic, hemodynamically significant aortic stenosis during prolonged follow-up. *Circulation.* 2005;111:3290-3295.

47. Dal-Bianco JP, Khandheira BK, Mookadam F, Gentile F, Sengupta PP. Management of asymptomatic aortic stenosis. *J Am Coll Cardiol.* 2008;52:1279-1292.

48. Greve AM, Gerdts E, Boman K, Gohlke-Baerwolf C, Rossebø AB, Devereux RB, Køber L, Ray S, Willenheimer R, Wachtell K. Impact of QRS duration and morphology on the risk of sudden cardiac death in asymptomatic patients with aortic stenosis: the SEAS (Simvastatin and Ezetimibe in Aortic Stenosis) Study. *J Am Coll Cardiol.* 2012;59:1142-1149.

49. Bonow RO, Carabello BA, Chatterjee K, de Leon AC Jr, Faxon DP, Freed MD, Gaasch WH, Lytle BW, Nishimura RA, O`Gara PT, O`Rourke RA, Otto CM, Shah PM, Shanewise JS. Focused update incorporated into the 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): Endorsed by the Society of Cardiovascular Anesthesiologists, Society for Cardiovascular Angiography and Interventions and Society of Thoracic Surgeons. *Circulation.* 2008;118:e523-e661.

50. Rosenhek R, Maurer G, Baumgartner H. Should early elective surgery be performed in patients with severe but asymptomatic aortic stenosis? *Eur Heart J.* 2002;23:1417-1421.

51. Vahanian A, Alfieri O, Andreotti F, Antunes MJ, Barón-Esquivias G, Baumgartner H, Borger MA, Carrel TP, De Bonis M, Evangelista A, Falk V, Iung B, Lancellotti P, Pierard L, Price S, Schäfers HJ, Schuler G, Stepinska J, Swedberg K, Takkenberg J, Von Oppell UO, Windecker S, Zamorano JL, Zembala M; ESC Committee for Practice Guidelines (CPG), Bax JJ, Baumgartner H, Ceconi C, Dean V, Deaton C, Fagard R, Funck-Brentano C, Hasdai D, Hoes A, Kirchhof P, Knuuti J, Kolh P, McDonagh T, Moulin C, Popescu BA, Reiner Z, Sechtem U, Sirnes PA, Tendera M, Torbicki A, Vahanian A, Windecker S; Document Reviewers:, Popescu BA, Von Segesser L, Badano LP, Bunc M, Claeys MJ, Drinkovic N, Filippatos G, Habib G, Kappetein AP, Kassab R, Lip GY, Moat N, Nickenig G, Otto CM, Pepper J, Piazza N, Pieper PG, Rosenhek R, Shuka N, Schwammenthal E, Schwitter J, Mas PT, Trindade PT, Walther T, . Guidelines on the management of valvular heart disease (version 2012): The Joint Task Force on the Management of Valvular Heart Disease of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS). *Eur Heart J.* 2012;33:2451-2496.

52. Otto CM. Valvular aortic stenosis. Disease severity and timing of intervention. *J Am Coll Cardiol.* 2006;47:2141-2151.

53. Baumgartner H, Hung J, Bermejo J, Chambers JB, Evangelista A, Griffin BP, Lung B, Otto M, Pellikka PA, Quinones M; American Society of Echocardiography; European Association of Echocardiography. Echocardiographic assessment of valve stenosis: EAE/ASE recommendations for clinical practice. *J Am Soc Echocardiogr.* 2009;22:1-23.

54. Iung B, Gohlke-Baerwolf C, Tornos P, Tribouilloy C, Hall R, Butchart E, Vahanian A. Recommendations on the management of the asymptomatic patient with valvular heart disease. *Eur Heart J.* 2002;23:1252-1266.

55. Hachicha Z, Dumesnil JG, Bogaty P, Pibarot P. Paradoxical low-flow, low-gradient severe aortic stenosis despite preserved ejection fraction is associated with higher afterload and reduced survival. *Circulation.* 2007;115:2856-2864.

56. Minners J, Allgeier M, Gohlke-Baerwolf C, Kienzle RP, Neumann FJ, Jander N. Inconsistencies of echocardiographic criteria for the grading of aortic valve stenosis. *Eur Heart J.* 2008;29:1043-1048.

57. Bahlmann E, Gerdts E, Cramariuc D, Gohlke-Baerwolf C, Nienaber CA, Wachtell K, Chambers JB, Kuck KH, Ray S,. Energy loss index as prognosticator in inconsistently graded asymptomatic aortic stenosis- (a SEAS substudy). *Circulation.* 2012;126:A12862.

58. Jander N, Minners J, Holme I, Gerdts E, Boman K, Brudi P, Chamber JB, Egstrup K, Kesäniemi AY, Malbecq W, Nienaber CA, Ray S, Rossebo A, Pedersen TR, Skjaerpe T, Willenheimer R, Wachtell K, Neumann FJ, Gohlke-Baerwolf C. Outcome of patients with low gradient "severe" aortic stenosis and preserved ejection fraction. *Circulation.* 2011;123:887-895.

59. Connolly HM, Oh JK, Schaff HV, Roger VL, Osborn SL, Hodge DO, Tajik AJ, . Severe aortic stenosis with low transvalvular gradient and severe left ventricular dysfunction:result of aortic valve replacement in 52 patients. *Circulation.* 2000;101:1940-1946.

60. Cramariuc D, Cioffi G, Rieck AE, Devereux R, Staal E, Ray S, Wachtell K, Gerdts E. Low-flow aortic stenosis in asymptomatic patients valvular-arterial impedance and systolic function from the SEAS substudy. *J Am Coll Cardiol Img.* 2009;2(4):390-399.

61. Bahlmann E, Cramariuc D, Gerdts E, Gohlke-Baerwolf C, Nienaber CA, Eriksen E, Wachtell K, Chambers J, Kuck KH, Ray S. Impact of pressure recovery on echocardio-

graphic assessment of asymptomatic aortic stenosis: a SEAS substudy. J *Am Coll Cardiol Img.* 2010;3:555-562.

62. Baumgartner H, Stefenelli T, Niederberger J, Schima H, Maurer G. "Overestimation" of catheter gradients by Doppler ultrasound in patients with aortic stenosis: a predictable manifestation of pressure recovery. *J Am Coll Cardiol.* 1999;33:1655-1661.
63. Clark C. The fluid mechanics of aortic stenosis - I. Theory and steady flow experiments. *J Biomech.* 1976;9:521-528.
64. Clark C. The fluid mechanics of aortic stenosis - II. Unsteady flow experiments. *J Biomech.* 1976;9:567-573.
65. Clark C. Relation between pressure difference across the aortic valve and left ventricular outflow. *Cardiovasc Res.* 1978;12(5):276-287.
66. Levine RA, Jimoh A, Cape EG. Pressure recovery distal to a stenosis: potential cause of gradient "overestimation" by Doppler echocardiography. *J Am Coll Cardiol.* 1989;13:706-715.
67. Gjertsson P, Caidahl K, Svensson G, Wallentin I, Bech-Hanssen O. Important pressure recovery in patients with aortic stenosis and high Doppler gradients. *Am J Cardiol.* 2001;88:139-144.
68. Volker W, Reul H, Stelzer T, Schmidt A, Karsch KR. Pressure recovery in aortic stenosis: an in vitro study in a pulsatile flow model. *J Am Coll Cardiol.* 1992;20:1585-1593.
69. Schoebel WA, Voelker W, Haase KK, Karsch KR. Extent, determinants and clinical importance of pressure recovery in patients with aortic valve stenosis. *Eur Heart J.* 1999;20:1355-1363.
70. Garcia D, Dumesnil J, Durand LG, Kadem L, Pibarot P. Discrepancies between catheter and Doppler estimates of valve effective orifice area can be predicted from the pressure recovery phenomenon. *J Am Coll Cardiol.* 2003;41:435-442.
71. Niederberger J, Schima H, Maurer G, Baumgartner H. Importance of pressure recovery for the assessment of aortic stenosis by Doppler ultrasound. Role of aortic size, aortic valve area and direction of the stenotic jet in vitro. *Circulation.* 1996;94(8):1934-1940.
72. Bahlmann E, Nienaber CA, Cramariuc D, Gohlke-Baerwolf C, Ray S, Devereux RB, Wachtell K, Kuck KH, Davidsen E, Gerdts E. Aortic root geometry in aortic stenosis patients (a SEAS substudy). *Eur J Echocardiogr.* 2011;12:585-590.
73. Kume T, Okura H, Kawamoto T, Watanabe N, Hayashida A, Neishi Y, Miyamoto Y, Imai K, Yamada R, Yoshida K. Clinical implication of Energy Loss Coefficient in patients with severe aortic stenosis diagnosed by Doppler Echocardiography. *Circ J.* 2008;72:1265-1269.
74. Spevack D, Almuti K, Ostfeld R, Bello R, Gordon G. Routine adjustment of Doppler echocardiographically derived aortic valve area using a previously derived equation to account for the effect of pressure recovery. *J Am Soc Echocardiog.* 2008;21:34-37.
75. Heinrich RS, Fontaine AA, Grimes RY, Sidhaye A, Yang S, Moore KE, Levine RA, Yoganathan AP. Experimental analysis of fluid mechanical energy losses in aortic valve stenosis: importance of pressure recovery. *Ann Biomed Eng.* 1996;24:685-694.
76. Garcia D, Pibarot P, Dumesnil J, Sakr F, Durand LG. Assessment of aortic valve stenosis severity: a new Index based on the Energy Loss Concept. *Circulation.* 2000;101:765-771.
77. Heinrich RS, Fontaine AA, Ensley AE, Gibson DE, Yoganathan AP. Valve orifice area alone is an insufficient index of aortic stenosis severity: effects of the proximal and distal geometry on transaortic energy loss. *J Heart Valve Dis.* 1999;8(5):509-515.
78. Braunwald E, Morrow AG. Obstruction to left ventricular outflow: current criteria for the selection of patients for operation. *Am J Cardiol.* 1963;12:53-59.
79. Frank S, Johnson A, Ross J Jr. Natural history of valvular aortic stenosis. *Br Heart J.* 1973;35:41-46.
80. Laskey WK, Kussmaul WG. Pressure recovery in aortic valve stenosis. *Circulation.* 1994;89:116-121.
81. Rahimtoola SH. Perspective on valvular heart disease: an update. *J Am Coll Cardiol.* 1989;14:1-23.
82. Bahlmann E, Gerdts E, Cramariuc D, Gohlke-Baerwolf C, Nienaber CA, Wachtell K, Seifert R, Chambers JB, Kuck KH, Ray S. Prognostic value of energy loss index in asymptomatic aortic stenosis. *Circulation.* 2013;127:1149-1156..