Accepted Manuscript

Impact of Flow and Left Ventricular Strain on Outcome of Patients with Preserved Left Ventricular Ejection Fraction and Low Gradient Severe Aortic Stenosis Undergoing Aortic Valve Replacement

Vasileios Kamperidis, MD, MSc, PhD Philippe J. van Rosendael, MD Arnold C.T. Ng, MBBS, PhD Spyridon Katsanos, MD, PhD Frank van der Kley, MD Philippe Debonnaire, MD Emer Joyce, MB BCh BAO, MRCPI Georgios Sianos, MD, PhD Nina Ajmone Marsan, MD, PhD Jeroen J. Bax, MD, PhD Victoria Delgado, MD, PhD

PII: S0002-9149(14)01858-X

DOI: 10.1016/j.amjcard.2014.09.030

Reference: AJC 20721

To appear in: *The American Journal of Cardiology*

Received Date: 21 July 2014

Revised Date: 15 September 2014

Accepted Date: 17 September 2014

Please cite this article as: Kamperidis V, van Rosendael PJ, Ng ACT, Katsanos S, van der Kley F, Debonnaire P, Joyce E, Sianos G, Marsan NA, Bax JJ, Delgado V, Impact of Flow and Left Ventricular Strain on Outcome of Patients with Preserved Left Ventricular Ejection Fraction and Low Gradient Severe Aortic Stenosis Undergoing Aortic Valve Replacement, *The American Journal of Cardiology* (2014), doi: 10.1016/j.amjcard.2014.09.030.

Impact of Flow and Left Ventricular Strain on Outcome of Patients with Preserved Left Ventricular Ejection Fraction and Low Gradient Severe Aortic Stenosis Undergoing Aortic Valve Replacement

Vasileios Kamperidis, MD, MSc, PhD,[a,b] Philippe J van Rosendael, MD,[a] Arnold C.T. Ng, MBBS, PhD,[c] Spyridon Katsanos, MD, PhD,[a] Frank van der Kley, MD,[a] Philippe Debonnaire, MD,[a,d] Emer Joyce, MB BCh BAO, MRCPI,[a] Georgios Sianos, MD, PhD,[b] Nina Ajmone Marsan, MD, PhD,[a] Jeroen J Bax, MD, PhD,[a] Victoria Delgado, MD, PhD[a]

[a]Department of Cardiology, Leiden University Medical Center, Leiden, The Netherlands, [b]Department of Cardiology, AHEPA University Hospital, Thessaloniki, Greece, [c]Department of Cardiology, Princess Alexandra Hospital, University of Queensland, Australia and [d]Department of Cardiology, Sint-Jan Hospital Bruges, Bruges, Belgium.

Short title: Flow, LV Strain and Outcome in AS

Corresponding author:
Victoria Delgado, MD, PhD
Department of Cardiology, Leiden University Medical Centre
Albinusdreef 2, 2333 ZA, Leiden, The Netherlands
P.O. Box 9600, 2300 RC Leiden, The Netherlands
Phone: +31 7 1526 6809, Fax: +31 7 1526 6809
Email address: v.delgado@lumc.nl

Disclosures:
The Department of Cardiology received grants from Biotronik, Medtronic, Boston Scientific Corporation, St Jude Medical, Sandra Lotus and GE Healthcare. V. Delgado received consulting fees from St. Jude Medical and Medtronic.

Funding Sources:
V. Kamperidis received a European Society of Cardiology training grant and a Hellenic Cardiological Society training grant. S. Katsanos received a Hellenic Cardiological Society training grant. P. Debonnaire received a Sadra Medical research grant (Boston Scientific) and a European Association of Cardiovascular Imaging research grant. E. Joyce received a European Society of Cardiology training grant and a national cardiovascular educational bursary from Merck Sharp & Dohme.

ABSTRACT

The prognostic implications of flow, assessed by stroke volume index (SVi), and left ventricular (LV) global longitudinal strain on survival of patients with low gradient severe aortic stenosis (AS) and preserved left ventricular ejection fraction (LVEF) are debated. The aim of this study was to evaluate the impact of flow and LV global longitudinal strain on survival of these patients treated with aortic valve replacement (AVR). Low gradient severe AS patients with preserved LVEF treated with AVR (N=134, age 76±10 years, 50% men) were included in the current study. Aortic valve hemodynamics and LV function were assessed with 2-dimensional, Doppler and speckle-tracking echocardiography pre AVR. Patients were dichotomized based on low (SVi≤35ml/m^2) or normal (SVi>35ml/m^2) flow and impaired (>-15%) or more preserved (≤-15%) global longitudinal strain. The end-point was all-cause mortality. During a median follow-up of 1.8 years (interquartile range 0.5-3 years) after AVR, 26 (19.4%) patients died. Survival was better for patients with SVi>35ml/m^2 or global longitudinal strain ≤-15% as compared with patients with SVi≤35ml/m^2 or global longitudinal strain >-15% (log-rank p=0.01). Atrial fibrillation (hazard ratio 5.40, 95% confidence interval 1.81-16.07, p=0.002) and chronic kidney disease (hazard ratio 3.67, 95% confidence interval 1.49-9.06, p=0.005) were the clinical variables independently associated with all-cause mortality. The addition of global longitudinal strain (X^2 19.87, p=0.029 and C-statistics 0.74) or SVi (X^2 29.62, p<0.001 and C-statistics 0.80) to a baseline model including atrial fibrillation and chronic kidney disease (X^2 14.52, C-statistics 0.68) improved risk stratification of these patients. In conclusion, flow and LV global longitudinal strain are independently associated with survival after AVR in low gradient severe AS patients with preserved LVEF.

Keywords: Low gradient severe aortic stenosis; Aortic valve replacement; Survival; Echocardiography

INTRODUCTION

The decision making of patients with low gradient (mean pressure gradient ≤40mmHg) severe aortic stenosis (AS) (aortic valve area index, AVAi ≤0.6cm^2/m^2) with preserved left ventricular (LV) ejection fraction (EF) (≥50%) has been source of debate.[1, 2] While some studies have reported better survival of these patients after aortic valve replacement (AVR),[3, 4] others have suggested that these patients have comparable prognosis to that of patients with moderate AS.[5] The underlying mechanisms influencing the outcome of these patients remain unclear. Despite having preserved LVEF, these patients have impaired LV mechanics as assessed with LV global longitudinal strain speckle tracking echocardiography and may have normal or low forward flow evaluated by stroke volume index (SVi).[3, 6] The influence of flow and LV global longitudinal strain on the prognosis of patients with preserved LVEF low gradient severe AS remains unexplored. The present evaluation assessed the relative merits of flow and LV global longitudinal strain to predict the outcome of patients with severe AS, low gradient and preserved LVEF who underwent AVR.

METHODS

Patients with symptomatic low gradient severe AS and preserved LVEF who underwent AVR were identified from an ongoing registry and were included in the current analysis (Figure 1).[7]

Patients were clinically evaluated and data were collected on a dedicated departmental Cardiology Information System (EPD-Vision®, Leiden University Medical Center, Leiden, The Netherlands) and analyzed retrospectively. Demographics, clinical symptoms (New York Heart Association (NYHA) functional class), cardiovascular risk factors, medications and presence of atrial fibrillation, chronic kidney disease (defined as moderately to severely decreased creatinine clearance <45ml/min)[8] and chronic pulmonary obstructive disease were collected. The Institutional Review Board approved this

retrospective analysis of clinically acquired data and waived the need for written patient informed consent.

All patients underwent a complete transthoracic echocardiogram using commercially available ultrasound systems (Vivid-7 and E9, General Electric, Horten, Norway) equipped with 3.5MHz or M5S transducers. Two-dimensional, colour-, pulsed-wave and continuous-wave Doppler data were acquired in the parasternal and apical views and were stored digitally and analyzed offline on a dedicated workstation (EchoPac 112.0.1, GE Medical Systems, Horten, Norway). LV dimensions and wall thickness were measured from the parasternal long-axis view according to current recommendations.[9] LV mass was estimated according to the formula by Devereux et al.[9] Relative wall thickness and the ratio of LV mass to LV end-diastolic volume were calculated as previously described.[10] LV end-diastolic and end-systolic volumes were measured in the apical 4- and 2-chamber views and indexed to body surface area and LVEF was derived using the Simpson's biplane method.[9] SVi was estimated by multiplying LV outflow tract area by LV outflow tract velocity time integral on pulse-wave Doppler recordings and then indexed to body surface area. Cardiac output was calculated as the product of stroke volume and heart rate. Stroke work was calculated by the formula (mean arterial pressure + mean peak gradient) x stroke volume x 0.0136 and indexed to LV mass.[11] Peak and mean pressure transaortic gradients were measured in the 3- or 5-chamber apical views according to the simplified Bernoulli equation. AVA was calculated with the continuity equation and then indexed to body surface area. In addition, energy loss index, valvulo-arterial impedance, systemic vascular resistance and systemic arterial compliance were calculated as previously described.[12]

For further evaluation of LV systolic function, offline 2-dimensional speckle tracking longitudinal strain analysis was performed at a workstation with commercially available software (EchoPac 112.0.1, GE Medical Systems, Horten, Norway). From the apical 3-, 4- and 2- chamber views, global longitudinal strain was measured and averaged. Transmitral pulsed-wave Doppler was used for assessment of LV diastolic function. Additionally, left

atrial volume was evaluated according to the biplane area-length method and then indexed to body surface area.[9] Co-existing valvular dysfunction was assessed based on the European Association of Echocardiography and the American Society of Echocardiography recommendations.[12]

Based on SVi patients were divided into two categories: low flow was defined as SVi≤35ml/m^2 and normal flow as SVi>35ml/m^2.[2, 6, 13, 14] Patients were also categorized as having an LV global longitudinal strain ≤-15% or >-15%.[7, 15-17]

The end-point of the study was all-cause mortality. All patients were followed-up after AVR. Survival data were collected either from the departmental Cardiology Information System (EPD-Vision®, Leiden University Medical Center, Leiden, the Netherlands), or by telephone interview or by the Social Security death index and were complete for all subjects included in the study.

Categorical variables are expressed as counts (frequency) and continuous variables as mean ± standard deviation. Continuous variables were compared between the 2 groups (survivors versus non-survivors) with the Student-t test or Mann-Whitney U test, as appropriate and categorical variables with the Chi-square test or Fisher exact test, as appropriate. The intra- and interobserver reproducibility of LV global longitudinal strain and SVi measurements were assessed by the intraclass correlation coefficient. The cumulative event rates were calculated based on Kaplan-Meier method and comparisons between groups were assessed by log-rank test. Cox proportional hazard ratio regression analyses were performed to investigate univariate and multivariate correlates of all-cause mortality. Hazard ratios and 95% confidence intervals were reported. Variables with univariate $p<0.10$ were entered in the multivariate analysis. The incremental value of flow and LV global longitudinal strain category over a baseline clinical model was estimated by the significant change in chi-square of the baseline model. The relative fit of each model was calculated with the –2 log likelihood. Moreover, C-statistics was used for model comparison. Statistical

significance was considered for p value <0.05. Statistical analysis was performed with the SPSS software version 20 (SPSS, Chicago, IL).

RESULTS

The baseline characteristics of 134 patients (75.5±9.9 years old, 50% male) are summarized in Table 1. Surgical AVR was performed in 71 (53%) patients and transcatheter AVR in the remaining 63 (47%). Echocardiographic data are summarized in Table 2. Low flow was identified in 48 (36%) patients and normal flow in 86 (64%) whereas an LV global longitudinal strain >-15% was observed in 67 (51%) patients and ≤-15% in 65 (49%). LV global longitudinal strain measurement was feasible in 132 (98%) patients. The intraclass correlation coefficients for intra and interobserver reprodcubility were 0.95 (95% confidence interval 0.69–0.99) and 0.87 (95% confidence interval 0.50-0.97) for LV global longitudinal strain, respectively, and 0.90 (95% confidence interval 0.60-0.97) and 0.88 (95% confidence interval 0.55-0.97) for SVi, respectively.

During a median follow-up of 1.8 years (interquartile range 0.5-3 years) after AVR, 26 (19.4%) patients died. There were no patients lost at follow-up. At baseline, patients who died exhibited more frequently associated co-morbidities (atrial fibrillation, chronic kidney disease, chronic pulmonary obstructive disease), previous cardiac surgery and worse NYHA functional class as compared with survivors (Table 1). Aortic valve hemodynamics were comparable between non-survivors and survivors. However, non-survivors had a higher LV global afterload, more concentrically remodelled LV, lower flow and more impaired LV global longitudinal strain than survivors (Table 2).

When dichotomizing the population based on low flow and normal flow, patients with low flow had higher mortality rates at 1, 2 and 3 years follow-up after AVR than patients with normal flow (16.7%, 25.0% and 33.3% vs. 2.3%, 3.5% and 4.6%, respectively, log-rank p<0.001). This difference remained significant after adjusting for age, atrial fibrillation, chronic pulmonary obstructive disease, chronic kidney disease, NYHA functional class and

LV global longitudinal strain; patients with normal flow had significantly better outcome than low flow patients (Figure 2). When dividing the population according to the pre-specified LV global longitudinal strain cut-off value, patients with more impaired global longitudinal strain (>-15%) had significantly increased mortality at 1, 2 and 3 years after AVR in comparison with patients with more preserved global longitudinal strain (≤-15%) (mortality rate 13.4%, 19.4% and 22.4% vs. 1.5%, 3.1% and 7.7%, respectively, log-rank p=0.01). Survival remained significantly higher in the cohort of patients with global longitudinal strain ≤-15% after adjusting for age, atrial fibrillation, chronic pulmonary obstructive disease, chronic kidney disease, NYHA functional class and SVi (Figure 3). Figure 4 shows the cumulative survival for patients grouped according to global longitudinal strain and flow. Patients with a global longitudinal strain >-15% and SVi≤35ml/m^2 had the worse prognosis. There were 6 patients who died within 30 days post AVR (50% had TAVR). All of them (100%) had impaired global longitudinal strain (>-15%) and 5 (83%) had low-flow. Perioperative mortality was significantly higher in the group with more impaired global longitudinal strain (>-15%) compared with the group with ≤-15% (log rank p=0.015) and in the low-flow compared to the normal-flow group (log rank p=0.014).

The univariate Cox-regression analysis demonstrated that the presence of atrial fibrillation, chronic pulmonary obstructive disease, chronic kidney disease, previous myocardial infarction and previous cardiac surgery were associated with increased all-cause mortality risk in this population (Table 3). From the echocardiographic variables, lower valvulo-arterial impedance and LV mass/LV end-diastolic volume ratio were associated with improved survival after AVR. Atrial fibrillation and chronic kidney disease were independently associated to mortality after AVR and were selected to build a baseline clinical model to test the independent association between flow and global longitudinal strain with survival (Table 3). Global longitudinal strain >-15% and each 1% impairment in global longitudinal strain were independently associated with all-cause mortality (Table 4). In addition, SVi ≤35ml/m^2

and each 5ml/m^2 decrease in SVi were independently associated with all-cause mortality (Table 4).

DISCUSSION

The present evaluation showed that patients with preserved LVEF, low gradient severe AS and normal flow or LV global longitudinal strain ≤-15% have better survival after AVR compared to their counterparts with low flow or global longitudinal strain >-15%. The addition of flow and LV global longitudinal strain to a clinical model improved the risk stratification of patients with preserved LVEF, low gradient severe AS treated with AVR.

Severe aortic stenosis based on AVAi calculation but with low gradient is observed in almost 35% of patients with preserved LVEF.[4-6, 10, 18, 19] Decision making in this subgroup of patients remains controversial. While several series have shown that surgical AVR in patients with severe AS with low gradient and preserved LVEF portends better prognosis compared with medical treatment,[11, 14, 20-22] other studies have shown that the prognosis of these patients medically treated is similar to that of patients with moderate aortic stenosis.[5, 10] The study by Hachicha et al. including 512 patients with severe AS and preserved LVEF, 62% of them with low gradient, showed that patients undergoing surgical AVR had better survival than patients treated medically.[3] Similarly, Ozkan et al. confirmed that patients with symptomatic severe AS, low gradient and preserved LVEF had better prognosis compared to medically treated patients (26% versus 40% mortality after 28 months of mean follow-up).[11] In contrast, Jander et al. demonstrated that patients with asymptomatic severe AS, low gradient and preserved LVEF had comparable outcome to patients with moderate aortic stenosis (major cardiovascular events 14.8±1.0% versus 14.1±1.5%, respectively; p=0.59).[5] Accordingly, the authors considered that patients with low gradient, preserved LVEF severe AS do not represent a true severe AS group and the progression of the disease is similar to moderate aortic stenosis.[5, 10]

These apparently conflicting results may be explained by differences within the group of patients with low gradient, preserved LVEF severe AS. Based on LV stroke volume, patients with preserved LVEF, low gradient severe AS can be further divided into low flow (≤35 ml/m^2) or normal flow (>35ml/m^2) and these two subgroups of patients have distinct clinical and echocardiographic characteristics: the former are more frequently female and older, have higher systemic vascular resistance, lower systemic compliance and higher LV global afterload than the normal flow patients.[4, 6, 21] In addition, low flow patients show smaller LV outflow tract and LV cavity dimensions, increased concentric remodelling and lower LVEF (although within the normal range) than normal flow patients.[4, 10] The increased concentric LV remodelling may have a significant impact on the LV mechanics that cannot be unmasked by LVEF alone. Two-dimensional speckle tracking longitudinal strain analysis can discriminate between these two groups of patients. Lancellotti et al showed that patients with preserved LVEF, low flow-low gradient severe AS had more impaired global longitudinal strain as compared with patients with normal flow-low gradient severe AS (-13.6±4.3% vs. -16.7±2.6%, p<0.001).[23] Therefore, low flow-low gradient severe AS may represent a more progressed disease status and the assessment of LV remodelling and global longitudinal strain may help distinguishing these two subgroups.

While the prognostic implications of flow (SVi) in patients with low gradient severe AS and preserved LVEF remains debated, the impact of LV global longitudinal strain on the outcome of these patients has not been evaluated. In the sub-study of the Simvastatin and Ezetimibe in Aortic Stenosis trial (including 435 patients with asymptomatic low gradient severe AS) Jander et al.[5] proposed that patients with low flow and patients with normal flow had comparable outcomes in terms of aortic valve and cardiovascular events and cardiovascular death. However, the outcome after AVR was not evaluated. In contrast, the studies by Hachicha et al.[4] and Ozkan et al.[11] suggested that survival after AVR is comparable between low flow and normal flow severe AS patients. Mehrotra et al.[10] provided further evidence to the association between flow and survival in patients with low gradient

severe AS and suggested that patients with low flow severe AS had worse survival than normal flow severe AS and patients with moderate aortic stenosis. However, flow was not independently associated with survival of patients with low gradient severe AS. Similarly, Mohty et al.[21] reported an independent association between flow and survival in patients with severe AS and after correcting for AVR (as time-dependent covariate), low flow-low gradient severe AS was associated with increased all-cause mortality risk (hazard ratio 1.84, p=0.014). The present study is in line with the results by Mohty et al.[21] demonstrating that flow status is independently associated with long-term outcome of patients with low gradient severe AS and preserved LVEF treated with AVR. However, the present study provides also incremental value by demonstrating the independent association between LV global longitudinal strain and outcome in this group of patients. After correcting for SVi, LV global longitudinal strain was associated with all-cause mortality. LV global longitudinal strain may be impaired in patients with low gradient severe AS and preserved LVEF possibly due to subendocardial ischemia, myocardial fibrosis, concentric remodelling or increased afterload.[6, 16, 24] LV global longitudinal strain can detect the subtle intrinsic myocardial systolic dysfunction and its impairment precedes LVEF reduction.[16, 25] However, randomized studies would be preferable to confirm the benefits of AVR in this subgroup of patients and impact on current practice guidelines.[1]

Several limitations should be acknowledged. Outcome and echocardiographic data were retrospectively analysed. In addition, patients underwent surgical or transcatheter AVR, introducing a important prognostic bias. We did not use a propensity score to account for this difference. Finally, we did not include a comparator group who were medically treated. However, the comparison of prognostic implications of medical treatment vs. AVR in this group of patients was beyond the scope of the present evaluation.

1. Nishimura RA, Otto CM, Bonow RO, Carabello BA, Erwin JP, 3rd, Guyton RA, O'Gara PT, Ruiz CE, Skubas NJ, Sorajja P, Sundt TM, 3rd, Thomas JD, American College of Cardiology/American Heart Association Task Force on Practice G. 2014 aha/acc guideline for the management of patients with valvular heart disease: Executive summary: A report of the american college of cardiology/american heart association task force on practice guidelines. *J Am Coll Cardiol* 2014;63:2438-2488

2. Joint Task Force on the Management of Valvular Heart Disease of the European Society of C, European Association for Cardio-Thoracic S, Vahanian A, Alfieri O, Andreotti F, Antunes MJ, Baron-Esquivias G, Baumgartner H, Borger MA, Carrel TP, De Bonis M, Evangelista A, Falk V, Iung B, Lancellotti P, Pierard L, Price S, Schafers HJ, Schuler G, Stepinska J, Swedberg K, Takkenberg J, Von Oppell UO, Windecker S, Zamorano JL, Zembala M. Guidelines on the management of valvular heart disease (version 2012). *Eur Heart J* 2012;33:2451-2496

3. Dumesnil JG, Pibarot P, Carabello B. Paradoxical low flow and/or low gradient severe aortic stenosis despite preserved left ventricular ejection fraction: Implications for diagnosis and treatment. *Eur Heart J* 2010;31:281-289

4. 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

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

6. Adda J, Mielot C, Giorgi R, Cransac F, Zirphile X, Donal E, Sportouch-Dukhan C, Reant P, Laffitte S, Cade S, Le Dolley Y, Thuny F, Touboul N, Lavoute C, Avierinos JF, Lancellotti P, Habib G. Low-flow, low-gradient severe aortic stenosis despite normal ejection

fraction is associated with severe left ventricular dysfunction as assessed by speckle-tracking echocardiography: A multicenter study. *Circ Cardiovasc Imaging* 2012;5:27-35

7. Ng AC, Delgado V, Bertini M, Antoni ML, van Bommel RJ, van Rijnsoever EP, van der Kley F, Ewe SH, Witkowski T, Auger D, Nucifora G, Schuijf JD, Poldermans D, Leung DY, Schalij MJ, Bax JJ. Alterations in multidirectional myocardial functions in patients with aortic stenosis and preserved ejection fraction: A two-dimensional speckle tracking analysis. *Eur Heart J* 2011;32:1542-1550

8. Inker LA, Astor BC, Fox CH, Isakova T, Lash JP, Peralta CA, Kurella Tamura M, Feldman HI. Kdoqi us commentary on the 2012 kdigo clinical practice guideline for the evaluation and management of ckd. *Am J Kidney Dis* 2014;63:713-735

9. Lang RM, Bierig M, Devereux RB, Flachskampf FA, Foster E, Pellikka PA, Picard MH, Roman MJ, Seward J, Shanewise JS, Solomon SD, Spencer KT, Sutton MS, Stewart WJ, Chamber Quantification Writing G, American Society of Echocardiography's G, Standards C, European Association of E. Recommendations for chamber quantification: A report from the american society of echocardiography's guidelines and standards committee and the chamber quantification writing group, developed in conjunction with the european association of echocardiography, a branch of the european society of cardiology. *J Am Soc Echocardiogr* 2005;18:1440-1463

10. Mehrotra P, Jansen K, Flynn AW, Tan TC, Elmariah S, Picard MH, Hung J. Differential left ventricular remodelling and longitudinal function distinguishes low flow from normal-flow preserved ejection fraction low-gradient severe aortic stenosis. *Eur Heart J* 2013;34:1906-1914

11. Ozkan A, Hachamovitch R, Kapadia SR, Tuzcu EM, Marwick TH. Impact of aortic valve replacement on outcome of symptomatic patients with severe aortic stenosis with low gradient and preserved left ventricular ejection fraction. *Circulation* 2013;128:622-631

12. Baumgartner H, Hung J, Bermejo J, Chambers JB, Evangelista A, Griffin BP, Iung B, Otto CM, Pellikka PA, Quinones M, American Society of E, European Association of E.

Echocardiographic assessment of valve stenosis: Eae/ase recommendations for clinical practice. *J Am Soc Echocardiogr* 2009;22:1-23

13. Tandon A, Grayburn PA. Imaging of low-gradient severe aortic stenosis. *JACC Cardiovasc Imaging* 2013;6:184-195

14. Herrmann HC, Pibarot P, Hueter I, Gertz ZM, Stewart WJ, Kapadia S, Tuczu EM, Babaliaros V, Thourani V, Szeto WY, Bavaria JE, Kodali S, Hahn RT, Williams M, Miller DC, Douglas PS, Leon MB. Predictors of mortality and outcomes of therapy in low flow severe aortic stenosis: a Placement of Aortic Transcatheter Valves (PARTNER) trial analysis. *Circulation* 2013;127:2316-2326

15. Yingchoncharoen T, Gibby C, Rodriguez LL, Grimm RA, Marwick TH. Association of myocardial deformation with outcome in asymptomatic aortic stenosis with normal ejection fraction. *Circ Cardiovasc Imaging* 2012;5:719-725

16. Pibarot P, Dumesnil JG. Improving assessment of aortic stenosis. *J Am Coll Cardiol* 2012;60:169-180

17. Lancellotti P, Tribouilloy C, Hagendorff A, Moura L, Popescu BA, Agricola E, Monin JL, Pierard LA, Badano L, Zamorano JL, European Association of E. European association of echocardiography recommendations for the assessment of valvular regurgitation. Part 1: Aortic and pulmonary regurgitation (native valve disease). *Eur J Echocardiogr* 2010;11:223-244

18. 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

19. Eleid MF, Sorajja P, Michelena HI, Malouf JF, Scott CG, Pellikka PA. Flow-gradient patterns in severe aortic stenosis with preserved ejection fraction: Clinical characteristics and predictors of survival. *Circulation* 2013;128:1781-1789

20. Tarantini G, Covolo E, Razzolini R, Bilato C, Frigo AC, Napodano M, Favaretto E, Fraccaro C, Isabella G, Gerosa G, Iliceto S, Cribier A. Valve replacement for severe aortic

stenosis with low transvalvular gradient and left ventricular ejection fraction exceeding 0.50. *Ann Thorac Surg* 2011;91:1808-1815

21. Mohty D, Magne J, Deltreuil M, Aboyans V, Echahidi N, Cassat C, Pibarot P, Laskar M, Virot P. Outcome and impact of surgery in paradoxical low-flow, low-gradient severe aortic stenosis and preserved left ventricular ejection fraction: A cardiac catheterization study. *Circulation* 2013;128:S235-242

22. Clavel MA, Dumesnil JG, Capoulade R, Mathieu P, Senechal M, Pibarot P. Outcome of patients with aortic stenosis, small valve area, and low-flow, low-gradient despite preserved left ventricular ejection fraction. *J Am Coll Cardiol* 2012;60:1259-1267

23. Lancellotti P, Magne J, Donal E, Davin L, O'Connor K, Rosca M, Szymanski C, Cosyns B, Pierard LA. Clinical outcome in asymptomatic severe aortic stenosis: Insights from the new proposed aortic stenosis grading classification. *J Am Coll Cardiol* 2012;59:235-243

24. Wiegers SE. Symptomatic low-gradient severe aortic stenosis with preserved left ventricular ejection fraction: Now less of a clinical conundrum. *Circulation* 2013;128:576-578

25. Blessberger H, Binder T. Two dimensional speckle tracking echocardiography: Clinical applications. *Heart* 2010;96:2032-2040

FIGURE LEGENDS

Figure 1. Patient population. AVAi, aortic valve area index; AVR, aortic valve replacement; LVEF, left ventricular ejection fraction; MPG, mean pressure gradient.

Figure 2. Impact of flow on survival of patients with low gradient severe aortic stenosis and preserved ejection fraction after aortic valve replacement. After adjusting for age, atrial fibrillation, chronic obstructive pulmonary disease, chronic kidney disease, New York Heart Association functional class and left ventricular systolic function assessed by global longitudinal strain, normal flow (stroke volume index>35ml/m^2) patients had better outcome than patients with low flow (stroke volume index≤35ml/m^2). CI, confidence interval; HR, hazard ratio.

Figure 3. Impact of left ventricular global longitudinal strain (GLS) on survival of patients with low gradient severe aortic stenosis and preserved ejection fraction after aortic valve replacement. After adjusting for age, atrial fibrillation, chronic obstructive pulmonary disease, chronic kidney disease, New York Heart Association functional class and flow expressed as stroke volume index, patients with better GLS (≤-15%) had better outcome than patients with GLS >-15%. CI, confidence interval; HR, hazard ratio.

Figure 4. Impact of flow and left ventricular global longitudinal strain (GLS) on survival of patients with low gradient severe aortic stenosis and preserved ejection fraction after aortic valve replacement. Patients with low flow and more impaired GLS (>-15%) had significantly worse outcome compared with the other groups.

Table 1

Baseline clinical characteristics

Variable	Overall (N=134)	Survivors (N=108)	Non-Survivors (N=26)	p-value
Age (years)	76 ± 10	75 ± 11	76 ± 5	0.24
Male	67 (50%)	53 (49%)	14 (54%)	0.66
Body mass index (Kg/m^2)	26 ± 4	26 ± 4	26 ± 4	0.92
Body surface area (m^2)	1.9 ± 0.2	1.8 ± 0.2	1.9 ± 0.2	0.64
Atrial fibrillation	10 (8%)	5 (5%)	5 (21%)	0.008
Chronic kidney disease	28 (21%)	16 (15%)	12 (46%)	0.001
Hypertension	98 (74%)	76 (71%)	22 (85%)	0.16
Diabetes mellitus	34 (25%)	24 (22%)	10 (39%)	0.09
Hyperlipidemia	69 (52%)	59 (56%)	10 (39%)	0.12
Smoker	44 (34%)	35 (33%)	9 (36%)	0.77
Family history of CAD	34 (27%)	28 (27%)	6 (24%)	0.75
Coronary artery disease	83 (69%)	67 (69%)	16 (67%)	0.76
Previous cardiac surgery	33 (25%)	22 (20%)	11 (42%)	0.02
Myocardial infarction	19 (14%)	13 (12%)	6 (23%)	0.15
Stroke	16 (12%)	11 (10%)	5 (20%)	0.17
Chronic obstructive pulmonary disease	35 (26%)	24 (22%)	11 (42%)	0.04
Logistic EuroSCORE (%)	14 ± 12	13 ± 11	18 ± 13	0.08
ACEi / ARB	66 (50%)	49 (46%)	17 (65%)	0.07
Beta-blocker	77 (58%)	64 (60%)	13 (50%)	0.36

Calcium channel blocker	39 (30%)	28 (26%)	11 (42%)	0.12
Statin	79 (59%)	64 (60%)	15 (58%)	0.84
Diuretics	62 (47%)	47 (44%)	15 (58%)	0.21
NYHA class I	40 (30%)	36 (33%)	4 (15%)	0.04
II	46 (34%)	37 (34%)	9 (35%)	
III	38 (28%)	30 (28%)	8 (31%)	
IV	10 (8%)	5 (5%)	5 (19%)	

ACEi, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; CAD, coronary artery disease; NYHA, New York Heart Association.

Hyperlipidemia, defined as serum total cholesterol ≥230 mg/dl and/or serum triglycerides ≥200 mg/dl and/or treatment with lipid lowering drugs. Family history of CAD, defined as first degree relatives of <55 years in men and <65 years in women who had a cardiac event. Coronary artery disease, defined as previous coronary artery bypass grafting or percutaneous coronary intervention or more than 50% stenosis at the coronary angiography.

Table 2

Baseline echocardiographic characteristics

	Overall (N=134)	Survivors (N=108)	Non-Survivors (N=26)	p-value
Aortic valve area (cm^2)	0.8 ± 0.1	0.8 ± 0.1	0.8 ± 0.2	0.13
Aortic valve area index (cm^2/m^2)	0.4 ± 0.1	0.5 ± 0.1	0.4 ± 0.1	0.12
Peak velocity (m/s)	3.6 ± 0.4	3.6 ± 0.4	3.6 ± 0.4	0.74
Mean gradient (mmHg)	32 ± 6	32 ± 6	32 ± 7	0.93
Energy loss index (cm^2/m^2)	0.5 ± 0.1	0.5 ± 0.1	0.4 ± 0.1	0.09
Valvulo-arterial impedance ($mmHg/ml/m^2$)	4.9 ± 1.5	4.7 ± 1.4	5.6 ± 1.5	0.004
Systemic vascular resistance (mmHg.min/l)	1741 ± 504	1695 ± 500	1932 ± 485	0.03
Systemic arterial compliance ($ml/mmHg/m^2$)	0.6 ± 0.2	0.6 ± 0.2	0.6 ± 0.1	0.16
Septal wall thickness in diastole (cm)	1.3 ± 0.2	1.3 ± 0.2	1.4 ± 0.3	0.11
Posterior wall thickness in diastole (cm)	1.2 ± 0.2	1.2 ± 0.2	1.3 ± 0.2	0.08
LVEDDi (cm/m^2)	2.5 ± 0.3	2.5 ± 0.3	2.5 ± 0.3	0.69
LVESDi (cm/m^2)	1.5 ± 0.4	1.5 ± 0.3	1.5 ± 0.4	0.62
Left ventricular mass index (g/m^2)	121 ± 32	118 ± 32	131 ± 31	0.06
Relative wall thickness (%)	56 ± 13	55 ± 13	58 ± 17	0.31
LVEDVi (ml/m^2)	49 ± 17	49 ± 17	47 ± 19	0.49
LVESVi (ml/m^2)	20 ± 8	20 ± 8	19 ± 8	0.85
Left ventricular mass / LVEDV ratio (g/ml)	2.7 ± 1.2	2.6 ± 1.1	3.2 ± 1.3	0.03
Ejection fraction (%)	61 ± 6	62 ± 6	59 ± 5	0.08
Stroke volume index (ml/m^2)	38 ± 10	39 ± 9	33 ± 10	0.001

Cardiac Output (l/min)	4.8 ± 1.1	4.9 ± 1.1	4.4 ± 0.9	0.03
Cardiac Index (l/min/m^2)	2.6 ± 0.6	2.6 ± 0.6	2.3 ± 0.5	0.02
Stroke Work (g.m)	124 ± 35	127 ± 34	110 ± 16	0.02
Stroke Work /100g (g.m)	60 ± 26	62 ± 25	48 ± 25	0.01
Global longitudinal strain (%)	-15 ± 3	-15 ± 3	-13 ± 3	0.005
E wave velocity (cm/s)	77 ± 28	76 ± 29	81 ± 25	0.39
Deceleration time (msec)	257 ± 100	263 ± 98	232 ± 106	0.15
Left atrial volume index (ml/m^2)	37 ± 15	37 ± 16	37 ± 15	0.95
Aortic regurgitation no/mild/moderate, n	56/66/12	42/54/12	14/12/0	0.13
Mitral regurgitation no/mild/moderate, n	67/53/14	55/41/12	12/12/2	0.71

LVEDDi, left ventricular end-diastolic diameter index; LVEDVi, left ventricular end-diastolic volume index; LVESDi, left ventricular end-systolic diameter index; LVESVi, left ventricular end-systolic volume index.

Table 3

Univariate and multivariate Cox regression analysis to identify determinants of all-cause mortality in patients with low gradient, preserved ejection fraction severe aortic stenosis after aortic valve replacement

	Univariate Analysis			Multivariate Analysis		
	HR	95% CI	p-value	HR	95% CI	p-value
Clinical Variables						
Age (years)	1.04	0.99-1.09	0.08	1.01	0.93-1.09	0.78
Male gender	1.49	0.68-3.29	0.32			
Body mass index (Kg/m^2)	1.01	0.91-1.13	0.81			
Transcatheter aortic valve replacement	1.69	0.74-3.89	0.21			
Logistic EuroScore (%)	1.03	1.00-1.06	0.03	0.98	0.92-1.06	0.69
Coronary artery disease	0.96	0.40-2.27	0.92			
Chronic kidney disease	2.60	1.18-5.74	0.02	3.20	1.10-9.31	0.03

Atrial fibrillation		3.45	1.26-9.40	0.02	4.63	1.22-17.62	0.02
Hypertension		2.28	0.78-6.69	0.13			
Diabetes		1.64	0.72-3.71	0.24			
Hyperlipidemia		0.63	0.28-1.43	0.23			
Previous cardiac surgery		2.37	1.06-5.29	0.04	0.97	0.20-4.71	0.97
Myocardial infarction		2.96	1.16-7.55	0.02	2.57	0.55-12.04	0.23
Stroke		2.08	0.76-5.65	0.15			
Chronic obstructive pulmonary disease		2.57	1.15-5.77	0.02	1.45	0.49-4.25	0.50
New York Heart Association, class	I	*Ref*		0.08			0.62
	II	3.20	0.96-10.47	0.06	1.75	0.45-6.80	0.42
	III	2.72	0.77-9.27	0.10	2.07	0.51-8.33	0.31
	IV	5.63	1.49-21.15	0.01	2.82	0.55-14.26	0.21

Echocardiographic Variables						
Aortic valve area index (cm^2/m^2)	0.06	0.001-5.18	0.21			
Mean pressure gradient (mmHg)	0.98	0.93-1.05	0.61			
Valvulo-arterial impedance ($mmHg/ml/m^2$)	1.26	1.02-1.57	0.03	1.08	0.80-1.49	0.66
Left ventricular mass index (g/m^2)	1.01	0.99-1.02	0.23			
Relative wall thickness (%)	1.02	0.99-1.05	0.12			
Left ventricular mass / LVEDV ratio (g/ml)	1.63	1.27-2.10	0.001	1.44	0.95-2.17	0.08
Left ventricular ejection fraction (%)	0.94	0.87-1.00	0.07	0.97	0.89-1.06	0.56
Left atrium volume index (ml/m^2)	0.99	0.97-1.02	0.71			

CI, confidence interval; HR, hazard ratio; LVEDV, left ventricular end-diastolic volume.

Table 4

Multivariate Cox regression analysis and c-statistics to test the value of flow (stroke volume index category > and ≤35ml/m^2 or increase per 5ml/m^2) and left ventricular systolic function (global longitudinal strain category > and ≤-15% or increase per +1%) on baseline model (please look at table 3) predicting mortality in low gradient, preserved ejection fraction severe aortic stenosis after aortic valve replacement

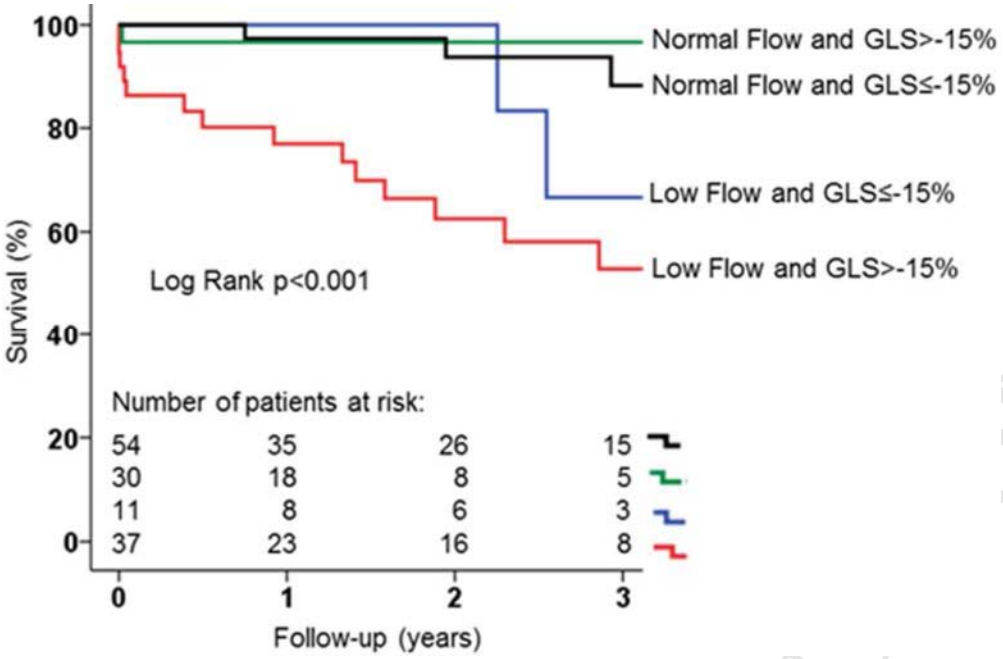
	Multivariate Analysis			Model Comparison			
	HR	95% CI	p-value*	Model -2Log Likelihood	Model x^2	p-value†	C-statistics
Baseline model				173.34	14.52	-	0.68
Atrial fibrillation	5.40	1.81-16.07	0.002				
Chronic kidney disease	3.67	1.49-9.06	0.005				
Baseline model + GLS category				166.80	19.87	0.029	0.74
Atrial fibrillation	4.03	1.33-12.18	0.014				
Chronic kidney disease	3.95	1.61-9.69	0.003				
Global longitudinal strain ≤-15%	0.37	0.14-0.94	0.036				
Baseline model + SVi category				158.06	29.62	<0.001	0.80
Atrial fibrillation	3.18	1.00-10.07	0.050				
Chronic kidney disease	3.59	1.41-9.11	0.007				
Stroke volume index >35ml/m^2	0.16	0.06-0.44	<0.001				

Baseline model + GLS 1% increase				164.09	22.29	0.006	0.78
Atrial fibrillation	3.49	1.11-10.92	0.03				
Chronic kidney disease	3.74	1.50-9.31	0.005				
Global longitudinal strain	1.21	1.05-1.39	0.007				
Baseline model + SVi 5ml/m^2 increase				167.86	19.77	0.019	0.77
Atrial fibrillation	3.16	0.93-10.45	0.07				
Chronic kidney disease	3.57	1.44-8.99	0.006				
Stroke volume index	0.77	0.61-0.97	0.03				

*p-value by multivariate Cox regression analysis

†p-value by likelihood ratio test vs. baseline model

CI, confidence interval; GLS, Global longitudinal strain; HR, hazard ratio; SVi, Stroke volume index.



Highlights

- Survival of low-gradient severe AS patients with preserved LVEF was evaluated.
- The prognostic association of flow and LV global longitudinal strain was assessed.
- Global longitudinal strain and flow were independently associated with survival after aortic valve replacement.