ORIGINAL ARTICLE

Prognostic Value of NT-proBNP in Asymptomatic Patients with Severe Aortic Stenosis and Preserved Left Ventricular Ejection Fraction

Utilidad del NT-proBNP en la evaluación pronóstica de pacientes con estenosis aórtica grave asintomáticos, con fracción de eyección ventricular izquierda preservada

CINTIA S. LAURENZANO[MTSAC, 1], DANIEL A. CHIRINO NAVARTA[MTSAC, 1], MARÍA F. CERDA JORGI[1], ALEJANDRA DIAZ CASALE[1]

ABSTRACT

Background: The aortic valve replacement (AVR) indication in asymptomatic patients with severe aortic stenosis (AS) and preserved function is being increasingly discussed.

Objective: The aim of this study was to evaluate whether the elevation of N-terminal fraction of the pro-B-type natriuretic peptide (NT-proBNP) predicts the occurrence of symptoms and the AVR indication in patients with severe AS and preserved left ventricular ejection fraction (LVEF), initially asymptomatic.

Methods: Asymptomatic patients with severe AS, preserved LVEF (≥55%) and no initial AVR indication were prospectively included. All patients underwent laboratory tests measuring NT-proBNP at baseline, and an echocardiogram with tissue Doppler recording the lateral wall S wave (lat. S) and the E/e´ ratio. The endpoint was the aortic valve replacement indication at follow-up.

Results: We included 133 patients aged 69 ± 8 years, 49% of which were women. After a follow-up of 570 (interquartile range 380-680) days, 23.3% (n=31) of them required aortic valve replacement. In the multivariate analysis, NT-proBNP value and the E/e' ratio were independent predictors of surgery (HR 1.02, 95% CI 1.001-1.03, p<0.001 and HR 1.42, 95% CI 1.21-2.45, p< 0.001, respectively). NT-proBNP presented an area under the curve (AUC) greater than the E/e' ratio (0.88 versus 0.64, p=0.02). The best NT-proBNP cut-off point was determined as >350 pg./mL (adjusted HR 1.55, 95% CI 1.38-2.01, p<0.001).

Conclusion: NT-proBNP value and the E/e' ratio were independent predictors of AVR requirement. NT-proBNP had a very good discrimination capacity, greater than the E/e´ ratio.

Keywords: Aortic Valve Stenosis- Biomarkers - Natriuretic Peptide, Brain

RESUMEN

Introducción: La indicación de reemplazo valvular aórtico (RVA) en pacientes con estenosis aórtica (EA) grave asintomáticos con función conservada es motivo de creciente debate.

Objetivo: Evaluar si la elevación del NT-proBNP predice la aparición de síntomas y la indicación de reemplazo valvular en pacientes inicialmente asintomáticos, con EA grave y fracción de eyección ventricular izquierda (FEVI) conservada.

Materiales y métodos: Se incluyeron en forma prospectiva pacientes con EA grave, FEVI conservada (≥55%) que fueron considerados asintomáticos, sin indicación inicial de RVA. A todos se les realizó laboratorio con medición de NT-proBNP en forma basal y ecocardiograma con Doppler tisular consignando la onda S de la pared lateral (S lat) y la relación E/e´. Se consideró como punto final el requerimiento de reemplazo valvular durante el seguimiento.

Resultados: Se incluyeron 133 pacientes con una edad de 69 ± 8 años, 49% mujeres. Luego de un seguimiento de 570 (rango intercuartilo 380-680) días, el 23,3 % (n=31) de los pacientes presentaron requerimiento de reemplazo valvular. En el análisis multivariado, el NT-proBNP y la relación E/e´ fueron predictores independientes de requerimiento de cirugía (HR 1,02, IC95% 1,001-1,03, p<0,001; y HR 1,42, IC95% 1,21-2,45, p<0,001, respectivamente). El NT-proBNP presentó un Área Bajo la Curva (ABC) mayor que la relación E/e´ (0,88 versus 0,64, p=0,02). Se estableció como mejor punto de corte de NT-proBNP un valor >350 pg/mL (HR ajustado 1,55, IC95% 1,38 – 2,01, p<0,001).

Conclusiones: El NT-proBNP y la relación E/e´ fueron predictores independientes de requerimiento de cirugía. El NT-proBNP presentó una muy buena capacidad de discriminación, mayor que la relación E/e´.

Palabras Clave: Estenosis de la válvula aórtica - Biomarcadores - Péptido Natriurético Encefálico

Argent J Cardiol 2023;91:24-30. http://dx.doi.org/10.7775/rac.v91.i1.20591

Received: 09/22/2022 – *Accepted:* 11/02/2022

Address for reprints: Cintia S Laurenzano, Tte. Gral. Juan Domingo Perón 2354, CABA. Phone 011-52764100. E-mail: cintia_cda@hotmail.com

[1] Jonas Salk OSECAC Outpatient Center, Buenos Aires, Argentina.

INTRODUCTION

Aortic stenosis (AS) is the most common valvular disease in Western countries. Prevalence increases with age, reaching 4-7% in patients over 65. (1) The only effective treatment is aortic valve replacement (AVR), either via surgery or percutaneously. AVR indication is evident and recommended in symptomatic patients with severe AS, as well as in patients with impaired ventricular function despite absence of symptoms. (2-4)

While it is recognized that symptoms are one of the main prognostic markers of severe AS, (5,6) some series show that natural progress in asymptomatic patients is not exempt from complications. (7,8) In addition, surgical mortality has reduced over the years, (9) and percutaneous aortic replacement has advanced. (10) This makes the risk/benefit ratio of early intervention increasingly favorable. It is also important to note that symptoms, as defined, are subjective features which are highly variable according to the patient. This makes them difficult to identify, especially in elderly patients.

Therefore, using biomarkers for risk stratification of patients with severe AS has become more appealing. The N-terminal fraction of the pro-B-type natriuretic peptide (NT-proBNP) is one of the most common biomarkers resulting in an adverse and more fatal prognosis when increased. (11,12)

The objective of this study is to assess whether increased NT-proBNP can predict symptoms and AVR indication in patients with severe AS and preserved left ventricular ejection fraction (LVEF), initially asymptomatic.

METHODS

An observational, prospective, single-site study was conducted enrolling patients with severe AS and preserved LVEF under outpatient follow-up in the site's Valvular Heart Disease Department, who were considered asymptomatic and had no initial indication of aortic valve replacement. Patients were enrolled from July 2017 to July 2021.

All the patients had an echocardiogram performed with the Esaote MyLab Seven equipment (Florence, Italy) with a multi-frequency probe (1.5 MHz to 2.6 MHz), and the following parameters were evaluated: aortic valve peak velocity (V max), mean pressure gradient (MG), aortic valve area (AVA) by continuity equation, LV diastolic and systolic diameters (LVDD and LVSD, respectively), left ventricular mass index (LVMI), pulmonary artery systolic pressure (PASP), and LVEF using Simpson's biplane formula. Furthermore, the lateral wall tissue S wave (lat. S) and E/e' ratio were determined.

Severe AS was defined as a V max ≥4 m/s, MG ≥40 mmHg, and AVA ≤1 cm2. Ventricular function was considered preserved if LVEF was ≥55%.

Exclusion criteria: Patients who were symptomatic upon assessment, or for whom the physical examination showed clinical signs of heart failure. Patients with suspected symptoms had an exercise stress test according to the Naughton protocol. Patients with symptoms or a systolic pressure flat curve during exercise were considered symptomatic and therefore excluded. Patients with impaired ventricular function (LVEF ≤55%) and dilated left ventricle (diastolic diameter >60 mm) were also excluded.

An NT-proBNP assessment was required for all patients in the site's laboratory using Vitros 5600 equipment after the first visit.

Follow-up was performed by means of clinic visits. The primary endpoint was the AVR requirement.

Statistical analysis

Continuous variables are expressed as mean ± standard deviation, or median and interquartile range (IQR) based on a normal or abnormal distribution, and categories are expressed as percentages. For continuous variables, group comparisons between AVR and non-AVR patients were performed using Student's t test for normal distributions and Mann-Whitney test for abnormal distributions. Categorical variables were compared using the chi-square test or the Fisher exact test when a variable showed an absolute <5 frequency.

The univariate analysis was performed using Cox regression, considering AVR as the dependent variable, and both NT-proBNP and several echocardiographic parameters as predictive variables. Those variables that were significant for the univariate analysis (considering $p<0.05$) were analyzed using a multivariate model through the proportional hazards regression method to assess variables that are independently associated with the AVR requirement.

Then, receiver operating characteristic (ROC) curves were developed, with the corresponding area under the curve (AUC), and the best cutoff point was established for significant variables in the multivariate analysis.

Finally, an event-free survival test was performed using the Kaplan-Meier method.

Statistix 7 and Epidat 3.1 softwares were used for the analysis.

Ethical considerations

This observational study was approved by the ethics committee of the institution and all the patients included, signed the informed consent.

RESULTS

One hundred seventy-five patients were evaluated, 27 of whom were excluded as they were considered symptomatic (19 upon the initial interview, and 8 after an exercise stress test); 13 patients had impaired ventricular function, and 2 could not have an NT-proBNP assessment. Therefore, 133 patients aged 69 ± 8 were enrolled, 49% were female (n=65). The most common cause of AS was sclerodegenerative aortic valve (70%, n=93), followed by bicuspid (25.5%, n=34) and rheumatic (4.5%, n=6) aortic valve. Table 1 shows the patients' clinical and echocardiographic characteristics.

The median follow-up was 570 days (IQR 380-680), and 23.3% (n=31) of patients required an AVR. As observed in Table 1, the group requiring AVR had a higher baseline NT-proBNP: 290 (IQR 75-450) vs. 85 (IQR 55-180) pg/mL , p=0.01, with a higher E/e' ratio (8.6 ± 2 vs. 7.1 ± 1.3, p=0.04), a tendency towards a lower tissue S wave (0.07 ± 0.01 m/s vs. 0.08 ± 0.01 m/s, p=0.07), and no difference for the remaining parameters.

Table 2 shows the univariate and multivariate

Table 1. Baseline demographics

	Total (n=133)	AVR requirement (n=31)	No AVR requirement (n=102)	P
Age	69 ± 8	69 ± 5	69 ± 8	0.45
Female	65 (49.1)	15 (48.3)	50 (49)	0.31
SBP (mmHg)	130 ± 28	128 ± 32	130 ± 27	0.32
Medical history				
Hypertension	95 (71.4)	22 (70.9)	73 (71.5)	0.72
Diabetes	29 (21.8)	7 (22.5)	22 (21.5)	0.89
Atrial fibrillation	13 (9.7)	3 (9.6)	10 (9.8)	0.77
Echocardiogram				
LVEF (%)	64 ± 4	65 ± 3	64 ± 3	0.23
LVDD (mm)	49 ± 5	49 ± 8	49 ± 7	0.83
IVS (mm)	12 ± 3	13 ± 3	12 ± 4	0.12
LVMI (g/m^2)	98 ± 38	99 ± 41	97 ± 39	0.42
LAA (cm^2)	26.9 ± 6.7	27.2 ± 6.9	26.5 ± 6.5	0.11
Doppler				
V max (m/sec)	4.2 ± 0.4	4.5 ± 0.8	4.2 ± 0.5	0.11
AVA index (cm^2/m^2)	0.58 ± 0.09	0.57 ± 0.1	0.58 ± 0.09	0.62
MG (mmHg)	45 ± 5	46 ± 4	45 ± 4	0.32
Tissue				
Lateral S wave (m/sec)	0.08 ± 0.01	0.07 ± 0.01	0.08 ± 0.01	0.07
E/e´ ratio	7.3 ± 1.5	8.6 ± 2	7.1 ± 1.3	0.04
NT-proBNP (pg./mL)	110 (62.3-310)	290 (75-450)	85 (55-180)	0.01

Categorical variables are presented as n (%). Continuous variables are presented as mean ± standard deviation or median (interquartile range) AVA index: aortic valvular area indexed according to body surface. IVS: intraventricular septum. LAA: left atrium area. LVDD: left ventricular diastolic diameter LVEF: left ventricular ejection fraction. LVMI: left ventricular mass index. MG: mean gradient. SBP: systolic blood pressure. V max : maximum aortic valve velocity.

analysis. In the univariate analysis, NT-proBNP, the E/e´ ratio and lat. S were predictors of the AVR requirement. In the multivariate analysis, NT-proBNP and E/e´ ratio were independent predictors of the surgery requirement: HR 1.02 (95% CI 1.001-1.03), p<0.001, and HR 1.42 (95% CI 1.21-2.45), p<0.001, respectively.

The AUC for NT-ProBNP was 0.88 (95% CI 0.81-0.91), and the best cut-off point was 350 pg./mL, while the AUC for the E/e´ ratio was 0.64 (95% CI 0.52-0.68), significantly lower than that of the NT-proBNP (p=0.02). See Figure 1.

The NT-proBNP >350 pg./mL showed an adjusted HR of 1.55 (95% CI 1.38-2.01), p<0.001. Figure 2 shows the corresponding Kaplan-Meier curve.

DISCUSSION

Our study found that an elevated NT-proBNP was associated with the AVR requirement in asymptomatic patients with severe AS and preserved ventricular function after a 1-year follow-up. The biomarker had a very good discrimination capacity (AUC 0.88), and a value higher than 350 pg./mL was associated with an increased AVR requirement higher than 50% (HR: 1.55). As acknowledged, NT-proBNP and the active BNP hormone are released in response to ventricular and/or atrial cardiomyocyte stretch, mainly as a result of increased filling pressures. (13) Several studies have previously evaluated the prognostic value of natriuretic peptides in AS. Recently, White et al. (12) published a meta-analysis to assess the prognostic role of several biomarkers in AS. They considered 33 studies evaluating the NT-proBNP in 8597 patients. In the combined analysis, an elevated NT-proBNP predicted mortality at follow-up (HR 1.73). All studies included both asymptomatic and symptomatic patients, as well as AVR and non-AVR patients.

In addition, several studies have shown that elevated BNP and NT-proBNP are associated with symptoms and a higher V max in patients with severe AS and preserved function. (14-16)

As regards AS without symptoms, in 2014 Clavel et al. (11) published an observational study of nearly 2000 patients with moderate or severe AS, 560 of whom were asymptomatic at baseline. In this subgroup, an increased BNP was an independent predictor of mortality at follow-up. BNP values ≥3 times the reference value represented an adjusted risk of event nearly 4

Table 2. Univariate and multivariate analysis

	Univariate analysis HR (95% CI)	p	Multivariate analysis HR (95% CI)	p
SBP	1.00 (0.96-1.04)	0.33	--	
LVEF	0.98 (0.97-1.12)	0.56	--	
LVMI	1.01 (0.93-1.05)	0.22	--	
V max	1.03 (0.99-1.12)	0.11	--	
MG	1.02 (0.89-1.23)	0.23	--	
LAA	1.32 (0.99-1.98)	0.09	--	
Lateral S wave	1.21 (1.115-1.88)	0.01	1.18 (0.97-1.72)	0.09
E/e´ ratio	1.52 (1.22-2.63)	<0.001	1.42 (1.21-2.45)	<0.001
NT-proBNP	1.04 (1.01-1.04)	<0.001	1.02 (1.001-1.03)	<0.001

LAA: left atrium area. LVEF: left ventricular ejection fraction. LVMI: left ventricular mass index. MG: mean gradient. SBP: systolic blood pressure. V max : maximum aortic valve velocity

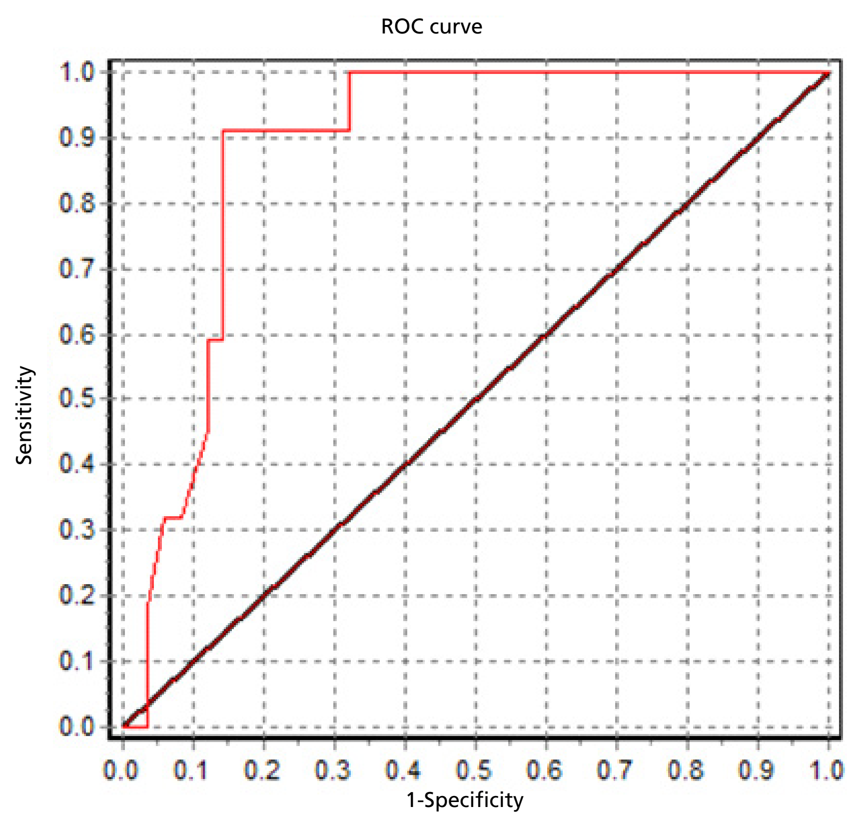
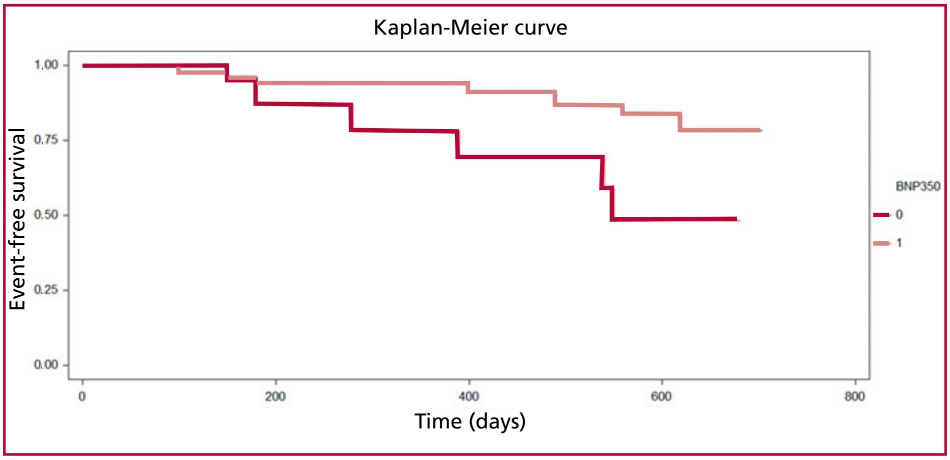


Fig. 1. ROC curve for the NT-proBNP.

times higher than normal BNP. In this sense, a Spanish study including 237 asymptomatic patients with moderate and severe AS evidenced that an increased NT-proBNP was an independent predictor of events (AVR requirement, mortality) at follow-up. (17) Unlike our study, they found a mild discrimination capacity (AUC 0.62). More recently, Henri et al. evaluated the purpose of a serial BNP measurement to predict events in asymptomatic patients with severe AS. (18) An annual 20 pg./mL increase in BNP was independently associated with a growing number of events at 3-year follow-up. A retrospective study of 74 patients found that NT-proBNP and the interventricular septum thickness were independent predictors of events (mortality and AVR requirement) at 4-year follow-up. (19) Previously, Monin et al. (20) found that BNP was associated with increased events and mortality in asymptomatic patients with severe AS and an AUC 0.74. They proposed

Fig. 2. AVR prediction based on the NT-proBNP value.



AVR: aortic valve replacement. BNP350: 0: ≤350 pg/mL. 1: >350 pg/mL

a risk score considering the BNP value, the V max, and the female sex, leading to better event prediction. This score was later validated by Farre et al., (17) using NT-proBNP instead of BNP. Based on these observations, the latest guidelines propose AVR as a Class IIA indication in patients with elevated natriuretic peptides. (3)

In our population, 23% of patients developed symptoms and required AVR during follow-up. This rate of events is lower than the rate reported in previous studies, where about half of the patients required AVR. The Spanish group (17) reported that 110 out of 237 patients required AVR in a follow-up similar to ours. In addition, they recorded a 12% mortality. This is remarkable, since they included a group with moderate AS. Our population was a little younger (69 versus 74 years old) and had a lower baseline NT-proBNP level (110 versus 490 pg./mL). This may partly explain the difference in events. Our patients were probably in an earlier stage of AS.

We also found that the E/e´ ratio was an independent predictor of AVR, with a mild predictive capacity (AUC 0.64). This is consistent with previous studies evaluating diastolic dysfunction parameters in AS. Especially the left atrium area (LAA) and the E/e´ ratio have been found to be independent markers of events in severe asymptomatic AS. (21,22) In our study, patients requiring AVR had a higher LAA than those who didn't; however, in the multivariate analysis, LAA lost independent predictive value, due to the E/e´ ratio and NT-proBNP. Something similar happened with the tissue S wave, which was significant in the univariate but not in the multivariate analysis. The V max is another parameter associated with worse AS progress. V max >5 m/sec indicates a very severe AS, and AVR is recommended in the absence of symptoms. (2,3) We have not found an association with the primary endpoint, probably because the average V max was 4.2 m/sec, and very few patients had a V max >5 m/sec.

The natural progress of severe AS and the time when AVR should be indicated while the disease is asymptomatic, is being increasingly discussed. The recommendation in the absence of adverse prognosis features is careful surveillance and immediate intervention as soon as symptoms occur. (2-4) The basis for this consensus is that the benefit of avoiding sudden death (1% per year in asymptomatic AS) may not be higher than AVR mortality. However, a recent retrospective study compared progress in patients with asymptomatic AS under a conservative treatment against a group of patients who had received AVR. Asymptomatic patients with no AVR at the beginning had higher mortality at 5-year follow-up than AVR patients. (23) Recently, the results of the RECOVERY study were published; (24) this study randomly assigned 145 asymptomatic patients with severe AS to early AVR versus a conservative treatment. The early AVR group had reduced events (death at surgery or within 30 days after surgery, or cardiovascular death during follow-up) versus the conservative treatment (1% vs. 15%, HR 0.09 and a large 95% CI, 0.01-0.67). However, this population was carefully picked, relatively young (aged 64), predominantly had a bicuspid etiology, and an average V max of 5.1 m/sec. Several randomized studies are currently being conducted to evaluate the early AVR strategy for asymptomatic AS: EARLY TAVR (NCT03042104), EASY-AS (NCT04204915), EVOLVED (NCT03094143) (clinicalstrials.gob).

As we have said, the value of natriuretic peptides increases with higher filling pressures. The increase in these and other biomarkers may serve to identify a subgroup of patients who, even if they are asymptomatic, are not so well adjusted to a higher afterload caused by AS, and therefore, have worse progress. This subgroup could benefit from early intervention. (25,26) In this sense, the study by Nakatsuma et al. (27) included 380 asymptomatic patients with severe AS and ventricular function that were divided based on their baseline BNP levels. The rate of events in the group with BNP <100 pg/mL was low both after a year and after 3 years (2.1% and 6.2 %, respectively), while in the group with BNP >300 pg./mL, the rate of events was considerably higher (22% and 42% after 1 and 3 years, respectively). The results of our study contribute to the hypothesis that natriuretic peptides may be a major factor when making decisions about asymptomatic patients with severe AS and preserved function.

Limitations

Our study has several limitations. It is a single-site study, so it is difficult to extrapolate results to other populations. Follow-up was relatively short; therefore, the impact of baseline NT-proBNP cannot be assessed in the long term, and the discrimination capacity of events might be overestimated. Nevertheless, one of the objectives was to evaluate factors helping to identify patients with a higher risk that might benefit from early intervention. As a result, we believe that a 36-month follow-up is sufficient for the study objectives. Lastly, as this is an observational prospective study, the NT-proBNP value may have affected the medical decision to perform an AVR, which may also help to overestimate the event discrimination capacity of the biomarker.

Conclusions

At follow-up, more than 20% of patients developed symptoms and required valvular replacement. The NT-proBNP and E/e´ ratio were independent predictors of the AVR requirement. The NT-proBNP had a very good discrimination capacity, higher than the E/e' ratio.

Conflicts of interest

None declared.

(See authors conflicts of interest forms in the website/ Supplementary material)

REFERENCES

1. Dweck MR, Boon NA, Newby DE. Calcific aortic stenosis: a disease of the valve and the myocardium. J Am Coll Cardiol 2012;60:1854-63. https://doi.org/10.1016/10.1016/j.jacc.2012.02.093.

2. Otto CM, Nishimura RA, Bonow RO, Carabello BA, Erwin JP 3rd, Gentile F, et al. 2020 ACC/AHA Guideline for the Management of Patients With Valvular Heart Disease: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. Circulation 2021;143:e72-e227. https://doi.org/10.1016/10.1161/CIR.0000000000000923.

3. Vahanian A, Beyersdorf F, Praz F, Milojevic M, Baldus S, Bauersachs J, et al. ESC/EACTS Scientific Document Group. 2021 ESC/EACTS Guidelines for the management of valvular heart disease. Eur Heart J 2022;43:561-632. https://doi.org/10.1016/10.1093/eurheartj/ehab395.

4. Stutzbach P, Lax J, Ciancuilli T, Granceli H, Piñeiro D, Prezioso D y cols. Sociedad Argentina de Cardiología. Consenso de Valvulopatías. Rev Argent Cardiol. 2015;83(supl 2). Disponible en: https://www.sac.org.ar/wp-content/uploads/2015/06/consenso-valvulopatias-suplemento-2-2015.pdf

5. Ross J Jr, Braunwald E. Aortic stenosis. Circulation 1968;38(1 Suppl):61-7. https://doi.org/10.1016/ 10.1161/01.cir.38.1s5.v-61.

6. Bach DS, Cimino N, Deeb GM. Unoperated patients with severe aortic stenosis. J Am Coll Cardiol 2007;50:2018-9. https://doi.org/10.1016/10.1016/j.jacc.2007.08.011.

7. Kitai T, Honda S, Okada Y, Tani T, Kim K, Kaji S et al. Clinical outcomes in non-surgically managed patients with very severe versus severe aortic stenosis. Heart. 2011;97:2029-32. https://doi.org/10.1016/10.1136/heartjnl-2011-300137.

8. Rosenhek R, Zilberszac R, Schemper M, Czerny M, Mundigler G, Graf S, et al. Natural history of very severe aortic stenosis. Circulation 2010;121(1):151-6. doi: 10.1161/CIRCULATIONAHA.109.894170.

9. Malaisrie SC, McCarthy PM, McGee EC, Lee R, Rigolin VH, Davidson CJ et al. Contemporary perioperative results of isolated aortic valve replacement for aortic stenosis. Ann Thorac Surg. 2010;89(3):751-6. doi: 10.1016/j.athoracsur.2009.11.024.

10. Durko AP, Osnabrugge RL, Van Mieghem NM, Milojevic M, Mylotte D, Nkomo VT, et al. Annual number of candidates for transcatheter aortic valve implantation per country: current estimates and future projections. Eur Heart J 2018;39:2635-42. https://doi.org/10.1016/10.1093/eurheartj/ehy107

11. Clavel MA, Malouf J, Michelena HI, Suri RM, Jaffe AS, Mahoney DW, et al. B-type natriuretic peptide clinical activation in aortic stenosis: impact on long-term survival. J Am Coll Cardiol. 2014;63(19):2016-25. https://doi.org/10.1016/10.1016/j.jacc.2014.02.581.

12. White M, Baral R, Ryding A, Tsampasian V, Ravindrarajah T, Garg P et al. Biomarkers Associated with Mortality in Aortic Stenosis: A Systematic Review and Meta-Analysis. Med Sci (Basel) 2021;9:29. https://doi.org/10.1016/10.3390/medsci9020029.

13. Steadman CD, Ray S, Ng LL, McCann GP. Natriuretic peptides in common valvular heart disease. J Am Coll Cardiol. 2010;55:2034-48. https://doi.org/10.1016/j.jacc.2010.02.021.

14. Gerber IL, Stewart RA, Legget ME, West TM, French RL, Sutton TM, et al. Increased plasma natriuretic peptide levels reflect symptom onset in aortic stenosis. Circulation. 2003;107:1884-90. https://doi.org/10.1016/10.1161/01.CIR.0000060533.79248.0C.

15. Bergler-Klein J, Klaar U, Heger M, Rosenhek R, Mundigler G, Gabriel H, et al. Natriuretic peptides predict symptom-free survival and postoperative outcome in severe aortic stenosis. Circulation. 2004;109:2302-8. https://doi.org/10.1161/01.CIR.0000126825.50903.18

16. Nessmith MG, Fukuta H, Brucks S, Little WC. Usefulness of an elevated B-type natriuretic peptide in predicting survival in patients with aortic stenosis treated without surgery. Am J Cardiol. 2005;96:1445-8. https://doi.org/10.1016/j.amjcard.2005.06.092.

17. Farré N, Gómez M, Molina L, Cladellas M, Blé M, Roqueta C, et al. Prognostic value of NT-proBNP and an adapted monin score in patients with asymptomatic aortic stenosis. Rev Esp Cardiol (Engl Ed). 2014;67:52-7. https://doi.org/10.1016/j.rec.2013.06.020.

18. Henri C, Dulgheru R, Magne J, Caballero L, Laaraibi S, Davin L, et al. Impact of Serial B-Type Natriuretic Peptide Changes for Predicting Outcome in Asymptomatic Patients With Aortic Stenosis. Can J Cardiol. 2016;32:183-9. https://doi.org/10.1016/j.cjca.2015.06.007

19. Campos I, Pereira J, Salome N, Pereira VH, Oliveira C, Marques Pires C, et al. Asymptomatic severe aortic stenosis: what is the current role of exercise stress test and NT-proBNP in patient risk stratification, Eur Heart J CardiovasC Imag 2021;22(Supplement 1) https://doi.org/10.1093/ehjci/jeaa356.053

20. Monin JL, Lancellotti P, Monchi M, Lim P, Weiss E, Piérard L, et al. Risk score for predicting outcome in patients with asymptomatic aortic stenosis. Circulation. 2009;120:69-75. https://doi.org/10.1161/CIRCULATIONAHA.108.808857

21. Lancellotti P, Moonen M, Magne J, O'Connor K, Cosyns B, Attena E, et al. Prognostic effect of long-axis left ventricular dysfunction and B-type natriuretic peptide levels in asymptomatic aortic stenosis. Am J Cardiol 2010;105:383-8. https://doi.org/10.1016/j.amjcard.2009.09.043

22. Lancellotti P, Donal E, Magne J, Moonen M, O'Connor K, Daubert JC, et al. Risk stratification in asymptomatic moderate to severe aortic stenosis: the importance of the valvular, arterial and ventricular interplay. Heart 2010;96:1364-71. https://doi.org/10.1136/hrt.2009.190942

23. Kvaslerud AB, Santic K, Hussain AI, Auensen A, Fiane A, Skulstad H, et al. Outcomes in asymptomatic, severe aortic stenosis. PLoS One 2021;16:e0249610. https://doi.org/10.1371/journal.pone.0249610

24. Kang DH, Park SJ, Lee SA, Lee S, Kim DH, Kim HK, et al. Early Surgery or Conservative Care for Asymptomatic Aortic Stenosis. N Engl J Med. 2020;382:111-9. https://doi.org/10.1056/NEJ-

Moa1912846.
25. Lindman BR, Dweck MR, Lancellotti P, Généreux P, Piérard LA, O'Gara PT, et al. Management of Asymptomatic Severe Aortic Stenosis: Evolving Concepts in Timing of Valve Replacement. JACC Cardiovasc Imaging 2020;13(2 Pt 1):481-93. https://doi.org/10.1016/j.jcmg.2019.01.036.
26. Généreux P, Stone GW, O'Gara PT, Marquis-Gravel G, Redfors B, Giustino G, et al. Natural History, Diagnostic Approaches, and Therapeutic Strategies for Patients With Asymptomatic Severe Aortic Stenosis. J Am Coll Cardiol. 2016;67:2263-88. https://doi.org/10.1016/j.jacc.2016.02.057.
27. Nakatsuma K, Taniguchi T, Morimoto T, Shiomi H, Ando K, Kanamori N, et al. CURRENT AS Registry Investigators. B-type natriuretic peptide in patients with asymptomatic severe aortic stenosis. Heart. 2019;105:384-90. https://doi.org/10.1136/heartjnl-2018-313746