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Exercise test in patients with asymptomatic aortic stenosis – clinically useful or not?

Short title: Exercise test in asymptomatic aortic stenosis

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What’s new?

In this manuscript, we revised the clinical value of exercise test in patients with asymptomatic aortic stenosis. We found that in patients with asymptomatic AS exercise test is safe but its value in decision of valve replacement in our group of patients was low. We also propose new clinical parameter that may be an equivalent of aortic stenosis symptoms – inability to achieve 85% of age adjusted maximal heart rate during exercise especially in patients treated with beta-blockers. Those who were treated with beta-blockers and did not achieve 85% of predicted maximal heart rate had a higher probability of AVR. The influence of beta blockers treatment on the decision of AVR in this small group of patients need further revision.
Abstract

Introduction: Aortic valve replacement (AVR) is recommended for symptomatic patients (pts) with severe aortic stenosis (AS). In asymptomatic AS (AAS) exercise testing (ET) is recommended but is controversial and varies among practicing clinicians.

Objectives: The aim of our study was to assess the importance of ET in AAS pts.

Patients and methods: 89 pts with AAS (53 men; age 59.5 yrs) underwent 244 symptoms-limited ET.

Results: All ET were clinically negative. During median follow-up 22(12) months 39 pts (22 men) became symptomatic - AVR group. This group was compared with the asymptomatic nonAVR 50 pts. In multivariable Cox analysis presence of maximal HR<85% (THR<85%) during ET was significantly related with AVR (p=0.01). After adjustment for the use of beta-blockers (BB) this was not statistically significant (p=0.08). In BB subgroup THR<85% was significantly related with AVR in univariable Cox analysis hazard ratio 2.2 (1.07-4.9) p=0.03 and after adjusting for age (p=0.047). This relationship was not observed in the group not treated with BB.

Conclusion: In patients with asymptomatic AS exercise test is safe but in our group of patients the results were not crucial in decision of AVR. Patients treated with beta-blockers who did not achieve 85% of predicted maximal heart rate had a higher probability of AVR. The influence of beta blockers treatment on the decision of AVR in this small group of patients need further revision.

Key words: asymptomatic aortic stenosis, exercise test, beta-blockers
Introduction

Aortic stenosis (AS) is one of the most common heart valve disease in developed countries. Studies investigating the natural history of AS in adults show that as stenosis increases, compensatory mechanisms fail and the symptoms: dyspnea, angina, syncope, and arrhythmias start to occur [1,2,3,4]. Once symptoms develop, the prognosis worsens [5,6]. Aortic valve replacement (AVR), either surgical or transcatheter, is recommended by current guidelines for symptomatic patients with severe AS [3,4]. In asymptomatic AS (AAS) patients with preserved left ventricular (LV) function defined as ejection fraction (EF) above 50%, the benefit of prophylactic AVR is still unproven and the optimal timing of intervention remains controversial [3-12]. International guidelines recommend exercise testing (ET) to unmask the pseudo-asymptomatic patients and those without self-reporting symptoms. In the past, ET was contraindicated in pts with severe AS because of concerns of life-threatening complications [3,4]. Nowadays, ET is still absolutely contraindicated in patients with symptomatic severe AS. As studies over the past 15 years have shown, in patients with AAS, ET supervised by an experienced cardiologist is safe and based on ESC and ACC/AHA guidelines should be prognostic useful [13-17]. In practice, the use of ET in asymptomatic AS is controversial and its use varies among practicing clinicians [15,16,18].

The aim of our study was to assess the safety and tolerability of ET in asymptomatic severe AS patients and an attempt to answer the question if standard ET is still of important clinical value in these group of patients.

Patients and Methods

We prospectively included 120 consecutive patients from the Outpatient Valve Disease Department with a diagnosis of asymptomatic, significant AS. Severe AS was defined by the aortic valve area (AVA≤1.0cm2), mean transvalvular pressure gradient ≥40 mm Hg, EF>50%. The inclusion criteria were: the absence of symptoms — major: dyspnea, angina
pectoris, syncope, and minor: dizziness, weakness, fatigue, exercise intolerance. Exclusion criteria: predominant aortic regurgitation or more than mild mitral/tricuspid regurgitation/stenosis, history of coronary artery disease (myocardial infarction, CABG, PCI), comorbid disease associated with symptoms that could interfere with clinical evaluation and preclude the performance of an exercise test (i.e. uncontrolled hypertension, disabilities, etc.). Hypertension was diagnosed as previously made by physician (with medications) or blood pressure values \( \geq 140 \text{mm systolic} \) or \( \geq 90 \text{mm diastolic} \) on 2 visits [18]. Diabetes was diagnosed as previous made by physician (with medications) or fasting blood glucose level \( \geq 7 \text{mmol/l} \) on \( \geq 2 \) blood samples [18]. Finally, the lack of symptoms was confirmed in 96 patients - after detailed examination and interview, twenty-four patients were classified as symptomatic. One patient was excluded from the study after the first test. Six patients denied participating in the study and AVR if necessary. Eighty-nine patients diagnosed as true asymptomatic AS agreed to participate in the study. The group consisted of 36 women and 53 men. The mean age was 59.5(11.7) yrs (range 25-77 yrs). All patients were informed about the procedures, benefits, and risks involved in participating in the study. Informed consent was obtained from each patient and the study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki as reflected in a priori approval by the institution’s human research committee. Patients were examined every 6 months (symptoms; echo and exercise test in asymptomatic pts). The follow-up was stopped at predefined time (31.12.2017) and the maximal follow-up was defined as 36 months.
Transthoracic echocardiography

The standardized examination comprised transthoracic echocardiograms. The severity of AS, LV wall thicknesses, chamber dimensions, and EF were measured according to the prevalent European and the United States guidelines.

Exercise testing

A symptom-limited ET test was performed using an electrical bicycle monitored by a cardiologist, according to the recommendation [19]. Every minute, patients were asked about their exhaustion (we use modified 0-10 Borg scale). The initial workload was 50 watts (W) with a gradual increase of 50 W every 3 minutes. The ET was conducted till the patient exhaustion (ie. 7th level in modified Borg scale). Target heart rate (THR) was calculated according to the formula: 220-age. Submaximal frequency corresponded to 85% of this value. The test was to stopped in case of:

- patient’s desire to finish the test
- significant breathlessness, chest pain
- systolic BP fall >20mmHg
- significant increase of ventricular ectopy – couplets, ventricular tachycardia
- supraventricular tachycardia, the onset of atrial flutter/fibrillation
- systolic BP≥250 mm Hg or diastolic BP≥115 mm Hg
- significant ST depression (>4mm) or ST elevation
- when patient achieves 100% of THR

To distinguish physiological and symptomatic breathlessness we verified the presence of additional symptoms like inability to speak, facial pallor, distress.

The ET was considered symptomatically positive if symptoms of AS occurred or if the patient stopped prematurely due to limiting breathlessness or dizziness or systolic BP drop > 20 mm Hg during exercise.
End points

The end point was defined as the decision of AVR

Statistical analysis

Statistical analysis was performed using SPSS version 11.0. Values are given as mean, standard deviation (SD) for continuous variables and as percentages for categorical variables. The data was tested for normality by Kolmogorov-Smirnov test. Comparison between groups was performed by unpaired t test, $\chi^2$, and Mann-Whitney tests. Correlates of the end point were identified by multivariable Cox regression models and presented as hazard ratio and 95% confidence intervals. In multivariable analysis, we included the parameters that achieve $p<0.1$ in univariable analysis, not more than four. In univariable analysis more than 4 variables had $p<0.1$. It is well known (and clearly seen in our results) that age was the strongest parameter related with aortic valve replacement so it was used as "basic". Variables like hypertension, hyperlipidemia, statins were strongly age related – what we verified firstly. This variables became not significant in multivariable analysis when age was one of variable. We clearly know that variables - Vmax, PAG and xAG are mathematically related each other so we took only one of them (most frequently used in publications) – PAG. The results of exercise test – Mets, heart rate are strongly age dependent. The % of target heart rate and presence of THR<85% are not – so we took one of them.

Results

A history of hypertension was noted in 56 pts, 26 pts had dyslipidemia and 13 were diabetic. Median follow up was 22 (first and fourth quartile 11-36) months. All of the patients finished and survived the follow-up period. During this time 39 from 89 patients, 17 women and 22 men, became symptomatic (it was recorded during periodic visits before the next exercise test) and the decision of AVR (AVR group) was made by the heart team.
Figure 1 presents the details of follow up. We performed 244 tests (Table 1). No significant differences were observed between consecutive tests performed every 6 months. All tests were finished because of pts fatigue (7/10 in Borg scale) or achievement of 100% of THR and were clinically negative, without blood pressure fall, or complex arrhythmias. The AVR group was compared with 50 patients - the nonAVR group (Table 2). Patients who remained asymptomatic had longer mean follow-up time, were younger and had less significant AS, less often had hypertension and more often were without medications.

When we compared the first tests performed in AVR patients with nonAVR group we found, that AVR group was characterized by lower exercise capacity in METs and lower heart rate during maximal effort compared with non AVR group. This was mostly caused by the age differences. Patients from AVR group more frequently become fatigued before they reached age-adjusted 85% of THR (Table 3).

This parameter was significant in univariable Cox analysis (Table 4). It might suggest new clinical parameter - an equivalent of AS symptoms ie. inability to achieve 85% of age adjusted THR during exercise. However, after adjustment for the use of beta-blockers this was not statistically significant (p=0.08).

Very interesting results, we observed when we analyzed patients treated and not treated with beta-blockers separately. Among 45 pts treated with beta-blockers 28 became symptomatic, 16 (57%) of them did not reach 85% of THR. Among 17 finally asymptomatic patients on beta-blocker, only 5 (29%) did not achieve it. In this beta-blockers subgroup THR<85% was significantly related with AVR in univariable Cox analysis - hazard ratio 2.2(1.07-4.9) p=0.03. This parameter was still significant after adjusting for age (p=0.047). This relationship was not observed in the group of 44 patients not treated with beta-blockers.

Eleven from 44 were finally qualified for AVR – only one had THR<85%. Among the rest 33 asymptomatic patients 7 did not reach 85% of THR (Figure 2).
Discussion

Despite advances in the diagnosis of valvular heart disease, indications for valve replacement in patients with significant asymptomatic AS are one of the most difficult clinical problems. Supporters of surgical treatment point out that even being asymptomatic, patients with severe AS have a poor prognosis with a high event rate and early elective surgery should be recommended based on observational studies [8,9,10,11,12,20,21]. It is reported that approximately half of the patients diagnosed with severe AS do not report symptoms at initial diagnosis [3,4,22]. On the other hand, it is known, that 3-11% of patients die soon after the onset of symptoms before AVR can be performed [23]. Traditional symptom-limited exercise testing should be helpful to determine whether patients who do not report symptoms are truly asymptomatic. In a retrospective analysis of prospectively collected data, Saeed et al. in 2018 found event-free survival at 1 year 87%±3% in patients who were asymptomatic on ET compared with 66%±4% in those with revealed symptoms [24]. The similar data presented the meta-analysis by Rafique; they found that asymptomatic patients with abnormal results on ET had a risk of cardiac events during follow up eight times higher than normal and risk of sudden death 5.5 times higher [25]. In 2017 Redfors summarized 20 publications about stress testing in AAS [15]. They presented a report with available data on a stress test in AS and its potential role in decision making for optimal timing of AVR. Only 7 of 20 publications concerned the treadmill stress test, there were no cycloergometric tests. The rest were stress echocardiogram and cardiopulmonary testing. The most assessed group consisted of severe but also moderate AS. The abnormal stress test was present in the majority of patients from 15 to even 67%. The authors summarized that positive ET was the strongest predictor of developing symptoms at follow-up. There was no explanation, why the patients with positive stress tests were not referred for surgery as recommended by guidelines.
The result of our study is completely opposite to those presented above. All of our tests were clinically negative. No symptoms were reported in 244 tests: The lack of a clinically positive ET in our group may be associated with a very careful selection of patients. The study group of 89 patients was selected from 120 patients referred to as AAS. At the beginning of the interview, all patients denied the symptoms. After a very careful examination, 25 of them confirmed symptoms. Perhaps those patients would be symptomatic during ET if performed. The lack of reporting the symptoms might be for various reasons. One of them is the self-limitation of physical activity. Some patients believed that reduced exercise tolerance, shortness of breath, chest pain, dizziness are age-related ailments, smoking, changes in the spine, etc. They have been adapted by decreasing their level of activity to avoid symptoms. They may also not recognize significant symptoms, often underestimate their severity, and only report when they become extremely limiting [15].

Assessment of absence of symptoms is based on information obtained from the patient, but also should be confirmed by the family. The exercise test is contraindicated in symptomatic patients. But it may happen that the patient is not telling the truth as in the case of one of our patients, who denied the symptoms because he wanted to be under the supervision of the granting physician. Despite the symptomatic (stenocardia, dizziness) significant AS, the stress test was performed without any symptoms reported by patient or complications. At the next visit, the patient refused to the test and confessed to the symptoms. Despite clinical and echocardiographic progression, the patient refused surgery and died at home because of heart failure. He was excluded from the study; he really did not fulfill the inclusion criteria.

Because of doubts about symptoms in classic exercise test new risk factors are searched for. Chambers [13] and co described a new exercise measurement with additional important prognostic implication, an early rapid rise in heart rate (RR-HR) defined as achieving at least 85% THR or >50% increase from baseline within the first 6 minutes. They
concluded that RR-HR is a compensatory mechanism to maintain cardiac output. This was associated with revealed symptoms later in the same test and predicted AVR. In the previous studies the authors showed also that stroke volume failed at the start of exercise and before symptoms developed in patients with severe AS [24].

Despite the lack of the symptoms during the test, we also tried to find out any differences in the result of ET between AVR and nonAVR group. AVR group was characterized by lower exercise capacity in METs and lower heart rate during maximal effort compared with nonAVR group. This difference might be easily explained by age because AVR patients were older. On the other hand, percent of maximal heart rate is age-adjusted and we found that patients from AVR group more frequently become fatigued before they reached 85% of predicted THR. Maximal heart rate below 85% of age-predicted was also presented as chronotropic incompetence and reported as important prognostic factor [26]. In our patients maybe it is a kind of equivalent of AS symptoms? In univariable Cox regression analysis THR<85% was related with higher probability of AVR. The significance persisted after adjustment to age. However after adjustment for the use of beta-blockers this parameter was no more statistically significant (p=0.08). Patients with asymptomatic AS do not need pharmacological treatment [3,4]. When they became symptomatic they need surgery. The prevalence of hypertension in pts with AS is up to 50% in some study – in our, younger group, it was about 30% [3,4, 27]. Hypertension was shown to accelerate the progression of aortic stenosis and may increase the risk of disease. Hypertension, by increasing the systemic vascular load had negative effect on hypertrophic remodeling in aortic stenosis [27,28]. However antihypertensive treatment in severe AS has been thought of a relative contraindication due to the risk of hypotension and hemodynamic collapse; nowadays there is no doubt that hypertension should be treated with caution. Antihypertensive treatment with beta blockers is frequently avoided because of fear of depression of left ventricular function.
This is in line with recent clinical practice guidelines recommendation with no mentioned of beta-blockers [3,4]. From the other hand recent studies have shown that use of beta-blockers are safe and may be even beneficial [27,28].

Pharmacological treatment in our group was used to treat hypertension or supraventricular arrhythmias. We found that presence of hypertension had no influence on survival/AVR, but beta-blockers treatment had. We found that patients treated with beta-blockers who did not achieve 85% of predicted maximal heart rate had a higher probability of AVR. This influence of beta-blockers treatment on AVR in this small group of patient need further revision.

Although ET has been performed in AAS for over 15 years there are still a lot of questions that causes the use of exercise testing controversial. In the Euro Heart Survey on Valvular Heart Disease in asymptomatic patients with aortic stenosis exercise test was performed only in 5.7% of patients [18]. This observation based on real clinical practice showed the present role of exercise test in this group of patients. Even in multicenter randomized controlled trial EVOLVED, AVATAR that compared early AVR to routine care in AAS, stress test was not used as a part of the study protocol to eliminate “pseudo-asymptomatic” patients [29,30]. The definitions of the clinically abnormal stress test in AAS also differ among reported studies [2,15,16,256]. Up to 20% of patients with AS are unable to perform a stress test due to poor mobility or impaired exercise capacity [21]. Nowadays AAS might be a different problem than it was observed 10-20 years ago - today, AS patients are elderly, often with multiple comorbidities, potentially more vulnerable to the hemodynamic derangements associated with severe AS [18,23,25]. Another issue to look out for is a very varied physical performance in the analyzed group. Some patients practiced amateur sports (tennis, cycling, climbing). A large percentage of the patients reported that they systematically attended the gym. But there were also patients who had a very conservative
"couch" lifestyle. Compared to the general population, patients with AS were rather low fitness group. This is the next indication to performed ET in AAS to establish also the safety of daily physical activities or occupational work.

Current guidelines recommend repeat clinical assessment and echocardiography every 6 to 12 months for severe AS but without information whether an ET should be repeated at each time of follow-up [3,4]. Like us, some authors stressed the limited usefulness of the repeated ET (apart from verifying the absence of symptoms) [16]. In our Institution, this is our practice to perform exercise stress testing in asymptomatic patients with aortic stenosis to verify the lack of symptoms.

Although additional technics like the echocardiographic assessment of LV function, cardiopulmonary test, risk score (CURRENT-AS), and biomarkers might improve diagnostic, their role in AAS management requires further investigation to justify a class I indication for surgery instead of classic ET [31-39].

**Study limitations**

Our hospital is dedicated to more difficult cases so the analyzed population may not be typical to general AAS patients. Cohort was highly selected due to National Institute of Cardiology is dedicated to more difficult cases so the analyzed population may not be typical to general asymptomatic AS patients. A limited number of patients may influence somehow statistical results.

We performed cycloergometric ET that was not previously so often reported in such studies so our results may not be comparable with the results of studies based on treadmill stress test examination. We also did not performed ergospirometric test with RER measurement to assess the real level of exercise.
It was impossible to assess how long after previous ET or how long before next ET patients develop symptoms. Despite being told to report the symptoms immediately, most of them waited for scheduled visit. It was also difficult to indicate most frequent symptom; sometimes it was dizziness, sometimes shortness of breath. Most complained of angina and more than one symptom. One patient had cardiac arrest with good result of resuscitation by family.

**Conclusion**

In patients with asymptomatic AS exercise test is safe but in our group of patients the results were not crucial in decision of AVR. Patients treated with beta-blockers who did not achieve 85% of predicted maximal heart rate had a higher probability of AVR. The influence of beta blockers treatment on the decision of AVR in this small group of patient need further revision.

**Contribution statement**

Ewa Orłowska-Baranowska – concept of the study, data collection, manuscript preparation

Rafał Baranowski – data collection, data analysis, revision of the manuscript

Tomasz Hryniewiecki – concept revision, revision of the manuscript

All authors accepted the final version of the manuscript.

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Table 1. Results of 244 exercise tests performed in asymptomatic patients with aortic stenosis.

| Parameter                        | Test 1 (n=89) | Test 2 (n=56) | Test 3 (n=39) | Test 4 (n=30) | Test 5 (n=23) | Test 6 (n=7) |
|----------------------------------|---------------|---------------|---------------|---------------|---------------|--------------|
| Time, minutes                    | 6.9(2.2)      | 6.9(2.4)      | 7(2.1)        | 7.1(2)        | 7.3(2.1)      | 7.5(2)       |
| Mets                             | 6.6(1.6)      | 6.4(1.5)      | 6.2(1.1)      | 6.6(0.9)      | 6.6(1.4)      | 6.7(0.9)     |
| Pre ET HR, bpm                   | 75(11)        | 77(15)        | 76(14)        | 79(13)        | 76(11)        | 81(13)       |
| Peak HR, bpm                     | 140(17)       | 143(18)       | 142(13)       | 144(17)       | 148(15)       | 152(19)      |
| % of THR                         | 89(8)         | 89(7)         | 90(7)         | 89(8)         | 91(6)         | 90(4)        |
| Pts (%) with THR<85%             | 29(32.6%)     | 10 (20%)      | 7 (17.9%)     | 8 (33.3%)     | 3 (15%)       | 1 (14.3%)    |
| HRR                              | 42(16)        | 42(11)        | 43(11)        | 48(23)        | 45(17)        | 42(9)        |
| Pre ET systolic BP               | 129(13)       | 126(15)       | 128(14)       | 127(17)       | 130(16)       | 120(15)      |
| Pre ET diastolic BP              | 80(11)        | 81(9)         | 78(17)        | 82(11)        | 81(10)        | 77(10)       |
| Peak systolic BP                 | 182(24)       | 187(26)       | 183(21)       | 181(24)       | 180(22)       | 179(20)      |
| Peak diastolic BP                | 96(13)        | 96(13)        | 100(12)       | 93(24)        | 95(14)        | 93(12)       |

**Abbreviations:** AVR, aortic valve replacement; BP, blood pressure, mm Hg; bpm, beats per minute; ET, exercise test; HR, heart rate; HRR, HR recovery; METs, exercise capacity; THR, Target heart rate.
Table 2. Comparison between asymptomatic and surgery patients

| Parameter                      | AVR (n=39)   | nonAVR (n=50) | p      |
|-------------------------------|--------------|---------------|--------|
| Age, yrs                      | 65.2(7.5)    | 54.9(12.5)    | 0.0001 |
| Male/Female                   | 22/17        | 31/19         | 0.66   |
| Hypertension n (%)            | 30 (77%)     | 28 (56%)      | 0.046  |
| Diabetes n (%)                | 6 (15%)      | 7 (14%)       | 0.99   |
| Hyperlipidemia n (%)          | 21 (54%)     | 14 (28%)      | 0.02   |
| No treatment n (%)            | 5 (13%)      | 20 (40%)      | 0.005  |
| Beta-blockers n (%)           | 28 (72%)     | 17 (34%)      | 0.001  |
| ACE-inhibitors n (%)          | 17 (44%)     | 19 (38%)      | 0.66   |
| Diuretics n (%)               | 13 (33%)     | 10 (20%)      | 0.22   |
| Statins n (%)                 | 23 (59%)     | 19 (38%)      | 0.057  |
| Follow up, months median      | 17(9-25)     | 36 (13-36)    | 0.001  |
| LVDD, mm                      | 43.7(6.5)    | 45.7(6.9)     | 0.17   |
| LVSD, mm                      | 27.2(4.7)    | 28.8(4.6)     | 0.12   |
| IVSD, mm                      | 14.7(2.4)    | 13.5(2.6)     | 0.03   |
| PWD, mm                       | 11.2(2.3)    | 10.9(2.1)     | 0.52   |
| LVM, g                        | 263(95)      | 257(91)       | 0.77   |
| LVMI, g/m2                    | 138(46)      | 133(40)       | 0.56   |
| EF, %                         | 68(4)        | 68(4)         | 0.89   |
| AVA, cm2                      | 0.8(0.2)     | 0.9(0.2)      | 0.11   |
| Vmax, m/sec                   | 4.8(0.7)     | 4.3(0.2)      | 0.02   |
| Abbreviation | Value 1 | Value 2 | p-value |
|--------------|---------|---------|---------|
| PAG, mmHg    | 88(24)  | 77(20)  | 0.02    |
| xAG, mmHg    | 52(16)  | 44(15)  | 0.03    |

**Abbreviations:** AVA, aortic valve area; EF, ejection fraction; IVSD, interventricular septum diameter; LV, left ventricle; LVDD, LV diastolic diameter; LVM, LV mass; LVMI, LV mass index; LVSD, LV systolic diameter; PAG, peak aortic gradient; PWD, posterior wall diameter; Vmax, peak velocity; xAG, mean aortic gradient.
**Table 3.** Results of the exercise test.

| Parameter                      | AVR pts (n=39) | nonAVR pts (n=50) | P=  |
|--------------------------------|----------------|-------------------|-----|
| Exercise duration, minutes     | 6.3(2.2)       | 7.3(2.7)          | 0.14|
| Mets                           | 6.2(1.5)       | 6.9(1.6)          | 0.04|
| Pre ET HR, bpm                 | 73(10)         | 77(11)            | 0.051|
| Peak HR, bpm                   | 133(14)        | 145(17)           | 0.001|
| THR, %                         | 87(8)          | 90(8)             | 0.09|
| THR<85%, n (%)                 | 17(43.5%)      | 12(24%)           | 0.04|
| HRR                            | 40(10)         | 44(19)            | 0.29|
| Pre ET systolic BP             | 130(13)        | 128(13)           | 0.43|
| Pre ET diastolic BP            | 78(6)          | 81(14)            | 0.29|
| Peak systolic BP               | 181(23)        | 183(24)           | 0.59|
| Peak diastolic BP              | 94(13)         | 97(12)            | 0.33|

**Abbreviations:** AVR, aortic valve replacement; BP, blood pressure mm Hg; bpm, beats per minute, HR, heart rate; HRR-HR recovery; METs, exercise capacity; THR, Target heart rate,
Table 4. Variables related with the decision of aortic valve replacement during follow-up.

Results of the Cox analysis

| Cox univariable analysis                        | Hazard ratio (95% CI) | p=       |
|------------------------------------------------|-----------------------|----------|
| Variable                                       |                       |          |
| Age                                            | 1.08 (1.04-1.1)       | p=0.0001 |
| PAG                                            | 1.02 (1.009-1.037)    | p=0.002  |
| Beta-blockers                                  | 2.8 (1.4-5.7)         | p=0.003  |
| <85%THR                                        | 2.27 (1.2-4.3)        | p=0.01   |

| Cox multivariable analysis                     |                       |          |
| Age                                            | 1.07 (1.026-1.1)      | p=0.001  |
| Beta-blockers                                  | 2.5 (1.23-5.1)        | p=0.01   |
| PAG                                            | 1.02 (1.003-1.036)    | p=0.02   |

**Abbreviations:** PAG, peak aortic gradient; THR, Target heart rate.
**Figure 1.** Results of the follow up

**Abbreviations:** AVR, aortic valve replacement; ExTest, exercise test; *patient was excluded before second test because he hid the symptoms during examination before the first exercise test. The test was asymptomatic."
Figure 2. The relationship of presence of target heart rate <85% and qualification to aortic valve replacement in whole patients, and in treated and not treated with beta blockers

**Abbreviations:** AVR, aortic valve replacement; HR, target heart rate <85%