UNIVERSIDAD AUTONOMA DE MADRID

Doctoral Thesis

Patient-Prosthesis Mismatch and risk of structural valve deterioration in patients undergoing bioprosthetic aortic valve implantation

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1. Abbreviations

AVR: aortic valve replacement

BSA: body surface area

CABG: coronary artery bypass grafting

EOA: effective orifice area

GOA: geometric orifice area

IEOA indexed effective orifice area

IGOA: indexed geometric orifice area

LV: left ventricle

LVEF: left ventricle ejection fraction

NYHA: New York Heart Association

PPM: patient-prosthesis mismatch

SVD: structural valve deterioration

2. Introduction

2.1 Aortic valve disease

The aortic valve separates the left ventricle from the aorta. It is constituted by three leaflets attached to a crown shaped annulus (fig 1).

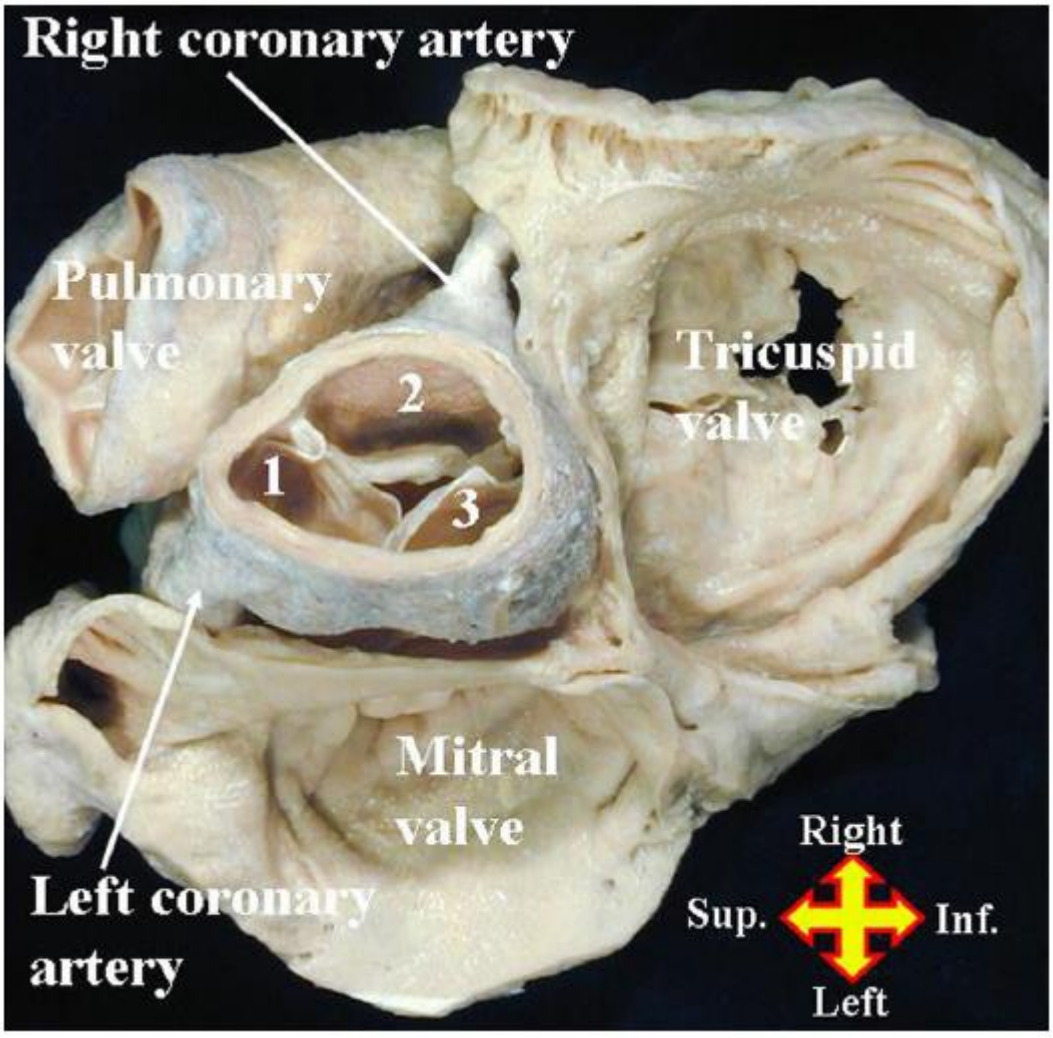


Fig 1.The dissection shows the three aortic valve leaflets (1: left coronary leaflet; 2: right coronary leaflet; 3: non coronary leaflet) and their anatomical relation with the coronary arteries. From Robert H. Anderson, The surgical anatomy of the aortic root, doi:10.1510/mmcts.2006.002527

Any condition which modifies the morphology and, consequently, the physiology of the aortic valve can be included at least in one of the two categories of aortic valve disease: aortic valve stenosis and aortic valve regurgitation[1].

The first condition, aortic valve stenosis, is a complex disease. About 2-7% of the population over 65 years of age is affected by its degenerative form[2]. Thus, as elderly people represent the fastest growing section of the population in western countries[3], aortic stenosis is the most frequent heart valve disease in Europe and US[4]. Old patients with degenerative aortic stenosis represent a heterogeneous population with specific comorbidities. The pathogeneses of some of them, such as arterial hypertension, coronary artery disease or impaired left ventricle function, are interrelated. For this reason degenerative aortic stenosis has been defined as a "systemic disease"[5]. The second cause of aortic stenosis is rheumatic disease.

Independently from the etiology, a stenotic aortic valve is characterized by diffuse leaflets thickening, fusion or calcification, with reduction of the orifice valve[6] (fig. 2).

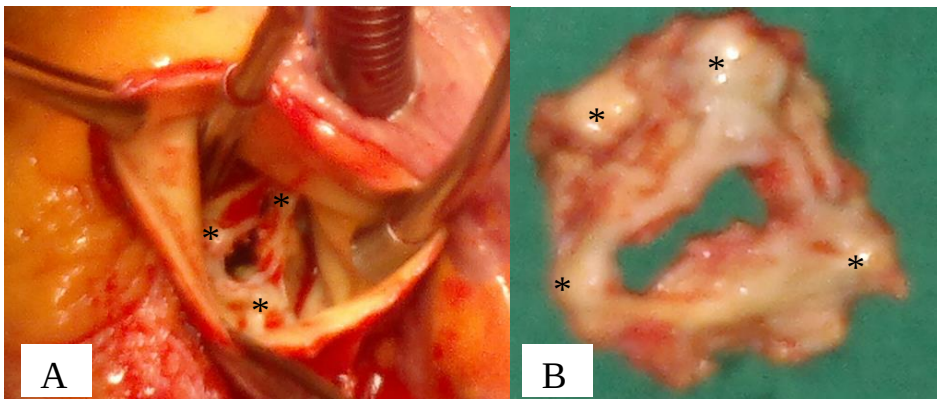


Fig. 2. A: stenotic aortic valve exposed after transection of the ascending aorta. Note the fusion of the commissures (*). B: aortic leaflet after surgical excision. Note the severe spherical calcifications (*). (Photographic files of the author).

The decrease of the aortic valve orifice area results in progressively greater left ventricular pressure overload and left ventricular hypertrophy[7]. Pressure overload itself increases left ventricular afterload, impairing ejection performance. Afterload is generally quantified as wall stress (σ) which is governed by the law of Laplace, in which $\sigma = pr/2t$, where "p" is left ventricular pressure, "r" is left ventricular radius, and "t" is left ventricular thickness. As pressure grows in the numerator of this equation it is offset by a rise in wall thickness (concentric left ventricular hypertrophy) in the denominator, keeping afterload (wall stress) normal (fig 3).

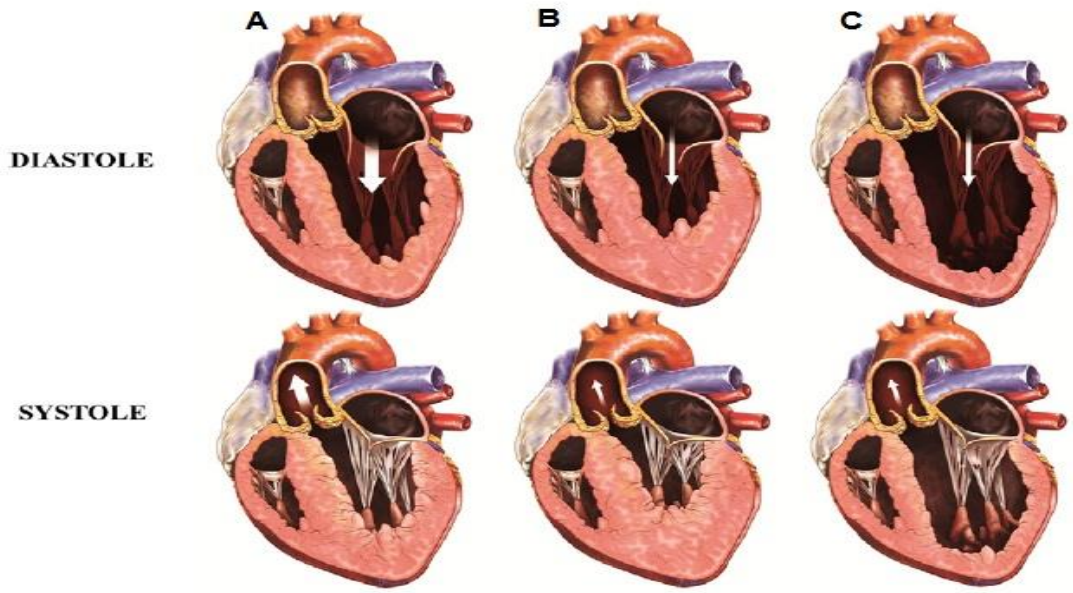


Fig 3. (A) Eighty percent of the patients with severe aortic stenosis (AS) presents with left ventricle hypertrophy with normal ejection fraction and normal left ventricular (LV) volume. (B) Ten percent of patients with AS presents with severe hypertrophic LV remodeling with reduced LV volume. (C) Another 10% of patients with AS, shows LV dilatation with decreased ejection fraction. From Urso et al. Asymptomatic severe aortic stenosis: a reopened debate. Med Clin (Barc), 2014 May 6;142(9):406-11.

Since afterload is a key determinant of ejection performance, its normalisation is important in maintaining normal ejection fraction and stroke volume[8]. Left ventricular hypertrophy has two hemodynamic consequences. First, it has been shown to decrease ventricular contractility and ejection performance[9]. Second, it leads to an abnormal coronary flow pattern and a decrease in coronary blood flow reserve leading to a state of relative myocardial ischemia[10]. The most frequent causes of aortic regurgitation are rheumatic disease, anuloaortic ectasia and endocarditis. In all these conditions, independently from the morphologic lesion, the competence of the aortic valve is affected. Patients with aortic regurgitation have combined volume and pressure overload of the left ventricle. Compensatory mechanisms are recruitment of preload reserve and LV hypertrophy[11].

The European Society of Cardiology/European Association of Cardiothoracic Surgery (ESC/EACTS) guidelines[12] recommend aortic valve surgery in patients with severe aortic valve stenosis in presence of symptoms (dyspnoea, angina and syncope) or left ventricle dysfunction (left ventricle ejection fraction [LVEF] <50%). Similarly, in patients with severe aortic regurgitation surgery is indicated in presence of symptoms (dyspnoea), or LV dysfunction (LVEF <50%) or LV dilatation (left ventricular end-diastolic diameter > 70 mm).

2.2 Aortic valve replacement and aortic valve prosthesis

The conventional surgical treatment of the aortic valve disease is aortic valve replacement (AVR), which produces LV hypertrophy regression[13] by eliminating the pressure/volume overload. AVR is carried out on cardiopulmonary bypass and with arrested heart. Standard surgical accesses to the aortic valve are represented by sternotomy, ministernotomy, and right minithoracotomy with support of videoscopy. The standard procedure consists in excision of the valve leaflets, decalcification of the aortic annulus and implantation of a biological valve prosthesis or a mechanical valve prosthesis.

The choice of the appropriate prosthetic valve has to take in consideration two factors. The first one is the evaluation of the span life of the prosthesis. Bioprostheses can be divided, according to their design, in stented (with metallic or polymer supporting stent) and stentless and, according to their components, in porcine (made of 3 porcine aortic valve leaflets crosslinked with glutaraldehyde) and pericardial (made from sheets of bovine pericardium mounted inside or outside a supporting stent)[14]. All bioprostheses, differently from the mechanical prostheses, undergo a process of structural valve deterioration, which represents the main determinant of their longevity. Indeed, the current guidelines by the European Association Cardiothoracic Surgery/ European Society of Cardiology suggest implanting aortic bioprosthesis in patients >65 years (class IIa), whose lifespan is supposed to be lower than the durability of the current bioprosthesis.

The second factor to take in consideration in choosing the prosthetic valve is the anticoagulation treatment which is mandatory in patients receiving mechanical prostheses. These have been evolving from the first generation of caged ball prostheses

trough the second monoleaflet generation to the third bileaflet generation (fig. 4). Still, because of their high thrombogenicity, they require lifelong anticoagulation.

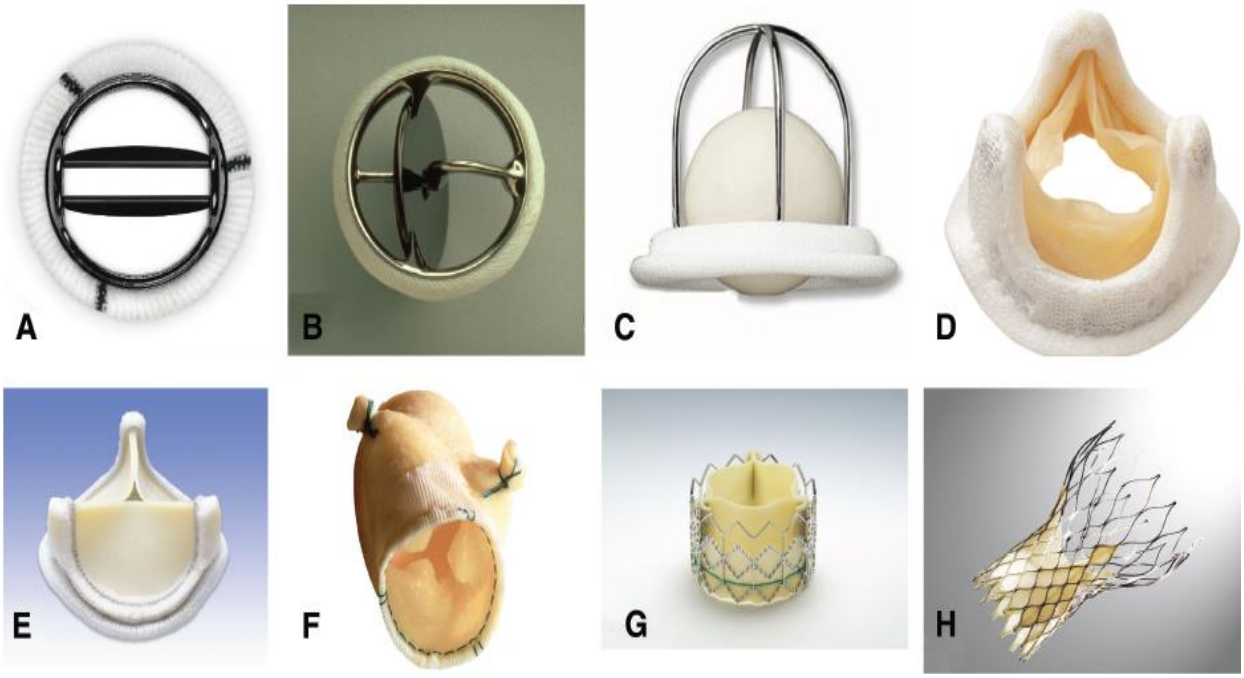


Fig.4 Different types of prosthetic valves. A, Bileaflet mechanical valve (St Jude); B, monoleaflet mechanical valve (Medtronic Hall); C, caged ball valve (Starr-Edwards); D, stented porcine bioprosthesis (Medtronic Mosaic); E, stented pericardial bioprosthesis (Carpentier-Edwards Magna); F, stentless porcine bioprosthesis (Medtronic Freestyle); G, percutaneous bioprosthesis expanded over a balloon (Edwards Sapien); H, self-expandable percutaneous bioprosthesis (CoreValve). From Pibarot P and Dumesnil JG Circulation. 2009 Feb 24;119(7):1034-48.

Recent data have shown that a growing proportion of patients undergoing AVR are represented by elderly patients[15], who are considered to be high risk patients. Nonetheless, the surgical risk of AVR has been reported to be decreasing. This phenomenon is the so-called paradoxical risk (the number of patients with high operative risk increases, but the overall surgical risk, in fact, decreases, thanks to the improvement of surgical, anesthesiologist and intensive care procedures).[16] This fact has been documented by the developers of the euroSCORE, a tool used to predict early mortality in patients undergoing cardiac surgery [17]. Recently the data of the Society for Cardiothoracic Surgery in Great Britain and Ireland National database, storing 41.227 patients underwent AVR, have been published[18]. This database reports hospital mortality of 4.1% for the whole population and of 8.1% of for the patients > 80 years old. Octogenarian patients are the subject of a recent meta-analysis[19] studying 13.261 elderly patients who underwent AVR. This study reports a 30 days mortality of 6.7%.

A relatively new therapeutic option for high risk patients with aortic stenosis is the transcatheter aortic valve implantation (TAVI). The TAVI is a percutaneous procedure, introduced in 2002[20], which allows implantation of aortic biological stentless prosthesis. This technique is currently reserved for those patients whose high risk profile discourages the use of extracorporeal circulation, required by the standard AVR surgery. TAVI needs to be performed in a hybrid operative suite by a dedicated multidisciplinary team, it is carried out under general anesthesia and it does not require extracorporeal circulation. TAVI can be performed by two approaches: retrograde and anterograde. The first one consists in the insertion of the delivery catheter through the common femoral artery. The catheter is progressed, under fluoroscopic and echocardiographic guide, to the aortic annulus, the aortic valve is ballooned, and the prosthesis is delivered. In the anterograde approach, the delivery catheter is inserted

though the LV apex, exposed by a small left anterior mini-thoracotomy. As percutaneous TAVI valves (Fig 4.H) have not stent, their hemodynamic performance and their durability are considered to be comparable with those of conventional stentless bioprostehsis. TAVI is currently reserved to patients with a predicted mortality, according to the euroSCORE, above 20%. A recent meta-analysis reporting on 3.519 patients undergoing TAVI shows a 30-day mortality of 7.8%.

2.3 The problem of the patient prosthesis mismatch

According to the original definition published by Rahimtoola in 1978 [21], "mismatch can be considered to be present when the effective prosthetic valve area, after insertion into the patient, is less than that of a normal human valve." This first subjective interpretation of mismatch was then replaced by using objective parameters able to detect how small has to be a prosthetic valve area to produce mismatch. There are two parameters used for the calculation of the prosthetic valve area: the effective orifice area (EOA) and the geometric orifice area (GOA). The EOA is the echocardiographic estimation of the flow area passing through the circular opening of the prosthesis itself. The GOA represents the inner area of the prosthesis, assumed to be circular and computed by the internal diameter of the prosthesis measured with a calliper. Dividing the EOA and the GOA for the body surface area, we obtain the indexed EOA (IEOA) and the indexed GOA (IGOA), which are currently used as reference parameters in mismatch analysis.

Pibarot[22], recently, has divided mismatch into 2 entities: severe mismatch defined by the presence of an indexed effective orifice area (IEOA) ≤ 0.65 cm^2/m^2 and moderate mismatch with IEOA value >0.65 and ≤ 0.85 cm^2/m^2. Severe patient-prosthesis mismatch (PPM) is a rare condition that has been reported to be an independent risk factor for overall 30-day mortality after aortic valve replacement (AVR)[23]. On the contrary, the question of whether the presence of moderate PPM does have an impact on post-operative survival is still open. In fact, since the introduction of its theoretical basis, the patient-prosthesis mismatch following aortic valve replacement has been the subject of a long debate. On one hand the persistence of post-operative trans-prosthesis gradients and the consequent delay of the left ventricular hypertrophy regression are

well documented in patients with mismatch[24]; on the other hand, its negative clinical impact is not widely recognized. The simultaneous publication of two retrospective studies [25] [26] reporting opposite conclusions about the impact of mismatch on mortality gives testimony of this controversy. Contradictory outcomes regarding this issue could be due to the lack of methodological standardization in studies about patient-prosthesis mismatch. A crucial point is the selection of the values for the EOA of the prosthetic valves. It has been suggested by Rahimtoola[27] that EOA values should be calculated from echocardiographic studies at 6 months in each patient undergoing aortic valve replacement. Many authors prefer not to use the EOA obtained by an early post-operative echocardiography (fig. 5). In fact, the EOA is a physiological parameter that may vary with flow rate, cardiac output and ventricular function, which could jeopardise its assessment in the immediate postoperative period. For these reason, most of the studies analysing the mismatch use the EOA values derived from the literature. These values are obtained from echocardiographic studies carried out after the first semester in a sample of patients who underwent AVR. Thus, in the literature it is possible to find the mean EOA of any prosthesis and of any size (table 1). Also, the use of literature-derived mean effective orifice area values has been reported to have the highest sensitivity in predicting mismatch[28]. At the same time, the GOA data have low prediction sensitivity because of their tendency to overestimate the EOA.

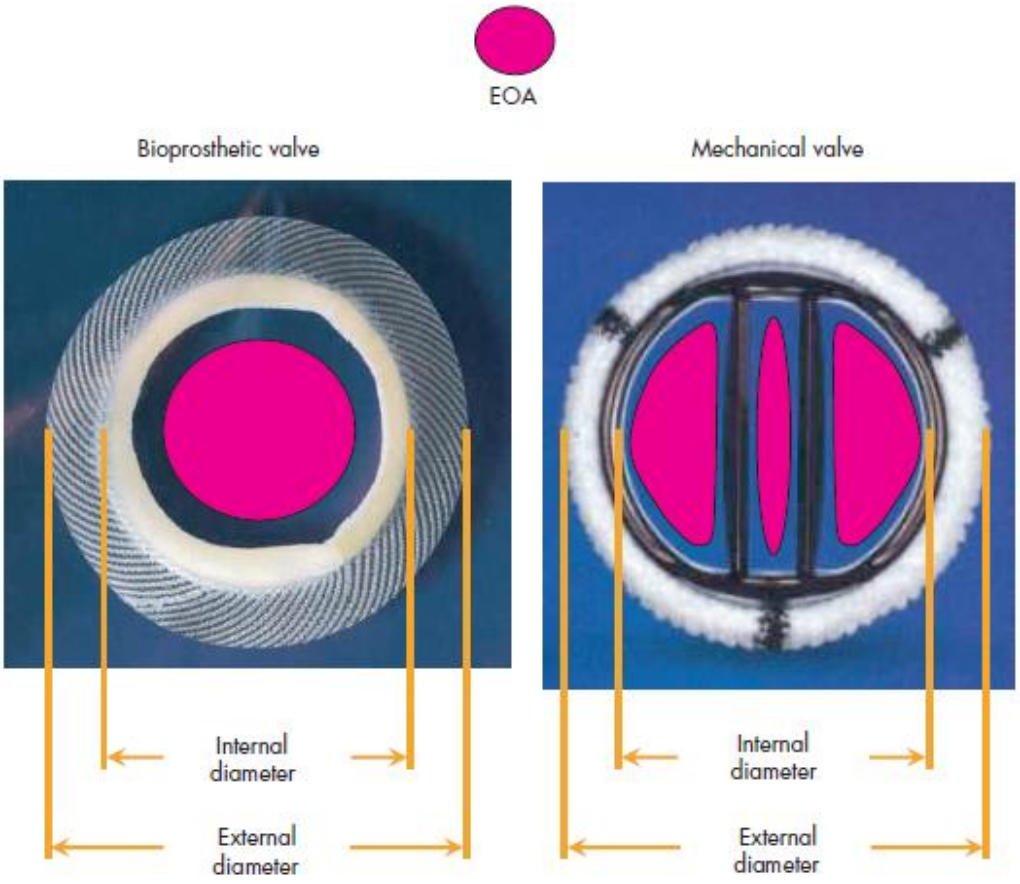


Fig 5.The effective orifice area (EOA) of a bioprosthesis represents the flow area passing through the circular opening of the prosthesis itself. In an open position bileaflet mechanical prostheses show three elliptic flow areas. The sum of them represents the EOA of the mechanical prosthesis. From Pibarot P, Dumesnil JG. Heart. 2006;92; 1022-9.

Prosthetic Valve Size, mm	19	21	23	25	27	29
Stented aortic bioprostheses						
Mosaic, mean (SD)	1.1 (0.2)	1.2 (0.3)	1.4 (0.3)	1.7 (0.4)	1.8 (0.4)	2.0 (0.4)
Hancock II, mean (SD)	–	1.2 (0.1)	1.3 (0.2)	1.5 (0.2)	1.6 (0.2)	1.6 (0.2)
Carpentier-Edwards Perimount, mean (SD)	1.1 (0.3)	1.3 (0.4)	1.50 (0.4)	1.80 (0.4)	2.1 (0.4)	2.2 (0.4)
Carpentier-Edwards Magna, mean (SD)	1.3 (0.3)	1.7 (0.3)	2.1 (0.4)	2.3 (0.5)	–	–
Biocor (Epic), mean (SD)	–	1.3 (0.3)	1.6 (0.3)	1.8 (0.4)	–	–
Mitroflow, mean (SD)	1.1 (0.1)	1.3 (0.1)	1.5 (0.2)	1.8 (0.2)	–	–
Stentless aortic bioprostheses						
Medtronic Freestyle, mean (SD)	1.2 (0.2)	1.4 (0.2)	1.5 (0.3)	2.0 (0.4)	2.3 (0.5)	–
St. Jude Medical Toronto SPV, mean (SD)	–	1.3 (0.3)	1.5 (0.5)	1.7 (0.8)	2.1 (0.7)	2.7 (1.0)
Mechanical aortic prostheses						
Medtronic-Hall, mean (SD)	1.2 (0.2)	1.3 (0.2)	–	–	–	–
Medtronic Advantage, mean (SD)	–	1.7 (0.2)	2.2 (0.3)	2.8 (0.6)	3.3 (0.7)	3.9 (0.7)
St. Jude Medical Standard, mean (SD)	1.0 (0.2)	1.4 (0.2)	1.5 (0.5)	2.1 (0.4)	2.7 (0.6)	3.2 (0.3)
St. Jude Medical Regent, mean (SD)	1.6 (0.4)	2.0 (0.7)	2.2 (0.9)	2.5 (0.9)	3.6 (1.3)	4.4 (0.6)
MCRI On-X, mean (SD)	1.5 (0.2)	1.7 (0.4)	2.0 (0.6)	2.4 (0.8)	3.2 (0.6)	3.2 (0.6)
Carbomedics Standard, mean (SD)	1.0 (0.4)	1.5 (0.3)	1.7 (0.3)	2.0 (0.4)	2.5 (0.4)	2.6 (0.4)

Tab 1. Effective orifice area values published by Pibarot and Dumesnil. Rev Esp Cardiol, 2010;63(4):387-9

The residual transvalvular pressure gradient (PG) is the most commonly used indicator to assess the residual obstruction of the prosthesis and is exponentially correlated with the IEOA. The IEOA can be decreased within a wide range without significantly changing the PG until reaching a value of 0.85 cm^2/m^2, when a steep increase in PG occurs[29]. On the basis of this hemodynamic principle, it is widely accepted that PPM (IEOA $\leq$0.85 cm^2/m^2) should be avoided. Pibarot and Dumesnil [30] proposed a 3-step algorithm for its prevention, as follows: a) calculate the patient's body surface area (BSA); b) determine the minimal valve EOA required to ensure an IEOA >0.85, >0.80, or >0.75 cm^2/m^2, given the patient's BSA as calculated in step 1; and c) select the type and size of prosthesis that has reference values for EOA greater than or equal to the minimal EOA value obtained in step 2.

Anyway there is not a unique definition of mismatch. Alternative in-vivo EOA cut-off values for definition of PPM are 0.90[31], 0.80[32], and 0.75 cm^2/m^2 [33]. The new European guidelines of heart valve disease[34], published in 2012, confirm the cut-off value of severe mismatch proposed by Pibarot as they state that "if the valve prosthesis– patient ratio is expected to be less than 0.65 cm^2/m^2, enlargement of the annulus to allow placement of a larger prosthesis may be considered".

Thus, in those patients with a large BSA and relatively small aortic annulus requiring AVR, the native annulus may not fit the size of the prosthesis required and so the surgeon faces the problem of whether to perform an annular enlargement procedure or to possibly compromise the surgical result by accepting PPM. A number of annular enlargement procedures have been described: the Nicks procedure[35], the Manouguian technique [36] and the Konno procedure[37]. These techniques allow for the implantation of prosthetic valves 1 or 2 sizes larger than the original size of the aortic annulus[38]. Although these procedures have been frequently performed with good results, some authors have reported increased operative mortality[39].

It is clear that when performing these types of procedures, there is an increase in cross-clamp time[40]. This variable has been suggested to be associated with increased mortality following AVR, particularly in the elderly[41]. The use of a stentless bioprosthesis has been proposed as an alternative to annulus enlargement when facing the possibility of PPM. This type of prosthesis has been said to have an excellent hemodynamic profile, and resembles native aortic valve function when assessed by transthoracic echocardiography (TTE) postoperatively[42]. Nevertheless, according to a recent meta-analysis, the clinical significance of this hemodynamic advantage is not very clear[43]. Thus, it seems that neither annular enlargement nor stentless prostheses are a perfect solution to the problem of PPM.

2.4 Mismatch as risk factor for post-operative survival: a review of the literature

As mismatch has been reported to increase mortality after aortic valve replacement, we carried out a literature search to identify the evidence supporting this hypothesis**.**

2.4.1 Search methodology

We searched Medline, Embase and Cochrane Library for publications containing the words: aorta (OR aortic OR AVR OR aortic valve replacement) AND mismatch (OR mismatched OR mismatching OR patient-prosthesis mismatch OR PPM) AND mortality, updated to August 2013. Inclusion criteria were: studies analyzing the impact on mortality of PPM in adult patients (≥18 years) undergoing AVR. The denomination of mismatch had to be based on IEOA, IGOA or Z value. We included data from only the last publication of centers that had produced sequential reports.

2.4.2 Search outcomes

A total of 389 papers were identified using the reported search of which 22 represented the best evidence according to the *Best Evidence Topics methodology (BETs)*[44].

The BETs are generated as a result of clinical questions, which in this case was: is PPM an independent risk factor for mortality after aortic valve replacement?

The BETs are developed through a review of Medline, Embase and Cochrane Library by a structured search strategy. The objective of the Best bets is to review the best available evidence by a "fast track" procedure. They are published regularly in

peer-reviewed journals (Emergency Medicine Journal, Archives of Disease in Childhood, Interactive Journal Cardiovascular and Thoracic Surgery).

The following studies are the best evidence according to the *Best Evidence Topics methodology.*

Bridges et al.[45] analyzed 42,310 patients, to our knowledge the largest sample population. Prosthesis with small GOA or EOA were reported to be associated with increased early operative mortality, but among patients receiving the same model and size prosthesis, elevations in BSA were associated with a decrease rather than an increase in operative mortality. The authors concluded that in AVR, priority should be given to prosthesis durability, surgeon experience, technical ease and speed of implantation. Once these factors have been considered, they have accepted it may be reasonable to give preference to higher projected in vivo EOA or GOA prosthesis. Blackstone et al.[46] reported that an indexed GOA $\leq$1.2 cm^2/m^2 increased 30-day mortality by 1–2%. However, the study was unable to identify mismatch as a predictor of late survival. It was speculated that the multifactorial nature of the reduced survival after AVR could have masked mismatch impact on long-term mortality.

Blais et al.[47] who, unlike the previous author, used IEOA instead of IGOA values, showed that both severe and moderate mismatch were independent predictors of short-term mortality. Also, the impact of PPM on survival was maximum when it was severe and in patients with left ventricle dysfunction.

Ruel et al.[48] confirmed the importance of left ventricle dysfunction in patients with moderate mismatch, showing clearly that this subgroup of patients had a higher late mortality than patients with PPM and normal ejection fraction.

Kohsaka et al.[49] and Tasca et al.[50] analyzed patients with pure aortic valve stenosis reporting a higher late-term mortality of patients with moderate mismatch. Equally, Walther et al.[51] were able to show that moderate mismatch was a predictor of adverse outcome after AVR.

Florath et al.[52] and Mohty et al.[53] showed independently that severe PPM, but not moderate PPM, was an independent risk factor for late mortality. Yap et al.[54] confirmed that severe PPM was independently associated with higher early mortality.

On the other hand, Mascherbauer et al.[55], Fuster et al.[56], Nozohoor et al.[57], Moon et al.[58], Flameng et al.[59], Frapier et al.[60], Bové et al.[61] and Rao et al.[62], did not analyze separately the conditions of severe and moderate PPM. None of these studies was able to show that PPM was an independent predictor of either early or late survival after AVR. Monin et al.[63] came to the same conclusions analyzing a sample population with low-gradient aortic stenosis. Milano et al.[64] analyzed a sample population receiving 19- or 21-mm mechanical prostheses. According to this study, IEOA was not an independent predictor of early or late mortality, but it was a predictor of cardiac events. A lack of impact of PPM on late survival was also reported by Medallion et al.[65], who used a multivariable hazard function to study risk factors for overall mortality after AVR.

According to the study of Howell et al.[66], and in contrast to the above mentioned study which focused on severe PPM, an IEOA <0.60 cm^2/m^2 did not affect either in-hospital mortality or late mortality. This finding could be explained by the fact that, as opposed to all other articles based on IEOA, this study used the in vitro EOA values and not the in vivo EOA values. In vitro EOA values have been shown to have a very low sensitivity to detect PPM [67] .

Table 1. Studies on mismatch selected according to *Best Evidence Topics methodology*.

Author, date and country, Study type (level of Evidence)	**Patient group**	**PPM prevalence**		**PPM as risk factor for mortality**	
		Moderate	**Severe**	**Early**	**Late**
Florath, 2008 Germany Prospective cohort study [52]	533 patients undergoing AVR. Mean age: 71.1 ± 9 years. Exclusion criteria: not specified.	52%	28%	Not evaluated	Severe PPM: Yes (HR: 1.9; 95% CI :1.08-3.21) Moderate PPM: No
		Moderate and severe PPM were studied separately. Severe mismatch but not moderate mismatch, was an independent predictor of late mortality after adjustment for age, left ventricular ejection fraction, atrial fibrillation, NYHA class, serum creatinine, and hemoglobin level. Mean follow-up time: 4.7 ± 2.2 years. EOA was studied by echocardiography.			
Kohsaka, 2008 U.S.A. Prospective cohort study [49]	469 patients undergoing mechanical AVR for aortic stenosis. Mean age: 56.1±11.5 years. Exclusion criteria: endocarditis, concomitant procedures other than CABG.	39%	4%	Not evaluated	Yes (HR: 1.6; 95% CI :1.4-2.3)
		Moderate and severe PPM were grouped together. Predictors of mismatch included small aortic valve sizes (19 and 21 mm) ($p<0.01$), obesity ($p<0.01$), and age > 65 years ($p<0.01$). Mismatch was a significant predictor of poorer survival, even after adjustment for all significant clinical predictors of late mortality. Median follow-up time: 7.9 years (interquartile range: 5.0–10.0 years). EOA was derived from published reference values.			
Mascherbauer, 2008 Austria Retrospective cohort study [55]	361 patients undergoing AVR for aortic stenosis. Mean age: 69.4±9.3 years. Exclusion criteria: aortic regurgitation.	51.3%	3%	No	No
		Moderate and severe PPM were grouped together. Patients with PPM were older ($p<0.0001$), more often female ($p<0.0001$) more symptomatic ($p=0.001$), more often suffered from coronary artery disease, ($p=0.04$), triple vessel disease ($p=0.03$) and hypertension ($p=0.01$) and presented with a higher euroSCORE ($p<0.0001$). Mismatch was not an independent predictor of early or late survival. Median follow-up time: 4.1 ±2 years. EOA was derived from published values			
Bridges, 2007 U.S.A Retrospective cohort study [44]	42,310 patients undergoing isolated AVR. Mean age: 66.6 ±10.1 years. Exclusion criteria: double valve replacement, concomitant surgical	Not evaluated	Not evaluated	Yes	Not evaluated
		PPM was studied mainly as a continuous variable. Prostheses with small GOA or EOA area are associated with increased operative mortality. But among patients receiving the same manufacturer's model and labeled size, increasing degrees of mismatch defined by decreasing the ratio of EOA/BSA or GOA/BSA are generally associated with better outcomes. For a patient with BSA = 2.0 m^2, a decrease in EOA from 2.00 cm^2 to 1.50 cm^2 is associated with			

Author, date and country, Study type (level of Evidence)	Patient group	PPM prevalence		PPM as risk factor for mortality	
		Moderate	Severe	Early	Late
	procedures other than CABG, stentless valves implantation, active endocarditis	increased mortality (OR: 1.35; 95% CI: 1.21-1.52). F-U time: within 30 days from surgery. EOA derived from published values.			
Fuster, 2007 Spain Retrospective cohort study [56]	743 patients undergoing AVR for predominant aortic valve stenosis. Mean age: 66.5±9.6 years. Exclusion criteria: previous AVR, emergent surgery, endocarditis, any concomitant procedure.	23.8%	3.9 %	No	No
		Moderate and severe PPM were grouped together. Mismatch increased early mortality only in the subgroup with high left ventricle mass index ($p<0.05$) and not the whole population. With regard to the late survival PPM was not an independent predictor of overall mortality, but it was an independent predictor of cardiac mortality (OR: 3.38, 95% CI: 1.37–8.31; $p<0.01$). Mean follow-up time: 6.9±2.4 years. EOA was derived from published reference values			
Yap, 2007 Australia Retrospective cohort study [54]	701 patients undergoing AVR. Mean age: 70.7±10.3 years. Exclusion criteria: not specified	Not evaluated	6.6%	Yes (OR: 6.07; 95% CI:1.66-22.16	Not evaluated
		Study focused on severe PPM. Severe PPM was independently associated with higher early mortality. Severe mismatch was not associated with stroke, prolonged ventilation, new renal failure, prolonged post-operative stay, prolonged ICU stay or readmission within 30 days. Follow-up time: within 30 days of surgery. EOA was derived from published reference values.			
Nozohoor, 2007 Sweden Retrospective cohort study [57]	1568 patients undergoing AVR. Mean age: 73.5 years Exclusion criteria: double valve replacement, concomitant surgical procedures other than CABG, stentless valves implantation, active endocarditis	49.5%	3.8%	No	No
		Moderate and severe PPM were grouped together. According to multivariable analysis, PPM was not a predictor of early or late overall mortality. Mismatch was associated with an increased risk of postoperative neurological events (OR 2.26, 95% CI 1.05-4.83, p = 0.037). Mean follow-up time: 4.3± 3.1 years. EOA was derived from published reference values.			

Author, date and country, Study type (level of Evidence)	Patient group	PPM prevalence		PPM as risk factor for mortality	
		Moderate	Severe	Early	Late
Monin, 2007 France Prospective cohort study [63]	139 patients with severe symptomatic aortic stenosis, mean transaortic pressure gradient <40 mm Hg, left ventricle ejection fraction ≤0.40% or cardiac index <3.0 L/min/m². Exclusion criteria: severe extra cardiac comorbidities, more than mild aortic or mitral regurgitation, atrial fibrillation.	5%	51.7%	No	No
		Moderate and severe PPM were grouped together. Neither label valve size, EOA or indexed EOA as continuous variables nor moderate–severe PPM as dichotomous variable were predictive of early or late all-cause mortality. Median follow-up time: 3.6 years (interquartile range: 2-5.6 years). Median age: 72. EO derived from published values			
Moon, 2006 USA Retrospective cohort study [58]	1,400 patients undergoing AVR Mean age: 67 ± 14 years. Exclusion criteria: homograft and autograft implantation. EOA was derived from published reference values.	37.7%	Not evaluated	No	No
		Study focused on moderate PPM. Mismatch was not an independent risk factor for early mortality or late mortality for the whole population. Mismatch was associated with impaired late survival in the following subgroups: patients <60 years old ($p < 0.005$), patients with a BSA 1.7 to 2.1 m² receiving bioprosthetic ($p < 0.05$) and mechanical ($p<0.005$) valves and patients with a BSA >2.1 m² receiving a mechanical prosthesis ($p<0.04$). Mean follow up time: 3.7± 3.1 years.			
Ruel , 2006 U.S.A Prospective cohort study [48]	805 patients undergoing AVR. Mean age: 63.9±12.4 years. Exclusion criteria: concomitant mitral valve surgery. EOA was derived from published reference values.	40.3%	Not evaluated	Not evaluated	No
		Study focused on moderate PPM. Mismatch was associated with impaired late survival only in the subgroup of patients with left ventricle ejection fraction < 50% (HR: 2.8 (95% CI, 1.1-8.0; p =0 .03). Mean follow-up time: 5.5 ± 3.5 years.			

Author, date and country, Study type (level of Evidence)	Patient group	PPM prevalence		PPM as risk factor for mortality	
		Moderate	Severe	Early	Late
Flameng, 2006 Belgium Retrospective cohort study [59]	506 patients undergoing single AVR and receiving a CE Perimount bioprosthesis. Mean age: 73.3 (range 57-87 years) Exclusion criteria: not specified	20.1%	0.2%	No	No
		Moderate and severe PPM were grouped together. According to multivariable analysis moderate mismatch was not an independent predictor of early mortality or late mortality. Mean follow-up time: 6.1±4.8 years. EOA values were derived from projection of EOA measured by echocardiography in 122 patients.			
Mohty, 2006 U.S.A Prospective cohort study [53]	388 patients receiving a 19- or 21-mm standard or Hemodynamic Plus (HP) SJM bileaflet mechanical prosthesis. Mean age: 62.0± 13 years Exclusion criteria: peri-operative death, or if a postoperative echocardiogram was not performed at the Author's Institution within 1 year after AVR.	43.3%	17.0%	Not evaluated	Severe PPM: Yes (HR: 2.18; 95% CI: 1.24-3.85) Moderate PPM: No
		Moderate and severe PPM were studied separately. According to multivariable analysis severe mismatch, but not moderate mismatch, was an independent predictor of late overall mortality. Mean follow-up time: 5.3±3.3 years. EOA assessed by transthoracic echocardiographic study performed at Author's institution.			
Tasca, 2006 Italy Prospective cohort study [50]	315 patients with pure aortic stenosis. Mean age: 70.8±9.5 years Exclusion criteria: not specified.	42.0%	5.0%	Not evaluated	Yes (HR: 4.2; 95% CI: 1.6-11.3)
		Moderate and severe PPM were grouped together. According to multivariable analysis mismatch was an independent predictor of overall late mortality and of cardiac events: cardiac death, sudden death, heart failure, syncope/lipothymia, angina (HR: 3.2; 95% CI: 1.5-6.8). Mean follow-up time: 3.7±1.7 years. EOA was derived from published reference except from Mitroflow. For this prosthesis, the EOA values were obtained by echocardiography an then they were projected to patients receiving it.			
Bové, 2006 Belgium. Retrospective cohort study [61]	255 patients undergoing AVR receiving bioprosthesis. Mean age: 75.8±6.7 years	27.9%	1.2%	No	No
		Moderate and severe PPM were grouped together. Mismatch was a predictor of late overall mortality according to bivariable analysis, but not according to multivariable analysis. Mean follow-up time: 4.3 years (range 1-11.3 years). EOA was derived from published			

Author, date and country, Study type (level of Evidence)	Patient group	PPM prevalence		PPM as risk factor for mortality	
		Moderate	Severe	Early	Late
	Exclusion criteria: pure aortic regurgitation, endocarditis.	reference values.			
Walther, 2006 Germany Prospective cohort study [55]	4,131 patients undergoing AVR. Mean age: 66.2±9.2 years Exclusion criteria: implant of stentless aortic prosthesis. EOA was derived from published reference values.	26.7%	2.3%	Yes (Odds Ratio no provided)	Yes (OR: 1.37; 95% CI 1.1 - 1.8)
		Moderate and severe PPM were grouped together. According to multivariable analysis mismatch was a predictor of adverse outcome after AVR, together with age > 70 years ($p = 0.002$), emergency indication ($p < 0.001$), EuroSCORE > 10 ($p < 0.001$), and requirement for additional procedures ($p < 0.001$). Mean follow-up: 5.2 ± 3.5 years.			
Howell, 2006 UK Prospective cohort study [66]	1,418 patients undergoing AVR. Mean age: 65.5 ±12.6 Exclusion criteria: procedures other than CABG, pre-existing valve prosthesis other than aortic valve, active endocarditis.	Not evaluated	10.6%	No	No
		Study focused on severe PPM. PPM did not affect in-hospital mortality neither in the whole sample nor in the subgroup with ejection fraction < 30%. Also PPM did not affect late survival neither in the whole sample population nor in the subgroup with pure aortic stenosis. Median follow-up time: 3 years (interquartile range 1.5—3.7 years). EOA was derived from manufacturers' in vitro data; GOA was calculated from the manufacturers'geometric internal valve orifice diameter.			
Blackstone, 2003 U.S.A Prospective cohort study [46]	13,258 undergoing AVR Mean age: 64.6 ±11.8. Exclusion criteria: preexisting valve prosthesis in a location other than aortic, endocarditis, emergency, concomitant procedures other than CABG.	Not evaluated	Not evaluated	Yes	No
		PPM was studied as a continuous variable. An IGOA values <1.2 cm^2/m^2 was an independent predictor of early mortality. IGOA < 1.2 cm^2/m^2 or standardized orifice size <-2.5 was associated with a 1% to 2% increase in 30-day mortality- After adjustment or balancing score an IGOA values < 1.1 cm^2/m^2 was not an independent predictor of intermediate-term or long-term survival. Mean follow-up: mean 5.3 ± 4.7 years. GOA was calculated from the manufacturers' geometric internal valve orifice diameter.			

Author, date and country, Study type (level of Evidence)	Patient group	PPM prevalence		PPM as risk factor for mortality	
		Moderate	Severe	Early	Late
Blais, 2003 Canada Prospective cohort study [51]	1,266 patients undergoing AVR. Mean age 69.7±8.5 years Exclusion criteria: no specified	36%	2%	Yes	Not evaluated
		Moderate and severe PPM were studied separately. In multivariable analysis severe and moderate mismatch were independent predictors of early mortality: moderate PPM HR 2.0; 95% CI: 1.1 – 3; severe PPM HR 12.6 95% CI: 4.3 - 37.0. For every category of PPM, the risk of mortality was greater in patients with a preoperative left ventricular ejection fraction <40%. Follow-up time: within 30 days after operation. EOA was derived from published reference values.			
Milano, 2002 Italy Retrospective cohort study [64]	229 patients undergoing AVR (with or without CABG) for aortic stenosis with 19 or 21 mm Jude Medical standard prosthesis. Mean age 63.7 ±12.5 Exclusion criteria: More than mild aortic regurgitation, concomitant mitral or tricuspid valve operations.	73.2%	8.1%	No	No
		IEOA studied as continuous and dichotomic variable. According to multivariable analysis IEOA was not an independent predictor of early mortality, late mortality, valve related complications, and valve related death. But IEOA at discharge was an independent predictor (p = 0.007) of cardiac events (new episodes of angina, myocardial infarction, congestive heart failure, and ventricular arrhythmia requiring hospitalization or leading to death). Mean follow-up time: 8 ± 5 years. EOA values were obtained by echocardiography.			
Frapier, 2002 France Retrospective cohort study [60]	90 patients undergoing AVR with Medtronic Intact valve. Mean age 72.6 ± 7.9 years Exclusion criteria: not specified.	71.1%	Not evaluated	Not evaluated	No
		Study focused on moderate PPM. According to multivariable analysis mismatch was not an independent predictor of late overall mortality or cardiac mortality. Mean follow-up time: 6.6 years. EOA derived from published values.			
Rao, 2000 Canada Retrospective cohort study [62]	2,154 patients undergoing isolated AVR with or without concomitant CABG Mean age 66.1 ± 1.9 years Exclusion criteria: not specified.	Not evaluated	10.5%	No	No
		Study focused on moderate PPM. According to multivariable analysis mismatch was not an independent predictor of early or late overall mortality. But prosthesis mismatch was an independent predictor of valve-related mortality (RR 1.46, 95% CI 0.95 to 2.24). Mean follow-up time: 6.2 ±4.1 years. EOA were obtained from the manufacturer's specifications			

Author, date and country, Study type (level of Evidence)	**Patient group**	**PPM prevalence**		**PPM as risk factor for mortality**	
		Moderate	**Severe**	**Early**	**Late**
Medallion, 2000 USA Retrospective cohort study [65]	892 patients undergoing AVR for aortic stenosis (with or without regurgitation) Mean age:64.1±12.1 Exclusion criteria: no concomitant procedures, such as CABG, previous cardiac surgery. GOA were obtained from the manufacturer's specifications	Not evaluated	Not evaluated	Not evaluated	No
		PPM was studied as a continue variable. There were too few in-hospital deaths to allow a meaningful examination of early risk factors. According to the hazard function no valve type or expression of valve size were identified as a risk factors for overall mortality in the constant or late phases after AVR. Mean follow-up time: 5.0 ± 3.9 years.			

Table1. **AVR**: Aortic valve replacement. **IEOA**: indexed effective orifice area; **IGOA**: indexed geometric orifice area; **PPM**: patient-prosthesis mismatch

2.5 Mismatch as risk factor for structural valve deterioration

One of the more active groups in mismatch analysis is the Leuven University which published the first report in 2006[53] analysing 506 patients undergoing AVR with a bioprosthesis. As above mentioned, in this initial study Flameng failed to show that PPM has an impact on post-operative survival. In 2010 the same group published a new report[68], analysing a sample population of 564 patients undergoing AVR with a bioprosthesis. This study reported, for the first time in the literature, that PPM increases independently the risk of structural valve deterioration (SVD) of biological aortic prosthesis. These data were confirmed by a third report published by the same group in 2013[69].

The SVD is the expression of intrinsic changes of a biological prosthesis, being the more frequent leaflet calcifications and leaflets tears. These intrinsic changes, producing potentially prosthesis stenosis or regurgitation, are the main determinant of the longevity of the bioprosthesis. A meta-analysis comprising 5,837 patients with porcine bioprostheses in aortic position published in 2001[70] showed the SVD begins at 8 years from AVR. According to the current literature, the age of the patient at the time of AVR is the most important determinant of SVD, being this event more frequent in patients who underwent surgery < 65 years old[71].

Patients with chronic renal failure or with dialysis present a more rapid rate of progression of native aortic valve stenosis and could present a potentially accelerated SVD[72]. This association could be explained by the altered calcium metabolism observed in patients with chronic renal failure with hypercalcemia and abnormalities of mineral metabolism. In this regard, it is well known that enhanced plasma levels of Fibroblast growth factor-23, parathormone, phosphate and decreased levels of vitamin D, may

promote vascular damage and calcification[73]. Anyway, there is no evidence suggesting that in patients with dialysis the SVD has an impact on post-operative survival. For this reason the last European guidelines for the management of patients with valvular heart disease [28], suggest that:" although SVD is accelerated in chronic renal failure, poor long-term survival with either type of prosthesis or an increased risk of complications with mechanical valves may favor the choice of a bioprosthesis in this situation".

2.6 Clinical summary

According to the current literature, patient prosthesis mismatch is a condition defined by an indexed effective orifice area ≤ 0.85 cm^2/m^2. To obtain the indexed orifice area, the EOA of the implanted prosthesis is divided for the body surface area of the patient. As previously mentioned the EOA can be obtained by published literature values or by a post-operative echocardiographic study. The former technique is the most common procedure of IEOA calculation in the current literature, basically because it is easy, it allows computing the pre-operative projection of the IEOA, and it has the highest sensitivity in predicting mismatch. Mismatch can be divided in two clinical entities: moderate mismatch (IEOA ≤0.85 cm^2/m^2 and >0.65 cm^2/m^2) and severe mismatch (IEOA ≤0.65 cm^2/m^2).

Moderate mismatch is a quite frequent clinical entity; it is present in up to 40% of patients who underwent AVR. Up to now moderate PPM has not been clearly demonstrated to increase the post-operative early or late mortality after aortic valve replacement, unless the patient presents with left ventricle dysfunction. In any case moderate mismatch can be associated with higher post operative trans-prosthetic gradient compared with patients without moderate mismatch.

Severe PPM is a rare entity; it is present in about 3% of the population who underwent AVR. Severe mismatch is an independent risk factor for early and late mortality after aortic valve replacement. Persistence of high trans-prosthesis gradients and lack of left ventricle mass regression are often observed in patients with severe PPM. For this reason the new European guidelines of heart valve disease [28], published in 2012, suggest that if the valve prosthesis– patient ratio is expected to be ≤0.65 cm^2/m^2, enlargement of the annulus to allow placement of a larger prosthesis may be considered. The

appropriate choice of the valve prosthesis is fundamental to get the maximal possible IEAO and to avoid, in most cases, severe PPM. Alternatively, there are different surgical techniques of aortic annulus enlargement which can be used to implant a larger prosthesis than that one which would fit anatomically. However, these techniques have a higher operative risk than the standard aortic valve replacement procedure.

Recently PPM, defined as IEOA ≤ 0.85 cm^2/m^2, has been reported by the Leuven University, to be associated with the SVD of the bioprosthesis. Because the SVD is a complex process whose determinants are still to be clearly identified, the possibility that mismatch has a negative impact on SVD represents, in our opinion, a very interesting hypothesis to be tested also in our population.

Recapitulación

Según la literatura actual, el desajuste paciente-prótesis es definido por un área efectiva de orifico indexado (AEOI) ≤ 0,85 cm^2/m^2. Para calcular el AEOI es necesario dividir el área efectiva de orificio (AEO) de la prótesis implantada por la el área de la superficie corporal del paciente. El AEO puede obtenerse a partir de artículos publicados en la literatura o de estudios ecocardiográficos realizados en el mismo paciente. La primera forma de calcular el AEO es la más utilizada, porque es más fácil, porque permite calcular en fase preoperatoria el AEOI para cada prótesis a implantar y porque el AEO así calculado presenta mayor sensibilidad en la predicción del desajuste.

El desajuste paciente-prótesis se puede dividir en dos entidades clínicas: moderado (AEOI ≤ 0,85 cm^2/m^2 y > 0,65 cm^2/m^2) y severo (AEOI ≤ 0,65 cm^2/m^2). El desajuste paciente-prótesis moderado es una entidad clínica relativamente frecuente y es diagnosticado hasta en el 40% de los pacientes intervenidos de recambio valvular aórtico (RVA). Hasta la fecha, no se ha demostrado de forma inequívoca que el desajuste moderado aumente la mortalidad post-operatoria, menos en el grupo de pacientes con disfunción ventricular izquierda. De todas formas, los pacientes con desajuste moderado presentan gradientes trans-protésicos más altos de los pacientes sin desajuste.

El desajuste paciente-prótesis severo es una entidad clínica poco frecuente, estando presente en el 3% de los pacientes intervenidos de RVA. El desajuste severo es un factor de riesgo para mortalidad a corto y a largo plazo después de un RVA. En este sentido, la persistencia de gradientes trans-protésicos altos y la falta de regresión de la hipertrofia del ventrículo izquierdo están presentes frecuentemente en los pacientes con desajuste severo. Por esta razón, la nuevas guías europeas sobre la patología valvular cardiaca, sugieren considerar la posibilidad de realizar una ampliación de la raíz aortica

en los pacientes cuyo AEOI calculado previamente a la cirugía sea ≤0,65 cm^2/m^2. De hecho, existen distintas técnicas quirúrgicas que permiten ampliar la raíz aórtica para implantar una prótesis que sea al menos una medida superior a la que cabría anatómicamente. De todas formas, estos procedimientos presentan un riesgo operatorio más alto que el RVA estándar. Recientemente la Universidad de Leuven ha demostrado que el desajuste paciente-prótesis, definido por un AEOI ≤0,85 cm^2/m^2 se asocia a un aumento de la tasa de degeneración estructural de las bioprótesis aórtica. Dado que la degeneración estructural protésica es un evento complejo cuyos determinantes no han sido aclarados del todo, la posibilidad que el desajuste paciente-prótesis pueda de alguna forma tener un impacto sobre este fenómeno, es una hipótesis muy interesante que queremos comprobar en nuestra población.

3. Hypothesis

All biological substitutes of heart valves undergo a process of structural valve deterioration (SVD), which represents the main determinant of their longevity. It has been reported that patient-prosthesis mismatch can increase the SVD process in patients receiving a bioprosthesis in aortic position[62].

In the present study we will test the following hypotheses:

1. Patient-prosthesis mismatch increases independently the risk of undergoing reoperation because of SVD in a Spanish population.

2. Patient-prosthesis mismatch increases independently 30-day and mid-term mortality after aortic valve replacement.

3. Different PPM degrees could have different impacts on post-operative mortality and on reoperation because of SVD.

4. Objectives

In a sample population of 387 consecutive adult patients who underwent aortic valve replacement with a biological prosthesis in the Fundación Jiménez Díaz from 1974 to 2009, we will analyze:

1. The incidence of patient-prosthesis mismatch in a Spanish population.
2. The impact of different patient-prosthesis mismatch degrees on post-operative mortality.
3. The impact of different patient-prosthesis mismatch degrees on reoperation because of SVD.

5. Materials and methods

In total, 387 consecutive adult patients who underwent aortic valve replacement with a bioprosthesis from 1974 to 2009 at the Fundación Jiménez Díaz were retrospectively reviewed. Follow-up information was obtained from the electronic database of the Cardiac Surgery Department. Patients status during follow-up was determined by hospital visit carried out on a yearly basis. Our database did not include echocardiographic data. Echocardiograms files were not recorded as electronic files before the year 2000. After this year, echocardiograms were electronically recorded and obtained routinely before discharge and periodically (generally yearly), and thereafter at the discretion of referring physicians. We were not able to find echocardiographic data of the 286 patients (74% of the whole sample population) who underwent surgery from 1974 to 1986. This important volume of missing data forced us to focus the study on the incidence of reoperation due to SVD instead of focusing on incidence of SVD itself.

The study was approved by the Local Ethics Committee.

A median sternotomy was performed via a standard approach, with cardiopulmonary bypass and mild systemic hypothermia (32ºC) being used in all patients.

Myocardial protection was achieved with a combination of antegrade intermittent cold blood o crystalloid cardioplegia and topical cooling. The prosthesis size was selected according to the size of the aortic annulus, as determined by the manufacturer's instructions. The largest suitable valve was always selected for any given patient. Valvular prostheses were implanted in the supra-annular position with mattress sutures, using Teflon pledgets.

5.1 Definitions

The patient's BSA was derived using the Dubois formula. The in-vivo EOA values were estimated by reference tables based on mean EOA values of the different prosthesis, type and size [74] [75] .

EOA published values of the Hancock standard were heterogeneous and sometimes even larger than those of the Hancock II (modified orifice) [76] [77]. For this reason we decided to be conservative and apply for the Hancock standard the same EOA values of the Hancock II, published by Pibarot et al.

The indexed effective orifice area (IEOA) was obtained by dividing the estimated EOA by the patient's BSA. Our mismatch analysis was focused on IEOA studied as continuous variable and as categorical variable. In particular we used three cut-off values: IEOA $\leq 0.85 cm^2/m^2$, IEOA $\leq 0.70 cm^2/m^2$ and IEOA $\leq 0.65 cm^2/m^2$.

Structural Valve Deterioration (SVD) was defined, according to the current guidelines for reporting mortality and morbidity in cardiac surgery[78], as "changes intrinsic to the valve, such as wear, fracture, poppet escape, calcification, leaflet tear, stent creep, and suture line disruption of components of a prosthetic valve".

5.2 Indications for bioprosthesis replacement

The first indication to replace the bioprosthesis was the presence of severe stenosis (mean trans-prosthesis gradient >50 mmHg) or regurgitation (3 or 4 out of 4) associated with heart failure symptoms or syncope. The second indication was a diagnosis of endocarditis. In all cases, diagnosis of SVD was carried out by the operating surgeons through macroscopic evaluation of the bioprosthesis according to two parameters: calcification: none (no calcification at all), mild (partial calcification of 1or 2 leaflets), moderate (partial calcification of the three leaflets), severe (complete calcification of the three leaflets), and leaflet tears (present/absent).

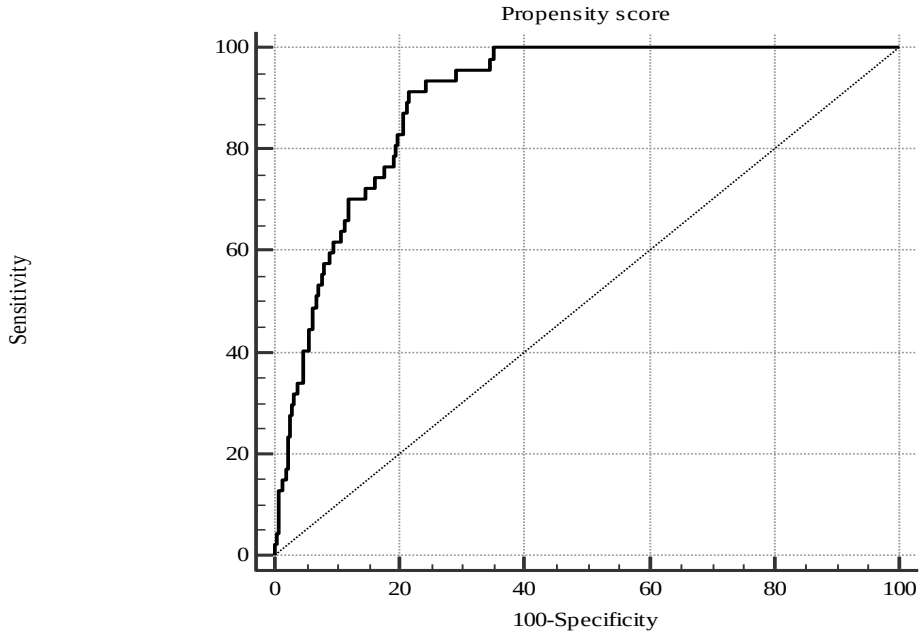
5.3 Statistical analysis

Continuous variables were expressed as median plus range, or mean ± standard deviation. Dichotomous categorical variables were indicated as absolute frequency (percentage). As a first step, all continuous data listed in table 1 were analyzed, one by one, by Student's t-test for independent samples or Mann-Whitney U-test, when appropriate. Categorical data were analyzed by chi-square test, or Fisher's exact test when appropriate to identify univariable predictors of 30-day mortality. Any variable with a p-value ≤ 0.10 in the univariate analysis was entered into a backward multivariable logistic regression model. From this model, independent predictors of 30-day mortality were obtained. As a second step, a standard single predictor and multivariable ($p < 0.10$= threshold to enter the variable in the model) Cox regression analysis was carried out to identify independent predictors of long-term mortality.

All data listed in table 2, were entered, one by one, in a Cox regression univariable model inserting "bioprosthesis replacement for SVD" as dependent variable. Any variable with a p-value ≤0.10 in the univariable analysis was entered into a backward multivariable Cox regression model (p >0.10 = threshold to remove the variable from the model). From this model the independent predictors of aortic bioprosthesis replacement for SVD of the whole sample population were obtained.

A propensity score was computed and used to reduce the selection bias related to the retrospective nature of this study. This was defined as the conditional probability of belonging to the PPM group versus the control group given the covariates. Hence, the propensity score was used to balance the differences on observed covariates between the two groups by a multivariable adjustment[79]. In other words, this analysis decreases the probability that differences in terms of incidence of aortic bioprosthesis replacement were due to differences of comorbidities between patients with mismatch and patients without mismatch.

Thus, all operative data listed in Table 2 predictive of group membership (p value ≤0.15) were entered into a logistic multivariable regression model with mismatch (1 = PPM group; 0 = control group) as the dependent variable. The variables used for the propensity score computation were: age, body surface area, body mass index, left ventricle ejection fraction, type of aortic lesion, clamp time, concomitant CABG, model bioprosthesis and type of bioprosthesis. The final model had an area under the receiver operating characteristic curve of 0.89.



Receiver Operating Characteristic (ROC) curves plotting the propensity score against the variable "group membership". Area under the curve: 0.89

As described in table 2, our sample population underwent surgery trough a 35 years long period (from 1974 to 2009). Because we cannot exclude that the variable "year of surgery" could have an impact in procedural details which could influence the rate of SVD over the years, we decided to use this variable in the analysis. In particular we transform the variable "year of surgery" in a dichotomic one: we assigned the value 1 to the dates ranging from 1974 to 1991, and the values zero to the dates ranging from 1992-2009. Then we forced this variable in the Cox regression model for calculation of predictors of reoperation because of SVD.

Unadjusted long-term survival and long term rates of freedom from aortic bioprosthesis replacement were calculated using the Kaplan-Meier method. The log-rank test was used to compare the curves of freedom from aortic bioprosthesis replacement for SVD of the two groups (PPM and control). The hazard ratio (HR) and the odds ratio (OR) values are shown with 95% confidence intervals (CIs). Proportional hazard assumption

was evaluated using the test based on the Schoenfeld residuals. The area under the curve (AUC) was used to measure how the regression logistic model predicted the outcome "30-day mortality". Statistical analyses were performed using the 2012 R statistics package (www.r-project.org). MedCalc for Windows (version 9.3.7.0; MedCalc Software, Mariakerke, Belgium) was used for graphics.

6. Results

Patients' characteristics are listed in Table 2.

	Total (n=387)	**IEOA≤0.70cm²/m²** **(n=47)**	**Control Group (n=340)**	***p value**
Clinical data				
Age	57.9±19.1	65.1±19.1	56.9±18.9	0.06
Female	118 (30.5%)	14 (29.8%)	104 (30.6%)	1
BSA (m²)*	1.70 ±0.17	1.9±1.3	1.7±0.17	<0.0001
BMI	23.9±3.9	27.4±3.8	23.5±3.7	<0.0001
IEOA	0.8±0.1	0.65±0.03	0.83±0.01	<0.0001
AF	26 (6.7%)	1 (2.1%)	25 (7.4%)	0.3
LVEF	55.3±12.1	61.0±10.6	54.5±12.1	<0.0001
NYHA III/IV	311 (80.4%)	39 (83%)	272 (80%)	0.8
Type of aortic valve lesion:				0.04
Aortic stenosis	177 (45.6%)	32 (68.1%)	144 (42.4%)	
Aortic regurgitation	159 (41.2%)	12 (25.5%)	147 (43.2%)	
Double lesion	51 (13.2%)	3 (6.4%)	48 (14.1%)	
Ethiology:				0.2
Rheumatic	295 (76.2%)	35 (74.5%)	260 (76.5%)	
Degenerative calcific	64 (16.5%)	11 (23.4%)	53 (15.6%)	
Endocarditis	28 (7.2%)	1 (2.1%)	27 (2.9%)	
Operative data				
REDO	27 (7.0%)	3 (6.4%)	24 (7.1%)	1
Urgency	17 (4.4%)	2 (4.3%)	15 (4.4%)	0.9
Clamp time	51.5±23.8	61.6±24.3	49.8±23.4	0.001
Concomitant CABG	37 (9.6%)	10 (21.3%)	27 (7.9%)	0.07

	Total (n=387)	IEOA≤0.70cm^2/m^2 (n=47)	Control Group (n=340)	*p value
Model of Bioprosthesis				Patients' Age (<0.0001)
Hancock (porcine; implantation years 1974-1982)	221 (57.1%)	14 (29.8%)	207 (60.9%)	Mean age: 45.1±14.6 (years)
Hancock II (porcine; implantation years 1983-2003)	45 (11.6%)	8 (17%)	37 (10.9%)	Mean age: 72.0±9.1 (years)
Carpentier Edwards supra-annular (porcine; implantation years 1983-1989)	20 (5.2)	0 (0%)	20 (5.9%)	Mean age: 77.6±5.0 (years)
Carpentier Edwards Perimount (bovine; implantation years 2001-2007)	97 (25.1%)	24 (51.1%)	73 (21.5%)	Mean age: 68.3±8.2 (years)
Carpentier Edwards Magna (bovine; implantation years 2006-2009)	4 (1)%	1 (2.1%)	3 (0.9%)	Mean age: 76.5±2.6 (years)
Type of Bioprosthesis				<0.0001
Bovine	101 (26.1%)	25 (53.2%)	76 (22.4%)	
Porcine	286 (73.9%)	22 (46.8%)	264 (77.6%)	

Table 2. Patients' characteristics. **AF**: atrial fibrillation; **BSA**: Body surface area; **CABG**: coronary artery; **IEOA**: indexed effective orifice area; bypass grafting; **LVEF**: left ventricle ejection fraction; **NYHA**: New York Heart Association Class. **REDO**: previous operation.

*P values computed by uni-variate analysis.

The mean value of the IEOA was 0.81 ± 0.11 cm^2/m^2.

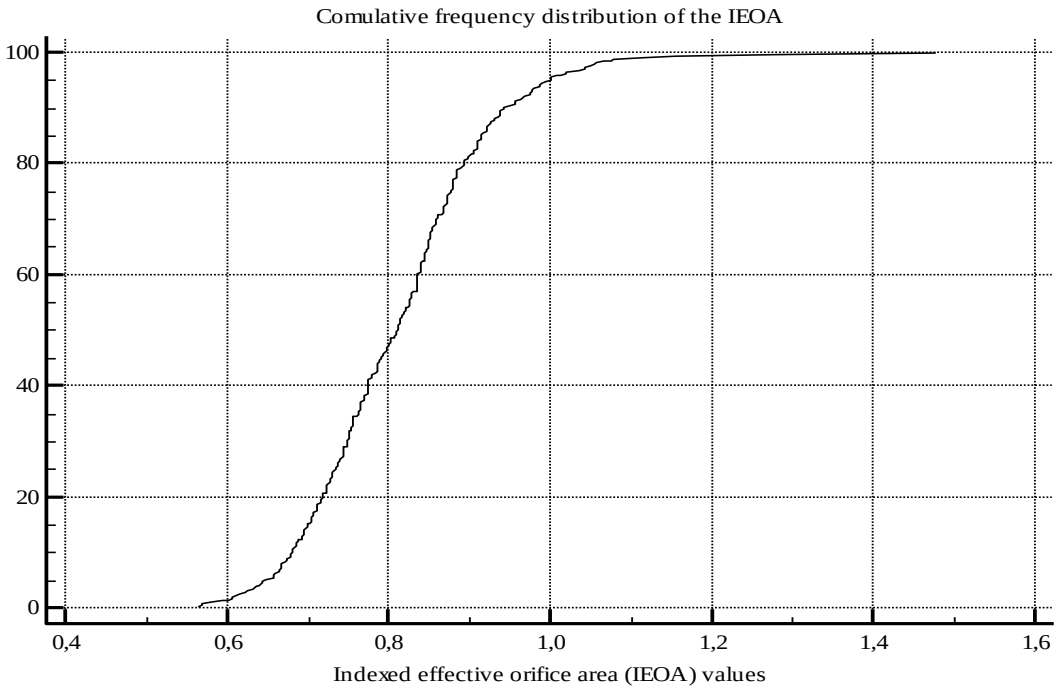


Fig 1A. Cumulative frequency distribution of the IEOA values.

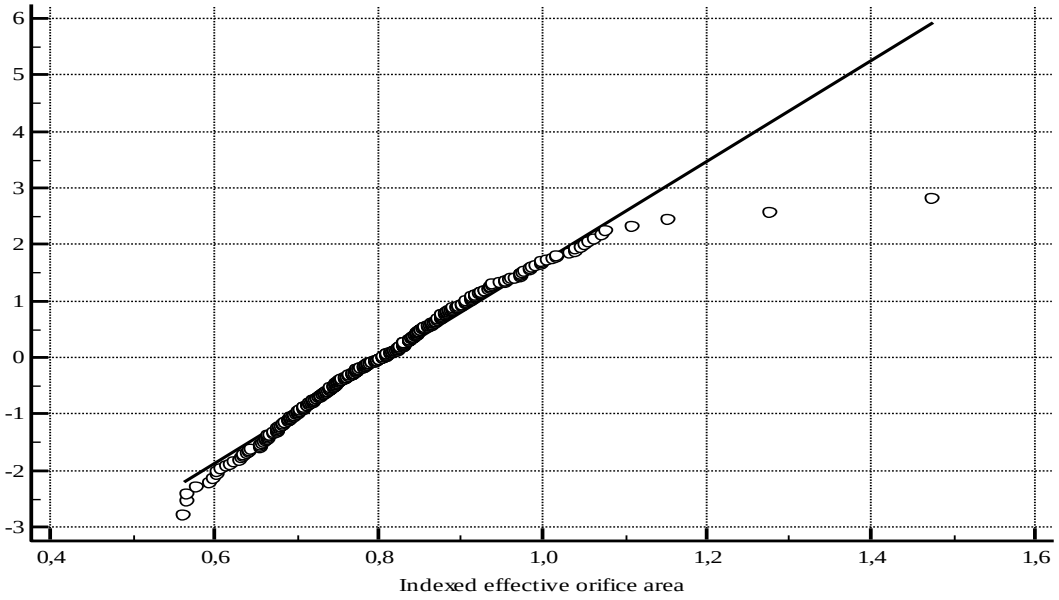


Fig 1B. Normal plot of the observed IEOA values (horizontal axis) and the z-scores of the observed IEOA. (Z-score =(x-mean)/SD).

The median follow-up period was 7.2 years (range: 0.5-22.5 years). Thirteen patients were lost to the follow-up, which was 97% complete.

Of the whole sample population, 66.7% (n=258) presented with IEOA ≤0.85 cm^2/m^2, 12.1% (47) had an IEOA ≤0.70 cm^2/m^2 and 5.2% (n=20) showed an IEOA ≤0.65 cm^2/m^2.

Thirty day mortality was 6.5% (total deaths=25). Multivariable logistic regression analysis revealed four risk factors of early mortality: urgency surgery, redo surgery, female sex and patients' age (table 3). The Area under the curve of the whole model was 0.74 (fig 2). IEOA was not an independent risk factor for 30-day mortality neither analyzed as continuous variable nor as categorical variable (IEOA ≤0.85cm^2/m^2, IEOA ≤0.70cm^2/m^2 and IEOA ≤0.65cm^2/m^2).

Variable	OR	Error	95% CI	P value
Age	1.026	0.0143	1.000 -1.057	0.0494
Urgency	5.811	4.1558	1.288 -22.491	0.0240
Redo Surgery	4.436	2.5222	1.352- 12.994	0.0159
Female sex	2.647	1.2552	1.051 -6.894	0.0389

Table 3. Independent predictors of 30-day mortality

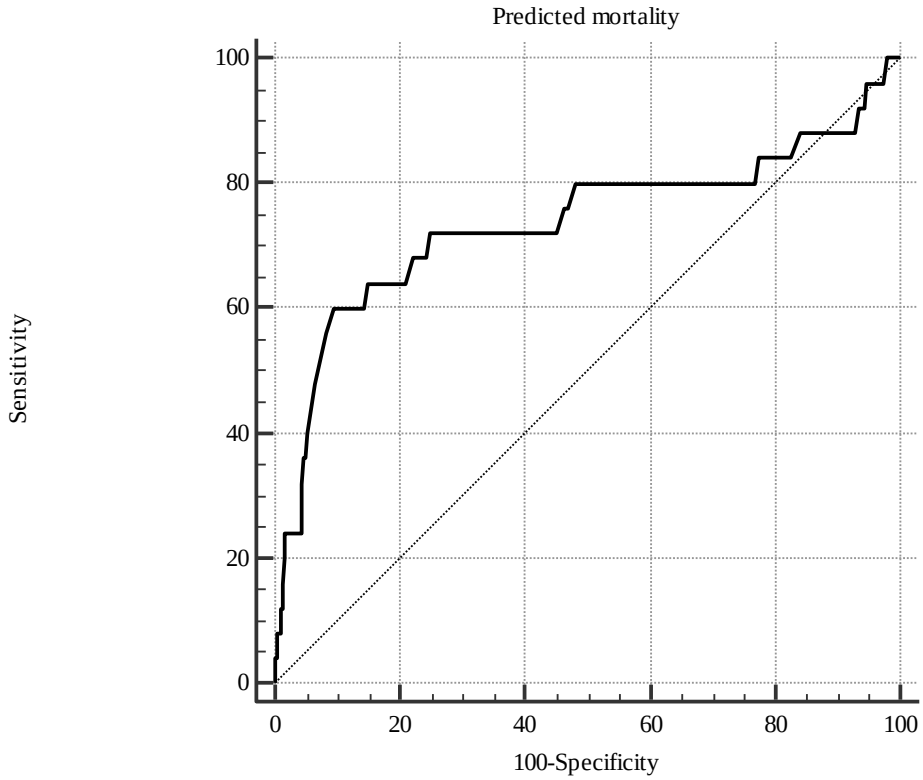


Fig 2. Receiver Operating Characteristic (ROC) curve showing the sensitivity of the multivariable model to predict the 30-day mortality. Area under the curve: 0.74.

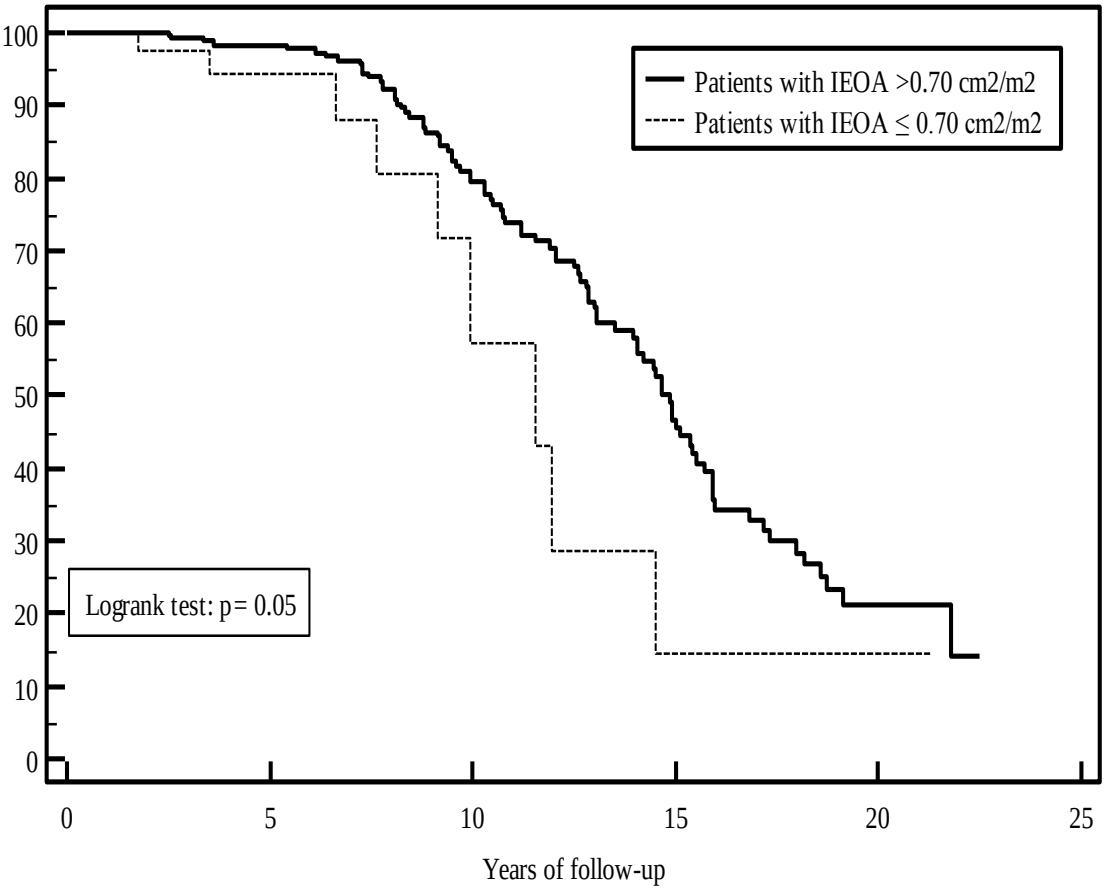
Of the 30-day survivors (n=362), 13 were lost at the follow-up. Among the remaining 349 patients, 85 deaths were recorded, of which only 34 (40%) were cardiac events, and 111 patients underwent reoperation for replacement of the aortic bioprosthesis. The median survival time of these 349 patients was 20.4 years. According to Kaplan Meier analysis ten years survival of the whole sample population was 74.4 ± 2.8 %. According to multivariable Cox regression analysis, there were four independent predictors of long term mortality. Female sex and left ventricle ejection fraction (LVEF) were identified as protector factors: female patients and patients with higher LVEF had a lower risk of late mortality compared with male patients and patients with lower LVEF. Patients' age and

urgency surgery were identified as risk factors (table 4). IEOA was not an independent risk factor for long-term mortality neither analyzed as continuous variable nor as categorical variable (IEOA $\leq 0.85 cm^2/m^2$, IEOA $\leq 0.70 cm^2/m^2$ and IEOA $\leq 0.65 cm^2/m^{2)}$.

Variable	HR	Error	95% CI	P value
Age	1.032	0.0074	1.017-1.046	<0.0001
Female sex	0.568	0.1619	0.324 -0.993	0.0383
Ejection Fraction	0.980	0.0092	0.962- 0.998	0.0297
Urgency	3.805	1.4243	1.827-7.925	0.0019

Table 4. Independent predictors of long-term mortality

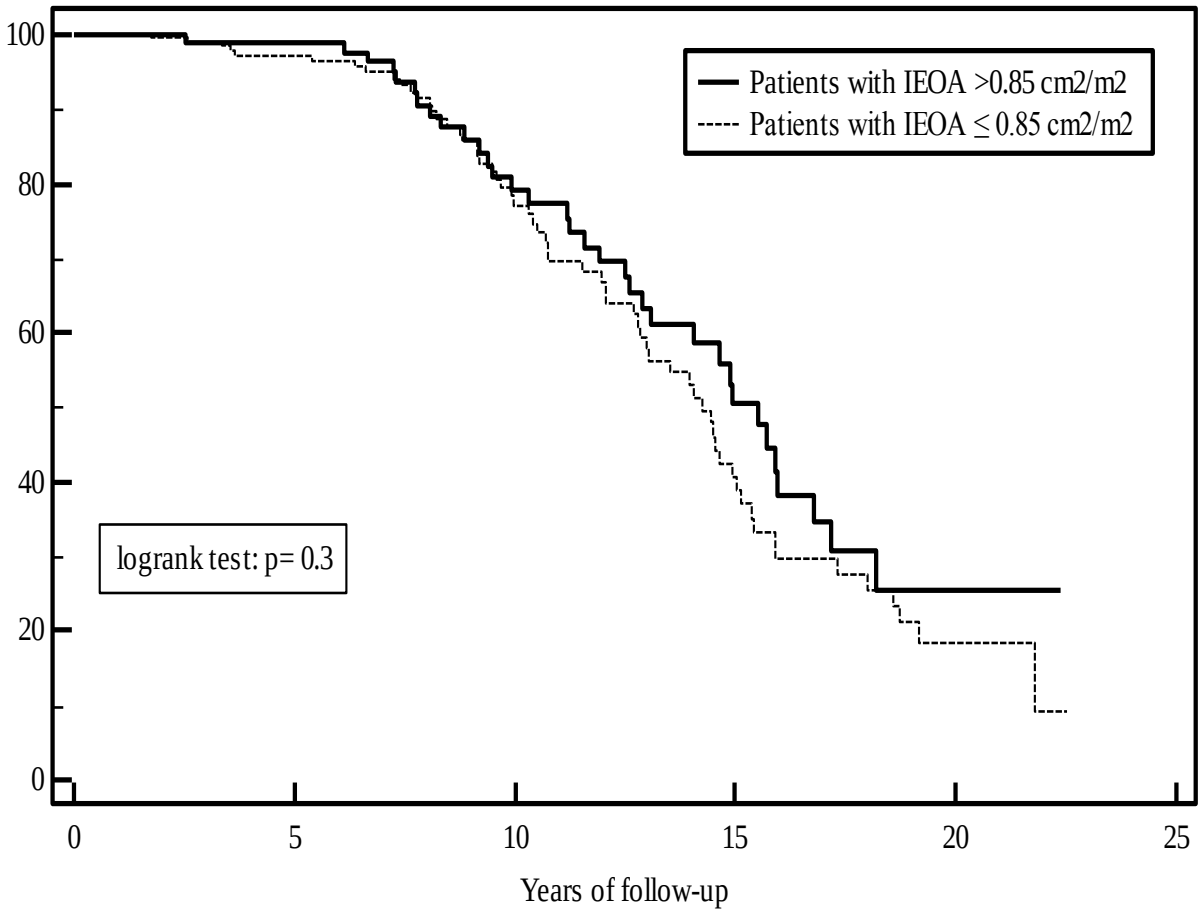
Ten year freedom from reoperation for aortic bioprosthesis reoperation was 74.3±3.2%. Causes of aortic bioprosthesis reoperation were structural valve deterioration of the bioprosthesis (n=96), paravalvular leak (n=10) and acute endocarditis (n=5). Of the 96 explanted bioprostheses because of SVD, 93 were Hancock I, 1 was Hancock II and 2 were porcine Carpentier Edwards. According to unadjusted Kaplan-Meier analysis (figure 3 A, B, C), only patients with IEOA ≤ 0.70 cm^2/m^2 (but not patients with IEOA$\leq$ 0.85 cm^2/m^2, nor patients with IEOA ≤ 0.65 cm^2/m^2) had a higher incidence of reoperation because of structural valve deterioration when compared with that one of patients without mismatch (log-rank "p" value= 0.05).



Number at risk

Group: Patients with IEOA >0.70 cm2/m2					
306	203	108	39	9	0
Group: Patients with IEOA ≤ 0.70 cm2/m2					
43	19	4	1	1	0

Figure 2A. Kaplan-Meier analysis of freedom from reoperation because of structural valve deterioration (SVD). Patients with IEOA $\leq$ 0.70 cm^2/m^2 were reoperated less often than those with IEOA >0.70 cm^2/m^2 (p=0.05).



Number at risk

Group: Patients with IEOA >0.85 cm2/m2					
118	84	46	18	5	0
Group: Patients with IEOA ≤ 0.85 cm2/m2					
231	138	66	22	5	0

Figure 2B. Kaplan-Meier analysis of freedom from reoperation because of structural valve deterioration (SVD). Patients with IEOA ≤0.85 cm^2/m^2 do not show any difference in term of rate of reoperation when compared with patients with IEOA >0.85 cm^2/m^2.

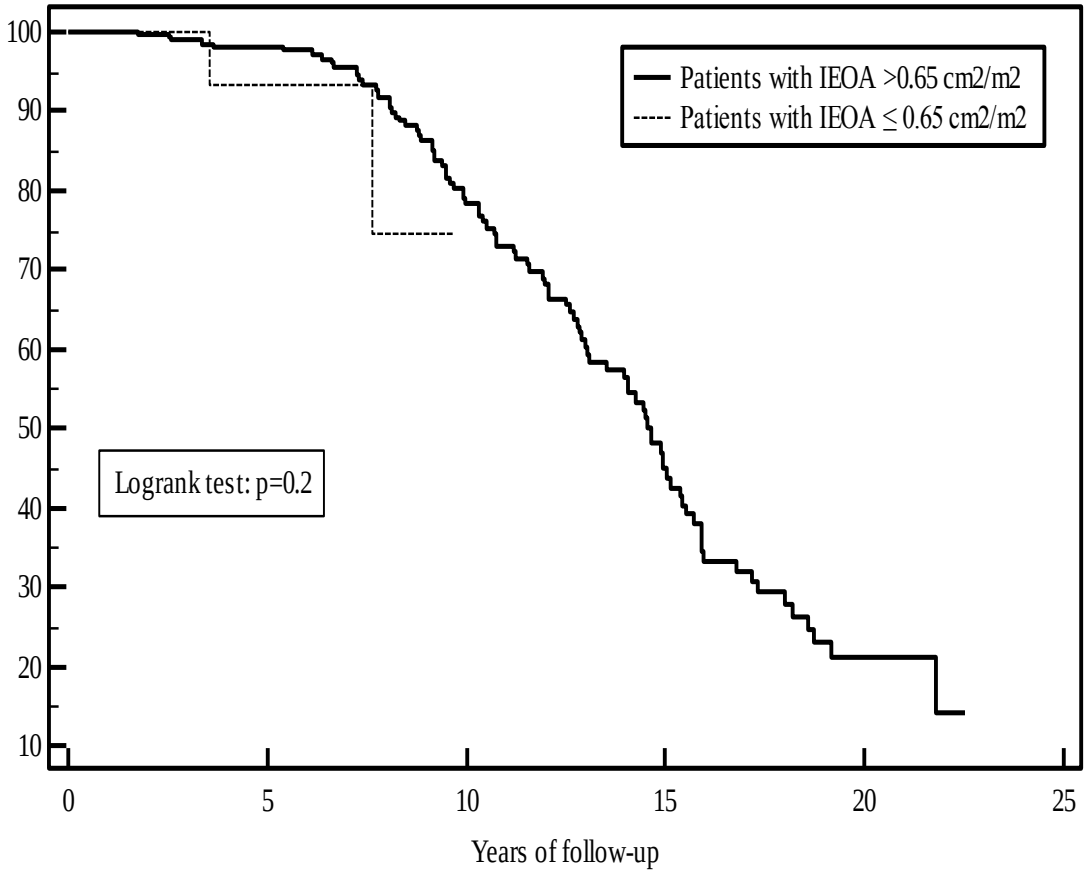


Figure 2C. Kaplan-Meier analysis of freedom from reoperation because of structural valve deterioration (SVD). Patients with IEOA ≤0.65 cm^2/m^2 do not show any difference in term of rate of reoperation when compared with patients with IEOA >0.65 cm^2/m^2.

This result was confirmed by the multivariable Cox regression analysis which identified two independent predictors of reoperation because of SVD: patients' age and IEOA ≤0.70 cm^2/m^2 (table 5). These results did not change significantly after forcing into the model the variable "year of surgery".

After adjusting for propensity score, "patients' age" maintained its statistical significance, while the variable "IEOA ≤0.70 cm^2/m^2" kept showing a hazard ratio of 2, with a statistical value just above the limit of statistical significance (p= 0.063).

Variable	**HR**	**Error**	**95% CI**	**P value**
IEOA ≤0.70 cm^2/m^2	2.161	0.355	1.079-4.329	0.030
Age	0.967	0.007	0.954-0.981	<0.0001
After forcing into the model the variable "year of surgery"				
IEOA ≤0.70 $cm^{2/}m^2$	2.268	0.354	1.1362-4.529	0.02
Age	0.970	0.007	0.956-0.984	<0.0001
After Propensity score adjustment				
IEOA ≤0.70 cm^2/m^2	2.033	0.382	0.962-4.295	0.063
Age	0.967	0.007	0.953-0.981	<0.0001

Table 5. Independent predictors of reoperation because of structural valve deterioration. IEOA: indexed effective orifice area.

According to our multivariable analysis, the variables IEOA ≤0.65 cm^2/m^2 (p value: 0.13), IEOA ≤0.85 cm^2/m^2 (p value: 0.86), and IEOA used as continuous variable (p value: 0.24), were not independent predictors of reoperation because of structural valve deterioration (SVD).

Surgical records on explanted degenerated bioprostheses were obtained in 95 cases over 96. Explanted bioprostheses were analyzed according to three parameters: prevalent lesion (based on echocardiographic records) presence of leaflet tear and presence of calcification (based on surgical records). Bioprostheses explanted from patients with IEOA ≤0.70 cm^2/m^2 had a trend to present a higher percentage of severe calcification (p=0.14), (table 6), that was not statistically significant.

	Mismatched Bioprosthesis (n=9)	**No Mismatched Bioprosthesis (n=86)**	**p values by bivariable analysis**
Type of bioprosthesis lesion:			0.8
Aortic stenosis	3 (33.3%)	22 (25.6%)	
Aortic regurgitation	4 (44.4%)	48 (55.8%)	
Double lesion	2 (22.2%)	16 (18.6%)	
Bioprosthesis leaflet tear	8 (88.9%)	65 (75.6%)	0.7
Severe bioprosthesis calcification	3 (33.3%)	12 (14.0%)	0.14

Table 6. Data of the explanted bioprosthesis for structural valve deterioration. Mismatched prosthesis: indexed effective orifice area ≤0.70 cm^2/m^2.

7. Discussion

7.1 Comment

All biological substitutes of heart valves undergo a process of SVD, which represents the main determinant of their longevity. Indeed, the current guidelines of the European Association Cardiothoracic Surgery/ European Society of Cardiology[80] and the American College of Cardiology/American Heart Association[81] on management of heart valve disease , suggest implanting aortic bioprosthesis in patients >65 years (class IIa), whose lifespan is supposed to be lower than the durability of the bioprosthesis itself. When the opposite happens, patients may require the replacement of the deteriorated valve prosthesis, a common event with first bioprosthesis generation.

In our database, 100% (n=96) of the reoperations for SVD were recorded in patients receiving a porcine bioprosthesis, and 97% (n=93) of these bioprostheses were Hancock standard. Thus, for statistical reasons (lack of model convergence), the first multivariable analysis developed to identify predictors of reoperation for bioprosthesis deterioration, could not include the variable “type of bioprosthesis”, neither the variable “model of bioprosthesis”. For this reason, a propensity score was computed with 9 variables, including the two ones mentioned above and used for multivariable adjustment. Thus, the propensity score analysis was performed to balance and mitigate the effect of observed covariates between the PPM and no-mismatch groups.

Also, because our study population underwent surgery along a 35 years period, it was decided to force the variable “date of surgery”, used as dichotomic variable, into the multivariable cox regression analysis for computation of predictor of reoperation.

The fact that the population receiving the Hancock standard was, almost exclusively, the one at risk of reoperation for SVD cannot be explained just by the higher deterioration rate which has been already documented in first generation porcine bioprosthesis[82].

In fact, the relatively high number of events in this group of patients, should be viewed in the light of three statistical considerations: patients with Hancock standard prosthesis represent, by far, the largest group of the sample population (57.1%), the youngest one, and the one with the largest follow-up (implantation years for each prosthesis and mean age of each group of patients are indicated in table 1).

Historically, the Hancock standard was used at our Institution in the seventies as the ideal choice in young patients and fertile women. Later, and because of the not convincing outcomes in terms of degeneration rate, the use of this bioprosthesis was mainly applied to patients over 65 years of age. These patients, since the 1980s, received the second generation bioprosthesis which had some advantages such as lower implant profile and a more sophisticated process of glutaraldheyde fixation and antimineralization treatment. For this reason, in our database, second generation prostheses were implanted in the oldest group of the sample population, which is also the smallest one, and the one with the shortest follow-up time.

In any case, the deterioration rate of Hancock standard bioprosthesis has produced enough number of events for risk factors analysis. In particular our model identified two predictors: age of the patients and IEOA ≤ 0.70 cm^2/m^2. Thus, according to our multivariable model, the younger the patients at the moment of the aortic valve replacement, the higher the risk of undergoing bioprosthesis replacement because of SVD. At the same time, patients with IEOA ≤ 0.70 cm^2/m^2 were twice as likely to

undergo reoperation for SVD than those with IEOA >0.70 cm^2/m^2. The propensity score adjusted model showed a not significant trend with similar findings.

We failed to show the IEOA used as continuous variable or as categorical variable with the specific cut off ≤0.85 cm^2/m^2 and ≤0.65 cm^2/m^2 has an impact on incidence of reoperation because of SVD. Looking at figures 2B and 2C, it is possible to note that in both cases patients with moderate (IEOA ≤0.85 cm^2/m^2) or severe (IEOA ≤0.65 cm^2/m^2) mismatch present with a lower freedom from reoperation compared with patient without mismatch. But this difference did not reach statistical significance.

There are two hypotheses which could explain this result. By one hand there could be a statistical power issue. In others words, the variable severe PPM and moderate PPM could have maintained their statistical significance in a larger sample population. In fact, only 18 patients in the analysis present with severe PPM (IEOA ≤0.65 cm^2/m^2).

On the other hand, if we analyze the cumulative frequency distribution and the normal plot of the IEOA (fig 1A and 1B) we can observe an almost perfect normal distribution around its mean value (0.81 cm^2/m^2) with a standard deviation of 0.11 cm^2/m^2. This means that the values are very well grouped around the mean. Thus the mean value of IEOA of the patients with IEOA ≤0.85 cm^2/m^2 is 0.75, and the mean value of IEOA of the patients with IEOA>0.85 cm^2/m^2 is 0.93. We can speculate that the difference of 0.18 cm^2/m^2 between the IEOA of the two groups of patients could be too small to show an impact in terms of rate of reoperation.

For this reason we thought that using an intermediate cut-off value of IEOA (0.70 cm^2/m^2) could have given the correct number of patients to solve the problem of statistical power. Also, the difference in terms of IEAO between the group with IEOA ≤0.70 cm^2/m^2 and the group with IEOA >0.70 cm^2/m^2 was 0.20 cm^2/m^2. This value was

large enough to create a visible difference in terms of rate of reoperation between the two groups.

The variable, patients' age, has been previously documented in literature as a risk factor for SVD[83 84 85]. Earlier SVD in young patients undergoing AVR has been classically related to the higher tissue valve hemodynamic stress[86]. Recently, SVD has been interpreted as a consequence of the intimate host-valve interaction process which, through specific genetic expression, can lead to activation of inflammation pathways. These phenomena are related to the calcification process which is a typical event in the SVD[87]. Young patients may be more exposed to these phenomena, and therefore to the risk of SVD. Also, SVD events are much more frequent in young patients undergoing AVR because these patients have a larger follow-up time than the older ones. For example, the follow-up mean time of our patients under 60 years old is 9.2 years. That one of our patients over 60 years old is 5.6 years. Thus, younger patients have an observation time, which is the period where it is possible to observe a time related event, almost double than that one of the older patients. In conclusion, the larger the follow-up time, the higher the probability to observe SVD.

The second risk factor is patient-prosthesis mismatch. Patients suffering from PPM have been traditionally documented to show a worse survival, compared with controls, after AVR[88]. Lack of left ventricle mass regression and persistence of higher transvalvular gradients, could be the hemodynamic basis of this event[89].

Recently, Flameng et al.[90] from Leuven University have shown the association between mismatch and higher incidence of bioprosthesis deterioration. The study analyzed echocardiographic and clinical follow-up data of a sample population 564 patients undergoing AVR from 1991 to 2003. Freedom from SVD, which was diagnosed on

echocardiographic findings, was 86.2% (40 patients) at 10 years. SVD was classified in stenosis type and regurgitation type. In the first case the bioprosthesis had to present with leaflet calcification o trans-prosthesis gradient > 55 mmHg. In the regurgitation type an increase of bioprosthesis regurgitation compared with the first post-operative echocardiography was documented (without calcification o severe gradient). According to this study SVD was prevalently "stenosis type" in patients with PPM (IEOA ≤0.85 cm^2/m^2). Also, according to multivariable analysis, independent predictors of SVD were PPM (HR 2.29,) anticalcification treatment (HR 0.34) and prosthesis size < 21mm (HR 2.35). Flameng et al. failed, as we did, to show that PPM is an independent risk factor for hospital mortality (5%) and for late mortality (survival at 10 year was 47.9%). In fact, the only predictor of early and late mortality was age of the patients (p value=0.010 and 0.0004 respectively).

These findings were later confirmed by a larger retrospective analysis carried out by the same group on 648 patients[91]. The authors speculated that PPM may predispose SVD through a process induced by abnormal flow profiles and prosthesis stress distribution.

There are several methodological differences between our study and that one of the group of Leuven University. We were not able to identify most of the echocardiographic data of the patients undergoing surgery in the seventies and in the eighties. For this reason, we were forced to use the rate of bioprosthesis explantation because of SVD instead of SVD diagnosed by echocardiography. In other words, in our patients we can image this chronological sequence: 1) bioprosthesis aortic valve implantation; 2) possible development of SVD; 3) diagnosis of SVD by echocardiography; 4) possible reoperation to replace the deteriorated bioprosthesis because of SVD. Flameng analyzed the incidence of the SVD diagnosed by echocardiography (point 3). We analyzed the rate of reoperation of deteriorated bioprosthesis (point 4). Thus we had to accept the risk

of underestimating the incidence of SVD. In fact we could have missed patients with an initial SVD, detectable by echocardiography (which data are missing), but not severe enough to require reoperation.

Our higher number of events (n=93) is probably due to the analysis of a population younger than that one analyzed by the Leuven University (57.9±19.1 years versus 73.6±5years). We also used a more strict IEOA cut off value for diagnosis of PPM (IEOA $\leq$0.70 cm^2/m^2). The variable "anticalcification treatment" was not analyzed because almost all the events occurred in the group receiving a first generation bioprosthesis (without anticalcification treatment). Despite these methodological differences our analysis suggested similar results: PPM seems to increase independently the risk of SVD. In particular if we compare the analysis of incidence of SVD events of the study by Flameng et al.[74] with our analysis (fig. 2 and 3) we can observe that in both cases the curves of patients with PPM and without PPM start diverging since the second post-operative year. Thus, patients with mismatch present with higher incidence of SVD events since the first years after surgery. The maximum divergence between the two curves is observable at about 9-10 years in the study of Flameng [74] and at about 12 years in our study.

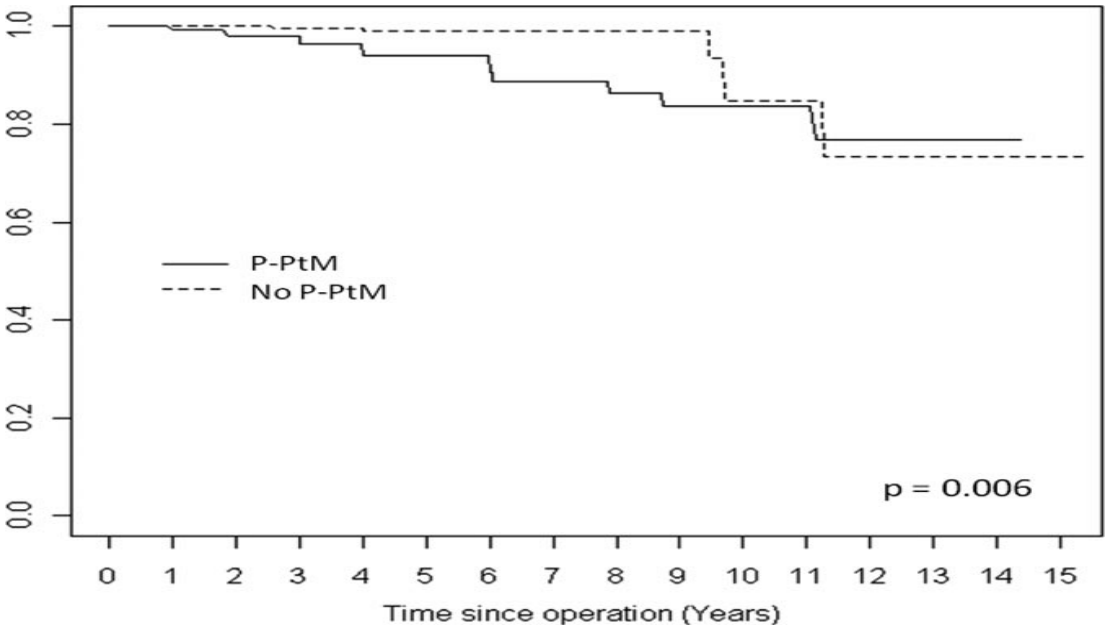


Fig 3. Nonparametric Turnbull estimate plotting freedom from structural valve deterioration. From Flameng et al. [74]

Behind 12 years in the Flameng[74] analysis and behind 15 years in our study, the divergence of the two curves starts gradually disappearing. In other words, SVD events in Flameng study[74] are visible earlier.

This difference in term of time of SVD presentation is probably due to the fact that we used as definition of SVD its clinical consequence: reoperation. Flameng used a definition based on a specific echocardiographic pattern, so his analysis was able to detect the SVD of bioprosthesis before this event may produce the necessity of a reoperation.

This hypothesis is corroborated by the second study about mismatch of Flameng[75] which showed (figure 4) the relation between freedom from reoperation and freedom

from SVD. This analysis shows clearly that echocardiographic diagnosis of SVD anticipates the need of reoperation.

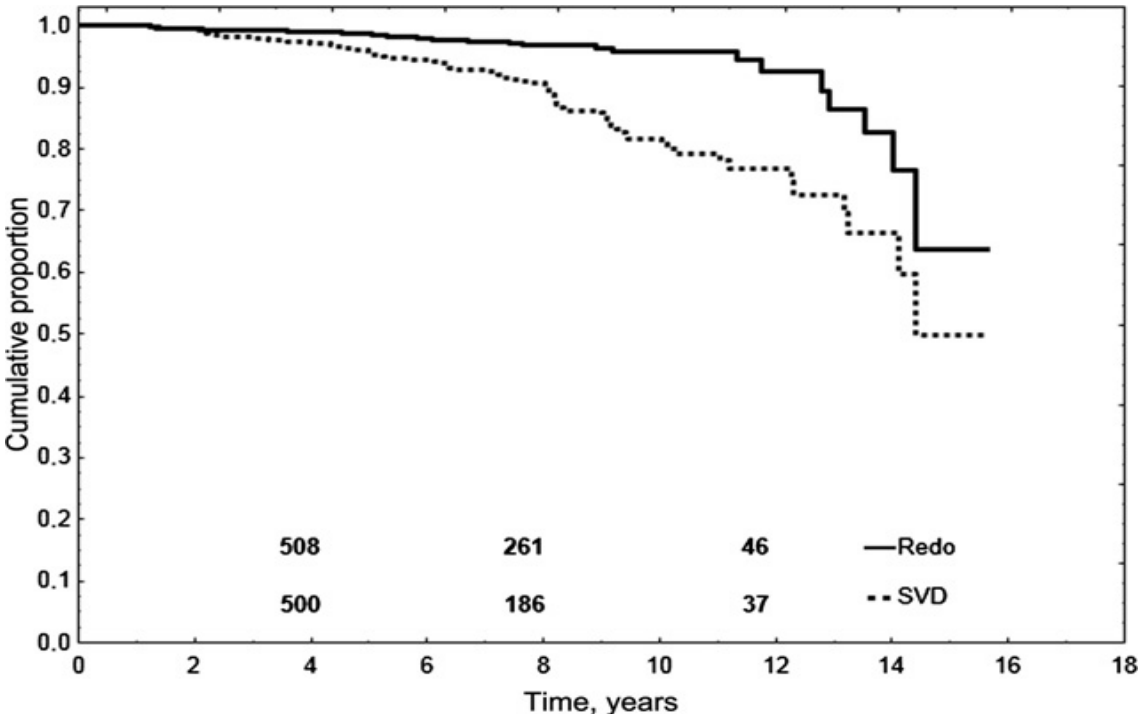


Fig.4. Freedom from reoperation (solid line) and SVD (dashedline). From Flameng et al. [75]

Important differences between the two analyses are present in term of overall freedom from SVD events. In our analysis at 10 years about 74 % of the population is free from reoperation for SVD. In the study of Flameng et.[74], at ten years about 86% of the population is free from SVD. This difference in term of freedom from SVD events, could be the expression of one important fact: almost 60% of our population is represented by young patients (mean age: 45.1 years) who received the first generation bioprosthesis (Hancock I, implanted from 1974 to 1982), the one with the highest

incidence of SVD. The Flameng series starts from 1991, and it is constituted by patients > 70 years old who received a second or a third generation bioprosthesis, which have anticalcification treatment and, consequently, a longer durability.

Because of the low number of mortality events, we were not able to carry out an appropriate analysis of the impact of PPM on 30-day survival. In fact, only 25 death events were recorded and, among the dead patients, only 3 presented with mismatch. The percentages of death events in each group were almost identical: 3 of the 47 patients with mismatch (6.4%) and 22 of the 340 patients without mismatch (6.5%) died in first 30 days after surgery. Thus no further analysis is allowed in this case.

As previously mentioned, we failed also to show an impact of mismatch on long term mortality. According to our multivariable model there were 4 independent predictors of late mortality: age, female sex, ejection fraction, and urgency. Thus, PPM was not a predictor of long-term mortality. According to Kaplan-Meier analysis, 10 year survivals of the group with PPM and the group without PPM were 60.5 ± 12.4% and 74.0 ± 3.0 %. This difference did not reach statistical significance, although this could have been due to the limited sample size. These data are consistent with the literature. The previously mentioned study of Flameng [74], despite analyzing a much lager sample population (n=564) than ours (n=387) identified, as the only risk factor for mortality, the variable "age of the patients". Looking at table 1 (page 18), which resumes the largest reports on PPM, it is possible to observe that, among the 19 studies analyzing long term survival, only 5 were able to show an impact of PPM on late mortality. Among the studies considered worthy of further comment and because of the large sample population evaluated and completeness of the statistical analysis, the following are included. Blackstone et al. [36] analyzed, by balancing score risk adjustment, a sample population of 13,258 patients undergoing AVR. In this study, an IEOA <1.2 cm^2/m^2

was shown to increase 30- day mortality by 1-2%. Yet, the study was unable to detect PPM as a risk factor for intermediate or long-term survival. It was speculated that the multifactorial nature of the reduced survival after AVR (anticoagulation- related complications, limited age span in elderly patients) may mask the impact of PPM on long-term mortality. A similar conclusion was reached by Moon et al.[48], who reported that PPM was associated with an impaired late survival only in patients aged <60 years. Most likely, Bridges et al. [35] have reported the largest study concerning PPM, by analyzing data acquired from a total of 42,310 patients undergoing isolated AVR. Prostheses with a small geometric orifice area or EOA were reported to be associated with an increased operative mortality. The most important finding of this study was that, among patients receiving the same model and size of prosthesis, those patients with a larger BSA had better outcomes. The authors suggested that the protective effect of a large BSA, which probably was related to surgical implant advantages, appeared more important than the hypothetical negative effect of PPM on survival. In conclusion, the impact of PPM on late mortality may be less important than several unmeasured confounding variables, including BSA.

Also we should remind that in our series only 40% of the deaths during follow-up were cardiac events. Thus in most of the cases, PPM could not play any role in late mortality. For all these reasons, we think that post-operative mismatch plays a minor role, if any, in long-term survival. The hypothetical negative impact which PPM could play in late mortality could be eclipsed by heavier risk factors, such as age of patients, a predictor of mortality present in most of long term analysis in valve surgery.

7.2 Conclusions

The incidence of mismatch defined as IEOA ≤0.85 cm^2/m^2 in our population was 66.7% (n=258), while the incidence of mismatch defined as IEOA ≤0.65 cm^2/m^2 was 5.2% (n=20). Forty-seven patients (12.1%) presented with IEOA ≤0.70 cm^2/m^2.

According to our multi-variable analysis patient-prosthesis mismatch was not an independent risk factor for 30-day mortality or for long-term mortality, independently from the type of IEAO variable analyzed (continuous variable or categorical variable according to the three cut-off values: IEOA ≤0.85cm^2/m^2, IEOA ≤0.70cm^2/m^2 and IEOA ≤0.65cm^2/m^2).

Our analysis suggests that two variables could play an important role in the degeneration process of heart valve bioprosthesis: the age of the patients at the time of aortic valve implantation, and the presence of mismatch. However, after propensity score adjustment, the statistical signification of mismatch was lost. This means that factors leading to mismatch, rather than mismatch itself, could be responsible of the process of structural valve deterioration. In any case the association we have documented could add one more mosaic tile in the understanding of the degeneration process of cardiac bioprostheses. We were not able to show any impact of PPM on early and late mortality.

Conclusiones

La incidencia en nuestra población del desajuste paciente-prótesis, definido por un AEOI ≤0,85 cm^2/m^2 fue del 66,7% (n=258); la incidencia del desajuste definido por un AEOI ≤0,65 cm^2/m^2 fue del 5,2% (n=20). Cuarenta y siete pacientes (12,1%) presentaron un AEOI ≤0,70 cm^2/m^2.

Según nuestro análisis multi-variable, el desajuste paciente-prótesis no fue un factor de riesgo independiente de mortalidad a corto o a largo plazo, tanto si se analizó como variable continua como si se estudió de manera categórica (AEOI ≤0,85cm^2/m^2, AEOI ≤0,70cm^2/m^2 y AEOI ≤0,65cm^2/m^2).

Nuestro análisis sugiere que dos variables podrían tener un papel importante en la degeneración de la bioprótesis aortica: la edad del paciente a la hora del RVA y la presencia de desajuste paciente-prótesis (AEOI ≤0,70cm^2/m^2). De todas formas, después del ajuste con el propensity score, la significatividad de la variable "desajuste paciente-prótesis" se perdió. Esto quiere decir que los factores que producen el desajuste, más que el desajuste mismo, pueden ser responsables del proceso de degeneración estructural de la bioprótesis. De todas formas, la asociación que documentamos puede añadir otro elemento en la comprensión del proceso de degeneración de las bioprótesis. No hemos podido demostrar ningún impacto del desajuste paciente-prótesis sobre la mortalidad precoz o tardía post operatoria.

7.3 Limitations

Given that there were not echocardiographic studies available of patients operated on between 1974 and 1986, we studied the incidence of reoperation because of SVD, an outcome that could be jeopardized by its subjective nature.

The indication to replace the aortic bioprosthesis was based on the quantitative evaluation of gradients, and on the qualitative clinical evaluation of the patient. Reoperation is a medical decision and therefore is subjected to bias.

The relative small size of the sample population and particularly the low number of patients with mismatch (12.1% of the whole sample population), limited the statistical power of the study especially on survival analysis.

8. Summary

Patient-prosthesis mismatch (PPM) has been identified as a risk factor for mortality after aortic valve replacement. Recently PPM has been also reported to increase the risk of structural valve degeneration (SVD) in patients receiving a bioprosthetic aortic valve. The aim of the present study was to compare the incidence of reoperation because of SVD in patients with mismatch to that of a population without mismatch.

Methods: In total, 387 adult patients undergoing aortic valve replacement with a bioprosthesis from 1979 to 2009 were retrospectively reviewed. Our mismatch analysis was focused on IEOA studied as continuous variable and as categorical variable. In particular we used three cut-off values: IEOA $\leq 0.85 cm^2/m^2$, IEOA $\leq 0.70 cm^2/m^2$ and IEOA $\leq 0.65 cm^2/m^2$. The median follow-up period was 7.2 years. Follow-up was 97% complete.

Results: Of the whole sample population, 66.7% (n=258) presented with IEOA ≤ 0.85 cm^2/m^2, 12.1% (47) had an IEOA ≤ 0.70 cm^2/m^2 and 5.2% (n=20) showed an IEOA ≤ 0.65 cm^2/m^2. Thirty day mortality was 6.5% (total deaths=25). Multivariable logistic regression analysis revealed four risk factors of early mortality: urgency surgery, redo surgery, female sex and patients' age. According to Kaplan Meier analysis ten years survival of the whole sample population was 74.4 ± 2.8 %. According to multivariable Cox regression analysis, there were four independent predictors of long term mortality: female sex, left ventricle ejection fraction (protector factors), and patients' age and urgency surgery (risk factors).

IEOA was not an independent risk factor for 30-day mortality or long term mortality neither analyzed as continuous variable nor as categorical variable (IEOA $\leq 0.85 cm^2/m^2$, IEOA $\leq 0.70 cm^2/m^2$ and IEOA $\leq 0.65 cm^2/m^2$).

Ten years freedom from reoperation for aortic bioprosthesis replacement was 74.3±3.2%. Thus, during follow-up, 111 patients underwent reoperation for aortic bioprosthesis replacement. Causes of aortic bioprosthesis replacement were SVD of the bioprosthesis (n=96), paravalvular leak (n=10) and acute endocarditis (n=5). According to unadjusted Kaplan-Meier analysis, patients with IEOA $\leq 0.70 cm^2/m^2$ had a higher incidence of reoperation because of SVD when compared with patients with IEOA $>0.70 cm^2/m^2$ (Log-rank test: p =0.05). This result was confirmed by multivariable Cox regression analysis which identified two independent predictors of reoperation because of SVD: age (HR= 0.967; 95% CI=0.954-0.981; p <0.0001) and IEOA $\leq 0.70 cm^2/m^2$ (HR=2.16; 95% CI=1.079-4.329; p=0.03). The propensity score adjusted model confirmed these results, although the risk factor "IEOA $\leq 0.70 cm^2/m^2$" was associated with a" p" value just above the significance limit (patients 'age: HR= 0.967, 95% CI= 0.953-0.981, p <0.0001; PPM: HR= 2.033, 95% CI= 0.962-4.295; p= 0.06). Thus, according to our multivariable models, the younger the patients at the moment of the aortic valve replacement, the higher the risk of undergoing reoperation because of SVD. At the same time, patients with IEOA $\leq 0.70 cm^2/m^2$ were twice as likely to undergo reoperation because of SVD than those with IEOA $>0.70 cm^2/m^2$.

In conclusion, besides the age of the patients, the presence of an IEOA $\leq 0.70 cm^2/m^2$ is an independent risk factor for reoperation because of SVD. The propensity score adjustment shows that factors producing an IEOA $\leq 0.70\ cm^2/m^2$, more than mismatch itself, could be a risk factor for reoperation because of SVD.

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Resumen

El desajuste paciente-prótesis ha sido identificado como factor de riesgo de mortalidad después del reemplazo de la válvula aórtica. Recientemente, este desajuste ha sido asociado con un aumento de la tasa de la degeneración estructural de las bioprótesis aorticas. El objetivo del presente estudio fue comparar la incidencia de reoperación por degeneración estructural de los pacientes con desajuste con los que no presentaban desajuste.

Se analizaron los datos de 387 pacientes adultos intervenidos con reemplazo valvular aórtico con una bioprótesis desde 1979 hasta 2009. Nuestro análisis ha sido enfocado sobre el área efectiva de orificio indexado (AEOI) estudiado como variable continua y como variable categórica según tres valores de corte: AEOI $\leq$0,85 cm^2/m^2, AEOI $\leq$0,70 cm^2/m^2y AEOI $\leq$0,65 cm^2/m^2. La mediana del periodo de seguimiento fue de 7,2 años. El seguimiento se completó en el 97% de los pacientes. La incidencia del desajuste paciente-prótesis en nuestra población, definido como AEOI $\leq$0,85 cm^2/m^2 fue del 66,7% (n=258) y la incidencia del desajuste definido por un AEOI $\leq$0,65 cm^2/m^2 fue del 5,2% (n=20). Cuarenta y siete pacientes (12,1%) presentaron un AEOI $\leq$0,70 cm^2/m^2. La mortalidad a corto plazo fue del 6,5%. La regresión logística multivariable demostró cuatro factores de riesgo de mortalidad precoz: cirugía urgente, operación previa, sexo femenino y la edad de los pacientes. Según el análisis de Kaplan-Meier, la supervivencia a 10 años fue del 74,4±2,8 %. En cuanto a la mortalidad a largo plazo, la regresión de Cox identificó cuatro variables asociadas de modo independiente con ella: sexo masculino, fracción de eyección del ventrículo izquierda (asociación inversa), la edad de los pacientes (asociación inversa) y la cirugía de urgencia.

El AEOI no fue un factor de riesgo independiente de mortalidad a corto o a largo plazo, tanto si se analizó como variable continua como si se estudió de manera categórica

(AEOI ≤0,85 cm^2/m^2, AEOI ≤0,70 cm^2/m^2 y AEOI ≤0,65 cm^2/m^2). Durante el seguimiento, 111 pacientes fueron reintervenidos para reemplazar la bioprótesis. Las causas de reoperación fueron degeneración estructural de la bioprótesis (n=96), fuga peri-protésica (n=10) y endocarditis aguda (n=5). Según el análisis de Kaplan-Meier, los pacientes con AEOI ≤0,70 cm^2/m^2 presentaron una incidencia más alta de reintervención por degeneración estructural comparados con los pacientes con AEOI >0,70 cm^2/m^2 (Log-rank test: p=0.05). Este resultado fue confirmado por la regresión de Cox que identificó dos predictores independientes de degeneración estructural: edad (HR= 0,967; 95% IC=0,954-0,981; p <0,0001) y AEOI ≤0,70 cm^2/m^2 (HR=2,16; 95% IC=1,079-4,329; p=0,03). El modelo multivariable ajustado con el propensity score, confirmó el valor predictor independiente de la edad, pero la variable "AEOI ≤0,70 cm^2/m^2" se asoció a un valor "p" justo por encima de la significación estadística (edad: HR= 0,967, 95% IC= 0,953-0,981, p <0,0001; AEOI ≤0,70 cm^2/m^2: HR= 2,033, 95% IC= 0,962-4,295; p= 0.06). Según nuestro modelo multivariable, cuanto más joven es el paciente en el momento del implante de la prótesis aórtica, mayor es el riesgo de ser reintervenido por degeneración estructural de la misma. Además, los pacientes con AEOI ≤0,70 cm^2/m^2 presentan un riesgo doble de ser reintervenidos por degeneración estructural comparados con los pacientes con AEOI >0,70 cm^2/m^2.

En conclusión, además de la edad de los pacientes, la presencia de un AEOI ≤0,70 cm^2/m^2 es un factor de riesgo de reoperación por degeneración estructural de la bioprótesis, aunque el "propensity score" muestra que posiblemente el AEOI ≤0,70 cm^2/m^2 en sí mismo no es un factor de riesgo, sino lo factores que llevan a la existencia de este desajuste entre el tamaño de la prótesis y la superficie corporal del paciente.

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