



**FACULDADE DE MEDICINA DA UNIVERSIDADE DE COIMBRA**

**MESTRADO INTEGRADO EM MEDICINA – TRABALHO FINAL**

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***Transcatheter aortic valve replacement in intermediate risk patients***

ARTIGO DE REVISÃO

ÁREA CIENTÍFICA DE CARDIOLOGIA

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JANEIRO/2018

## **Index**

Abbreviations .....	3
Abstract .....	6
Introduction .....	8
Materials and methods .....	11
Results .....	13
-Risk stratification tools.....	13
-Different routes of vascular access.....	18
-Valves and recent inovations.....	23
-Mortality outcomes and adverse events .....	28
-Pharmacological treatment following TAVR.....	36
-Cost-effectiveness analysis of TAVR .....	39
Discussion .....	42
Conclusion.....	45
Acknowledgements .....	46
References .....	47

## **Abbreviations**

ACS – acute coronary syndrome

AKI – acute kidney injury

AF – atrial fibrillation

AS – aortic stenosis

AR – aortic regurgitation

AUC – area under the curve

AVR – aortic valve replacement

CAB – coronary artery bypass

DAPT – dual antiplatelet therapy

DWI – diffusion weighted imaging

EP – embolic protection

GDF-15 – growth differentiation factor 15

GFR – glomerular filtration rate

IL - interleukin

LV – left ventricle

LVAD – left ventricle assist devices

LVEF – left ventricle ejection fraction

MACCE – major adverse cardiac and cerebrovascular events

MeSH – medical subject headings

MI – myocardial infarction

MRI – magnetic resonance imaging

NACE – net adverse clinical and cerebral events

NYHA – new york heart association

NLR – neutrophil lymphocyte ratio

NT pro-BNP – N-terminal pro-B type natriuretic peptide

PCR – C-reactive protein

PLR – platelet lymphocyte ratio

PM – pacemaker

PPM – patient prosthesis mismatch

QALY – quality adjusted life years

QoL – quality of life

SAPT – single antiplatelet therapy

SAVR – surgical aortic valve replacement

STS – Society of Thoracic Surgeons

TA – transapical

TAo – transaortic

TAVI – transcatheter aortic valve implantation

TAVR – transcatheter aortic valve replacement

TCvl - transcaval

TF – transfemoral

TSc – transsubclavian

VARC – valve academic research consortium

VKA – vitamin K antagonist

## **Abstract**

Introduction – TAVR is recommended for high surgical risk or inoperable patients, with symptomatic aortic stenosis, since it has shown lower mortality and fewer adverse events than its alternative, SAVR. Recently, owing to its good clinical performance, TAVR has been proposed to treat intermediate risk patients; however, the expansion of the use of TAVR mandates rigorous clinical validation. This paper will focus on collecting all the available data on extending TAVR to intermediate risk populations, discussing recent technical innovations, clinical outcomes and mortality effects of TAVR against its comparator, SAVR.

Methods – A PUBMED search was performed with the following keywords: “aortic stenosis”, “transcatheter aortic valve replacement”, “surgical aortic valve replacement”, “aortic valve”, “risk”, “intermediate risk” and “transcatheter aortic valve implantation”. Articles were excluded if they were not written in English, published in the last 10 years or did not discuss the intermediate risk category. A total of 91 papers were analysed.

Results – Heart team has a primordial importance in adequating the best therapy to each patient; however, no risk score has proved good clinical accuracy to stratify procedure/surgery-related risk. Between the available vascular approaches, TF is the safest one. Although valves are being constantly improved, currently, balloon and self expandable appear to be safer than mechanically-expandable valves. In terms of mortality and adverse events, the majority of trials demonstrated that TAVR is noninferior, or can be superior, to surgery. The cost related to TAVR, the precise estimation of valve durability, and deciding which is the best pharmacological treatment post-TAVR are not yet established for the percutaneous procedure.

Conclusion – TAVR, owing to its good outcomes, should be studied in more randomized clinical trials in the intermediate risk population, with longer follow-up and larger cohorts. Future efforts should be placed on estimating prosthetic valves durability, diminishing valve costs and establishment of the best medical treatment post-TAVR.

## **Introduction**

Among heart valve disease, aortic valve stenosis is the most prevalent,<sup>1</sup> affecting 2 to 7% of the population above 65 years.<sup>2</sup> After symptoms arise (dyspnoea, angina or syncope), the prognosis is very poor, and approximately 50% of patients die in 3 to 5 years.<sup>3</sup>

Severe AS consists of an aortic valve area smaller than  $1.0 \text{ cm}^2$ , or an aortic valve area index of less than  $0.6 \text{ cm}^2$  per square meter of body surface area, a mean gradient of more than 40 mmHg, or a maximum aortic flux of more than 4 meters per second, at rest or with dobutamine provocation, in patients with a left ventricular ejection fraction of less than 55% or a Doppler velocity index of less than 0.25 on resting echocardiography.<sup>4</sup> There are 3 main patterns for aortic stenosis: the normal flow high gradient, occurring in 60 to 70% of AS patients, whose development is associated with myocardial hypertrophy; the “paradoxical” low-flow low-gradient, that arises when the compensatory mechanisms are overcome – LV dilates and LVEF decreases, while LV filling pressure and pulmonary pressure both increase (5 to 25% of patients); and the “classic” low-flow low-gradient (5 to 10% of patients), which is truly severe.<sup>5</sup>

In patients with severe symptomatic aortic stenosis, the substitution of the valve is preconized, to impede the natural progression of the disease and to promote a better quality of life. In the past, the only available option for valve substitution was surgical aortic valve replacement (SAVR). In 2002, transcatheter aortic valve replacement (TAVR) was first performed, becoming an option for patients with severe symptomatic aortic valve stenosis.<sup>1</sup>

TAVR consists in a minimally invasive procedure based on inserting a new valve through a catheter to the place where the stenotic one is. In ideal conditions, this new valve fully adapts itself to the older, allowing no blood regurgitation, and a restoration of the normal bloodstream through the aortic valve. There are many different approaches to insert the new



valve: transfemoral (TF), transapical (TA), transaortic (Tao), transsubclavian (TSc), and transcaval (TCvl),<sup>6</sup> being TF the most widely performed. Furthermore, TAVR can be performed without extracorporeal circulatory support, general anesthesia, mechanical ventilation, or need for intubation, which gives it some advantages over SAVR.<sup>7</sup>

However, there are some absolute contraindications to TAVI: the absence of a “heart team” or on-site cardiac surgery; a life expectancy lower than one year; a low likelihood of improvement in quality of life (QoL); severe concomitant disease of other valves – also requiring surgery; inadequate annulus size (<18 mm or >29 mm); presence of left ventricular thrombus; active endocarditis; high risk of coronary obstruction; large plaques with mobile thrombi in the ascending aorta or arch or inadequate vascular access.<sup>8</sup>

Studies have been conducted comparing TAVR and SAVR in different populations. The Placement of Aortic Transcatheter Valve (PARTNER) 1A study, CoreValve and NOTION trials have shown that TAVR is able to compete in terms of mortality with SAVR in high risk cohorts, and it is now a class I guideline (Fig.1) to perform a TAVR in this population, and also in people who are deemed inoperable, due to technical reasons (porcelain aorta, hostile chest wall, or presence of bypass graft in proximity to the sternum, for instance).<sup>1,9,10</sup> In terms of intermediate risk population, TAVR is considered a class IIa guideline (Fig.1), while SAVR is still considered the gold-standard approach.<sup>11</sup>

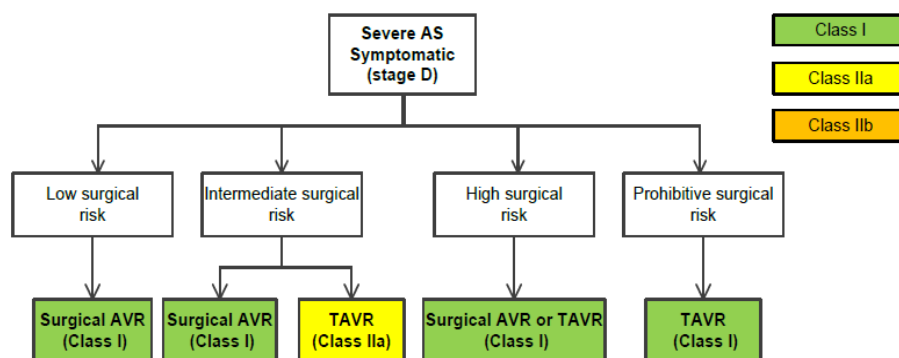


Figure 1 – Adapted from Nishimura et al.<sup>11</sup> Guidelines for the treatment of severe symptomatic AS.

In the last couple of years, there seems to be a trend towards referring lesser risk patients to TAVR procedures.<sup>12-14</sup> However, in this lower risk population, generally younger and with less comorbidities (namely rates of previous bypass surgeries, stroke, peripheral vascular disease, renal failure or frailty scores),<sup>15</sup> there are no particular recommendation on whether TAVR is the best possible therapeutic option.

This paper will focus on collecting all the available data on extending TAVR to intermediate risk populations, discussing recent technical innovations, clinical outcomes and mortality effects of TAVR against its comparator, SAVR.

## **Materials and methods**

Article search was performed through PUBMED database, in July 2017, using the following MeSH terms: “aortic stenosis”, “transcatheter aortic valve replacement”, “surgical aortic valve replacement”, “aortic valve” and “risk”. The keywords “intermediate risk” and “transcatheter aortic valve implantation”, although not considered MeSH terms, were also added to the search, as they were deemed relevant to enlarge our data base. There were no restrictions regarding the type of study included - meta-analysis, systematic reviews, reviews or expert opinions were taken into consideration.

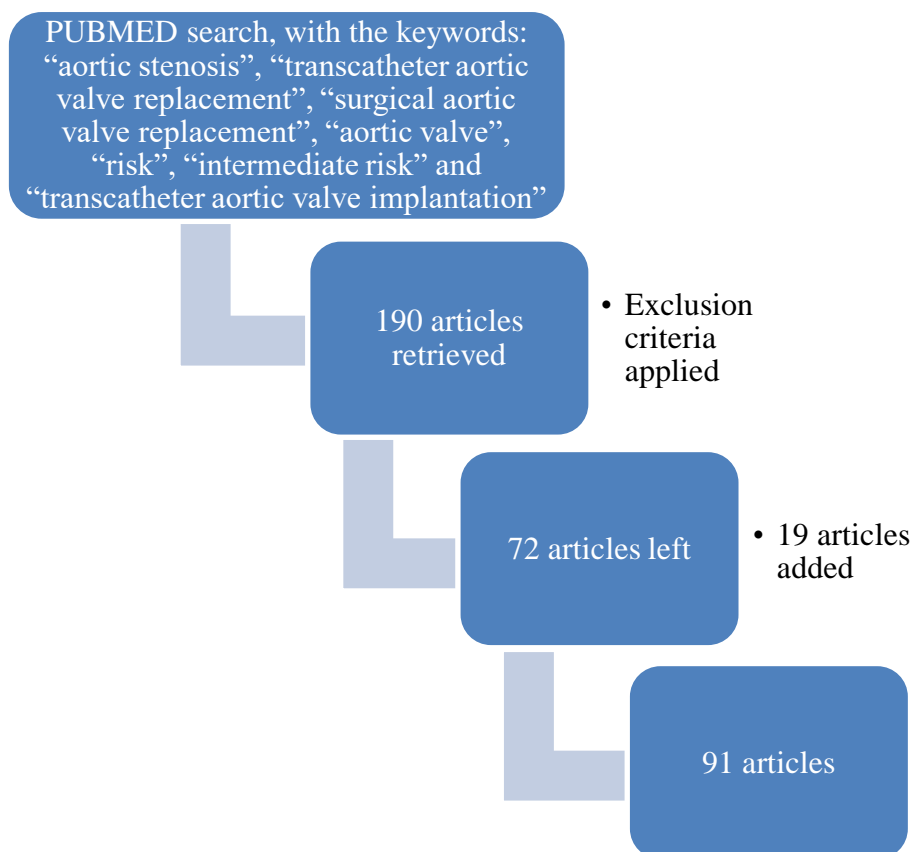
Papers were afterwards excluded from our database if they were not written in English, published in the last 10 years, or if they did not discuss the intermediate risk category for transcatheter aortic valve replacement, therefore articles targeting solely high risk or low risk populations were ruled out.

The initial literature search retrieved 190 articles. According to the exclusion criteria, 72 papers were selected, based on their relevance and pertinence. After analysing the 72 articles, another 19 were added, consisting of references from the previous ones that were considered adequate to include our database. In the end, a total of 91 articles were analysed throughout the development of this study.

Our search was divided in different areas, and consequently different variables were analysed in each of them. In terms of risk stratification tools, correlations between estimated and observed outcomes were considered. Regarding routes of access, trials considering transfemoral, transapical, transaortic, transsubclavian and transcaval routes have been considered. In valve analysis, SAPIEN 3 (Edwards Lifesciences) and SAPIEN XT (Edwards Lifesciences) ballon-expandable, Corevalve Evolut R (Medtronic) self-expandable and Lotus (Boston Scientific Corporation) mechanically-expandable devices were evaluated.

While comparing routes of access, different valves, different risk cohorts and TAVR vs SAVR, the outcomes of interest were all-cause mortality, disabling stroke rates, echocardiographic parameters, length of hospitalization, quality of life assessments, and adverse events, namely stroke, vascular complications, myocardial infarction, major bleeding, acute kidney injury, atrial fibrillation, neurological events, requirement for pacemaker implantation and aortic regurgitation – in the analysed trials, clinical endpoints were defined by VARC, or VARC-2 criteria.<sup>16</sup>

In terms of costs, TAVR and SAVR were compared regarding the price of devices, procedures and follow-up. Considering pharmacological treatment post-TAVR, dual or single antiplatelet therapy, as well as anticoagulant strategies have been taken into consideration.



## **Results**

While addressing the possibility of extending TAVR indications to intermediate risk patients, there are several issues that must be considered. In order to do so, the results of this study were organized in different sections.

### **- Risk stratification tools**

It is of paramount importance to correctly stratify each patient in terms of surgical risk, before deciding which treatment suits them best. Clinical judgment, based on the Heart Team, should be the primary tool for decision making.<sup>17</sup> A Heart Team is a multidisciplinary group, composed of an interventional cardiologist, a cardiac surgeon, an anesthesiologist, a radiologist and the referring cardiologist, among others, whose main purpose is to discuss and select the best possible approach to each singular patient.

The application of different scores has been very helpful in guiding physicians to make the best treatment option. However, the vast majority of risk scores used with this finality, were developed to predict the risk for cardiac surgery and not for TAVR. The STS score takes into account 39 factors – it is the most complex, being one of the most used among all these classifications. Logistic Euroscore I is also used very often, taking into consideration 17 parameters, it has been designed to predict early mortality after major cardiac surgeries. Generally, intermediate risk classification consists of STS scores between 4 and 8%, or Logistic Euro SCORE I between 10 and 20%. Other classifications, not as used as the ones mentioned above, are: Euro SCORE II (was developed based on Euro SCORE I, including 18 factors), Ambler score (consisting of 14 variables), and ACEF (a simpler score, with only 3 parameters). All of these variables are present in the table below (Table 1).<sup>18</sup>

However, they do not take into consideration many factors that could increase the risk related to surgery: patient frailty, cognitive impairment, liver disease, risk of delirium or anatomical characteristics (i.e. porcelain aorta).<sup>19</sup> Among these, frailty seems to be the most important one, since it is very common in the elderly population (constitutes the majority of patients referring to TAVR/SAVR), can lead to worse QoL outcomes and greater adverse events;<sup>20,21</sup> it is currently evaluated through the use of Katz score, gait speed or five minutes walk, which can lead to different results depending on the test conducted.<sup>22,23</sup> Consequently, these risk classifications do not predict as accurately as desired the risk for patients to enroll in these procedures, and can lead to over (logistic Euro SCORE I) or underestimations (STS score) of the actual risk incurred.<sup>18</sup>

<b>Mortality to 30 days</b>	<b>9.6% (44)</b>
Logistic EuroSCORE I	22 ± 13.5%
EuroSCORE II	7.0 ± 5.9%
STS-PROM	7.9 ± 5.7%

Table 1 – Adapted from Silaschi et al..<sup>23</sup> Comparison between observed and estimated mortality between EuroScore and STS scores.

A new classification, specifically for TAVR, has been developed to fulfil the need to correctly stratify risk patients. The Survival post TAVI Score (STT score), unlike the above mentioned scales, takes into consideration other variables that have proved to be related to adverse events after TAVR, particularly history of previous stroke, depressed renal function, high pulmonary arterial pressures and elevated LV pressure. Comparing the ability to predict 1 year all-cause death, the AUC of STT score was 0.66, similar to the STS score, however better than Euro SCORE I (AUC 0.62). In terms of 30-day mortality the AUC for Euro SCORE, STS and STT score were, respectively, 0.68, 0.67 and 0.66.<sup>24</sup> Nevertheless, STT has some limitations: it was derived from a small cohort of a thousand patients; and it does not

include features usually evaluated in patients during preoperative assessment of aortic stenosis (i.e. porcelain aorta).<sup>19</sup> One other classification, SURTAVI score, included predictors of adverse events of TAVR present in the literature, such as: frailty, pulmonary disease, peripheral artery disease, diabetes mellitus, neurological dysfunction, renal disease and pulmonary hypertension. Since the SURTAVI score is based upon literature’s available clinical predictors, and the STT represents observational data from a large worldwide cohort, the two can be seen as complementary to each other.<sup>24</sup>

The Observant Score is a simple score used to predict 30-day mortality after TAVR. It is based on 7 preprocedural variables, namely GFR, critical preoperative state, New York Heart Association (NYHA) class, pulmonary hypertension, diabetes mellitus, previous balloon aortic valvuloplasty and left ventricular ejection fraction. Although having shown a good global accuracy and being a simpler score than the ones above, it still lacks validation in larger cohorts.<sup>25</sup>

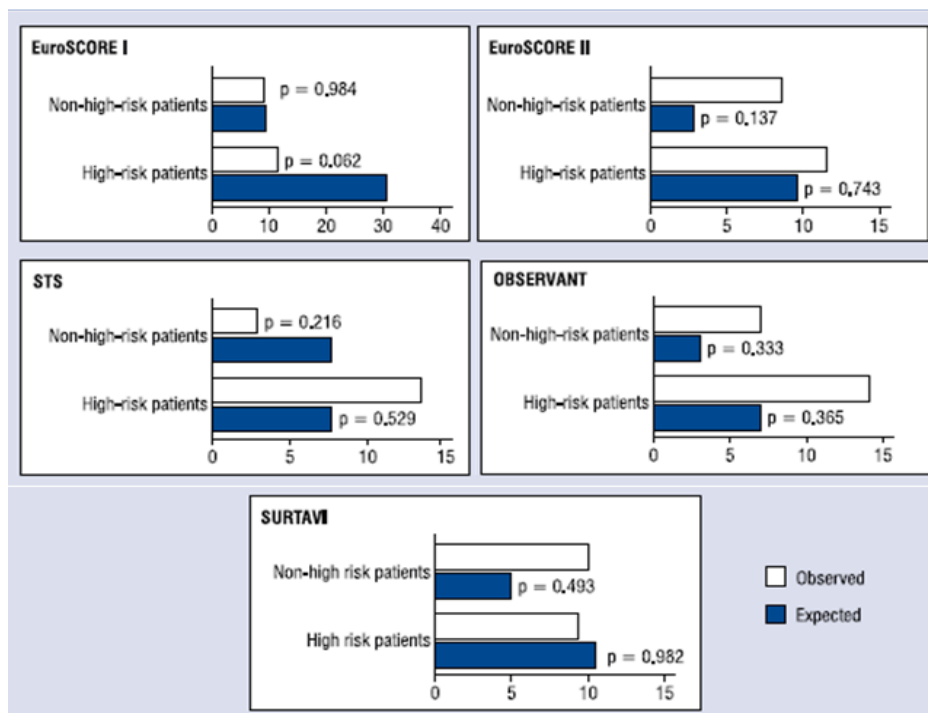


Figure 2 – Adapted from Zbroński et al..<sup>18</sup> Rates of observed vs expected mortalities, between Logistic Euro SCORE I, Euro SCORE II, STS, OBSERVANT and SURTAVI.

	Euro- SCORE I	Euro- SCORE II	STS	ACEF	Ambler's	OBSERVANT	SURTAVI
<b>Patient characteristics</b>							
Age	+	+	+	+	+		
Sex	+	+	+		+		
Height			+				
Weight			+				
Body mass index					+		
Ethnicity			+				
<b>Co-morbid conditions</b>							
Diabetes		+	+			+	+
Hypertension			+		+		
Chronic lung/pulmonary disease	+	+	+				+
Extracardiac arteriopathy	+	+	+				
Peripheral vascular disease			+				+
Neurological dysfunction	+		+				+
Frailty							+
Cerebrovascular accident			+				
Creatinine clearance		+				+	+
Serum creatinine	+		+	+	+		
Dialysis-dependent renal failure			+		+		
Immunosuppressive therapy			+				
Poor mobility		+					
<b>Cardiac history</b>							
NYHA classification		+	+			+	
Unstable angina	+		+				
CCS class IV angina		+					
Recent myocardial infarction	+	+	+				
Arrhythmias			+		+		
Previous cardiac surgery	+	+			+		+
Previous CABG			+				
Previous valvular disease			+				
Previous PCI			+				
Previous balloon aortic valvuloplasty						+	
Active endocarditis	+	+	+				
Number of diseased coronary vessels			+				
Type and severity of valvular disease	+						
<b>Hemodynamic state</b>							
Pulmonary hypertension	+	+				+	+
Ejection fraction	+	+	+	+	+	+	+
Critical preoperative state	+	+				+	
Cardiogenic shock			+				
Resuscitation			+				
Inotropic agents			+				
Intra-aortic balloon pump			+				
<b>Procedure</b>							
Emergency	+	+	+				
Surgery on thoracic aorta	+	+	+				
Aortic valve surgery		+	+		+		
Mitral valve surgery			+		+		
Aortic and mitral valve surgery			+		+		
Tricuspid valve surgery			+				
Surgery for CHD			+				
Rhythmological surgery			+				
Concomitant CABG			+		+		
Concomitant tricuspid valve surgery			+		+		
Post-infarct septal rupture	+						

CABG — coronary artery by-pass grafting; CCS — Canadian Cardiovascular Society; CHD — congenital heart disease; NYHA — New York Heart Association; PCI — percutaneous coronary intervention; TAVI — transcatheter aortic valve implantation

Table 2 – Adapted from Zbroński et al.<sup>18</sup> Variables included in each risk classification.

While these different classifications have been proposed to stratify risk in these patients, none has proved to be sufficiently accurate to be chosen as the preconized tool for TAVR patients – in a trial comparing all the referred scores, in terms of predicting 30-day mortality neither of them had an AUC over than 0.60;<sup>18</sup> one other study also concludes that due to the lack of precision of the above mentioned scores, the Heart Team is fundamental to guide the decision process.<sup>23</sup>



New efforts have recently been made in pursuit of the best possible classification for patients. Five biomarkers of inflammation and/or myocardial dysfunction (growth differentiation factor 15 – GDF-15, interleukin-6 – IL-6, interleukin-8 – IL-8, high sensitivity C-reactive protein – PCR, and N-terminal pro-B type natriuretic peptide – NT pro-BNP) were tested in addition to the referred risk scores, as they reflect different aspects of cardiovascular and noncardiovascular disease pathophysiology. Even though patients who died or had more rehospitalizations presented with higher biomarker concentrations, GDF-15 and IL-8 were the only ones that offered statistically significant improvements, with GDF-15 being the most promising predictor of poor outcome.<sup>26</sup> This biomarker is a cytokine, produced in response to inflammation and tissue injury that, apart from the widely known NT- proBNP – that is produced almost exclusively in the heart, can also reflect extracardiac disease manifestations in heart failure, which may be more helpful to predict adverse events in these situations.

Neutrophil lymphocyte (NLR) and platelet lymphocyte ratios (PLR), have also been studied for risk stratification. Both these indicators are systemic inflammation markers, and it has been proven that their elevation is correlated with higher mortality, and a higher occurrence of 30 day adverse outcomes. Being non-invasive, widely available and easily obtained, NLR and PLR could be well suited as risk markers.<sup>27</sup>

Despite all recent efforts to create a risk tool as accurate as possible, there is no consensus about which score should be used to predict mortality and adverse events in TAVR, and it is of utmost importance that future studies develop more specific clinical tools to guide medical judgement in TAVR.<sup>23</sup> Some conditions have been identified as predictors of 30 day or midterm mortality (namely AKI stage 2 or more, periprocedural acute myocardial infarction and increased pro-BNP), and, among many factors, these ones should be considered for the development of new classifications for risk assessment.<sup>28</sup> While these are not available, risk stratification should highly rely on the Heart Team.

- **Different routes of vascular access**

There are several routes of vascular access available allowing TAVR implantation, and the most appropriate route must be chosen in each case, to minimize complications and to achieve the highest success rate. A complete analysis of the peripheral vascularity, aorta, aortic annulus and left ventricle plays a key role in the process of choosing the best route, and multimodality imaging has been increasingly used to correctly evaluate the patient's vascular status.<sup>8</sup>

Generally TF approach is considered default, since it is the least invasive and it can be performed with local anesthesia, resulting into a shorter procedural time, hospital stay and earlier mobilization.<sup>8</sup> On the other hand, it has a significant risk of peripheral vascular complications, it may expose to an increased risk of stroke (atherosclerotic debris from the aortic arch and ascending aorta may be released) and the amount of contrast agent used is higher than in other routes.<sup>29</sup>

A TA approach has been used as the main alternative to the TF route. Patients who generally undergo TA TAVR have a higher prevalence of peripheral artery disease or previous procedures in the aortoiliac arteries.<sup>29</sup> This strategy has some advantages: a direct pathway to the aortic valve and a lower risk of peripheral vascular injury. However, it is much more invasive than the previous approach, leading to higher rates of myocardial injury (greater cardiac biomarker release, lesser improvement in LVEF, arrhythmias and apical wall motion abnormalities), bleeding, hospital stay (it requires general anesthesia and the recovery is lengthier) and need for orotracheal intubation.<sup>8</sup> It is also argued that TA can be considered a significant predictor of readmission and in hospital mortality.<sup>30</sup> Clinical results of TA approach in TAVR vary among operators experience, with superior results being reported from single centers performing only this technique.<sup>30</sup>

In more specific trials, comparing either TF or TA TAVI with SAVR in intermediate risk patients, results have underlined the benefits of TF approach (Fig. 3). Two meta-analysis have demonstrated lower mortality and adverse event rates (stroke and AKI) in TF TAVI, while the transapical route showed similar, or worse, results than SAVR.<sup>19,31</sup>

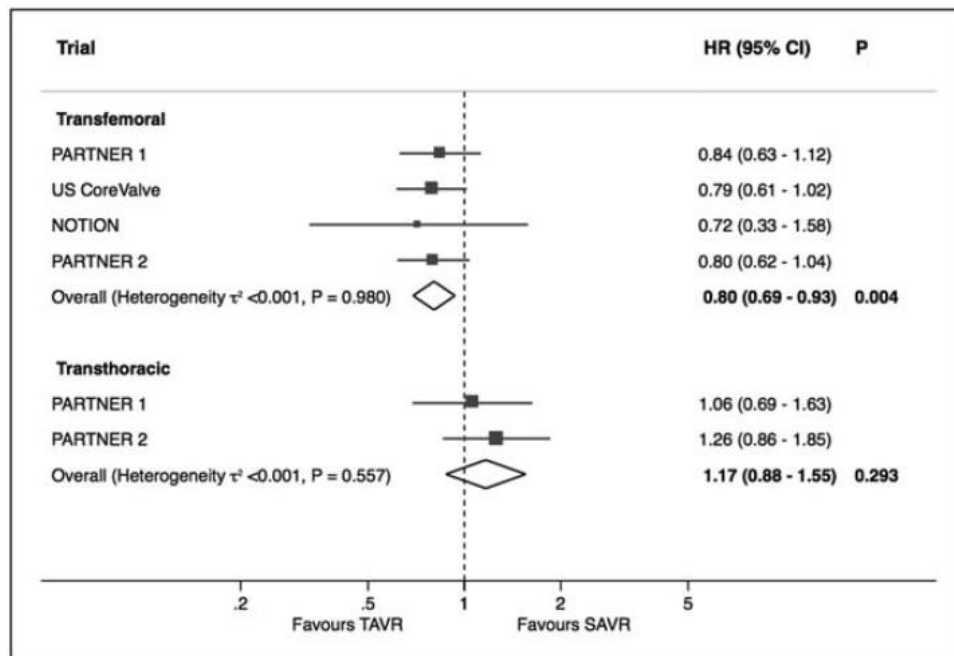


Figure 3 – Adapted from Praz et al.<sup>10</sup> Comparison of 2-year death from any cause between TF and Transthoracic outcomes.

Others approaches are more uncommon and rarely used, since they tend to have worse outcomes and more adverse events. The transaortic (TAo) approach has been recently reported has a feasible alternative to the TF or TA approaches. A study comparing TF, TA and TAo routes demonstrated that, in high risk cohorts, 1-year survival tended to be better in the TAo cohort than in TA (Fig. 4), while the TF approach had the best survival rate, however with no significant differences.<sup>32</sup> A meta-analysis has also been conducted, comparing TAo and TA routes, and equivalent outcomes in 30-day mortality, major bleeding, stroke incidence and paravalvular leak have been reported.<sup>33</sup>

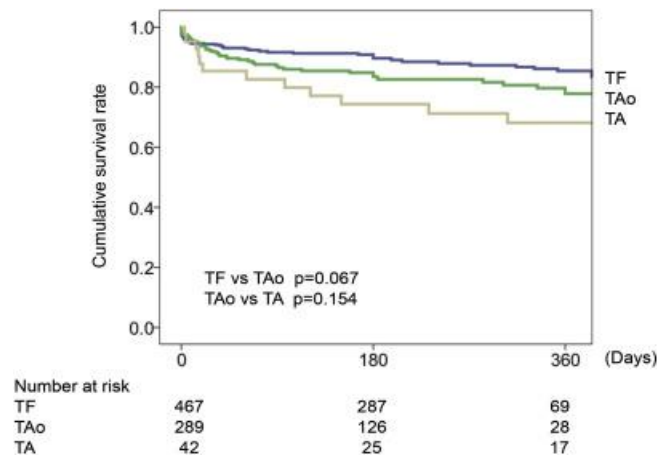


Figure 4 – Adapted from Arai et al.<sup>33</sup> Comparison of cumulative survival between TF, TAO and TA approaches.

The transsubclavian (TSc) route has also been studied regarding TAVR procedures. In a trial comparing it with the TF approach, in-hospital complications rates, namely AKI, major bleeding and in-hospital mortality, were similar between both approaches, and freedom from events at 6 months was higher in the transsubclavian population, but with no significant differences (Table 3).<sup>34</sup> Another trial, comparing cumulative survival between TF, TSc, TA and TAO routes, claimed that transsubclavian access survival was not significantly different from TF, and both had significantly higher survival rates than the other two approaches (Fig. 5).<sup>30</sup>

Adverse Events at 6 months	Total (n=514)	Femoral (n=460)	Transsubclavian (n=54)	P
Death, %	89.1±1.5	88.6±1.6	93.3±3.8	0.49
Cardiac death, %	95.8±0.9	95.5±1.0	97.9±2.1	0.41
MACCEs, %	86.3±1.6	85.5±1.7	93.9±3.4	0.25

Table 3 – Adapted from Petronio et al.<sup>34</sup> Comparison of adverse events at 6 months between TF and TSc cohorts.

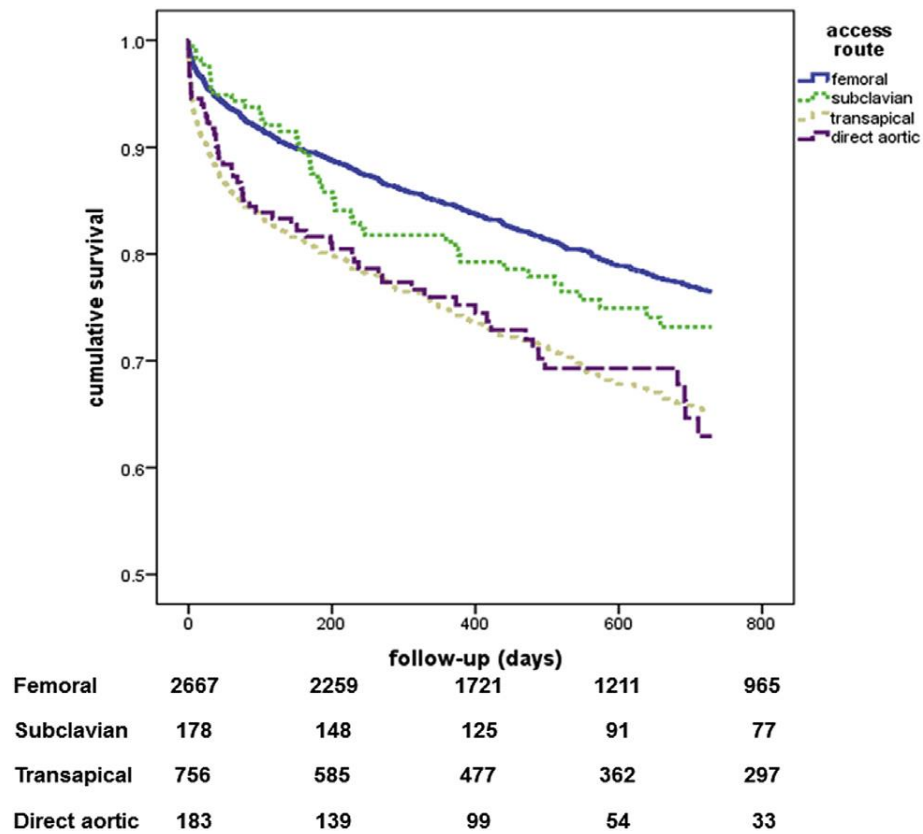


Figure 5 – Adapted from Fröhlich et al.<sup>30</sup> Cumulative survival, comparing TF, TSc, TA and TAO approaches.

The transcaval (TCvl) access has also been used as an alternative to the TF route.<sup>35</sup> In a trial with 100 patients undergoing TAVR with TCvl approach, 30-day survival was 92% and bleeding and major vascular complications were 7% and 13%, respectively, suggesting TCvl route as an interesting strategy to be considered in some patients.<sup>36</sup>

However, all these studies about these different routes (TAo, TCvl and TSc) were conducted in high risk cohorts (STS scores over than 8%, and Logistic Euro SCORE over than 20%), and future studies considering lower risk populations, and greater cohorts are needed.

Nevertheless, there is an unavoidable selection bias in the TF strategy, compared to the others, since it is generally chosen in the first place. Furthermore, patients who undergo TAVR through TF route are usually healthier than the ones who undergo alternative approaches - higher risk scores, higher incidence of cerebrovascular disease and peripheral artery disease (Table 4).<sup>6</sup>

Characteristic <sup>a</sup>	All (N = 595)	TF (n = 337)	Non-TF (n = 258)	p Value
Age, y	81.67 ± 8.29	82.35 ± 7.95	80.79 ± 8.65	0.02
Female	293 (49)	152 (45)	141 (55)	0.02
Caucasian	532 (89)	294 (87)	238 (92)	0.05
STS PROM %	11.0 ± 5.5	10.5 ± 5.3	11.7 ± 5.7	0.01
STS <8%	182 (31)	113 (34)	69 (27)	0.05
STS 8%–15%	298 (50)	169 (50)	129 (50)	
STS >15%	115 (19)	55 (16)	60 (23)	
BMI, kg/m <sup>2</sup>	26.70 ± 5.86	27.13 ± 5.63	26.13 ± 6.12	0.04
Chronic lung disease				
None	285 (48)	162 (48)	123 (48)	0.66
Mild	131 (22)	77 (23)	54 (21)	
Moderate	72 (12)	36 (11)	36 (14)	
Severe	107 (18)	62 (18)	45 (17)	
Diabetes	260 (44)	144 (43)	116 (45)	0.61
Renal dialysis	18 (3.0)	11 (3.3)	7 (2.7)	0.99
Hypertension	575 (97)	329 (98)	246 (95)	0.14
Coronary artery disease	202 (34)	108 (32)	94 (36)	0.31
Prior cardiac operation				
Any	259 (44)	130 (39)	129 (50)	<0.01
CABG	211 (35)	105 (31)	106 (41)	0.01
Cerebrovascular disease	180 (30)	88 (26)	92 (36)	0.01
Peripheral arterial disease	213 (36)	76 (23)	137 (53)	<0.01
Serum creatinine, mg/dL	1.37 ± 1.18	1.37 ± 1.31	1.36 ± 1.00	0.87
Hemoglobin, g/dL	11.46 ± 1.81	11.38 ± 1.52	11.54 ± 2.13	0.33
Echocardiogram data				
Ejection fraction	0.55 (0.40–0.60)	0.55 (0.40–0.60)	0.55 (0.40–0.60)	0.82
Aortic valve area, cm <sup>2</sup>	0.66 ± 0.18	0.67 ± 0.19	0.64 ± 0.17	0.05
Mean aortic gradient, mm Hg	45.42 ± 14.34	46.17 ± 15.57	44.45 ± 12.50	0.14
Pre-MR moderate/severe	281 (49)	161 (48)	120 (47)	0.99
Pre-TR moderate/severe	215 (38)	131 (39)	84 (33)	0.30
Pre-AR moderate/severe	148 (25)	83 (25)	65 (25)	0.98








Table 4 – Adapted from Jensen et al..<sup>6</sup> Comparison of preoperative characteristics between TF and non-TF routes.

Due to its lower mortality and adverse events, transfemoral strategy is considered the safest strategy for TAVR procedure; transaortic and transsubclavian routes may be more successful than the transapical access.<sup>30,32</sup>

- **Valves and recent innovations**

Many studies have compared outcomes in populations with different risk scores, undergoing the same procedure, or undergoing either SAVR or TAVR. In order to ease comparisons in clinical trials, Valve Academic Research Consortium (VARC) criteria was published, in 2011, and later modified in 2012, giving birth to VARC-2. Clinical endpoints, such as mortality, stroke, myocardial infarction, bleeding complications, acute kidney injury and vascular complications were defined, providing a standardization for posterior studies, and promoting a clearer way to interpret them.<sup>16</sup>

Over the last couple of years, TAVR has had an impressive advancement, and newer devices have been constantly developed, in order to reduce the delivery catheter profile, facilitate deployment and enable repositioning and retrieval capability, in order to obtain the desired position for the valve, and reduce adverse events. Currently, there are 3 types of valves available for TAVR procedures: the balloon-expandable, the self-expanding and the mechanically-expandable (Fig. 6), each of them with their own characteristics (Table 5).<sup>37</sup>

Balloon-expandable devices				Device Name	Valve Structure	Access Route, Delivery System, and Valve Size	Reference Access Vessel Diameter	Repositionable?	Fully Retrievable?
Sapien XT	Sapien 3								
				Sapien 3 (Edwards Lifesciences)	Bovine pericardial tissue valve balloon-expandable cobalt-chromium frame	TF: Edwards eSheath 14 F (20, 23, 26 mm), 16 F (29 mm); TA, TAO: Certitude 18 F (20, 23, 26 mm), 21 F (29 mm)	≥ 5 mm (Sapien 3: 23, 26 mm), ≥ 5.5 mm (Sapien 3: 29 mm)	No	No
Self-expanding devices				Evolut R (Medtronic)	Porcine pericardial tissue valve; self-expanding nitinol frame	TF, TAO, TSc: EnVeo R 14 F outer diameter (23, 26, 29, 34 mm)	≥ 5 mm (Evolut R: 23, 26, 29 mm) ≥ 5.5 mm (Evolut R: 34 mm)	Yes	Yes
Evolut R	Acurate Neo	Portico	Allegra	Portico (St. Jude Medical, Inc.)	Bovine pericardial tissue valve; self-expanding nitinol frame	TF, TAO, TSc: 18 F (23, 25 mm) 19 F (27, 29 mm)	≥ 6 mm	Yes	Yes
				Acurate Neo (Symetis)	Porcine pericardial tissue valve; self-expandable nitinol alloy stent	TF: 18 F outer diameter (small, medium, large); TA: sheathless 28 F (small, medium, large)	≥ 6 mm	No	No
Mechanically-expandable devices				JenaValve (JenaValve Technology GmbH)	Porcine pericardial tissue valve; self-expanding nitinol stent	TA: sheathless 32 F (23, 25, 27 mm)	-	Yes	No
Lotus				Lotus (Boston Scientific Corporation)	Bovine pericardial tissue valve; self-expanding, braided nitinol frame	TF: 18 F (23 mm), 20 F (25, 27 mm)	≥ 6 mm (Lotus: 23 mm) ≥ 6.5 mm (Lotus: 25, 27 mm)	Yes	Yes
				Allegra (NVT AG)	Bovine pericardial tissue valve (annular skirt and leaflets); self-expanding nitinol stent	TF: 18 F (23, 27, 31 mm)	≥ 6 mm	Yes	Yes

Abbreviations: TA, transapical; TAO, transaortic; TF, transfemoral; TSc, transsubclavian.

Figure 6 and Table 5 – Adapted from Todaro et al..<sup>37</sup> Types of valves and technical characteristics.

Among percutaneous valves, the SAPIEN 3 (Edwards Lifesciences), the Corevalve Evolut R (Medtronic) were used more frequently in clinical trials.<sup>4,38,39</sup>

The SAPIEN 3 (Edwards Lifesciences) balloon expandable valve has been developed with lower-profile delivery catheters than the previous prothesis (SAPIEN XT, Edwards Lifesciences), in order to ease delivery and promote a more precise positioning, and also with a polyethylene terephthalate outer skirt, to proportionate a better adjustment of the new valve to the stenotic one, decreasing the likelihood of paravalvular leaks.<sup>40</sup> A trial, comparing the clinical outcomes between these two valves, concluded that despite the SAPIEN 3 (Edwards Lifesciences) system reduced significantly residual paravalvular leakage, there was no significant difference in 30-day mortality.<sup>41</sup>

The Corevalve Evolut R (Medtronic), when compared with the previous generation of CoreValve devices, provides several improvements, namely annular sealing, durability and the capability to be repositioned and recaptured.<sup>37</sup>

The CHOICE study enrolled high-risk surgical patients (STS above 10%, or logistic EuroSCORE above 20%) with severe aortic stenosis, suitable for TF TAVR; patients were randomly assigned to receive a balloon-expandable valve (Sapien XT, Edwards Lifesciences) or self-expandable valve (Corevalve, Medtronic). Among this cohort, the use of a balloon-expandable valve resulted in significantly greater rates of device implantation success (composite end point including successful vascular access, correct position of the device and intended performance of the valve),<sup>16</sup> less occurrence of aortic regurgitation and less need for pacemaker placement, than the use of a self-expandable valve, while there were no significant differences regarding other outcomes, in a 30-day follow up (Tables 6 and 7).<sup>42</sup>



	No./Total No. (%)		Relative Risk (95%CI)	P Value
	Balloon-Expandable Valve (n = 121)	Self-expandable Valve (n = 120)		
Immediate procedural mortality	0/121 (0)	0/120 (0)	-	-
Final aortic regurgitation				
Angiography <sup>a</sup>				
None/trace	75/121 (62.0)	42/120 (35.0)	1.77 (1.34-2.35)	<.001
Mild	41/121 (33.9)	56/120 (46.7)	0.73 (0.53-0.99)	
Moderate	4/121 (3.3)	17/120 (14.1)	0.23 (0.08-0.67)	
Severe	1/121 (0.8)	5/120 (4.2)	0.20 (0.02-1.67)	
Echocardiography <sup>b</sup>				
None/trace	88/121 (66.1)	59/120 (49.2)	1.48 (1.20-1.83)	.005
Mild	39/121 (32.2)	54/120 (45.0)	0.72 (0.52-0.99)	
Moderate	1/121 (0.8)	7/120 (5.8)	0.14 (0.02-1.13)	
Severe	1/121 (0.8)	0/120 (0)		
Aortic regurgitation index, mean (95% CI) <sup>c</sup>	29.0 (27.7-30.3)	27.3 (26.0-28.7)		.08
Coronary obstruction	2/121 (1.6)	0/120 (0.0)		.49
Annular rupture	0/121 (0)	0/120 (0)		
Left-to-right shunt	2/121 (1.6)	2/120 (1.7)	0.99 (0.14-6.93)	.99
Device success (primary endpoint)	116/121 (95.9)	93/120 (77.5)	1.24 (1.12-1.37)	<.001

Variable	No./Total No. (%)		Relative Risk (95% CI)	P Value
	Balloon-Expandable Valve (n = 121)	Self-expandable Valve (n = 117)		
Death				
Any cause	5/121 (4.1)	6/117 (5.1)	0.81 (0.25-2.57)	.77
Cardiovascular causes	5/121 (4.1)	5/117 (4.3)	0.97 (0.29-3.25)	.99
Stroke	7/121 (5.8)	3/117 (2.6)	2.26 (0.60-8.52)	.33
Myocardial infarction	1/121 (0.8)	0/117 (0.0)		.99
Bleeding				
Life threatening	10/121 (8.3)	14/117 (12.0)	0.69 (0.32-1.49)	.35
Major	23/121 (19.0)	17/117 (14.5)	1.31 (0.74-2.32)	.36
Minor	11/121 (9.1)	9/117 (7.7)	1.18 (0.51-2.74)	.70
Major or minor	34/121 (28.1)	26/117 (22.2)	1.26 (0.81-1.97)	.30
Vascular complications				
All	17/121 (14.0)	15/117 (12.8)	1.10 (0.57-2.09)	.78
Major	12/121 (9.9)	13/117 (11.1)	0.89 (0.42-1.88)	.76
Minor	5/121 (4.1)	2/117 (1.7)	2.42 (0.48-12.21)	.28
Acute kidney injury	5/121 (4.1)	11/117 (9.4)	0.44 (0.16-1.23)	.13
Repeat procedure for valve-related dysfunction	1/121 (0.8)	2/117 (1.7)	0.48 (0.04-5.26)	.62
Combined safety end point <sup>d</sup>	22/121 (18.2)	27/117 (23.1)	0.79 (0.48-1.30)	.42
Major adverse cardiovascular and cerebrovascular events <sup>e</sup>	8/121 (6.6)	4/117 (3.4)	1.93 (0.60-6.25)	.38
Rehospitalization for heart failure	0/119 (0.0)	5/117 (4.3)		.02
NYHA class improvement	100/106 (94.3)	91/105 (86.7)	1.09 (1.00-1.19)	.06
Quality of life				
Score, mean (95% CI)	71.0 (68.2-73.9)	65.9 (62.4-69.5)		.02
Score change, median (IQR)	12.5 (0-20)	10 (0-20)		.19
New permanent pacemaker	19/110 (17.3)	38/101 (37.6)	0.46 (0.28-0.74)	.001

Table 6 and 7 – Adapted from Abdel-Wahab et al..<sup>42</sup> Procedural and 30-day outcomes.

In terms of 1 year follow-up, despite the higher device success rates with the balloon-expandable valve, the great majority of clinical outcomes were not statistically different between both devices (Table 8 and Fig. 7).<sup>43</sup>

	Balloon-Expandable Valve (n = 121)	Self-Expandable Valve (n = 117)	p Value
Death			
Of any cause	21/121 (17.4)	15/117 (12.8)	0.37
Of cardiovascular causes	15/121 (12.4)	11/117 (9.4)	0.54
Stroke			
Major stroke	7/121 (5.8)	4/117 (3.4)	0.54
Minor stroke	4/121 (3.3)	0/117 (0.0)	0.12
Ischemic stroke	8/121 (6.6)	4/117 (3.4)	0.38
Hemorrhagic stroke	3/121 (2.5)	0/117 (0.0)	0.25
Repeat hospitalization for heart failure	9/121 (7.4)	15/117 (12.8)	0.19
Myocardial infarction	1/121 (0.8)	1/117 (0.9)	1.00
Bleeding			
Life threatening	17/121 (14.0)	15/117 (12.8)	0.85
Major	26/121 (21.5)	17/117 (14.5)	0.18
Minor	13/121 (10.7)	9/117 (7.7)	0.50
Vascular complications			
Major	14/121 (11.6)	14/117 (12.0)	1.00
Minor	5/121 (4.1)	2/117 (1.7)	0.45
Endocarditis	2/116 (1.7)	1/111 (0.9)	1.00
Valve thrombosis	4/116 (3.4)	0/111 (0.0)	0.12
Repeat procedure for valve-related dysfunction	2/121 (1.6)	3/117 (2.6)	0.68
New pacemaker	26/111 (23.4)	38/100 (38.0)	0.02
New-onset atrial fibrillation	8/82 (9.8)	8/85 (9.4)	1.00
Combined efficacy endpoint	24/116 (20.7)	31/111 (27.9)	0.22
MACCE	13/121 (10.7)	8/117 (6.8)	0.36
NYHA functional class improvement	82/95 (86.3)	85/95 (89.5)	0.66
Quality-of-life score	65 ± 22	67 ± 20	0.49

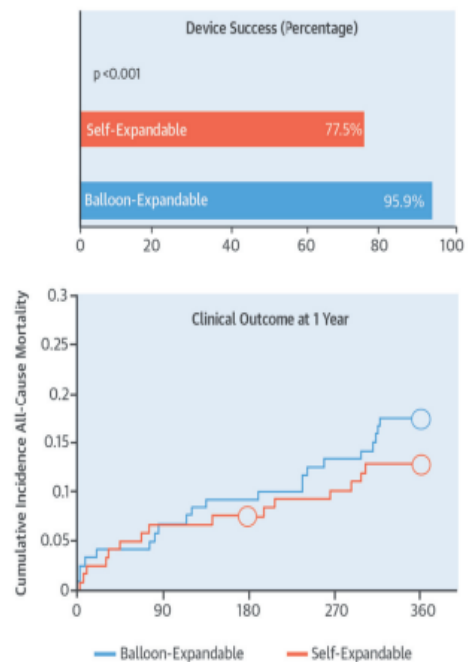


Table 8 and Figure 7 – Adapted from Abdel-Wahab et al..<sup>43</sup> 1-year follow up and clinical outcomes of balloon-expandable and self-expandable devices.

Considering mechanically-expandable devices, a trial conducted in intermediate risk patients (STS score between 3% and 8%, or Euro SCORE II between 2% and 10%), with Lotus (Boston Scientific Corporation) device, sustained its great rates of device success – 97.4%, in a 30-day follow up, while the rate for pacemaker (PM) implantation were still higher than desired – 27.9%. On the other hand, this analysis also demonstrated that this PM implantation rate can be minimized, if attention is given to both the implantation depth (<4 mm) and rate of oversizing (<1.05) – if taken into consideration, the reported PM rate is 12.8%.<sup>44</sup>

In terms of device success, mortality, stroke and vascular complication rates are comparable between the three types of valves. Although the SAPIEN 3 (Edwards Lifesciences) balloon expandable valve is associated with less major stroke, the Lotus (Boston Scientific Corporation) valve is associated with less vascular complications. In contrast, when using Lotus (Boston Scientific Corporation) valve, rates of aortic regurgitation are significantly lower, while there is a considerable higher rate of conduction disturbances requiring PM (Fig. 8).<sup>37</sup>

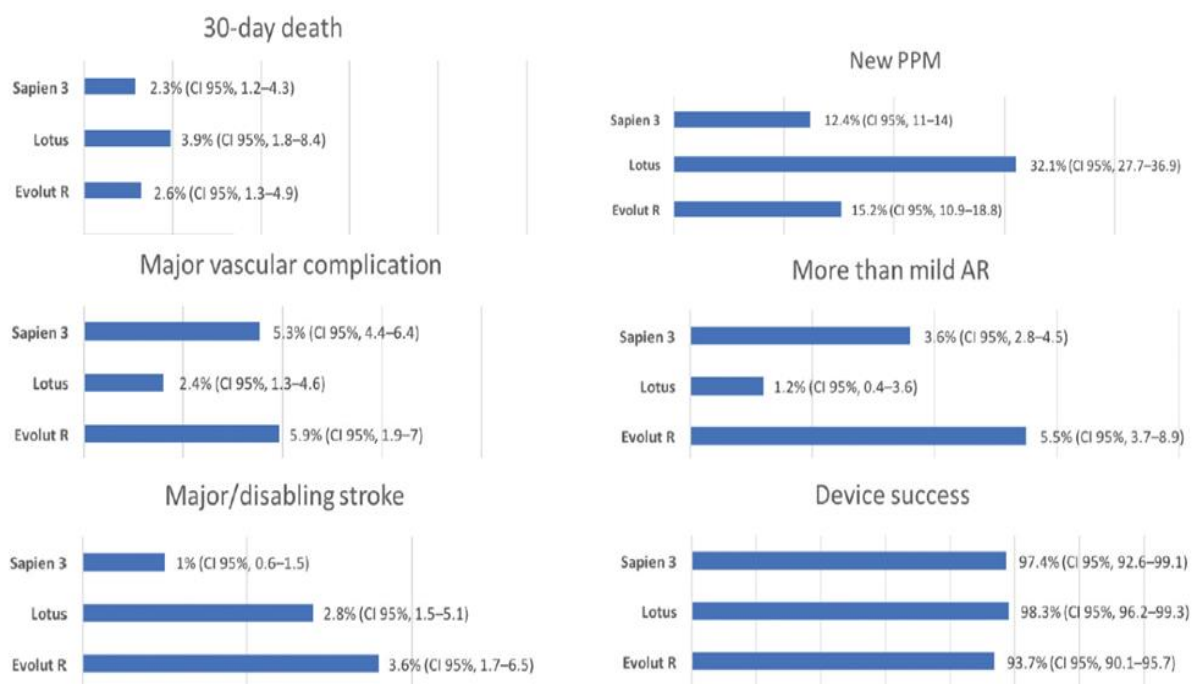


Figure 8 – Adapted from Todaro et al..<sup>37</sup> Clinical outcomes comparing TAVR devices.

Two recent studies have compared the results of stentless valve application and TAVR, in intermediate risk populations. These new valves have some advantages: i) its unique design, allowing suprannular impantation and reducing the risk of atrioventricular block; ii) less time consuming procedure, granting a reduction of aortic crossclamp time; and iii) shorter length of stay in Intensive Care units. Data gathered suggested that both techniques have excellent hemodynamic outcomes, although TAVR has showed higher short term mortality, pacemaker implantation and aortic regurgitation rates (Fig. 9).<sup>45,46</sup> Nevertheless, data comparing comparing TAVR and stentless valves is limited and no recommendation has been made regarding the generalized use of stentless valves.

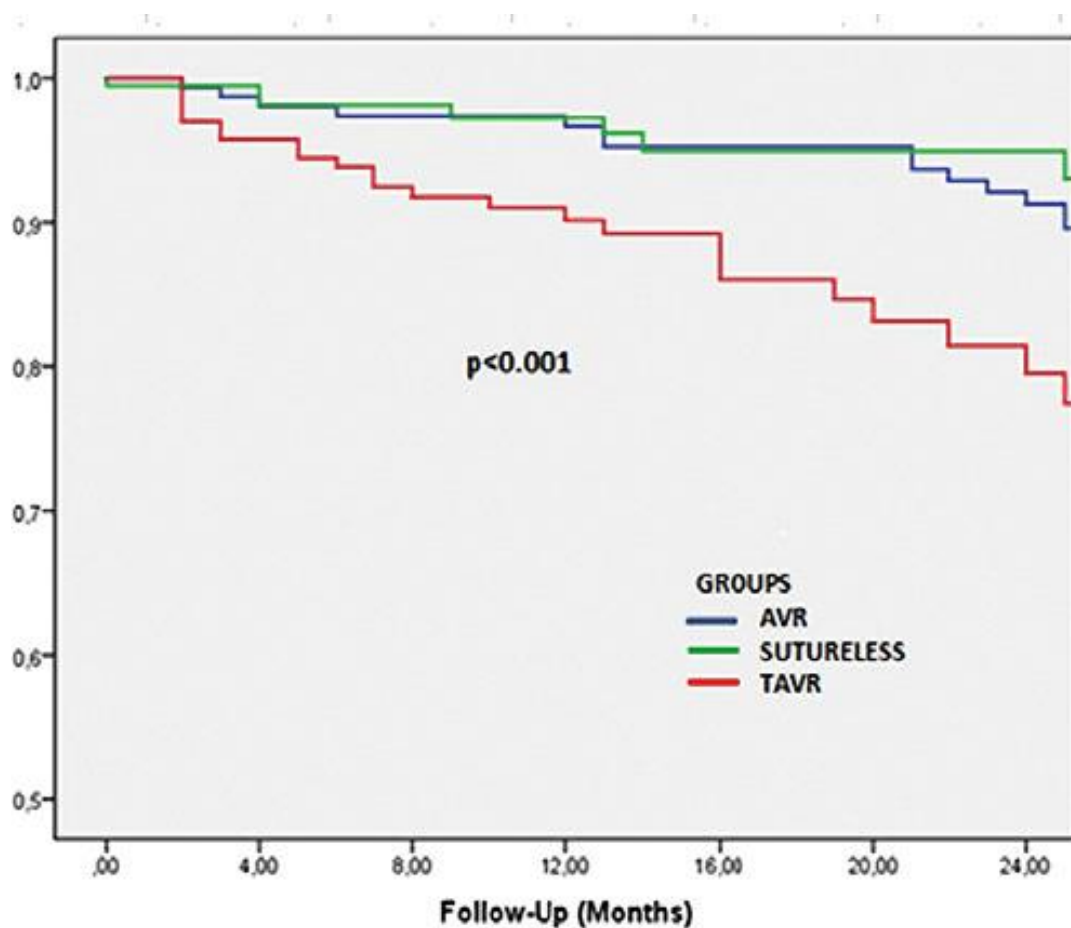


Figure 9 – Adapted from Muneretto et al..<sup>46</sup> Overall survival comparison between AVR, sutureless valves and TAVR.

- **Mortality outcomes and adverse events**

The PARTNER 2 trial compared two similar cohorts of intermediate risk patients, with STS score between 4 and 8%, that were randomly assigned to undergo either TAVR or SAVR with the SAPIEN XT (Edwards Lifesciences) valve. Mortality rates from any causes, or disabling stroke at 2 years, were similar in both groups – 19.3% for TAVR, vs 21.1% for surgery (p=NS). If only transfemoral access was considered, its outcomes were better than in the SAVR population – 16.8% vs 20.4% (p=0.05). TAVR resulted into larger aortic valve areas, lower rates of acute kidney injury (1.3% vs 3.1%, p=0.006), severe bleeding (10.4% vs 43.4%, p<0.001) and new onset atrial fibrillation (9.1% vs. 26.4%, p<0.001), in addition to a more rapid recovery – shorter duration of stay in the intensive care unit and hospital. Conversely, surgery led to fewer major vascular complications (5.0% vs 7.9%, p=0.0008) and less number and severity of paravalvular leaks. Nevertheless, only moderate or severe paravalvular aortic regurgitation was associated with higher mortality in the follow up (Fig.10).<sup>47</sup>

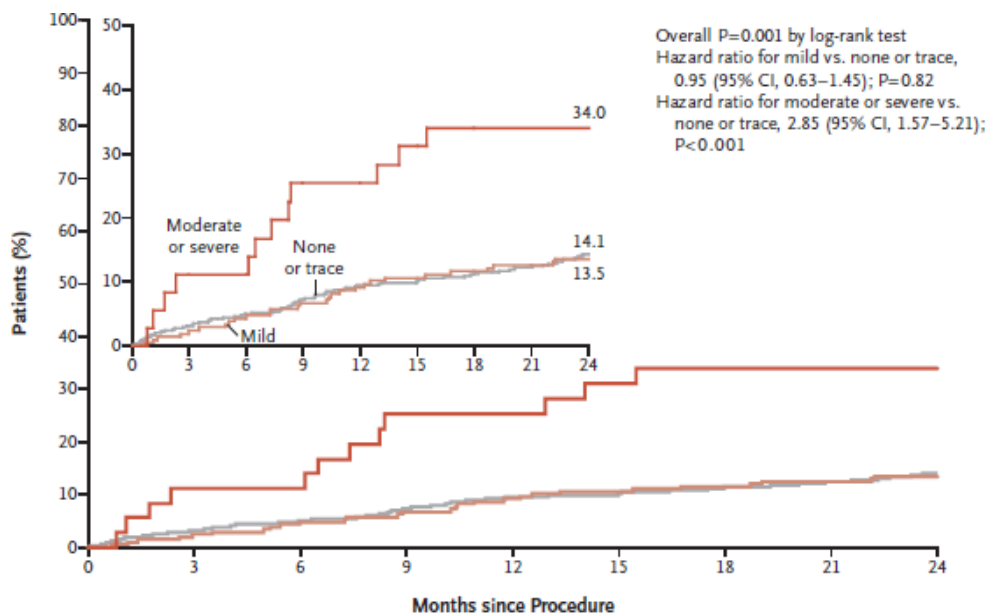


Figure 10 – Adapted from Leon et al..<sup>47</sup> Overall mortality comparison between none, mild and moderate or severe AR.

The SURTAVI trial analysed the outcomes of an intermediate risk population - STS score between 3 and 15% - undergoing either SAVR or TAVR, in an arbitrary way, with no differences in the baseline clinical features. A self-expanding biovalve, mostly the CoreValve (Medtronic) was used. Rates of the primary composite endpoint (death from any cause or disabling stroke at 2 years) were 12.6% in the TAVR group and 14.0% in the surgical one (p=NS). In this study, TAVR patients had lower mean gradients and larger aortic valves, higher rates of aortic regurgitation and need for PM. In the SAVR cohort, acute kidney injury, atrial fibrillation and transfusional requirements were more frequent. The NYHA class and quality of life (measured by the Kansas City Cardiomyopathy Questionnaire) improved significantly in both cohorts. TAVR was reported noninferior to surgery in patients at intermediate risk.<sup>4</sup>

The Nordic Aortic Valve Intervention trial (NOTION) randomly assigned patients with severe aortic valve stenosis to TAVR - CoreValve (Medtronic) - or SAVR. There were no differences in all-cause mortality, cardiovascular death and adverse events (stroke or myocardial infarction) at 2 years. Afterwards, patients were divided based on their STS score into 2 categories (< or > 4%). Both groups showed no statistically significant differences in the former clinical outcomes, with a general trend towards superiority for TAVR. In the low-risk population 14.7% TAVR patients had intercorrences (stroke or myocardial infarction) or died, versus 16.8% in SAVR (p=NS), whereas in the intermediate risk population 21.1% transcatheter patients had any intercorrences/died, versus 27.1% in SAVR (p=NS).<sup>38</sup>

The CoreValve trial performed an analysis of a population, whose STS score was 7% or less, randomly undergoing transcatheter replacement, with the CoreValve (Medtronic) prosthesis or surgical substitution. The two year all cause mortality was 15.0% for TAVR, and 26.3% for SAVR ( $p=0.01$ ), while the two year stroke rate was 11.3% for TAVR, and 15.1% for SAVR ( $p=NS$ ). Also at 2 years, hemodynamic results (encompassing orifice areas, aortic valve gradients), PPM rates, new onset of atrial fibrillation and AKI data also favoured TAVR. On the contrary, major vascular complications and PM requirement were more common in the percutaneous group. Quality of life benefits were similar for both cohorts.<sup>48</sup>

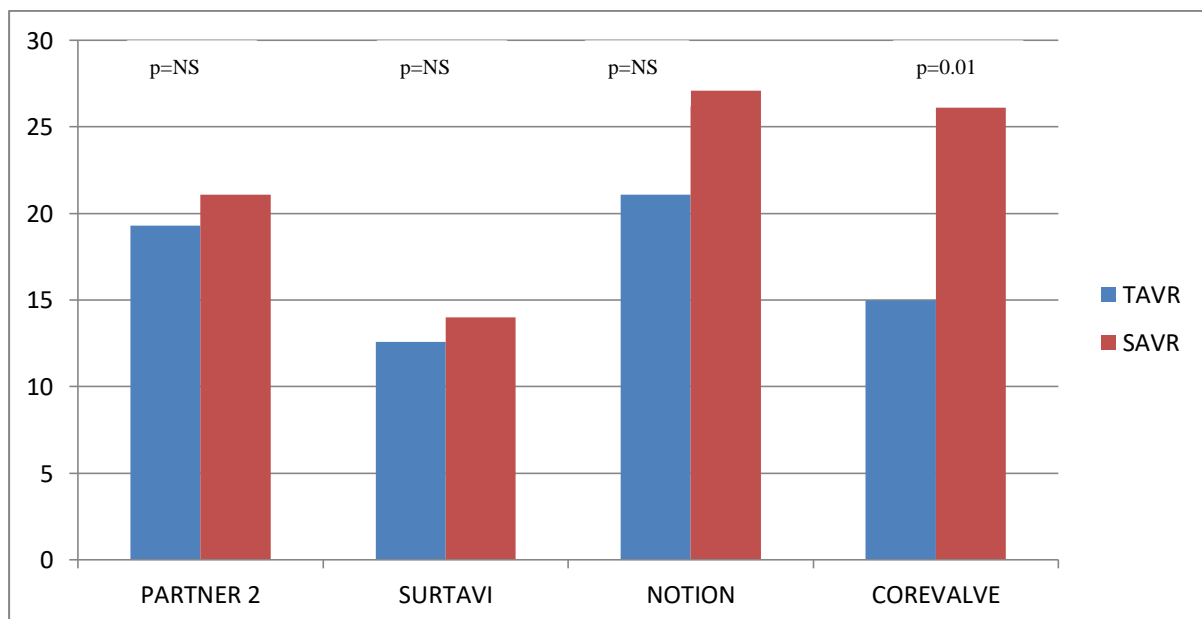


Figure 11 – Death/disabling stroke percentages, according to each of the previous trials

Another trial was conducted by the PARTNER investigators group, this time with the new Edwards SAPIEN 3 (Edwards Lifesciences) valve, either in high (STS > 8%) or intermediate risk patients (STS between 4 and 8%). In the higher risk cohort, the rates of 30-day all cause mortality and cardiovascular mortality were 2.2% and 1.4% respectively; while in the intermediate risk group were 1.1% and 0.9%.<sup>22</sup> Adverse events proportions were similar between both cohorts (Table 9) .

<b>SAPIEN 3 TAVI 30-day Adverse Events</b>	<b>High risk population</b>	<b>Intermediate risk population</b>
<b>Major/disabling stroke</b>	0.9%	1.0%
<b>Major bleeding</b>	14.0%	10.6%
<b>Major vascular complications</b>	5.1%	6.1%
<b>Requirement for permanent pacemaker</b>	13.3%	10.1%

Table 9 – Adapted from Kodali et al.<sup>22</sup> Percentage of adverse events, in each cohort.

Comparing mortality and adverse events at 1-year of follow-up, showed that TAVR approach was, respectively, non-inferior and superior to SAVR.<sup>40</sup>

The OBSERVANT study compared results in an intermediate risk population, with logistic EuroSCORE I of 9.1±9.9%, undergoing TAVR with the CoreValve (Medtronic) system, against SAVR. Thirty day mortality (3.8%) and the incidence of myocardial infarction (0.%) were similar between both groups, while the occurrence of stroke was higher in the surgical cohort (0% vs 1.5% p=0.156), as well as the requirement for blood transfusion (36.1% vs 49.6% p=0.026). Significantly greater incidences of major vascular damage (5.3% vs 0%, p=0.007), and permanent atrioventricular block requiring PM implantation (12.0% vs 0.8%, p=0.001) were reported in the TAVR group. So, despite showing similar mortality rates, adverse events were quite different, depending on which technique was performed.<sup>39</sup> A post hoc analysis of the OBSERVANT trial compared the outcomes of two groups of propensity matched intermediate risk patients, aged 80 and over, undergoing either TAVR or SAVR. The results showed that the early and midterm mortality were similar between the two groups, while significant differences were found regarding adverse events: more vascular

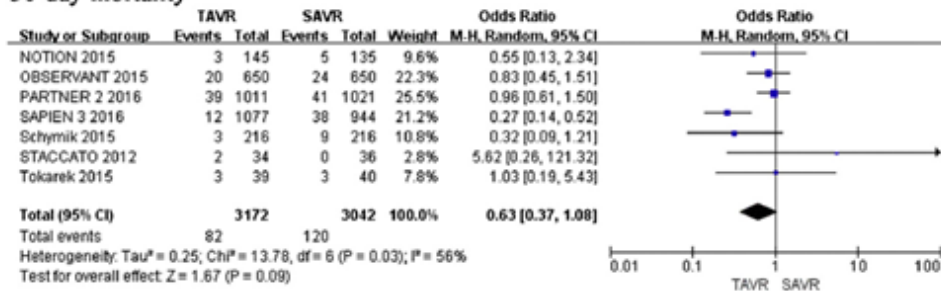
complications (6.0% vs 0.5%,  $p < 0.0001$ ), PM implantation (13.4% vs 3.7%,  $p < 0.0001$ ), and paravalvular leak (8.9% vs 2.4%;  $p < 0.0001$ ) occurred in the transcatheter cohort. Surgical patients required more often transfusion (34.5% vs 63.2%,  $p < 0.0001$ ) and AKI (3.9% vs 9.6%;  $p = 0.001$ ).<sup>49</sup>

The GARY (German Aortic Valve Registry) study focused on intermediate surgical risk – logistic EuroSCORE I between 10 and 20% - undergoing either TAVR or SAVR. The first results reported were unbalanced, with noticeable advantage for SAVR in terms of 1 year mortality rates – 8.9% vs 16.6% ( $p < 0.001$ ). However, the 2 cohorts differed significantly in terms of baseline risk profile. The authors repeated the analysis using propensity score matching, nonetheless resulting in a higher mortality rate for TAVR – 15.5% vs 10.9%,  $p = 0.002$ . By analysing the TF TAVR cohort only, the authors reported a 14.3% mortality rate, which was still statistically higher than the surgical mortality ( $p = 0.021$ ).<sup>50</sup>

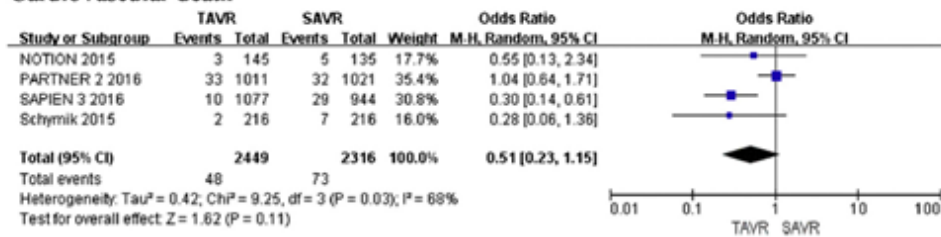
Several meta-analysis and systematic reviews have argued that there is no difference, in the intermediate risk population, between SAVR and TAVR in terms of 30-day and late mortality (Fig. 12).<sup>7,51-54</sup> Regarding complications, it is argued that SAVR has a higher risk of early stroke, atrial fibrillation, major bleeding, AKI, and a greater length of hospitalization.<sup>7,51,53,55</sup> Conversely, TAVR predisposes to a higher risk of PM implantation, aortic insufficiency and major vascular complications.<sup>7,18,51,53,54</sup> Furthermore, data regarding stroke is inconsistent, since some clinical studies pointed out an increased risk of stroke in TAVR,<sup>54</sup> while others showed no difference between both techniques.<sup>7,19</sup>



### 30 day mortality



### Cardiovascular death



### Death form any cause

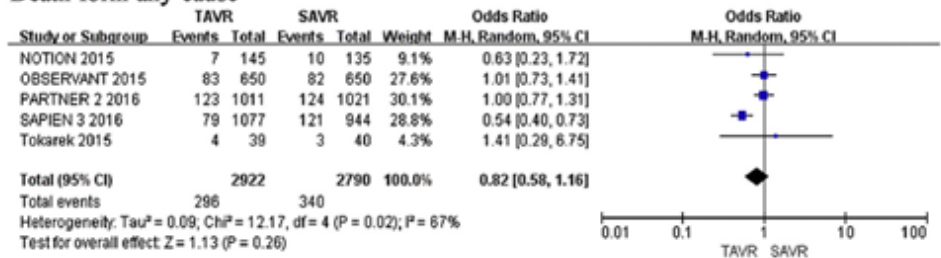


Figure 12 – Adapted from Zhou et al..<sup>53</sup> Rates of 30-day all cause and cardiovascular mortalities, and 1-year death from any cause.

Several studies have suggested that TAVR outcomes in the female gender are better (Fig. 13), with higher rates of 1-year survival, however with a higher 30-day mortality and vascular complications.<sup>55</sup> There are many possible explanations for these findings: i) since women have a smaller body surface, they consequently have smaller iliofemoral diameters and annulus sizes, making them more prone to early vascular complications and patient-prosthesis mismatch, and consequently, early deaths;<sup>56</sup> ii) after valve replacement, women tend to develop a more remarkable regression of myocardial hypertrophy, and, in addition, their collagen synthesis is not as pronounced as in men, making it easier for women to recover left ventricular function;<sup>10</sup> iii) finally, the longer life expectancy in the female gender can also have a role in the higher survival rate reported.

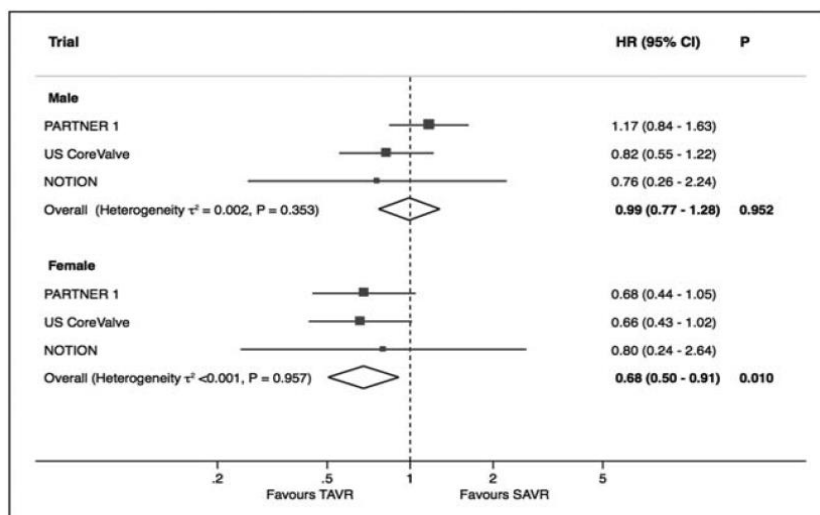


Figure 13 – Adapted from Praz et al.<sup>10</sup> Comparison between death at 2 years, in both genders, in TAVR vs SAVR.

Neurological injuries are among the greatest concerns in patients who are undergoing TAVR. In high risk cohorts, subclinical damage can be reported in up to 75% of the patients. A trial assessed neurological injuries using brain MRI, including diffusion weighted imaging (DWI), in an intermediate risk population undergoing TAVR, both preprocedure and 2 to 4 days post procedure. The authors reported 68 new DWI lesions in 60% of the patients, which were associated with a significant impact in early cognition, whereas in longer follow up at 6 months, no effects on cognition, QoL or functional capacity were reported.<sup>57</sup> One other study comparing intermediate risk patients in TAVR and SAVR, analysed acute ischemic injuries detected by DWI. The results showed similar incidence of new brain injuries (45.0% in TAVR vs 40.7% in SAVR,  $p=NS$ ), however TAVR was associated with a lower number of lesions ( $p=0.02$ ). The use of a vitamin-k antagonist was found to be protective ( $p=0.037$ ), independently of the type of intervention, while “older age” was a predictor of new acute brain lesions ( $p=0.01$ ). Moreover, no changes were observed in cognitive scores after the procedures, and no association was reported between the number and total volume of these lesions and intellectual loss. It is also argued that cognitive decline in this cohort may be more related to the primary characteristics of patients, rather than to the procedures themselves.<sup>58</sup>

In order to prevent embolization of thrombotic debris during TAVR and diminish stroke rates, embolic protection (EP) techniques have been developed.<sup>59</sup> Various trials and meta-analysis, regarding these new devices have been performed, and their use was associated with a significantly lower total lesion volume, as well as smaller number of new ischemic brain lesions (Fig. 14), and a nonsignificantly lower risk for stroke and all-cause mortality, when compared with the control group.<sup>60,61</sup>

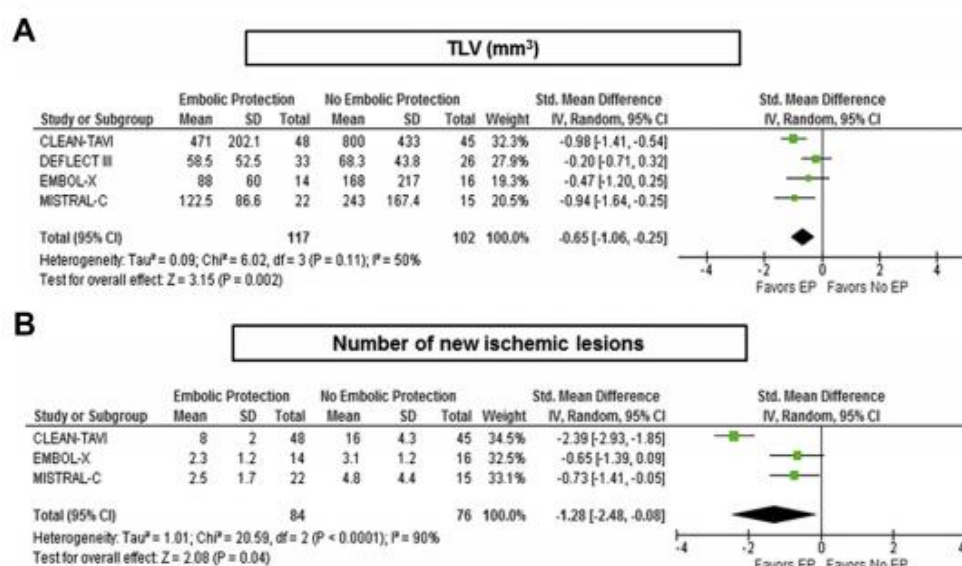


Figure 14 – Adapted from Giustino et al.<sup>60</sup> Total lesion volume and number of new ischemic lesions, in trials with EP.

Among these devices, Sentinel Cerebral Protection System (Claret Medical) has been the most frequently used one. It consists of a catheter with deployable proximal and distal filters and an articulating sheath, which are percutaneously placed from the right radial or brachial artery, over a guide wire; these two filters are placed in the brachiocephalic and left common carotid arteries, and block the passage of any debris to the cerebral circulation. Owing to its interesting clinical results in reducing stroke rate (by 63%, in the first 72 hours – when most strokes occur) and strong safety profile, the use of this technique has been cleared by the US FDA to be used in all TAVR patients, regardless of surgical risk.<sup>62</sup>

## - **Pharmacological treatment following TAVR**

Selection of the most appropriate antithrombotic treatment after TAVR has been an issue of debate, since it may prove difficult to balance prevention of ischemic events and bleeding risks.<sup>5</sup> Dual antiplatelet therapy (DAPT), with low-dose aspirin and a thienopyridine (usually clopidogrel), followed by aspirin or thienopyridine alone, is recommended for patients who undergone TAVR and have no indication for anticoagulation.<sup>63</sup>

Recent trials comparing the safety and outcomes of dual or single (SAPT) antiplatelet therapy, reported inconsistent results. In terms of 30-day clinical outcomes, a meta-analysis suggested that there is no difference between both approaches in terms of mortality, stroke or myocardial infarction (MI) rates, while there was a trend towards a higher bleeding risk when using DAPT.<sup>64</sup> The ARTE study compared 300 TAVR patients, who were randomly assigned to a SAPT with aspirin alone (for at least 6 months), or to a combination of aspirin (for at least 6 months) and clopidogrel (for 3 months). This trial demonstrated that SAPT tended to reduce the occurrence of major adverse outcomes, namely death, ischemic or bleeding events, while not increasing the risk for MI or stroke in the 3 months following the procedure.<sup>65</sup> Nevertheless, no significant differences were found between both antitrombotic strategies. There are no other similar trials with larger cohorts or longer follow up.

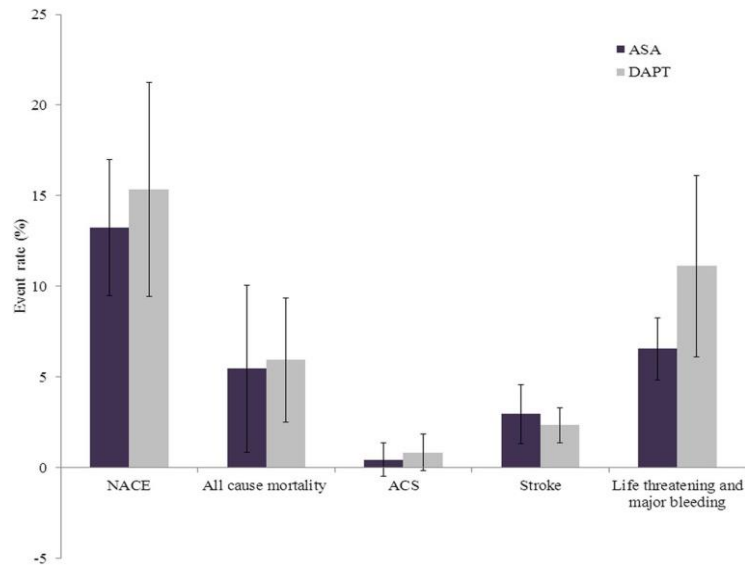


Figure 16 – Adapted from Hassell et al.<sup>66</sup> Comparison of 30-day outcomes, between DAPT and ASA (aspirin only therapy), in terms of net adverse clinical and cerebral events (NACE): mortality, acute coronary syndrome, stroke and major bleeding.

In patients with a new onset of atrial fibrillation (AF) after TAVR, a combination of vitamin K antagonist (VKA) and aspirin or thienopyridine is generally used, but should be weighted against increased risk of bleeding.<sup>2</sup> A trial comparing the safety and efficacy of apixaban compared to VKA, demonstrated that there was a trend towards lower 30-day all cause mortality, stroke and AKI rates in patients treated with apixaban (Fig. 17).<sup>67</sup>

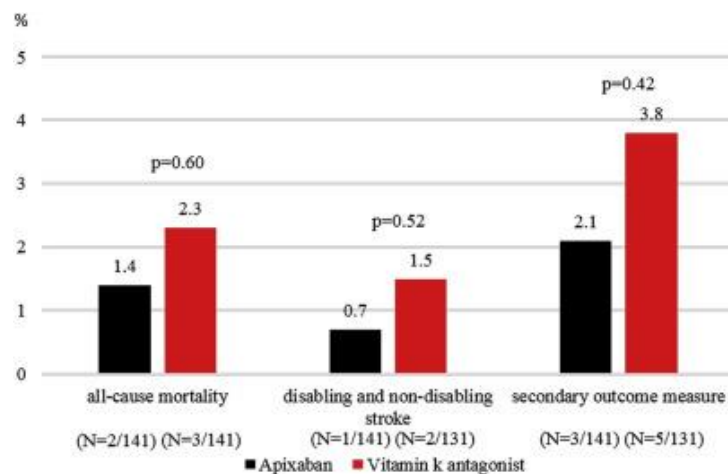


Figure 17 – Adapted from Seeger et al.<sup>67</sup> 30-day outcomes of patients with AF post-TAVR with either apixaban or VKA treatments (secondary outcome measure is a composite of all-cause mortality and all-stroke).

While some studies argue that anticoagulant therapy reduces the incidence of subclinical thrombosis and valve deterioration,<sup>68</sup> others argue that there is no advantages in terms of stroke, bleedings, 30-day overall mortality,<sup>69</sup> or even early (30-day) valve degradation,<sup>70</sup> when oral anticoagulation was added to antiplatelet therapies. A systematic review of randomized controlled trials and observational studies on the effect of different pharmacological treatments after TAVR, regarding stroke, bleeding and death, demonstrated similar outcomes between most studies, with no advantage from the addition of anticoagulation therapy.<sup>71</sup>

The upcoming GALILEO trial will compare rivaroxaban to an antiplatelet-based strategy after TAVR. The primary endpoint is the composite of all-cause death, stroke, MI, symptomatic valve thrombosis, pulmonary embolism, deep venous thrombosis and systemic embolism.<sup>72</sup> Some other studies concerning the antithrombotic strategy after TAVR are in progress, and their results will help to guide future recommendations about medical treatments post TAVR.<sup>68</sup>

- **Cost-effectiveness analysis of TAVR**

There are 2 main concerns about extending TAVR indications to lower risk populations: the cost of the procedure and the longevity of the prosthetic valves.<sup>54,73</sup>

In order to compare the cost-effectiveness of the percutaneous and surgical procedures, QALY (quality adjusted life years) can be used as the primary tool. It consists of a composite of the extra years of life, gained with a treatment and the quality of life (where 0 is no different than death and 1 is perfect health). The cost-effectiveness of TAVR in the PARTNER trial was a QALY cost of 61889\$, much higher than the QALY cost for many other procedures (Table 10), which raised concerns on whether it is reasonable to expand TAVR indications.<sup>74</sup>

Procedure	QALY
TAVR (PARTNER Cohort B)	\$61,889
AVR (octogenerians)	\$27,182
CAB (BARI data)	\$14,294
Stenting (BARI data)	\$15,179
Heart Transplantation	\$38,000
Lung transplantation	\$77,000
Liver transplantation	\$26,000
LVAD	\$78,000
Driver side air bag	\$24,000

Table 10 – Adapted from Reardon et al..<sup>74</sup> A comparison between QALY costs in different procedures/devices.

TAVR has proved to be significantly more expensive than SAVR, for in-hospital costs (Table 11) and for the total costs at the 1-year (Fig. 15). While TAVR can be cheaper in terms of blood products, operating room use and length of stay (for intensive care and ward stay); the cost of the transcatheter valve clearly surpasses all the latter advantages – the cost of the materials is 4 times higher in TAVR (22055\$, in TAVR, vs 5162, in SAVR,  $p < 0.001$  – Figura 15).<sup>75</sup> As more valves are being developed and the percutaneous technique gets increasingly used, it is likely that the costs of the TAVR tends to decrease.<sup>12</sup>

Parameter (mean $\pm$ standard error of the mean)	TAVR (n = 42)	SAVR (n = 42)	p Value
Preoperative costs	2,024 $\pm$ 0	1,538 $\pm$ 0	
Procedure costs	28,785 $\pm$ 1014	13,096 $\pm$ 315	<0.001
Operating room use	1,124 $\pm$ 60	453 $\pm$ 18	<0.001
Personnel	2,303 $\pm$ 117	2,431 $\pm$ 90	0.41
Materials	22,055 $\pm$ 869	5,162 $\pm$ 0	<0.001
Blood products	176 $\pm$ 41	1,869 $\pm$ 223	<0.001
Overhead and housing	3,127 $\pm$ 48	3,181 $\pm$ 38	0.40
Total stay	8,545 $\pm$ 776	17,409 $\pm$ 3,116	<0.001
ICU stay	2,458 $\pm$ 168	9,991 $\pm$ 2,820	0.008
Ward stay <sup>a</sup>	6,087 $\pm$ 733	7,418 $\pm$ 544	0.087
Academic hospital	6,023 $\pm$ 715	4,208 $\pm$ 370	0.016
General hospital	64 $\pm$ 64	3,210 $\pm$ 446	<0.001
Postoperative tests	545 $\pm$ 50	674 $\pm$ 108	0.31
Postoperative blood products	136 $\pm$ 43	63 $\pm$ 27	0.17
Additional procedures	768 $\pm$ 273	573 $\pm$ 209	0.56
Total in-hospital costs	40,802 $\pm$ 1,399	33,354 $\pm$ 3,357	0.010

Table 11 – Adapted from Osnabrugge et al..<sup>75</sup> In hospital costs, in TAVR and SAVR.

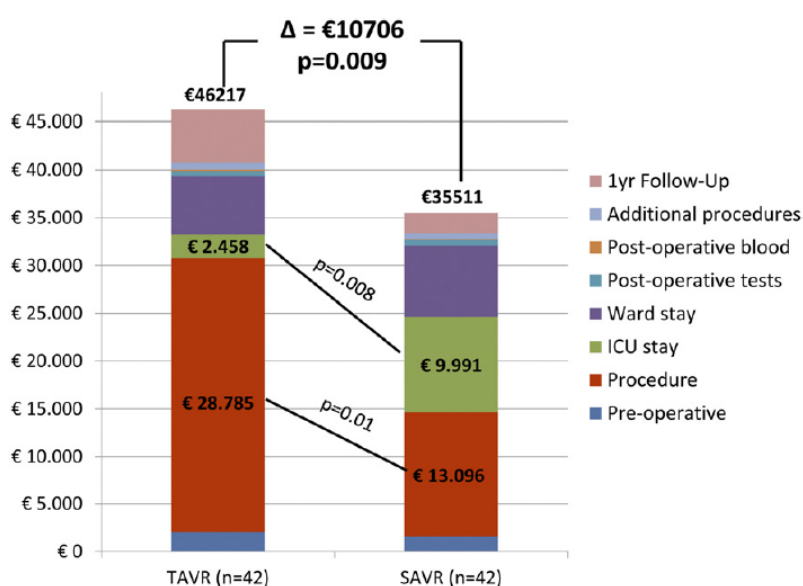


Figure 15 – Adapted from Osnabrugge et al..<sup>75</sup> Total 1-year costs, in TAVR and SAVR.



If considering only the TA approach, costs are even worse. TA approach has higher rates of requirement for cardiopulmonary bypass, which increases the costs when compared with other routes.<sup>76</sup> TA TAVR need further studies to determine whether it can be cost-effective, when compared to TF TAVR and SAVR (Table 12).<sup>77</sup>

Resource Category	TA-TAVR (n = 101)	AVR (n = 91)	Difference (95% CI)	p Value
Procedural costs	40,368 ± 12,651 [37,853]	15,076 ± 2,665 [14,592]	25,292 (23,091 to 28,145)	<0.001
Nonprocedural costs	44,909 ± 34,603 [30,091]	57,827 ± 44,815 [39,103]	-12,918 (-24,763 to -1,805)	0.03
Physician fees	5,642.22 ± 1,890.62 [4,929]	6,121 ± 2,418 [5,302]	-479 (-1,145 to 103)	0.13
Total admission costs	90,919 ± 39,397 [74,721]	79,024 ± 47,343 [61,395]	11,896 (-1,013 to 24,304)	0.06

Table 12 – Adapted from Reynolds et al..<sup>77</sup> Costs of TA TAVR and SAVR.

Concerning valve durability, some recent studies have been carried out to give a reasonable estimation.<sup>78</sup> As lower risk patients tend to be younger and have a higher life expectancy, it is fundamental that these prothesis are resistant enough to allow a longterm life without future valve complications. An older study found no valve deterioration or migration at five years; however, it represents a very diminutive experience when compared with the long term results of SAVR valve.<sup>79</sup> A clearer estimation of long term valve longevity has been also limited by the non-valve related deaths, which pose as the majority of causes of mortality in these patients.<sup>80</sup>

## Discussion

With the increasing use of TAVR in many centers/hospitals, the technique has been refined, and, as a consequence, its results and approaches have improved. As shown above, the vast majority of recent trials, namely SURTAVI,<sup>4</sup> OBSERVANT,<sup>39</sup> NOTION,<sup>38</sup> CoreValve,<sup>48</sup> and PARTNER 2,<sup>47</sup> and also some meta-analysis,<sup>7,51-54</sup> performed in the intermediate risk population, concerning mortality rates and adverse events, consider TAVR as a noninferior or even superior alternative to surgery. So, in a near future, TAVR should be further studied and developed in order to extend, as soon as possible, its recommendations to intermediate risk patients.

More specifically, regarding adverse events, there is a different pattern associated with each procedure: SAVR tends to be more associated to atrial fibrillation, bleeding, PPM and AKI, whereas TAVR has a higher risk of pacemaker implantation, aortic insufficiency and major vascular complications. The effect of these conditions should be greater evaluated in the future, and considering each patient in particular.

Despite all the efforts that should be placed in developing more and more suitable risk stratification tools, to guide medical decision, the last call will always belong to the Heart Team. In terms of risk stratification tools, in the mean time, for the intermediate risk population, Logistic Euro SCORE I and STS seem the most adequate,<sup>18</sup> but they must be used taking into consideration their limitations – a complementary frailty assessment should always be done, patients' cognitive impairment should be beared in mind, among others.<sup>19</sup>

In this intermediate risk population, the TF route seems a valid option, due to its lower mortality rate and adverse events. On the other hand, when this approach is not available (because of peripheral vascular disease, or small vessel caliber, for instance), TAO, TSc and TCvl approaches may be feasible, as they have had encouraging results in recent trials.

However, TA route, must be cautiously assessed, since in this lower risk cohort the worse outcomes associated may have bigger consequences for a longer term survival. So, while patients are likely to perceive benefit with TF TAVI versus SAVR, the same may not be applicable to other routes, and future studies should focus on this matter,<sup>31</sup> and on developing these “emergence” routes of access. It must always be taken in mind each center/hospital results on TAVR approaches, and also on SAVR, since outcomes highly rely on operator’s experience – once again, the Heart Team is fundamental in adequating the best treatment available, to each patient.

Valve technology has had some great improvements, and reduced adverse events and higher device success rates have been achieved recently. So far, ballon-expandable valves appear to have the best outcomes, followed by the self-expandable valves, and the choice to use one or the other may depend on the experience of the operator. The mechanically-expandable devices still have a high rate of PM implantation associated, so they tend to be less used than the others.

Neurological impact, particularly, must be further studied, as its associated risk may be acceptable in higher risk cohorts, but since we are discussing lower risk populations, this side effect has to be taken into account.<sup>57</sup> The use of EP techniques particularly, the Sentinel™ Cerebral Protection System (Sentinel; Claret Medical, Santa Rosa, CA, USA), has been decreasing the rates of these injuries, and they may become mandatory for future TAVR interventions. With the generalisation of the use of these EP devices, stroke occurrence may hopefully become a problem of the past.

Another aspect to be cleared in posterior trials is the selection of the most adequate medical treatment post-TAVR, since so far results have demonstrated that SAPT may be (at least) as valuable as DAPT. Regarding TAVR costs, they are likely to diminish, since more and more valves will eventually be produced, as this technology becomes more adopted. In terms of valve durability, while by one hand it has been difficult to estimate, by the other questions arise whether we should wait for this information, or if TAVR should already start to be recommended to intermediate risk cohort, since results have been really good, so far.<sup>78</sup>

The greatest limitations about this study are the short follow-ups (maximum 2 years), the small number of patients enrolled in the majority of the mentioned trials, the fact that some trials were performed not only in intermediate risk cohorts, and also the absence of standardized statistical criteria to compare TAVR trials, or TAVR vs SAVR.

## **Conclusion**

Overall, TAVR, regarding recent studies, can become a reliable alternative to SAVR, in intermediate risk patients, in a near future. However there are still many breaches regarding this technique, and future studies should focus on the adverse events, costs, valve durability, and medical treatments post-TAVR, while taking into consideration the limitations already described – trials considering intermediate-risk patients are necessary, with longer follow-ups and larger cohorts.

## **Acknowledgements**

First of all, I thank my tutor, Professor Doutor Lino Manuel Martins Gonçalves, for all the help and guidance throughout the making of this work.

Secondly, I thank my co-tutor, Doutor Luís Manuel de Vilardouro e Paiva, for his cooperation and advice.

In addition, I thank the library of the Centro Hospitalar e Universitário de Coimbra, namely to Doutora Helena Donato, for the help in the article research.

Finally, I thank Laura, for her help in the English review, and for her support, as well as my family and friends, for all the motivation.

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