STATE OF ART ON TRANSCATHETER AORTIC VALVE IMPLANTATION (TAVI) FOR THE TREATMENT OF AORTIC STENOSIS

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ABSTRACT

Transcatheter Aortic Valve Implantation (TAVI) technique represents a real revolution in the field of interventional cardiology and medicine, in particularly for the treatment of aortic valve stenosis in elderly patients, or in patients when the periprocedural risk for the traditional surgical option is considered too high, as an alternative to the traditional aortic valve replacement.

From the year 2002, when Cribier, in France, performed the first transcatheter aortic valve implantation (TAVI), in a period of just over a decade, this technique has become a reality in clinical practice of cardiologists interventionists worldwide.

The data of follow-up in the long term are currently available mainly for the valves of the first generation. These data show an excellent, also at long term, hemodynamic performance.

Although experience on the valves of the last generation is still limited in time, the data currently available are definitely in the direction of a minimum hospital mortality (1%), as well as to a drastic reduction in the incidence of complications, compared to the devices of the previous generation. Finally, the evolution of specified materials of the newest generation have greatly enhanced safety and efficacy of TAVI procedures in the last years

Key words: *Transcatheter Aortic Valve Implantation, TAVI, Aortic Stenosis, A.S., Endovascular Procedures, Interventional Cardiology Procedures.*

Was the year 2002, when Cribier, in France, performed the first transcatheter aortic valve implantation[1]. Since then, in a period of just over ten years, TAVI (transcatheter aortic valve implantation), has become a reality in the clinical practice of the interventional cardiologists of all the world. Patients with severe aortic valvular stenosis at high surgical risk, which until not many years ago were treated by medication or by the simple aortic valvuloplasty, letting the disease follows to run its natural course, currently they have the chance of a targeted therapy for the elimination of aortic stenosis with an acceptable periprocedural risk.

PARTNER studies[2,3] have explained, respectively, that a) the TAVI confers a significant improved outcomes in patients who are not candidates to traditional surgery and that b) the 2-year mortality in patients at high surgical risk (EuroSCORE logistic> 20) does not differ from that of replacement aortic valve surgically. The indications for TAVI were recently drafted from the European Society of Cardiology/European Association for Cardio-Thoracic Surgery and the American College of Cardiology/American Heart Association Task Force on Practice Guidelines in 2012 and 2014, respectively[4,5].

Briefly, TAVI can be performed in elderly, frail patients, or in patients when the periprocedural risk for the traditional surgical option is considered too high (essentially do to patient comorbility), as an alternative to the traditional aortic valve replacement, as an alternative to traditional aortic valve replacement. The claim to final TAVI and the decision on the individual patient must be decided by a Heart Team which is responsible for assess the individual risk profile and the anatomical suitability.

Based on these guidelines, the TAVI is currently feasible to about 20% of all patients with aortic valve stenosis, with two-thirds of the population of patients referred for conventional surgery and remaining always managed with medical therapy.

The valve types mainly used currently in most centers are the transcatheter valve balloon-expandable Edwards Sapien (Edwards Lifesciences, Irvine, CA, USA) and the self-expanding valve CoreValve (Medtronic Inc., Minneapolis, MN, USA).

The Sapien valve of the first generation was designed for insertion through both transfemoral and transapical approach (through the apex of the left ventricle). Structurally, it is composed of three cusps of bovine pericardium sutured on a stainless steel stent. The implant for transfemoral approach is performed using a dedicate delivery system, the diameter of which varies from 22-24F according to the size of the valve. The transapical implant instead it provides an introducer 26 F. As reported in SOURCE registry, which enrolled 1,038 patients, the success probability of this device is greater 90% for both types of approach[6]. There were no differences between the two groups, regarding the rate of stroke and the need for a permanent pacemaker. Conversely, vascular complications were five times more frequent in patients who had received a transfemoral valve implantant (22.9 vs 4.7%), this due to the high profile of the introducer of the valve.

This limitation has been almost overcome by the evolution of SAPIEN valve to the next generation, that is the Edwards SAPIEN XT. The modifications of valve implantation device, the design of a delivery system with a lower profile together with an introducer with a further reduction than previous versions, have helped to reduce the rate of vascular complications. In fact, in one study of 120 patients, there was an event rate vascular 3 times lower (11.1% vs. 33%; p = 0.004) in group of patients treated with the SAPIEN XT compared to the valve of the first generation[7]. These data are confirmed in the PARTNER IIB trial, one randomized trial comparing SAPIEN XT vs SAPIEN in inoperable patients, where there was a significant reduction in major vascular complications (9.6% vs 15.5%, p = 0.04) in favor of the newer generation valve[8].

Long-term results

Like all innovations in medicine, also TAVI has suffered some initial skepticism. A main objection was the lack of results in the long term. Much of our uncertainties about today disappeared, since we can refer to reasonably long term follow-up. Moreover, independently by the conditions of cardiac base, the patients undergoing TAVI are still subject to high risk, they have multiple comorbidities, and are on average over eighty.

The long-term data currently available cover, in large part, the Edwards SAPIEN valve of the first generation. In one of the first experiences of long term follow-up Gurvitch et al. reported in 2010 data from a cohort of 77 patients with survival more than 30 days that had been subjected between the 2005 and 2006 the implant of Cribier-Edwards valve or Sapien of first generation (with a logistic EuroSCORE average 31.7 ± 16, STS score 9.6 ± 3.5)[9]. An average follow-up of 3.7 years, the pressure gradient Transvalvular aortic increased from 10.0 mmHg (interquartile range 8.0 to 12.0 mmHg) immediately after the procedure to 12.1 mm Hg, with an interquartile range from 8.6 to 16 mm Hg after 3 years (p = 0.03), while the valve area decreased average 1.7 ± 0.4 cm 2 after the procedure, to 1.4 ± 0.3 cm 2 after 3 years of follow-up (p <0.01).

Two years later, i.e. in 2012, Rodés-Cabau et al, have reported follow-up data to 3 years and a half of 188 patients treated with implant of SAPIEN Edwards valve of first generation or SAPIEN XT[10]. The mortality at 42 ± 15 months was 55.5%, in most cases of non-cardiac causes (59.2%), followed by cardiovascular mortality (23.0%) or unrecognized (17.8%). The echocardiographic 2 years follow-up data have confirmed a slight decrease of the valve area during the time, which, however, did not decrease further up to a follow-up of 4 years, without reported cases of severe dysfunction of the valve. The picture do not change much with the follow-up to five years reported by Toggweiler et al. in 2013 in 88 patients predominantly with the SAPIEN valve of the first generation[11]. The average transvalvular gradient passed by 10 ± 4.5 mmHg after implantation to 11.8 ± 5.7 mmHg after 5 years (P for trend = 0.06). At 5 years, 3 patients (3.4%) showed

dysfunction of the prosthetic valve. The survival rates from 1 to 5 years of follow-up were respectively of 83%, 74%, 53%, 42% and 35%, with a duration life median of 3.4 years (95% 2.6 to 4.3 confidence interval).

Major complications of TAVI

Most of the results on the use of the first two versions of the Edwards SAPIEN transcatheter valve derived from different multicentre registers (6,12-18) and by the two multicentre prospective randomized PARTNER study[2-3]. In this case, the patients included in the multicenter registers were considered inoperable or at very high surgical risk, with logistic EuroSCORE average> 20% and STS score> 8%. These were patients mostly octogenarians, about half of them with history of coronary artery disease, with a third with chronic renal failure and about a quarter with chronic obstructive pulmonary disease or peripheral vascular disease. Overall, the probability of procedural success was above 90% in all studies.

Here we will focus on complications closely related to the structural aspect of the valve, omitting others, such as acute renal failure and post-procedural myocardial infarction.

Mortality

In multicenter registries periprocedural mortality was less than 10% in patients treated with the transfemoral approach and ranged from 9.9% to 16.9% in patients treated with the transapical approach, probably in relation to the higher risk profile of this second category of patients[6,9-14]. One year follow-up, survival rates were around 80% (75-85%) for the transfemoral approach and around 70% (63-78%) for the transapical approach. In thr cohort of inoperable patients of the PARTNER study[2], the 30-day mortality was 5.0% in the TAVI group (Transfemoral approach in all patients) and 2.8% in the group of medical treatment (p = 0.41). It's important point out that, up to 84% of patients in the group of medical treatment was subjected to at least one procedure of aortic valvuloplasty during the study period. In the cohort of patients at high risk of the PARTNER study[2,8] the 30-day mortality was 3.4% in the TAVI group, compared to 6.5% in group receiving conventional surgery (p= 0.07). Among the predictors of periprocedural or to one year mortality are included both basal cardiovascular factors i.e. lower left ventricular ejection fraction, pulmonary hypertension and severe mitral regurgitation

and periprocedural complications i.e. low cardiac output, major vascular complications, cardiac tamponade, switch to cardiac surgery, acute renal failure, stroke, and residual moderate to severe aortic regurgitation[6,12,14,19-23]. By contrast, noncardiac comorbidities, such as chronic obstructive pulmonary disease, chronic renal failure and liver dysfunction are important predictors of mortality during the period of follow-up rather than periprocedural mortality[6,12,14,19-23]. The 2-year mortality was 33.9% in the cohort at high risk and 43.3% in the inoperable cohort[24,25].

Vascular complications

The use of large introducers (18-24 F), in most cases in patients over eighty, is inevitably associated with a high rate of major vascular complications during TAVI procedures, about of 5-10% in most cases. An accurate assessment of the anatomy of the iliac-femoral arterial axes before the procedure by CT angiography and / or angiography and the use of alternative access to transfemoral approach in prohibitive cases, has an essential role in avoiding / reducing these complications[26]. Similarly, it is to recommend a proper puncture of the vessel, performed before and in a disease-free, segment of the common femoral artery, preferably under angiographic control. Is important underline that the occurrence of serious vascular complications is an independent predictor of 30-day mortality. The TAVI team should be able to treat these complications rapidly and in an appropriate manner, through intravascular procedure or directly with the intervention of the vascular surgeon.

Stroke

The occurrence of cerebrovascular events is one of the most fearsome complications of TAVI. The rate of stroke at 30 days varies from 1.2% to 6.7% in multicenter registries[6,12-18] and in the PARTNER trial[2,3]. In the cohort of high risk of the PARTNER study, the number of strokes tended to be higher in the TAVI group compared to group of patients undergoing aortic valve replacement by surgery (4.6% vs 2.4%, p = 0.12 to 30 days and 6.0% vs 3.2%, p = 0.08 at 1 year follow-up)[2]. At two years the difference in stroke between the two groups was no more significant (p = 0.52)[25]. In the same way, also in the cohort of inoperable patients of the PARTNER study has been observed a higher rate of stroke or transient ischemic attack at 30 days (6.7% vs. 1.7%, p = 0.03) and at 1 year of follow-up

(10.6% vs. 4.5%, p = 0.04) among patients who underwent to TAVI than those treated conservatively with medical therapy, always remembering that they were facing aortic valvuloplasty in 84% of cases[3]. Although studies using transcranial Doppler have demonstrated that the cerebral embolism can occur in any time during the TAVI procedure, the phase at greatest risk is undoubtedly that of the implant of the prosthetic valve, which would lead to identify emboli of elements of calcium of the native valve the leading cause of cerebral embolism associated with TAVI[27]. It should also be remembered that the PARTNER data indicate that half of cerebrovascular events happen more than 24 hours after the procedure[2,3], but also that at 3 years of follow-up there were no differences among patients treated percutaneously or surgically[28]. The combination of clopidogrel and aspirin was empirically recommended as treatment after TAVI[12-18], but future studies will have to determine the optimal antithrombotic regimen after these procedures.

Coronary obstruction

The obstruction of the coronary ostia, and in particular of the common trunk of the left coronary artery, is a serious complication of the TAVI procedure, but the overall incidence of this life threatening complication it is very low (<1%)[12-18]. The basic mechanism is linked to the dislocation a leaflet of the native aortic valve to the ostium of the coronary artery during the implantation of the valve. The risk of this complication is higher in patients with severely calcified leaflet, with low implantation of the coronary ostia, a long aortic cusp and obliterated Valsalva sinus. In patients considered at risk for this complication, as assessed by CT during work-up prior to TAVI, performing aortography during valvuloplasty before implantation of the valve, may be useful for predicting a possible mechanical obstruction of coronary ostia at implant of the valve itself.

Intraventricular conduction abnormalities

The appearance of disorders of intraventricular conduction, in particular, the left bundle branch block, is a rather common occurrence after TAVI[2,3,6,12-18]. It should be emphasized that the balloon-expandable SAPIEN valve have been associated to a probability of occurrence of left bundle branch block significantly lower than self-expandable CoreValve® (3.4 to 18% vs. 30-83%)[29-35]. In particular, the study of Erkapic of 2012, a Literature

analysis on 5258 patients, reported an incidence of implants of pacemaker 6.5% in SAPIEN patients and 25.8% in patients CoreValve (36). The principal mechanism of this complication is to be identified in direct mechanical damage and inflammation of the left bundle branch induced by the stent that supports the valvular prosthesis. Interestingly Nuis et al. have reported that about half of these conduction disturbances occur during valvuloplasty prior to implantation[34]. It is not surprising that the presence of a block of right branch before the procedure results in an important predictor of complete atrioventricular block and subsequent pacemaker implantation after TAVI[33-35]. In PARTNER studies rate of pacemaker implantation after TAVI with the Edwards SAPIEN valve was 3.4% and 3.8% in inoperable cohorts and high risk, respectively, with no difference compared to medical therapy (5.0%) and aortic valve replacement by surgery (3.6%)[2,3].

Paravalvular leak

As before explained, the hemodynamic results after TAVI are excellent, with transvalvular gradient values average remaining <15 mmHg and aortic valve areas >1.5 cm2, hemodynamic results that remain in medium to long term[9-11]. In addition, Clavel et al. have demonstrated that the hemodynamic results associated with TAVI, using the valves Cribier-Edwards and Edwards Sapien were higher than those obtained with surgical tissue graft and stentless valves, especially in patients with aortic annulus <20 mm[37]. By contrast, the incidence of regurgitation associated with Sapien valve, mostly paravalvular, is quite common (65-89%), although it is negligible or mild in most cases, moderate or moderate to severe in a relatively low percentage, variable between 5% and 17% of the cases. Specifically, in high-risk cohort of the study PARTNER[2] a certain degree of paravalvular leaks occurred in 77% (12% moderate or severe) of patients in the TAVI compared with 26% (0.9% moderate or severe) in the group underwent aortic valve replacement (p <0.001). Several studies have shown that the degree of residual paravalvular and transvalvular aortic regurgitation remains stable at medium-term (one year) follow-up, but studies with a long follow-up are needed to provide additional assessments.

Two meta-analyzes have shown a difference in incidence of moderate or severe paravalvular leak in patients receiving valve balloon-epandable (Sapien) and selfexpandable (CoreValve). In the study of

Athappan[38], on 12,926 patients, the incidence of this complication occurred in 16.0% of cases with the valve self-expandable vs 9.1% of the latest balloon-expandable valve (p = 0.005). O'Sullivan meta-analysis has confirmed this fact: of 5910 patients: 15.75% with CoreValve, vs. 3.93% with Sapien[39].

The latest generation of TAVI device

Research and technological development in the field of TAVI have kept in close consideration the limitations that have emerged in the use of the valves of the previous generation, which we have described above, the hemodynamic results and prognosis. From this has come, after the phases of design and testing started in 2010, the availability to the clinical use of the last generation TAVI devices, which the Sapien 3 Edwards, is the first device made of this generation and which is also that for the most part used. Essentially, the valves of the last generation have been designed to have a profile and overall dimensions lower than the previous, and also exhibit structural devices such as to reduce the risk of paravalvular leak. It has also obtained an evolution of the introducers required to implant procedure, in fact they are of average size smaller and more flexible than in the past, these features that reduce the risk of vascular lesion at the arterial access during the endovascular progression of the valve introducer in the implantation procedure. Finally updates made in delivery systems and positioning of the prosthetic valve to aortic annulus level represent a further development of the TAVI materials, tending to the overall optimization of the implant procedures.

As for the clinical results obtained with this last generation TAVI devices, the first data available[40] seem to be very promising and indicate a 30-day mortality of 1.1%, and incidence of stroke 1%. Furthermore, major vascular complications, reduced compared to the previous generation, are 5.2%. and 7.4%, respectively, for the transfemoral and transapical approach. Probably this improvement is mainly due to the reduction in the size of the catheter introducer valve. The incidence of paravalvular leak showed a significant reduction over the previous generation of valves: 0% severe leak; moderate leak 3.4% (2.6% in the trans-femoral) and 24.1% mild. In over 70% of cases the result was comparable to the surgical replacement of the aortic valve in terms of residual insufficiency. The new devices also show a probability of positioning at the desired point of 99.3%, without the need for additional maneuvers, the latter often associated with major complications. The experience on the valves of the last generation is very gradually increased from when they enter clinical use. Clinical data on the TAVI procedures are the subject of multicenter prospective, randomized studies, currently in progress in several countries[41]. In more than 70% of the procedures performed, it was possible to use the trans-femoral tapproach, much less invasive for the patient compared to the trans-apical. This is because, thanks to the overall improvements made in the materials of the latest generation TAVI, the introducers used are of average size smaller than those of the previous one. Almost 40% of the cases the patients were also treated merely with a mild sedation, which may prospectively reduce the time of hospitalization and recovery after the procedure. Even more exciting are the outcome data, with more than 99% of survival in the procedure. This is probably due to a reduced risk of malposition of the valve (0.3%) or of its embolization (0.1%). The special shape of the valve also has minimized the degree of periprosthetic regurgitation, problem which was one of the weaknesses of TAVI in the long period follow-up in the first generation of devices. Finally the updates made on TAVI materials have made the whole procedure in general, and the correct positioning of the valve in particular, much smoother than the previous generation.

Conclusions

The TAVI represents a real revolution in the field of interventional cardiology and medicine, for the treatment of severe aortic stenosis in elderly patients, or in high-risk surgical patients, as an alternative to traditional aortic valve replacement.

The data of follow-up in the long term are currently available mainly for the valve of the first generation. These data show an excellent, also at long term, hemodynamic performance.

Although experience on the valves of the last generation is still limited in time, the data currently available are definitely in the direction of a minimum hospital mortality (1%), as well as to a drastic reduction in vascular complications and paravalvular leak. Finally, the new TAVI materials made the implant much simpler and easier for the operators, they confer even more features that improve also the precision in the execution of the procedure. For all these reasons the TAVI materials of the newest generation have greatly enhanced safety and efficacy of

TAVI procedures in the last years.

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