

TAVI for Pure Native Aortic Regurgitation: Are We There Yet?

Eduardo A Arias,¹ Amit Bhan,² Zhan Y Lim³ and Michael Mullen²

1. Interventional Cardiology Department, National Institute of Cardiology Ignacio Chávez, Mexico City, Mexico;

2. Barts Heart Centre, St Bartholomew's Hospital, London, UK; 3. Cardiology Department, Khoo Teck Puat Hospital, Singapore

Abstract

Treatment of degenerative aortic stenosis has been transformed by transcatheter aortic valve implantation (TAVI) over the past 10–15 years. The success of various technologies has led operators to attempt to broaden the indications, and many patients with native valve aortic regurgitation have been treated 'off label' with similar techniques. However, the alterations in the structure of the valve complex in pure native aortic regurgitation are distinct to those in degenerative aortic stenosis, and there are unique challenges to be overcome by percutaneous valves. Nevertheless some promise has been shown with both non-dedicated and dedicated devices. In this article, the authors explore some of these challenges and review the current evidence base for TAVI for aortic regurgitation.

Keywords

Aortic valve stenosis, native aortic valve regurgitation, second generation TAVI device, TAVI, transcatheter valve interventions, valvular heart disease

Disclosure: The authors have no conflicts of interest to declare.

Received: 12 November 2018 **Accepted:** 7 January 2019 **Citation:** *Interventional Cardiology Review* 2019;14(1):26–30. **DOI:** <https://doi.org/10.15420/icr.2018.37.1>

Correspondence: Eduardo Arias, National Institute of Cardiology Ignacio Chávez, Juan Badiano 1, Col Sección XVI, Tlalpan, Mexico City, Mexico.

E: dreduardoarias@gmail.com

Open Access: This work is open access under the CC-BY-NC 4.0 License which allows users to copy, redistribute and make derivative works for non-commercial purposes, provided the original work is cited correctly.

During the past decade, transcatheter aortic valve implantation (TAVI) has revolutionised the interventional treatment of aortic stenosis (AS).¹ It has rapidly evolved from a treatment used on a compassionate basis for inoperable patients to being the standard of care in high-risk AS.^{2,3} In that cohort it has proven to be non-inferior to surgical aortic valve replacement (SAVR) in terms of mortality, and superior to optimal medical treatment (OMT) in terms of mortality and rehospitalisations.^{4,5} Evidence and indications are now moving towards its suitability for intermediate and low-risk profiles.

Randomised trials such as Placement of Aortic Transcatheter Valves (PARTNER 2) and Surgical or Transcatheter Aortic-Valve Replacement in Intermediate-Risk Patients (SURTAVI) have shown that TAVI is a safe and effective treatment option for people with intermediate risk; being non-inferior to SAVR overall and superior to surgery when it is performed using the transfemoral approach.^{6,7} The randomised controlled Nordic Aortic Valve Intervention (NOTION) trial, which included intermediate and low-risk patients, has also confirmed the safety and efficacy in a low-risk setting.⁸ It is important to clarify that low-risk patients are not necessarily younger patients (the mean age in all the mentioned studies was about 80 years). This leaves unanswered questions about valve durability; as far as we know the incidence of structural valve deterioration after 5 years is very low, but information beyond this time is scarce.^{9–12}

The use of TAVI is continuing to evolve worldwide. Transcatheter heart valves (THV) are being used for valve-in-valve treatment in failing bio-prostheses, treatment of bicuspid aortic valves in younger patients with

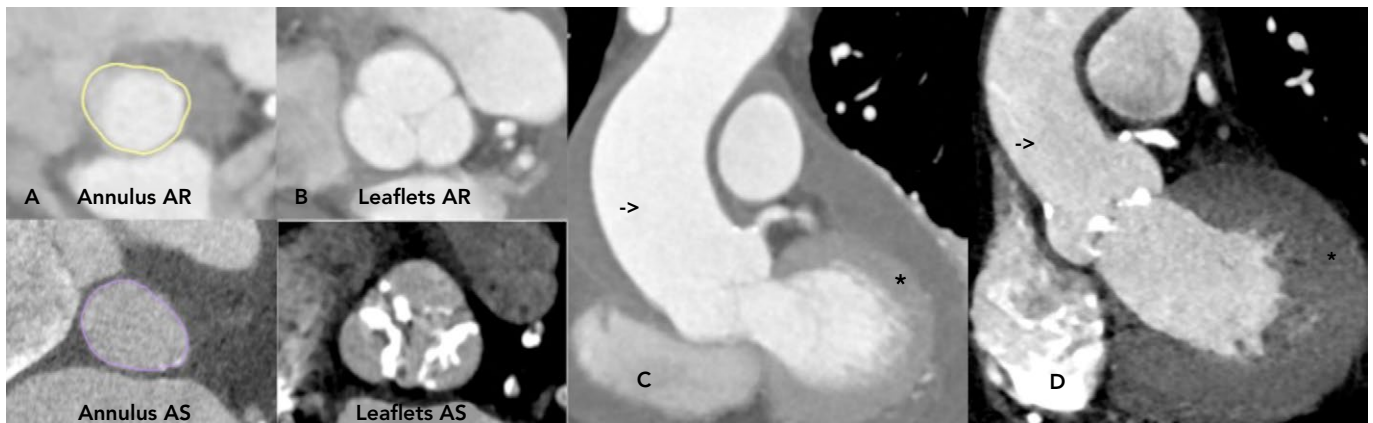
complex anatomical features and for native pure aortic regurgitation (NPAR). This is currently an off-label indication as it poses multiple challenges with variable and unpredictable immediate and long-term results.^{13–15} The aim of this review is to describe: the main differences between AS and NPAR; its impact on procedure complexity; the THVs available for NPAR treatment and current evidence regarding success and short-term results.

Native Aortic Valve Regurgitation

From a pathophysiological point of view, severe AS is characterised by pressure overload with consequent concentric hypertrophy and afterload mismatch.¹⁶ In most cases, after TAVI is performed and this mismatch corrected, left ventricular ejection fraction increases and there is regression of left ventricular (LV) hypertrophy.¹⁷ This explains why patients have the clear benefits of quality of life and life expectancy after TAVI.

On the other hand, severe NPAR is characterised by volume overload and eccentric hypertrophy (increased ventricular volume with little increase in wall thickness and increased LV wall stress) associated with LV cavity structural modifications and progressive LV dysfunction.¹⁸ These structural modifications are due to cardiomyocyte enlargement triggered by multiple growth factors that modulate cardiac output by means of the Frank-Starling mechanism. Once the Frank-Starling mechanism is lost, LV function is irreversibly impaired.^{19,20} From an anatomic point of view, degenerative AS results from progressive calcification of the aortic valve leaflets and annulus, while NPAR is usually the result of leaflet

Figure 1: Main Differences Between Aortic Stenosis and Aortic Regurgitation on CT Scan



A: Spherical and dilated aortic annulus in AR compared with a more elliptical one in AS; B: Absence of calcium on leaflets in AR compared with heavily calcified leaflets on AS; C: Severe aortic regurgitation (* eccentric LV hypertrophy; -> dilated aortic root); D: Severe aortic regurgitation (* eccentric LV hypertrophy; -> dilated aortic root). AR = aortic regurgitation; AS = aortic stenosis.

Table 1: Available Non-dedicated and Dedicated Transcatheter Aortic Valve Implantation Devices for Native Aortic Valve Regurgitation

Valve name	Mechanism	Use in AR	Company
SAPIEN 3 transcatheter heart valve	Balloon expandable	Non-dedicated	Edwards Lifesciences
ACURATE neo™	Self-expandable	Non-dedicated	Boston Scientific
LOTUS	Self-expandable	Non-dedicated	Boston Scientific
CoreValve™ Evolut™ R	Self-expandable	Non-dedicated	Medtronic
JenaValve™	Self-expandable	Dedicated	JenaValve Technology
J-Valve™	Self-expandable	Dedicated	JC Medical

degeneration or incompetence, aortic root dilatation with aortic annulus enlargement, or both. These anatomical differences pose particular challenges for TAVI, which we will discuss later. *Figure 1* depicts the main anatomical differences between AS and AR.

Current Management of Aortic Regurgitation

Prevalence of AR increases with age and it affects about 13% of patients with isolated, native left-sided valvular heart disease.²¹ Symptoms related to AR tend to appear late in the history of the disease, once LV dilatation and systolic dysfunction have set in. Patients with severe AR and an ejection fraction <30% have an annual mortality risk of 20%, but unfortunately only 5% of these patients are given SAVR according to data from the Euro Heart Survey on Valvular Heart Disease.²¹

According to current European and US guidelines, patients with symptomatic moderate/severe AR and decreased LV systolic function (<50%) or severe LV dilatation (LV end-systolic diameter >50 mm; LV end-diastolic diameter >65–70 mm; LV end-systolic volume index >45 ml/m²) should be considered for SAVR.^{2,3} Nonetheless, there is a high-risk subgroup who are inoperable and who could be considered for TAVI, taking into account the multiple procedural challenges and the fact that it still is an off-label indication.²² To date, the standard of care for severe NPAR is SAVR with TAVI emerging as an option for high-risk or inoperable patients.

Technical Challenges During TAVI for NPAR

The main challenge that interventionists face during TAVI for NPAR is the absence of annular and leaflet calcification, which is necessary for device anchoring and stabilisation during deployment. The lack

of calcium, the increased stroke volume secondary to severe AR and the presence of aortic root dilatation makes device positioning and deployment very difficult and there is a predisposition to embolisation or malposition of the prosthesis with subsequent moderate to severe post-procedural AR (associated with worst clinical outcomes).²³ Valve migration can occur to the aorta or deep into the LV up to several hours after implantation.²⁴ Valve oversizing has been proposed to reduce the risk of valve migration. Published data recommend a 15–20% oversize when selecting the THV size with the caution not to oversize beyond 20% due to the risk of annular rupture and conduction system abnormalities.^{25,26}

THV Devices Available for NPAR

Second generation THVs that have been used for TAVI for NPAR can be divided into non-dedicated devices: CoreValve Evolut R (Medtronic), Sapien 3 (Edwards Lifesciences), Lotus valve (not commercially available at time of writing) and ACURATE neo (Boston Scientific) and dedicated devices: JenaValve (JenaValve) and the J-Valve (JC Medical).²⁷ Non-dedicated devices are widely used for TAVI for AS (their mechanisms are dependent on annulus and leaflet calcification for fixation), while the dedicated devices have been developed to be implanted in non-calcified valves anchoring in the aortic annulus and clipping the native valve leaflets for stability.²⁸

Self-expandable THVs have been the preferred non-dedicated devices used for TAVI for NPAR with CoreValve being the most widely studied. Self-expandable THVs can be recaptured and repositioned which theoretically make the prosthesis behave in a more predictable manner.^{29,30} Experience with ACURATE neo

Table 2: Main Results of Recent Retrospective Studies Evaluating Early Generation Devices Versus New Generation Devices

Author, year	Patients (n)	EGD	NGD	Device Success (EGD/NGD)	CV Mortality (EGD/NGD)	Second Valve (EGD/NGD)	AR >Moderate (EGD/NGD)
Roy et al. 2013 ⁴¹	43	100%	NA	74.4%/NA	10.7%*/NA	18.6%/NA	4.7%/NA
Yoon et al. 2017 ⁴⁹	331	36%	64%	61.3%/81.1%	23.6%/9.6%*	24.4%/12.7%	18.8%/4.2%
De Backer et al. 2018 ⁴⁸	254	43%	57%	47%/82%	12%/7%†	40.4%/9.4%	31%/4%
Sawaya et al. 2017 ⁵⁰	78	47.4%	52.6%	54%/85%	11%/5%†	24%/10%	29%/2%
Silaschi et al. 2018 ⁴⁹	30	NA	100%	NA/96.7%	NA/10%	NA/0%	NA/0%

* 1-year mortality; †30-day mortality. AR = aortic regurgitation; CV = cardiovascular; EGD = early generation device; NGD = new generation device.

(transfemoral) is limited to successful case reports and there is a small series of eight patients treated with ACURATE TA (transapical) that showed good results based on its hourglass design, stabilisation arches and upper crown that ensure coaxial alignment and device stability during deployment.^{31,32} The first successful transfemoral implantation of a Lotus valve in pure NPAR was reported in 2016 and the authors warrant its use based on its repositionability and retrievability.³³

Sapien 3 valve (balloon expandable) implantation has been shown to be feasible for NPAR in three cases reported in 2016. Deployment position was more ventricular than that recommended for AS and the annulus oversizing ratio was >15% using from 3 to 10 mm extra volume according to the LV outflow tract dimensions.^{34,35}

The JenaValve, a self-expanding, 32Fr transapical valve with three integrated locators was the first dedicated device to get the CE mark for NPAR based on its anatomically correct positioning in the native cusps and clipping of the THV onto the native leaflets.^{36,37} Since June 2016, the transapical system is no longer available but development of a new generation transfemoral system is underway and has been used successfully for NPAR in a first-in-human case report in 2017.³⁸ The Longterm Safety and Performance of the JenaValve (JUPITER) registry showed a procedural success rate of 96.7% with 0% incidence of valve malposition and moderate to severe post-procedural AR.³⁹

Another NPAR-dedicated second generation TAVI device is the J-Valve, which has a unique system composed of three U-shape graspers that facilitate intuitive self-positioning implantation providing axial and radial fixation by embracing the native valve leaflets. A successful first-in-human implantation was reported in 2015 but currently, the device is only available in Asia.⁴⁰ Table 1 shows the different THVs available for NPAR.

TAVI for NPAR: Evidence on Early Generation Devices

The first use of TAVI for NPAR was reported by Roy et al. in 2013 and included the retrospective analysis of 43 patients at 14 centres who had TAVI for severe inoperable NPAR. All cases used CoreValve prosthesis and as part of the procedure protocol two pigtail catheters in different sinuses of Valsalva were used to guide THV delivery under rapid pacing. Results included a 97.7% success rate (according to protocol and not VARC-2 guidelines), in 18.6% of the cases a second valve was required during the index procedure for residual AR (all of which had absent valve calcification) and the one-year all-cause mortality was 21.4%.⁴¹ Multiple studies followed using early generation devices (CoreValve being the most used followed by Sapien/Sapien

XT, JenaValve, Direct flow and ACURATE TA), and in 2016 Franzone et al. published a meta-analysis of 13 studies with a total of 237 severe inoperable NPAR patients without AS treated with TAVI.⁴²⁻⁴⁴ In 80% of the cases a self-expandable valve was used and less than 25% of the cases were treated with devices approved for AR. Device success ranged from 77% to 100% with a 7% incidence of second valve implant due to either device migration or severe post-procedural AR. The primary endpoint of all-cause mortality at 30 days ranged from 0 to 30% with a summary estimate rate of 7%. Moderate to severe post-procedural AR was reported in up to 88% of patients with a summary estimate rate of 9%.⁴⁵ The JenaValve subgroup had a 0% incidence of moderate to severe post-procedural AR. Given the heterogeneity of the groups and procedural aspects, no solid conclusions in terms of safety and efficacy can be drawn from these initial experiences but all of them showed that TAVI for NPAR is complex, with success rates below those reported for AS and a high incidence of valve malposition and moderate to severe post-procedural AR.

TAVI for NPAR: Evidence on New Generation Devices

New generation devices (NGDs) such as CoreValve Evolut R, ACURATE neo, Lotus valve and Sapien 3 have features that distinguish them from their predecessors. Characteristics such as retrievability and repositioning in the case of the self-expandable valves and the adaptive seal or skirt found in Sapien 3 and Lotus valve offer a more controlled and predictable TAVI procedure.^{46,47} Three recent retrospective studies have analysed the use of new generation TAVI devices for NPAR and compared their results with early generation devices.

De Backer et al. reported the early safety and clinical efficacy of TAVI for NPAR in 254 patients from 46 centres with an EGD/NGD proportion of 43% and 57%, respectively. Overall device success according to Valve Academic Research Consortium (VARC-2) criteria was 67%, being higher with NGD (82% versus 47% when compared with EGD).⁹ NGD use was associated with less valve malpositioning and less moderate to severe post-procedural AR. Cardiovascular mortality was also lower with NGD. As part of the study they focused on THV CT-scan sizing and found a significant increase on the incidence of device embolisation with relative THV under or oversizing when compared with neutral sizing. The authors found no causal explanation for this phenomenon other than valve design and absence of calcification.⁴⁸

Yoon et al. reported 331 severe NPAR patients from 40 centres (36% EGD and 64% NGD). Primary endpoint was all-cause and cardiovascular mortality at one year. Overall device success was 74.3% and again, second valve implantation, moderate to severe post-procedural AR

and cardiovascular mortality were significantly lower with NGD (12.7% versus 24.4%; 4.2% versus 18.8% and 9.6% versus 23.6%, respectively) when compared with EGD. They also found that the absence of calcium or the presence of mild calcification was associated with less frequent device success with EGD but not with NGD. A larger annulus (>25.2mm) was associated with less frequent device success either with EGD or NGD. Finally, they showed that a higher degree of perimeter oversizing index (>15%) was associated with less frequent moderate to severe AR.⁴⁹

Sawaya et al. performed a retrospective analysis of 78 patients with severe NPAR treated with TAVI. The majority of cases were done under general anaesthesia via transfemoral access with CoreValve; given its radial force at both the annular level and ascending aorta and also because it could be significantly oversized without risk of annular rupture. Results were consistent with those that we have previously described. NGD showed a lower incidence of valve malposition, a lower degree of AR and cardiovascular mortality versus EGD. They also found that a BMI <20kg/m², Society of Thoracic Surgeons score >8%, major vascular complication or new left bundle branch block, and more than moderate AR were independent predictors of mortality and New York Heart Association III–IV at 30 days after TAVI for NPAR.⁵⁰ All of these findings were confirmed in a recent meta-analysis.⁵¹ Table 2 summarises the main results of these three studies.

Interventional Tips and Tricks for TAVI for NPAR

The following recommendations are made based on personal experience and information gathered from published cases. The first and one of the most important steps before TAVI for NPAR is a pre-procedural CT assessment with focus on the annulus area, sinuses of Valsalva and aortic root diameters and device size selection keeping in mind that a 15–20% oversizing index is recommended in this setting (oversizing index formula: [(device nominal perimeter/area) / (annulus/perimeter area measured by CT) – 1] x 100.⁵² The procedure should be carried out preferably under general anaesthesia, as it can be lengthy and complicated. Transoesophageal echocardiogram can be used to help with valve positioning but more importantly to accurately evaluate

the degree of post-procedural AR. Given the absence of calcification and fluoroscopic landmarks many operators use two pigtail catheters in different sinuses of Valsalva, or CT fusion-guided imaging for valve deployment. Balloon predilatation should not be performed unless it is used to measure the annulus when there is no available CT. Rapid pacing is mandatory for balloon expandable valves and it can also be used with self-expandable valves to reduce the stroke volume, helping to stabilise the aortic annulus and limit THV motion by reducing the regurgitant jet. While deploying the valve, always pay close attention to the haemodynamic profile, particularly to the waveform, the aortic diastolic pressure.⁵³ Whenever using a balloon-expandable valve, keep in mind that variable amounts of extra volume should be added to avoid valve embolisation. Finally, based on the evidence we have presented, the use of NGD should be mandatory in TAVI for NPAR.

Conclusion

Patients with NPAR who are candidates for TAVI tend to be in a poorer clinical condition than many contemporary AS patients, due to LV dilatation and dysfunction. These facts alongside the technical difficulties met during the procedure and the lack of transfemoral dedicated devices make TAVI for NPAR an 'off-label' treatment. Even though better results are achieved with NGD in terms of lower rates of valve malposition/second valve insertion during index procedure and lower incidence of moderate to severe post-procedural AR, clinical results are far from those achieved with TAVI for AS. To date there are no randomised clinical trials and all the evidence we have comes from retrospective studies with heterogeneous populations and no standardised TAVI protocol for NPAR.

New dedicated devices are being designed and those available are evolving to transfemoral as we continue to gain experience of using non-dedicated devices for this patient group. Nonetheless, TAVI for NPAR has to be considered the treatment of choice for inoperable severe AR patients because it offers a better prognosis than optimal medical treatment. TAVI has been established for inoperable or high-risk patients, but we need to improve. TAVI is not yet the standard of care for NPAR, but it is likely to be established as such in time. ■

- Perrin N, Frei A, Noble S. Transcatheter aortic valve implantation: Update in 2018. *Eur J Intern Med* 2018;55:12–9. <https://doi.org/10.1016/j.ejim.2018.07.002>; PMID: 30180946.
- Vahanian A, Alferri O, Andreotti F, et al. Guidelines on the management of valvular heart disease (version 2012): the Joint Task Force on the Management of Valvular Heart Disease of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS). *Eur J Cardiothorac Surg* 2012;42:S1–44. <https://doi.org/10.1093/ejcts/ezs455>; PMID: 22922698.
- Nishimura RA, Otto CM, Bonow RO, et al. 2017 AHA/ACC focused update of the 2014 AHA/ACC Guideline for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *J Am Coll Cardiol* 2017;70:252–89. <https://doi.org/10.1016/j.jacc.2017.03.011>; PMID: 28315732.
- Leon MB, Smith CR, Mack M, et al. Transcatheter aortic-valve implantation for aortic stenosis in patients who cannot undergo surgery. *N Engl J Med* 2010;363:1597–607. <https://doi.org/10.1056/NEJMoa1008232>; PMID: 20961243.
- Eltchaninoff H, Prat A, Gilard M, et al. Transcatheter aortic valve implantation: early results of the FRANCE (French Aortic National CoreValve and Edwards) registry. *Eur Heart J* 2011;32:191–7. <https://doi.org/10.1093/eurheartj/ehq261>; PMID: 20843959.
- Leon MB, Smith CR, Mack MJ, et al. Transcatheter or surgical aortic-valve replacement in intermediate-risk patients. *N Engl J Med* 2016;374:1609–20. <https://doi.org/10.1056/NEJMoa1514616>; PMID: 27040324.
- Reardon MJ, Van Mieghem NM, Popma JJ, et al. Surgical or transcatheter aortic-valve replacement in intermediate-risk patients. *N Engl J Med* 2017;376:1321–31. <https://doi.org/10.1056/NEJMoa1700456>; PMID: 28304219.
- Sondergaard L, Steinbrüchel DA, Ihlemann N, et al. Two-year outcomes in patients with severe aortic valve stenosis randomized to transcatheter versus surgical aortic valve replacement: the all-comers nordic aortic valve intervention randomized clinical trial. *Circ Cardiovasc Interv* 2016;9:e003665. <https://doi.org/10.1161/CIRCINTERVENTIONS.115.003665>; PMID: 27296202.
- Kumar A, Sato K, Banerjee K, et al. Hemodynamic durability of transcatheter aortic valves using the updated Valve Academic Research Consortium-2 criteria. *Catheter Cardiovasc Interv* 2018. <https://doi.org/10.1002/ccd.27927>; PMID: 30312995; epub ahead of press.
- Eltchaninoff H, Durand E, Barbanti M, Abdel-Wahab M. TAVI and valve performance: update on definitions, durability, transcatheter heart valve failure modes and management. *EuroIntervention* 2018;14(Suppl AB):AB64–73. <https://doi.org/10.4244/EIJ-D-18-00653>; PMID: 30158097.
- Holy EW, Kebernik J, Abdelghani M, et al. Long-term durability and haemodynamic performance of a self-expanding transcatheter heart valve beyond five years after implantation: a prospective observational study applying the standardised definitions of structural deterioration and valve failure. *EuroIntervention* 2018;14:e390–6. <https://doi.org/10.4244/EIJ-D-18-00041>; PMID: 29741488.
- Barbanti M, Petronio AS, Ettori F, et al. 5-year outcomes after transcatheter aortic valve implantation with corevalve prosthesis. *JACC Cardiovasc Interv* 2015;8:1084–91. <https://doi.org/10.1016/j.jcin.2015.03.024>; PMID: 26117458.
- Takagi H, Mitta S, Ando T. Meta-analysis of valve-in-valve transcatheter versus redo surgical aortic valve replacement. *Thorac Cardiovasc Surg* 2018. <https://doi.org/10.1055/s-0038-1668135>; PMID: 30114716; epub ahead of press.
- Das R, Puri R. Transcatheter treatment of bicuspid aortic valve disease: imaging and interventional considerations. *Front Cardiovasc Med* 2018;5:91. <https://doi.org/10.3389/fcvm.2018.00091>; PMID: 30073170.
- De Backer O, Sondergaard L. Challenges when expanding transcatheter aortic valve implantation to younger patients. *Front Cardiovasc Med* 2018;5:45. <https://doi.org/10.3389/fcvm.2018.00045>; PMID: 29868611.
- Grossman W, Paulus WJ. Myocardial stress and hypertrophy: a complex interface between biophysics and cardiac remodeling. *J Clin Invest* 2013;123:3701–3. <https://doi.org/10.1172/JCI69830>; PMID: 23999445.
- Kasapkala HA, Ayhan H, Sari C, et al. Impact of transcatheter aortic valve implantation on the left ventricular mass. *Cardiol J* 2015;22:645–50. <https://doi.org/10.5603/CJ.a2015.0025>; PMID: 26004938.
- Guadalajara JF, Gual J, Martinez SC, et al. [Myocardial hypertrophy in aortic insufficiency as a compensation mechanism. Implications for surgical indication]. *Arch Inst Cardiol Mex* 1992;62:351–60 [in Spanish]. PMID: 1417354.
- Harvey PA, Leinwand LA. The cell biology of disease: cellular mechanisms of cardiomyopathy. *J Cell Biol* 2011;194:355–65. <https://doi.org/10.1083/jcb.201101100>; PMID: 21825071.
- Mannacio V, Guadagno E, Mannacio L, et al. Comparison of left ventricular myocardial structure and function in patients with aortic stenosis and those with pure aortic regurgitation. *Cardiology* 2015;132:111–8. <https://doi.org/10.1159/000431283>; PMID: 26139515.
- Lung B, Baron G, Butchart EG, et al. A prospective survey of patients with valvular heart disease in Europe: the Euro Heart Survey on Valvular Heart Disease. *Eur Heart J* 2003;24:1231–43. [https://doi.org/10.1016/S0195-668X\(03\)00201-X](https://doi.org/10.1016/S0195-668X(03)00201-X); PMID: 12831818.
- Spina R, Anthony C, Muller DW, Roy D. Transcatheter aortic valve replacement for native aortic valve regurgitation. *Interv Cardiol* 2015;10:49–54. <https://doi.org/10.15420/icr.2015.10.1.49>; PMID: 29588674.

23. Maeno Y, Yoon SH, Abramowitz Y, et al. Effect of ascending aortic dimension on acute procedural success following self-expanding transcatheter aortic valve replacement: a multicenter retrospective analysis. *Int J Cardiol* 2017;244:100–5. <https://doi.org/10.1016/j.ijcard.2017.05.120>; PMID: 28622944.
24. Fankhauser CD, Nietlispach F, Emmert MY, Maisano F. Antegrade valve embolization after transcatheter treatment for pure aortic regurgitation. *Eur Heart J* 2016;37:856. <https://doi.org/10.1093/eurheartj/ehv237>; PMID: 26084683.
25. Alkhouli M, Sengupta P, Badhwar V. Toward precision in balloon-expandable tavr: oversizing tight versus just right. *JACC Cardiovasc Interv* 2017;10:821–3. <https://doi.org/10.1016/j.jcin.2017.03.003>; PMID: 28427599.
26. Dvir D, Webb JG, Piazza N, et al. Multicenter evaluation of transcatheter aortic valve replacement using either SAPIEN XT or CoreValve: degree of device oversizing by computed-tomography and clinical outcomes. *Catheter Cardiovasc Interv* 2015;86:508–15. <https://doi.org/10.1002/ccd.25823>; PMID: 25573784.
27. Treede H, Rastan A, Ferrari M, et al. JenaValve. *EuroIntervention* 2012;8(Suppl Q):Q88–93. <https://doi.org/10.4244/EIJV8SQA16>. PMID: 22995119.
28. Puri R, Chamandi C, Rodriguez-Gabella T, Rodes-Cabau J. Future of transcatheter aortic valve implantation – evolving clinical indications. *Nat Rev Cardiol* 2018;15:57–65. <https://doi.org/10.1038/nrcardio.2017.116>; PMID: 28836620.
29. Bruschi G, Colombo P, Nava S, et al. Evolut R implantation to treat severe pure aortic regurgitation in a patient with mitral bioprosthesis. *Ann Thorac Surg* 2016;102:e521–4. <https://doi.org/10.1016/j.athoracsur.2016.05.054>; PMID: 27847071.
30. Bruschi G, De Marco F, Martinelli L, Klugmann S. CoreValve® transcatheter self-expandable aortic bioprosthesis. *Expert Rev Med Devices* 2013;10:15–26. <https://doi.org/10.1586/erd.12.64>; PMID: 23278219.
31. Wendt D, Kahlert P, Pasa S, et al. Transapical transcatheter aortic valve for severe aortic regurgitation: expanding the limits. *JACC Cardiovasc Interv* 2014;7:1159–67. <https://doi.org/10.1016/j.jcin.2014.04.016>; PMID: 25129668.
32. Cerillo AG, Griese D, Berti S. Successful percutaneous implantation of symetis ACURATE neo transcatheter aortic bioprosthesis for the treatment of pure aortic regurgitation. *Catheter Cardiovasc Interv* 2016;88:319–23. <https://doi.org/10.1002/ccd.26402>; PMID: 26762474.
33. Wohrle J, Rodewald C, Rottbauer W. Transfemoral aortic valve implantation in pure native aortic valve insufficiency using the repositionable and retrievable lotus valve. *Catheter Cardiovasc Interv* 2016;87:993–5. <https://doi.org/10.1002/ccd.26062>; PMID: 26110426.
34. Urena M, Himbert D, Ohlmann P, et al. Transcatheter aortic valve replacement to treat pure aortic regurgitation on noncalcified native valves. *J Am Coll Cardiol*; 2016;68:1705–6. <https://doi.org/10.1016/j.jacc.2016.07.746>; PMID: 27712786.
35. Kaneko H, Hoelschermann F, Tambor G, et al. Rescue valve-in-valve transcatheter aortic valve replacement for pure aortic regurgitation. *JACC Cardiovasc Interv* 2017;10:e23–4. <https://doi.org/10.1016/j.jcin.2016.11.031>; PMID: 28109871.
36. Treede H, Mohr FW, Baldus S, et al. Transapical transcatheter aortic valve implantation using the JenaValve system: acute and 30-day results of the multicenter CE-mark study. *Eur J Cardiothorac Surg* 2012;41:e131–8. <https://doi.org/10.1093/ejcts/ezs129>; PMID: 22508111.
37. Seiffert M, Bader R, Kappert U, et al. Initial German experience with transapical implantation of a second-generation transcatheter heart valve for the treatment of aortic regurgitation. *JACC Cardiovasc Interv* 2014;7:1168–74. <https://doi.org/10.1016/j.jcin.2014.05.014>; PMID: 25129672.
38. Schafer U, Schirmer J, Niklas S, et al. First-in-human implantation of a novel transfemoral self-expanding transcatheter heart valve to treat pure aortic regurgitation. *EuroIntervention* 2017;13:1296–9. <https://doi.org/10.4244/EIJ-D-17-00502>; PMID: 28846544.
39. Silaschi M, Conradi L, Wendler O, et al. The JUPITER registry: one-year outcomes of transapical aortic valve implantation using a second generation transcatheter heart valve for aortic regurgitation. *Catheter Cardiovasc Interv* 2018;91:1345–51. <https://doi.org/10.1002/ccd.27370>; PMID: 29171730.
40. Zhu D, Hu J, Meng W, Guo Y. Successful transcatheter aortic valve implantation for pure aortic regurgitation using a new second generation self-expanding J-Valve™ system – the first in-man implantation. *Heart Lung Circ* 2015;24:411–4. <https://doi.org/10.1016/j.hlc.2014.10.007>; PMID: 25465513.
41. Roy DA, Schaefer U, Guetta V, et al. Transcatheter aortic valve implantation for pure severe native aortic valve regurgitation. *J Am Coll Cardiol* 2013;61:1577–84. <https://doi.org/10.1016/j.jacc.2013.01.018>; PMID: 23433565.
42. Frerker C, Schewel J, Schewel D, et al. Expansion of the indication of transcatheter aortic valve implantation – feasibility and outcome in ‘off-label’ patients compared with ‘on-label’ patients. *J Invasive Cardiol* 2015;27:229–36. PMID: 25929299.
43. Schlinghoff F, Schafer U, Frerker C, et al. Transcatheter aortic valve implantation of a second-generation valve for pure aortic regurgitation: procedural outcome, haemodynamic data and follow-up. *Interact Cardiovasc Thorac Surg* 2014;19:388–93. <https://doi.org/10.1093/icvts/ivu155>; PMID: 24893871.
44. Testa L, Latib A, Rossi ML, et al. CoreValve implantation for severe aortic regurgitation: a multicentre registry. *EuroIntervention* 2014;10:739–45. <https://doi.org/10.4244/EIJV10I6A127>; PMID: 25330506.
45. Franzoni A, Piccolo R, Siontis GC, et al. Transcatheter aortic valve replacement for the treatment of pure native aortic valve regurgitation: a systematic review. *JACC Cardiovasc Interv* 2016;9:2308–17. <https://doi.org/10.1016/j.jcin.2016.08.049>; PMID: 28026742.
46. Pesarini G, Lunardi M, Piccoli A, et al. Effectiveness and safety of transcatheter aortic valve implantation in patients with pure aortic regurgitation and advanced heart failure. *Am J Cardiol* 2018;121:642–8. <https://doi.org/10.1016/j.amjcard.2017.11.042>; PMID: 29329825.
47. Nakamura Y, Teffy P, Kiaii B, et al. Transcatheter aortic valve implantation in a patient with severe aortic insufficiency and minimal aortic annular calcification. *Can J Cardiol* 2013;29:1138.e9–11. <https://doi.org/10.1016/j.cjca.2012.11.037>; PMID: 23465340.
48. De Backer O, Pilgrim T, Simonato M, et al. Usefulness of transcatheter aortic valve implantation for treatment of pure native aortic valve regurgitation. *Am J Cardiol* 2018;122:1028–35. <https://doi.org/10.1016/j.amjcard.2018.05.044>; PMID: 30072124.
49. Yoon SH, Schmidt T, Bleiziffer S, et al. Transcatheter aortic valve replacement in pure native aortic valve regurgitation. *J Am Coll Cardiol* 2017;70:2752–63. <https://doi.org/10.1016/j.jacc.2017.10.006>; PMID: 29191323.
50. Sawaya FJ, Deutsch MA, Seiffert M, et al. Safety and efficacy of transcatheter aortic valve replacement in the treatment of pure aortic regurgitation in native valves and failing surgical bioprostheses: results from an international registry study. *JACC Cardiovasc Interv* 2017;10:1048–56. <https://doi.org/10.1016/j.jcin.2017.03.004>; PMID: 28521923.
51. Rawasia WF, Khan MS, Usman MS, et al. Safety and efficacy of transcatheter aortic valve replacement for native aortic valve regurgitation: A systematic review and meta-analysis. *Catheter Cardiovasc Interv* 2018 [Epub ahead of print]. <https://doi.org/10.1002/ccd.27840>; PMID: 30269437.
52. Zhu D, Chen W, Peng L, Guo Y. Valve sizing for pure aortic regurgitation during transcatheter aortic valve replacement: deformation dynamic of the aortic annulus in different valve pathology may be different. *JACC Cardiovasc Interv* 2015;8:372–3. <https://doi.org/10.1016/j.jcin.2014.11.011>; PMID: 25700760.
53. Ozpelit E, Dursun H, Gencpinar T, et al. Transcatheter aortic valve implantation for severe pure aortic regurgitation: looking beyond the image. *Anatol J Cardiol* 2015;15:681–2. <https://doi.org/10.5152/AnatolJCardiol.2015.6412>; PMID: 26301356.