

# COMMENTARY OUTCOME OF PERMANENT PACEMAKER IMPLANTATION IN TRANSCATHETER OR SURGICAL AORTIC VALVE REPLACEMENT: A STILL UNSOLVED PROBLEM.

Antonio Totaro<sup>1</sup>, Antonio Calafiore<sup>1</sup>, Cosimo Sacra<sup>1</sup>, and Gianluca Testa<sup>2</sup>

<sup>1</sup>Gemelli Molise

<sup>2</sup>University of Molise Department of Medicine and Health Sciences Vincenzo Tiberio

September 4, 2022

## Abstract

Despite advances in technologies and clinical experience, conduction disorders, after TAVR or SAVR, represent the weak point of these procedures, requiring permanent pacemaker implantation (PPI) till 37.7% of patients in TAVR recipients. The role of PPI in TAVR and SAVR remains controversial in mid- and long-term outcomes. Indeed, many studies have been published with contradictory results, leaving doubts rather than certainties.

## OUTCOME OF PERMANENT PACEMAKER IMPLANTATION IN TRANSCATHETER OR SURGICAL AORTIC VALVE REPLACEMENT: A STILL UNSOLVED PROBLEM.

Antonio Totaro MD <sup>a-b</sup>, Antonio Maria Calafiore MD<sup>a</sup>, Cosimo Sacra MD <sup>a</sup>, Gianluca Testa MD PhD <sup>b</sup>

a. Department of Cardiovascular Sciences, Gemelli Molise Hospital, Campobasso, Italy

b. Department of Medicine and Health Sciences “V. Tiberio”, University of Molise, Campobasso, Italy

## ABSTRACT

Despite advances in technologies and clinical experience, conduction disorders, after TAVR or SAVR, represent the weak point of these procedures, requiring permanent pacemaker implantation (PPI) till 37.7% of patients in TAVR recipients. The role of PPI in TAVR and SAVR remains controversial in mid- and long-term outcomes. Indeed, many studies have been published with contradictory results, leaving doubts rather than certainties.

## COMMENTARY

Transcatheter aortic valve replacement (TAVR) has become a well-established therapy for patients with severe aortic stenosis, preferred, in many cases to surgical aortic valve replacement (SAVR). However, despite advances in technologies and clinical experience, conduction disorders represent the weak point of this procedure, requiring permanent pacemaker implantation (PPI) till 37.7% of patients (1).

In a single-centre retrospective study, Bin Mahmood et al. (2) sought to discover the impact of PPI on mid-term mortality in SAVR and TAVR patients. Prevalence of PPI was 7.2% and 18.1% in SAVR and TAVR,

respectively. In this examination there was no correlation between PPI and mid-term mortality in both SAVR (HR 0.69, CI 0.21-2.30;  $p=0.56$ ) and TAVR (HR 0.70, CI 0.42-1.17  $p=0.18$ ) patients. Median follow-up duration was 1.9 years and 2.5 years in the SAVR and TAVR group, respectively. This study provides reassuring conclusions about outcomes in TAVR and SAVR patients treated with PPI. One important limitation is the short-term follow-up that may not be enough to detect a negative effect of PPI on clinical outcomes.

The role of PPI in TAVR and SAVR remains controversial in mid- and long-term outcomes. Indeed, many studies have been published with contradictory results, leaving doubts rather than certainties. The prevalence of PPI in TAVR patients is high. A recent meta-analysis (3) showed, in 40,181 patients, a PPI rate of 19.2% in balloon-expandable, 24.7% in self-expandable and 34.8% in mechanically-expandable valves. In SAVR patients, on the contrary, PPI prevalence is 4%, as found analysing 5,600 patients undergone SAVR in Netherlands from 2013 to 2019 (4). This explains why any PPI-related problem is more carefully evaluated in TAVR patients.

Buellesfeld et al. (5) reported a similar outcome in patients with or without PPI at 12 months follow up, as other Authors (6) (7) did. Recently Rück et al. (8) after a median follow-up period of 2.7 years (2.5-11.8) years, found no difference in long-term survival between patients who did and did not require PPI after TAVR.

On the other hand, J. Lopez-Aguilera et al. (9) found that, after TAVR with CoreValve, there was a significant difference in overall all-cause mortality, with a decreased survival of patients in PPI group at 3-3.5 years, while there was no longer a significant difference in survival curves, at 5-6 years. These results were consistent with a study of Dizon et al. (10) and were confirmed in a recent meta-analysis (11), that found, at a follow-up longer than 1 year, a negative impact on all-cause mortality and heart failure rehospitalization in PPI group in patients undergone TAVR, without difference in long-term cardiovascular mortality.

The same contradictions can be found in the SAVR. Greason et al. observed worse long-term survival among patients who underwent PPI after SAVR (12), while Bagur et al. (13) came to a different and opposite conclusion.

It is not easy to understand why results are different and often contradictory. First of all, we know that permanent right ventricular pacing can impact negatively on mortality and hospitalization for heart failure. In the Dual-Chamber and VVI Implantable Defibrillation (DAVID) trial (14), patients treated with a rate responsive pacing (DDD 70 bpm) instead of back-up pacing (VVI 40 bpm) had a significant increase in the composite end point of mortality and hospitalization for heart failure (HR 1.61; 95% CI 1.06–2.44). This means that the deleterious impact of PPI on cardiac function is stronger if cumulative time of ventricular pacing is higher, especially in patients with long-term pacing percentage [?] 40%; the impact of PPI on late mortality is then depending also from the rate of pacing, with a low impact on mortality if time of pacing is low (15) (16). Moreover, conduction abnormalities in TAVR might also be transient, as it has been demonstrated that up to 50% of the TAVR patients who implanted a PPI did not need any pacing with time (17). We then have patients with PPI who will have the same outcome than patients without, but still included in PPI group. It is possible that the outcome of both groups (with and without PPI) could be similar. As a matter of fact, information on ventricular pacing was not available in most of the studies.

This means that we cannot translate the results of the DAVID trial into patients undergoing TAVR. Another question is still unanswered: which is the the optimal timing for PPI after TAVR? Should it to be postponed beyond the 7 days currently recommended after SAVR to determine if rhythm disturbances are temporary or permanent?

Another point to take into consideration is that patients undergone TAVR are old (18). The potential protective effects of PPI with respect to lethal bradyarrhythmias may counterbalance the negative effects of ventricular pacing. Furthermore, after the treatment of aortic stenosis, improvement of left ventricular function may compensate for the deleterious effects of right ventricular pacing. Due to advanced age, most of the studies have a short follow up and reflect the natural history of aged patients where a single factor

(PPI) cannot be such to cause a difference in a survival that is, anyway, short.

Indeed, studies on SAVR have a longer follow up. In a recent study (19) that evaluated PPI in SAVR, the mean and maximum follow-up periods were 7.3 years and 22.0 years, respectively, and at 10 years and 20 years after surgical treatment, all-cause mortality was statistically significantly increased in the PPI group compared with the non-PPI group. This conclusion is however questioned by the study by Bin Mahmood et al (2), who found no difference in survival, but with a shorter follow up.

To date, the impact of PPI in TAVR or SAVR recipients is still unclear and management of conduction abnormalities after TAVR is challenging. As stated by 2021 ESC Guidelines on cardiac pacing (20), the impact of PPI on late outcomes after TAVR remains controversial. Unnecessary PPI has to be minimized, especially in an era when transcatheter AVR is used among younger patients at lower risk.

## BIBLIOGRAPHY

1. van Rosendaal PJ, Delgado V, Bax JJ. Pacemaker implantation rate after transcatheter aortic valve implantation with early and new-generation devices: a systematic review. *Eur Heart J.* (2018) 39:2003–13. doi: 10.1093/eurheartj/ehx785
2. Bin Mahmood SU MBBS, Mori M MD, Amabile A MD, Prescher L DO, Forrest J MD, Kaple R MD, Geirsson A MD, Mangi AA MD. Risk Factors and Mortality associated with Permanent Pacemaker after Surgical or Transcatheter Aortic Valve Replacement: Early versus Late Implantation, *Journal of Cardiac Surgery.* 2022 Sept. JOCS-2022-ORIG-1145.R1
3. Ravaux JM, Di Mauro M, Vernooy K, Kats S, Mariani S, Ronco D, Actis Dato G, Simons J, Hof AWV, Maessen JG, Lorusso R. Permanent pacemaker implantation following transcatheter aortic valve implantation using self-expandable, balloon-expandable, or mechanically expandable devices: a network meta-analysis. *Europace.* 2021 Dec 7;23(12):1998-2009.
4. Ravaux JM, Van Kuijk SM, Di Mauro M, Vernooy K, Bidar E, Mariani S, Dato GA, Van T Hof AW, Veenstra L, Kats S, Housterman S, Maessen JG, Lorusso R; Cardiothoracic Surgery Registration Committee of the Netherlands Heart Registration. Incidence and predictors of permanent pacemaker implantation after surgical aortic valve replacement: Data of the Netherlands Heart Registration (NHR). *J Card Surg.* 2021 Oct;36(10):3519-3527.
5. Buellesfeld L, Stortecky S, Heg D, Hausen S, Mueller R, Wenaweser P et al. Impact of permanent pacemaker implantation on clinical outcome among patients undergoing transcatheter aortic valve implantation. *J Am Coll Cardiol* 2012;60:493–501
6. De Carlo M, Giannini C, Bedogni F, Klugmann S, Brambilla N, De Marco F et al. Safety of a conservative strategy of permanent pacemaker implantation after transcatheter aortic CoreValve implantation. *Am Heart J* 2012;163:492–9
7. Urena M, Webb JG, Tamburino C, Muñoz-García AJ, Cheema A, Dager AE et al. Permanent pacemaker implantation after transcatheter aortic valve implantation: impact on late clinical outcomes and left ventricular function. *Circulation* 2014;129:1233–43
8. Rück A, Saleh N, Glaser N, Outcomes Following Permanent Pacemaker Implantation After Transcatheter Aortic Valve Replacement: SWEDEHEART Observational Study, *JACC: Cardiovascular Interventions*, Volume 14, Issue 19, 2021, Pages 2173-2181
9. López-Aguilera J, Segura Saint-Gerons JM, Sánchez Fernández J, Mazuelos Bellido F, Pan Álvarez-Ossorio M, Suárez de Lezo J, Romero Moreno M, Ojeda Pineda S, Pavlovic D, Mesa Rubio D, Rodriguez Diego S, Ferreira C, Durán E, Chavarría J, Moya González J, Suárez de Lezo J. Long-term clinical impact of permanent cardiac pacing after transcatheter aortic valve implantation with the CoreValve prosthesis: a single center experience. *Europace.* 2018 Jun 1;20(6):993-1000. doi: 10.1093/europace/eux046. PMID: 28472387
10. Dizon JM, Nazif TM, Hess PL, Biviano A, Garan H, Douglas PS et al. Chronic pacing and adverse outcomes after transcatheter aortic valve implantation. *Heart* 2015;101:1665–71
11. Xu S, Zhang E, Qian Z, Sun J, Zou F, Wang Y, Hou X and Zou J (2022) Mid- to Long-Term Clinical and Echocardiographic Effects of Post-procedural Permanent Pacemaker Implantation After Transcatheter

- Aortic Valve Replacement: A Systematic Review and Meta-Analysis. *Front. Cardiovasc. Med.* 9:911234. doi: 10.3389/fcvm.2022.911234
12. Greason KL, Lahr BD, Stulak JM, et al. Long-term mortality effect of early pacemaker implantation after surgical aortic valve replacement. *Ann Thorac Surg.* 2017;104(4):1259-1264.
  13. Bagur R, Manazzoni JM, Dumont É, et al. Permanent pacemaker implantation following isolated aortic valve replacement in a large cohort of elderly patients with severe aortic stenosis. *Heart.* 2011;97(20):1687-1694.
  14. Wilkoff BL, Cook JR, Epstein AE, et al. Dual-chamber pacing or ventricular backup pacing in patients with an implantable defibrillator: the Dual Chamber and VVI Implantable Defibrillator (DAVID) Trial. *JAMA* 2002;288:3115-23
  15. De Sisti A, Márquez MF, Tonet J, Bonny A, Frank R, Hidden-Lucet F. Adverse effects of long-term right ventricular apical pacing and identification of patients at risk of atrial fibrillation and heart failure. *Pacing Clin Electrophysiol.* (2012) 35:1035-43. doi: 10.1111/j.1540-8159.2012.03371.x
  16. Sweeney MO, Hellkamp AS, Ellenbogen KA, Greenspon AJ, Freedman RA, Lee KL, et al. Adverse effect of ventricular pacing on heart failure and atrial fibrillation among patients with normal baseline QRS duration in a clinical trial of pacemaker therapy for sinus node dysfunction. *Circulation.* (2003) 107:2932-7. doi: 10.1161/01.Cir.0000072769.17295.B1).
  17. Bjerre TJ, Loh PH, Cholteesupachai J, et al. Reevaluation of the indications for permanent pacemaker implantation after transcatheter aortic valve implantation. *J Invas Cardiology.* 2014;26: 94-99. Pereira E, Ferreira N, Caeiro D, et al. Transcatheter aortic valve implantation and requirements of pacing over time. *Pacing Clin Electrophysiol.* 2013;36:559-569
  18. D'Ancona G, Pasic M, Unbehaun A, et al. Permanent pacemaker implantation after transapical transcatheter aortic valve implantation. *Interact Cardiovasc Thorac Surg.* 2011;13:373-376.
  19. Glaser N, Persson M, Dalén M, Sartipy U. Long-term Outcomes Associated With Permanent Pacemaker Implantation After Surgical Aortic Valve Replacement. *JAMA Netw Open.* 2021;4(7):e2116564.
  20. Glikson M, Nielsen JC, Kronborg MB, Michowitz Y, Auricchio A, et al, ESC Scientific Document Group, 2021 ESC Guidelines on cardiac pacing and cardiac resynchronization therapy: Developed by the Task Force on cardiac pacing and cardiac resynchronization therapy of the European Society of Cardiology (ESC) With the special contribution of the European Heart Rhythm Association (EHRA), *European Heart Journal*, Volume 42, Issue 35, 14 September 2021, Pages 3427-3520