JACC: CARDIOVASCULAR INTERVENTIONS
© 2015 BY THE AMERICAN COLLEGE OF CARDIOLOGY FOUNDATION
PUBLISHED BY ELSEVIER INC.

VOL. 8, NO. 1, 2015
ISSN 1936-8798/$36.00
http://dx.doi.org/10.1016/j.jcin.2014.09.010

EDITORIAL COMMENT

Permanent Pacemaker Implantation Following Transcatheter Aortic Valve Replacement

Still a Concern?*

Marina Urena, MD, Josep Rodés-Cabau, MD

Transcatheter aortic valve replacement (TAVR) has become the first-choice therapy for patients with symptomatic aortic stenosis and contraindications for cardiac surgery and a therapeutic alternative for those at high-risk of perioperative mortality. TAVR has experienced a very rapid worldwide expansion in recent years, and ongoing studies are currently evaluating its application in intermediate-risk populations. However, several limitations of this technology have been identified, some of which could potentially jeopardize its expansion to the treatment of a lower-risk population.

SEE PAGE 60

The occurrence of new conduction disturbances after TAVR, particularly left bundle branch block and the need for permanent pacemaker (PPM), is still a matter of concern because of the very high frequency of these complications and their potential negative impact on late outcomes (1). The results from the PARTNER (Placement of Aortic Transcatheter Valve) trial (randomized and nonrandomized continuous access cohorts) regarding the occurrence, predictors, and impact of PPM implantation following TAVR are reported by Nazif et al. (2) in this issue of *JACC: Cardiovascular Interventions*. In a cohort of 1,973 patients undergoing TAVR with a balloon-expandable Edwards SAPIEN valve (Edwards Lifesciences, Irvine, California), PPM was required in 8.8% of patients due to the occurrence of complete atrioventricular block (AVB) in most cases. Of note, a much higher incidence of PPM was observed in the more recent nonrandomized continuous access cohort (9.6%) than in the earlier randomized cohort (5.6%), and such differences persisted after further adjustment for potential confounders in a multivariate analysis. Although the reasons for such a significant increase in PPM implantation over time are poorly understood, this finding indicates that this complication of TAVR is not going to be solved only by increasing the centers'/operators' experience. In addition, although enhanced antiparavalvular leak properties and improved retrievability/repositionability capabilities are expected with newer balloon- and self-expandable TAVR technologies, no specific features seem to have been implemented to reduce this complication.

The spatial proximity between the aortic valve and the conduction system (atrioventricular node and left bundle branch block), which lies in the ventricular septum a few millimeters below the aortic root complex (3), explains the risk of AVB when the stent frame of the transcatheter valve prosthesis mechanically interacts with the ventricular septum. In fact, an indirect measurement of the pressure exerted by the stent frame on the ventricular septum (prosthesis diameter/left ventricular outflow tract diameter ratio) was an independent predictor of the occurrence of AVB in the work by Nazif et al. (2), along with other well-known predictors such as the presence of right bundle branch block (1,2,4). Unfortunately, the depth of the valve prosthesis, 1 of the most important factors associated with PPM in prior studies (1), was not available in the study by Nazif et al. (2), and whether or not valve oversizing predicted

*Editorials published in *JACC: Cardiovascular Interventions* reflect the views of the authors and do not necessarily represent the views of *JACC: Cardiovascular Interventions* or the American College of Cardiology.

From the Quebec Heart & Lung Institute, Laval University, Quebec City, Quebec, Canada. Dr. Rodés-Cabau is a consultant for Edwards Lifesciences Inc. and St. Jude Medical. Dr. Urena has reported that she has no relationships relevant to the contents of this paper to disclose.

TABLE 1 Main Studies Assessing the Effect of PPM Implantation After Cardiac Surgery and Transcatheter Aortic Valve Replacement

First Author, Year (Ref. #)	N	Intervention	Age, yrs	LVEF, %	Incidence PPM, %	Mean/Median Follow-Up, yrs	Endpoints	Results (PPM vs. no PPM)	Long-Term Pacing
Bagur et al., 2011 (16)	780	SAVR	77 ± 4	60 ± 13	3.2	3.3	Mortality	4% vs. 26%, p = 0.12	NA
Raza et al., 2011 (17)	6,268	Any cardiac surgery	66 ± 10	50 ± 10	2.2	7.2 ± 5.0	Mortality	Adjusted HR: 1.30, p = 0.17	40%
D'Ancona et al., 2011 (14)	322	TAVR (ES)	79 ± 8	51 ± 15	6.2	1	Mortality	16% vs. 19%, p = 0.30	NA
Buellesfeld et al., 2012 (15)	352	TAVR (ES, CV)	83 ± 6	51 ± 15	32.1	1	Mortality Death, stroke, and MI	Adjusted HR: 1.06, p = 0.90 Adjusted HR: 0.98, p = 0.98	NA
De Carlo et al., 2012 (13)	275	TAVR (CV)	82 ± 6	52 ± 12	26.9	1.8	Mortality	12.5% vs. 11.8%, p = 0.90	NA
Urena et al., 2014 (12)	1,516	TAVR (ES, CV)	80 ± 8	55 ± 14	15.4	1.9 ± 1.4	Mortality Death or rehospitalization for HF	Adjusted HR: 0.98, p = 0.87 Adjusted HR: 1.0, p = 0.98	66.9% (on ECG)
Nazif et al., 2014 (2)	1,763	TAVR (ES)	84 ± 7	54	8.8	1	Mortality Death and any rehospitalization	26% vs. 18%, p = 0.08 42% vs. 33%, p = 0.007	50.5% (on ECG)

Values are n, mean ± SD, or %, unless otherwise indicated.

CV = CoreValve (Medtronic, Minneapolis, Minnesota); ECG = electrocardiogram; ES = Edwards Sapien (Edwards Lifesciences, Irvine, California); HF = heart failure; HR = hazard ratio; LVEF = left ventricular ejection fraction; MI = myocardial infarction; NA = not available; PPM = permanent pacemaker; SAVR = surgical aortic valve replacement; TAVR = transcatheter aortic valve replacement.

PPM independently of prosthesis implantation depth needs to be confirmed. In fact, a higher (more aortic) implantation of the transcatheter valve has been the only maneuver associated with a reduction in the need for PPM after TAVR (5), although perhaps at the price of a potential increase in the risk of valve embolization or malpositioning.

Solid evidence supports pacing-induced heart disease (6). The electrical and mechanical dyssynchrony associated with right ventricular pacing leads to an acute increase in left ventricular filling pressures, a decrease in cardiac output, an increase in sympathetic activation, abnormalities in myocardial perfusion, and ultimately, a chronic adverse left ventricular remodeling (6,7). These pathophysiological effects of right ventricular pacing translate into an increased risk of atrial fibrillation, clinical heart failure, and even mortality, with patients with pre-existing heart failure or left ventricular dysfunction at highest risk (8-11). To date, however, studies assessing the impact of PPM implantation after both cardiac surgery and TAVR have failed to demonstrate a negative effect of PPM on clinical outcomes (**Table 1**) (2,12-17). There may be several reasons for this discrepancy. First, the profile of patients included in studies assessing the impact of right ventricular pacing differs from those included in surgical aortic valve replacement and particularly TAVR studies, who tend to be older and to more frequently experience severe noncardiac comorbidities. Second, it has been shown that the clinical effect of right ventricular pacing becomes apparent first in patients with left ventricular dysfunction, and long periods of ventricular pacing (usually >3 years) are required for the occurrence of clinically-overt heart failure in patients with normal left ventricular function (9,18,19), who in fact currently represent approximately two-thirds of patients undergoing TAVR. Indeed, the longest reported follow-up for TAVR patients in studies assessing the effect of PPM implantation is <2 years, probably not long enough to see such clinical consequences. Third, the percentage of cumulative pacing has been shown to be a strong predictor of the occurrence of heart failure (20-22), and more than 50% of patients requiring PPM after TAVR are not pacing-dependent at 1-year follow up (23).

Unlike previous TAVR studies (12-15), Nazif et al. (2) reported poorer clinical outcomes in patients needing PPM implantation after TAVR, with an increased rate of the combined endpoint of 1-year all-cause mortality or repeat hospitalization for any cause (42.0% vs. 32.6%, p = 0.007) and a trend toward a higher risk of 1-year all-cause mortality (26.3% vs. 20.8%, p = 0.08) in patients requiring PPM. It is noteworthy that this excess mortality was driven (surprisingly) by noncardiovascular deaths, whereas no differences were observed in cardiovascular deaths (7.6% vs. 9.0% in the PPM vs. no PPM groups, respectively, p = 0.52). Although this study has the strengths of including a large number of patients and using an event adjudication committee to ensure data quality, the results were not adjusted