New Conduction Abnormalities After Transcatheter Aortic Valve Replacement An Innocent Bystander or a Serious Adverse Event Indeed?

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EDITORIAL COMMENT

New Conduction Abnormalities After Transcatheter Aortic Valve Replacement

An Innocent Bystander or a Serious Adverse Event Indeed?*

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There is no need for ample resourcefulness to know and understand that transcatheter aortic valve replacement (TAVR) will be the first-choice treatment modality for patients with aortic stenosis including surgical candidates, thereby supplanting surgical aortic valve replacement. It is sufficient to consider the results of the already conducted landmark randomized clinical trials (RCTs) with balloon- and self-expanding valves and the ongoing RCTs comparing TAVR and surgical aortic valve replacement in low-risk patients, and the backing of this minimally invasive treatment by the medical community and controlling authorities (e.g., the U.S. Food and Drug Administration, the European Medicines Agency), as well as patients and their relatives; the technology is therefore rightfully termed disruptive (1-4). Yet treatment must be safe and effective, and TAVR has come a long way (5). As a result of substantial improvement in clinical and technical (i.e., valve performance) outcomes, the Achilles' heel is no longer paravalvular leakage but the occurrence of perioperative new conduction abnormalities (CAs) eventually leading to new permanent pacemaker implantation (PPI).

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In this issue of *JACC: Cardiovascular Interventions*, Jørgensen et al. (6) elegantly addressed the latter in a carefully conducted single-center, prospective, observational study in which they assessed all-cause mortality and heart failure hospitalization during a median follow-up period of approximately 2.5 years in patients with aortic stenosis treated with balloon-expandable, self-expandable, or mechanical expanding valves. Patients with bundle branch block (BBB) or pacemaker implantation before TAVR were excluded from the index population (n = 348 of 1,190 [29%]). The exposure variable (i.e., new BBB or new PPI) was defined at 30 days post-TAVR (time 0), at which the survival analysis commenced in the remaining 816 patients, divided into those with 1) absence of CAs (n = 437 [54%], the reference population); 2) new BBB (n = 247 [30%], of whom 237 had left BBB [LBBB] and 10 had right BBB); and 3) new PPI (n = 132 [16%]). Vital status, hospital information, and date and indication of PPI were collected via the Danish Civil Registration and National Patient Registry and the Danish Pacemaker Registry. By Kaplan-Meier and Cox regression analysis, the main findings are that new BBB was associated with early and late all-cause mortality (hazard ratio for new BBB vs. no CAs: early mortality, 2.8 [95% confidence interval: 1.2 to 3.7]; late mortality, 1.8 [95% confidence interval: 1.2 to 2.6]), while new PPI was associated with late but not early all-cause mortality (hazard ratio for new PPI vs. no CAs: early mortality, 1.6 [95% confidence interval: 0.7 to 3.7]; late mortality, 1.6 [95% confidence interval: 1.0 to 2.5]). Interestingly, the slopes of the Kaplan-Meier curves indicate that new BBB represents a continuous risk, and patients with single-ventricular pacemakers and pacing rates >40% had higher risk for first heart failure hospitalization than those with pacing rates ≤40% (hazard ratio: 2.8; 95% confidence interval: 1.3 to 6.5).

The study population and methods are well defined, the data and findings are clearly presented, and the discussion is balanced with a comprehensive

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review of published research. If there is one comment to be made, it is that the investigators did not determine to what extent cardiac mortality contributed to the increased risk for all-cause mortality, as first reported by Houthuizen et al. (7,8) and subsequently confirmed when focusing on persistent new LBBB and cardiac mortality.

There is currently debate and controversy as to whether TAVR-induced new CAs, including new PPI, are associated with a dismal prognosis and whether they should be considered a serious adverse event or a complication. The cause of this debate stems from conflicting findings discussed by Jørgensen et al. (6). This conflict is most likely due to the profound differences in the methods and definitions among studies, precluding a sound meta-analysis despite statistical methods to cope with heterogeneity. To appreciate the previously published findings, one needs to start by carefully comparing the patients who were included and excluded from analyses, the timing of the diagnosis of new BBB and whether it persisted beyond discharge, in addition to the indication, timing, and mode of new PPI, and finally the methods of analysis (reference group, statistics, single-composite endpoints, etc.). Also, one needs to understand that despite obvious reasons for subdividing patients into various risk groups (e.g., new BBB with or without new PPI, new PPI), these patients may differ from one another and from the reference group (no BBB, new PPI) for variables that were or could not have been collected. Moreover, differences in the management of patients' post-discharge may confound outcomes as well.

Currently, the best available (indirect) evidence comes from post hoc subgroup analyses from RCTs, because RCT have by nature the highest quality data because of, among other factors, the prospective collection of pre-defined variables and independent analysis of outcomes. In 2014, the PARTNER (Placement of Aortic Transcatheter Valve) study group (using a valve known to have the lowest risk for new LBBB and new PPI) reported that new LBBB was not associated with an increased risk for 1-year all-cause or cardiac mortality or repeat hospitalization but failure of ejection fraction to improve and a lower left ventricular ejection fraction at 6 months to 1 year (52.8% vs. 58.1%, $p = 0.001$) (9). Yet when taking a somewhat different approach, the same group of investigators reported in 2015 that compared with no PPI, prior PPI, new PPI, and LBBB and no PPI were all associated with significantly higher mortality and combined mortality or rehospitalization at 1 year, which was confirmed in a sensitivity analysis (10). In a Cox regression analysis in which patients with LBBB and no PPI were excluded, new and prior PPI were both found to independently predict 1-year mortality (10).

In light of seemingly conflicting results, it may help to consider pathophysiologic observations. LBBB induces interventricular dyssynchrony, which in turn affects ventricular systolic and diastolic performance and may lead to increased end-systolic volumes, abnormal septal perfusion, and hypertrophy (11–13). Also, LBBB may progress to atrioventricular block and, therefore, sudden death (14). With respect to PPI-induced dyssynchrony, the BLOCK HF trial revealed that in patients with atrioventricular block and impaired left ventricular function, biventricular pacing had a lower incidence of all-cause mortality or late heart failure in comparison with right ventricular pacing, confirming the findings in patients with preserved left ventricular function (15). The MOST study revealed that heart failure hospitalization increased by 20% for every 10% increase in right ventricular pacing and a ventricular pacing rate ≥40% was associated with a 2.5-fold higher risk for hospitalization for heart failure in comparison with patients with pacing rates <40% (16).

Similar to a more refined assessment of new PPI and prognosis using pacing rate, we may gain more insight in the relationship between new LBBB and prognosis if new LBBB is used as a continuous variable (e.g., increase in QRS duration). In 63 BC, Cicero opened his discourse to Catalina with the words "Quo usque tandem abutere, Catalina, patientia nostra…." Translated to the current topic: How much evidence do we still need before considering new LBBB and/or new PPI as an event that affects prognosis and quality of life and thus worthy to be considered a serious adverse event post-TAVR? This is once more underscored by the findings of Jørgensen et al. (6).

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