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ABOUT COVER

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Current knowledge for the risk factors of early permanent pacemaker implantation following transcatheter aortic valve replacement and what is next for the primary prevention?

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Abstract

In this editorial, we comprehensively summarized the preoperative risk factors of early permanent pacemaker implantation after transcatheter aortic valve replacement (TAVR) among patients with severe aortic stenosis from several renowned clinical studies and focused on the primary prevention of managing the modifiable factors, *e.g.*, paroxysmal atrial fibrillation before the TAVR.

Key Words: Permanent pacemaker implantation; Transcatheter aortic valve replacement; Interventricular conduction delay; Diabetes; Supraventricular arrhythmia

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INTRODUCTION

In this issue of the *World Journal of Cardiology*, Nwaedozie *et al*[1] explored clinical outcomes associated with early permanent pacemaker (PPM) implantation following transcatheter aortic valve replacement (TAVR) in high-risk patients with aortic stenosis. At the end of 1 year follow-up, as compared to those without PPM implantation, those with PPM implantation had a higher risk of heart failure (HF) hospitalization and nonfatal myocardial infarction (MI) [odds ratios (ORs): 2.2 and 3.9, respectively]. In contrast, in the study conducted by Fadahunsi *et al*[2], early PPM implantation after TAVR was associated with a greater risk of a composite of all-cause mortality or HF admission [hazard ratio (HR): 1.33], while not with HF admission alone. Despite the disparity in observational studies, the 1-year adverse outcomes associated with early PPM implantation after TAVR were unquestionable. Therefore, it is crucial to know the modifiable predictors of early PPM implantation in high-risk patients with severe AS before the procedure of TAVR, and a pre-procedural preventive measure may be of great interests for future trials to be taken for reducing the possibility of PPM implantation and improving the clinical outcomes.

Previous studies have shown several risk predictors of early PPM implantation after TAVR (Table 1). In this state of the art study, three novel pre-procedural predictors were added including nonspecific interventricular conduction delay (IVCD), type 2 diabetes and supraventricular arrhythmia[1] (ORs: 2.18, 2.16, and 1.82, respectively). It has been acknowledged that right bundle branch block (RBBB) is an independent electrocardiographic predictor of post-TAVR PPM implantation (ORs: 1.36-8.61)[3-5]. In this study[1], the association between RBBB and post-TAVR PPM implantation was borderline (OR: 2.15, $P = 0.081$), while the association between IVCD (QRS duration ≥ 120 ms) and post-TAVR PPM implantation was significant (OR: 2.18, $P = 0.045$). In addition, this study also demonstrated a dose-response association for each 20 ms increase in the pre-procedural QRS duration > 100 ms (ORs: 2.44, 3.25, and 6.98 for the QRS duration: 101-120 ms, 121-140 ms, and 141-160 ms, respectively). To the best of our knowledge, the development of RBBB and IVCD may be due to conduction system calcification and pressure overload in the left ventricle in severe AS[5]. The prevalence of RBBB and IVCD and the QRS duration were observed higher with increasing AS severity, and the presence of RBBB and wider QRS duration (per each 10 ms increase) was associated with greater risk of all-cause mortality (HRs: 1.59 and 1.06, respectively) in patients with AS[6]. In a large study among consecutive patients who completed 24-h Holter electrocardiography (ECG) for variety of indications[7], RBBB was an independent predictor for arrhythmia requiring further treatment which was in line with the present study findings. Obviously, the nature course in those with AS having abnormal ECG features, *i.e.*, RBBB and IVCD is consistently with poor prognosis across different groups regardless of receiving TAVR. Moreover, a prior study showed that if the QRS duration is less than 120 ms throughout the first day after TAVR, the occurrence of late atrioventricular conduction abnormalities is relatively low[8].

Diabetes mellitus has been regarded as a risk factor of cardiovascular mortality, mainly due to HF (HR: 2.61) in patients with severe AS, while not in those with mild or moderate AS[9]. The relative risk was close to the finding in this study (OR: 2.16). In addition, type 2 diabetes and insulin use were found with an association with late overall mortality (5-10 years) in patients with AS receiving surgical aortic valve replacement (HRs: 1.39 and 1.76, respectively)[10]. Furthermore, those with type 2 diabetes has been found with a 1.56-fold higher risk of PPM implantation as compared to those free of type 2 diabetes[11], and those with diabetes after PPM implantation had a greater risk of cardiovascular events[12]. Based on current evidence, the finding for diabetes mellitus as a risk factor of PPM implantation following TAVR for patients with severe AS in this study[1] was reasonable to explain the higher risk of incident HF hospitalization and nonfatal MI events.

Finally, this study also demonstrated an increased possibility of pre-procedural supraventricular arrhythmia for early PPM implantation following TAVR. As is known, the presence of atrioventricular node dysfunction in any grades were associated with a higher risk of atrial fibrillation (AF)[13]. It is notable that more than 95% of the pre-procedural supraventricular arrhythmia in patients with severe AS was AF. However, there were a discrepancy in case numbers between those with a history of AF ($n = 156$) and those with pre-procedural AF ($n = 84$), indicating that at least 47% of patients with paroxysmal or persistent AF in this study. In a meta-analysis of 981168 patients undergoing TAVR, the presence of AF was associated with a modestly increased risk of PPM implantation after TAVR (relative risk: 1.10)[14]. It would be of great interests for physicians to know if a conversion of paroxysmal or persistent AF to sinus rhythm prior to the procedure of TAVR may reduce the risk of PPM implantation in patients with severe AS or not, and a randomized clinical trial would be helpful to verify the effect. With the results of the PARTNER 3 trial for the long-term outcome (5 years) coming out[15], we can expect that in the following a few years, not only high-risk patients but also low-risk patients with severe AS will be eligible for TAVR. More observational studies to clarify the risk factors of early PPM implantation in low-risk patients undergoing TAVR are necessary in the future.

CONCLUSION

Since early PPM implantation following the TAVR is linked to poor prognosis among patients with aortic stenosis, it is crucial to clarify those potential modifiable risk factors, *e.g.*, paroxysmal AF that can be managed before the TAVR for the primary prevention of early PPM implantation.

Table 1 Established pre-procedural risk factors of early permanent pacemaker implantation following transcatheter aortic valve replacement

Pre-procedural risk factors	Age, yr	Male sex	Prior MI	DM	Risk ratio	Ref.
Prior conduction defect						[2-5,15]
RBBB	80-85	43%-52%	25%-45%	29%-37%	2.50-3.10	
Mobitz type 1 AV block					3.10	
Left anterior hemiblock					1.20-1.40	
Bifascicular block					2.40-2.60	
Peri-procedural AV block	Meta-analysis of 75 cohort studies[5]				4.17	[5]
Age ≥ 80 yr	Meta-analysis of 75 cohort studies[5]; meta-analysis of 239 cohort studies [15]				1.07-1.19	[2,5,15]
Self-expanding valve	Meta-analysis of 32 clinical trials[4]; meta-analysis of 239 cohort studies[15]				1.94-7.56	[2,4,5]
Aortic valve area < 0.75 cm ²	84	52.0%	26.4%	36.4%	1.21	[2]
≥ Moderate operative risk	84	52.0%	26.4%	36.4%	1.85	[2]
Atrial fibrillation	Meta-analysis of 75 cohort studies[5]; meta-analysis of 239 cohort studies [15]				1.05-1.10	[5,15]

AV: Atrioventricular; DM: Diabetes; MI: Myocardial infarction; RBBB: Right bundle branch block.

FOOTNOTES

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