Editorial

The Lotus dilemma—respond to paravalvular leakage, but not answering pacemaker implantations?

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The treatment of symptomatic aortic valve stenosis has been revolutionized by transcatheter aortic valve replacement (TAVR), evolving from a last resort therapy to the standard treatment of patients at intermediate or high risk for conventional surgery (1,2). The continuous evolution of transcatheter heart valves (THV) and delivery systems along with a considerable increase in operator experience has led to a steady improvement of outcomes with a 30-day mortality approaching the 1% threshold. Continuous iterations of balloon-expandable and self-expanding devices as well as the pursue of alternative implantation technologies to address limitations of earlier generations such as paravalvular leakage (PVL), requirement for new permanent pacemaker implantations (PPI), and vascular complications have been performed.

Among alternative implantation technologies, the Lotus Valve System™ (Boston Scientific, Marlborough, Massachusetts, USA) is the first commercially available THV, employing a technology best described as mechanical expansion. This device consists of a braided single-wire nitinol frame with three bovine pericardial leaflets and features an adaptive polymer membrane seal at the lower half to reduce PVL. The Lotus valve is available in three sizes (23, 25, and 27 mm) and is delivered via an 18-F (for the 23 mm size) and 20-F introducer (for the 25 and 27 mm sizes). Guided by a tantalum marker, the device is mechanically expanded in the desired position and allows for full reposition after careful evaluation of the initial result and is locked after reaching the final position.

The Lotus valve system has been studied in a considerable number of studies most of which included small to intermediate-sized populations. The REpositionable Percutaneous Replacement of Stenotic Aortic Valve Through Implantation of Lotus™ Valve System—Randomized Clinical Evaluation (REPRISE)-I study (3) was an early feasibility trial including 11 patients and laid out the path for the larger REPRISE-II study, which eventually led to CE-approval of the device (4,5). In REPRISE-II, 120 high-risk patients from Europe and Australia were included, where a 30-day and a 1-year mortality of 4.2% and 10.9% were found, respectively. With only 1%, the rate of moderate to severe PVL was very low. After completion, the REPRISE-II study was extended to a cohort of 250 patients and was published as REPRISE-IIE (6). In this extended cohort, PVL rate was also remarkably low with 0.6% of the patients displaying moderate to severe PVL. Nevertheless, despite these very promising achievements in the near abolishment of PVL, the REPRISE program also clarifies a major problem of this novel THV: the need of PPI in over 30% of pacemaker naive patients. This worrisome PPI rate has been confirmed by numerous independent groups with PPI rates ranging from 24–38% (7-10). A summary of selected studies

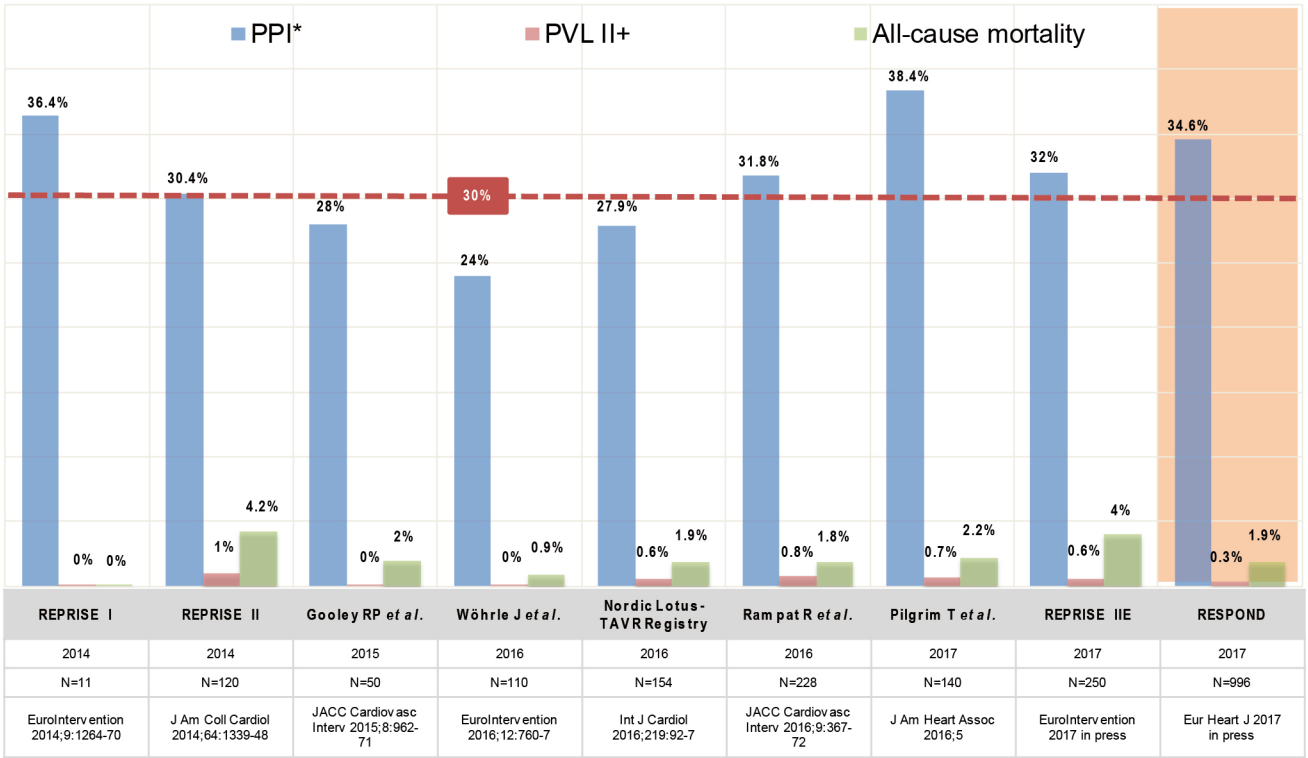

Figure 1 Thirty-day event rate of selected LOTUS trials. *, patients w/o pacemaker at baseline as denominator (if available).

on the Lotus valve system is displayed in *Figure 1*. Prompted by these findings, considerable effort has been invested to elucidate the underlying mechanisms of this elevated PPI rate of the Lotus valve system. In a study by Rampat *et al.*, excluding patients with a pacemaker at baseline, new PPI rate was 32% and was only predicted by baseline conduction abnormalities (11). In a recent subanalysis of the REPRISE IIE trial, implantation technique (implantation depth >5 mm) and annular oversizing (defined as LVOT overstretch of >10%) were identified as predictors for new PPI (6).

The recently published REpositionable Lotus Valve System—POst-Market EvaluatioN of Real WorlD Clinical Outcomes (RESPOND) study (12), is a prospective, open-label, single-arm, multicenter study, which assesses the safety and efficacy of the Lotus THV in routine clinical practice in a large cohort of patients. Of 1014 patients included in the study, 996 patients received the Lotus THV and were included in the as-treated population. In almost 30%, repositioning of the Lotus THV was successfully attempted. As expected from the intermediate risk patients and the remarkable expertise of participating operators, 30-day all-cause mortality and disabling stroke rate were 2.6% and 2.2%, respectively. Further, this study confirms results from smaller, earlier trials with a very low rate of PVL (0.3%) and a very high rate of PPI (34.6%).

In the case of the Lotus THV, it becomes clear that there seems to exist a dilemma between the achievement of low PVL rates at the expense of PPI. With PVL rates ranging between 0-1%, the Lotus THV has taken the lead in the field among competitors, such as SAPIEN 3, Evolut R and ACURATE neo, having PVL II+ rates of 2.6–3.7% (13,14), 1.9–5.3% (15-17) and 4.1–4.8% (18), respectively. PPI rates of several "next-generation" THVs are considerably different. It ranges from around 10% with Symetis ACURATE neo (18), 12–13% with SAPIEN 3 (13,14), 15–20% with Evolut R (15-17) and about 30% with the Lotus valve system (12).

Although in earlier studies moderate or severe PVL has been linked to poorer outcomes after TAVR (19,20), the impact of PPI on long-term outcome remains controversial. While no difference has been observed in earlier studies (21) recent data from the PARTNER consortium has revealed chronic pacing as a predictor of mortality (22,23). Therefore, it is important to note that RESPOND will provide us with long-term follow-up to clarify the prognostic impact of PVL and PPI in patients treated with Lotus valve system.

Additionally, among other reasons, elevated PPI rates have prompted the development of the next generation of Lotus valve system, Lotus Edge which has received CE-Mark in September 2016. In comparison to the Lotus valve system, this next iteration provides a more flexible and lower profile catheter equipped with Depth Guard™, a feature to prevent deep implantation in order to reduce new PPI rate.

The ongoing REPRISE-III trial (NCT02202434) has recently completed enrolment and constitutes a head-to-head randomized controlled comparison of Lotus/Lotus Edge versus CoreValve/Evolut R in a 2:1 fashion. This trial includes 1,032 patients in up to 60 centers in North America, Europe and Australia and will further elucidate the comparative effectiveness of the Lotus valve system and will also include new insights on Lotus Edge.

However, as of today the Lotus valve system has been recalled from the market due to problems with the devices locking system resulting in excess tension in the pin mechanism and is expected to be back on the market in the last quarter of 2017.

In conclusion, the RESPOND trial showed that the Lotus THV can be safely used in routine daily practice. With a favorable safety profile and the lowest PVL rate to date, but quite high new PPI rates, the comparative effectiveness of the Lotus valve system needs to be determined in direct randomized comparison, such as the recently completed REPRISE-III trial. Long-term follow-up after Lotus implantation is warranted in order to assess the prognostic impact of the elevated PPI rate.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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