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***Retrospective Study***

**Comparison between the SAPIEN S3 and the SAPIEN XT transcatheter heart valves: A single-center experience**

Sawaya F *et al*. Comparison between the S3-THV and the XT-THV

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**Abstract**

***AIM***

To investigate the clinical outcomes of transcather aortic valve implantation (TAVI) with the SAPIEN 3 transcatheter heart valve (S3-THV) *vs* the SAPIEN XT valve (XT-THV).

***METHODS***

We retrospectively analyzed 507 patients that underwent TAVI with the XT-THV and 283 patients that received the S3-THV at our institution between March 2010 and December 2015.

***RESULTS***

Thirty-day mortality (3.5% *vs* 8.7%; OR = 0.44, *P* = 0.21) and 1-year mortality (25.7% *vs* 20.1%, *P* = 0.55) were similar in the S3-THV and the XT-THV groups. The rates of both major vascular complication and paravalvular regurgitation (PVR) > 1 were almost 4 times lower in the S3-THV group than the XT-THV group (major vascular complication: 2.8% *vs* 9.9%, *P* < 0.0001; PVR > 1: 2.4% *vs* 9.7%, *P* < 0.0001). However, the rate of new pacemaker implantation was almost twice as high in the S3-THV group (17.3% *vs* 9.8%, *P* = 0.03). In the S3 group, independent predictors of new permanent pacemaker were pre-procedural RBBB (OR = 4.9; *P* = 0.001), pre-procedural PR duration (OR = 1.14, *P* = 0.05) and device lack of coaxiality (OR = 1.13; *P* = 0.05) during deployment.

***CONCLUSION***

The S3-THV is associated to lower rates of major vascular complications and PVR but higher rates of new pacemaker compared to the XT-THV. Sub-optimal visualization of the S3-THV in relation to the aortic valvular complex during deployment is a predictor of new permanent pacemaker.

**Key words:** S3 valve; Vascular complications; Permanent pacemaker; Lack of coaxiality; Paravalvular regurgitation

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**Core tip:** The SAPIEN 3 transcatheter heart valve (S3-THV) is associated to lower rates of major vascular complications and PVR but higher rates of new pacemaker compared to the SAPIEN XT valve (XT-THV). Sub-optimal visualization of the S3-THV in relation to the aortic valvular complex during deployment is a predictor of new permanent pacemaker (PPM). Our findings highlight the increased importance to adequately visualize the S3-THV in relation to the aortic valvular complex during deployment, in order to improve device positioning and potentially mitigate new PPM requirements.

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**INTRODUCTION**

Transcatheter aortic valve implantation (TAVI) has gained rapid acceptance for patients with severe aortic stenosis[1-4] and has recently been associated with excellent short-, mid- and long-term outcomes in patients at intermediate risk[5-7]. However, TAVI is still associated with a higher incidence of paravalvular regurgitation (PVR), permanent pacemaker implantation (PPM) and vascular complications[8-12] when compared to surgical aortic valve replacement. In order to justify the extension of the procedure to lower risk patients, these adverse outcomes have to be mitigated. The development of novel transcatheter heart valves (THVs) and further iterations of delivery systems and prostheses have contributed to the decrease in complications rates in TAVI[13]. One of the recent developments is the balloon-expandable Sapien 3 transcatheter heart valve (S3-THV; Edwards Lifesciences, Irvine, CA). It has been designed with a lower profile to be delivered in a 14 French sheath (for sizes 23 and 26 mm), and with an external sealing cuff. The lower profile should diminish vascular complications while the sealing cuff should diminish PVL[14,15].

Despite positive procedural and short-term outcomes in small single center series and registries, large reports comparing the S3-THV to its predecessor, the Sapien XT (XT-THV), are lacking[16,17]. Recent reports suggest an increased rate of new PPM implantation following TAVI with the S3-THV, compared to the XT-THV[16,17]. Whether procedural characteristics such as depth of implant are related to PPM implantation with this new device remains unclear[18].

The objective of this analysis was to retrospectively compares the procedural outcomes, 30-d clinical outcomes and one-year mortality of TAVI with the S3-THV *vs* the XT-THV in patients with symptomatic severe aortic stenosis in a single high-volume center. We also explored clinical and procedural predictors of new PPM in the S3-THV group.

**MATERIALS AND METHODS**

***Patient population and procedure***

To compare clinical outcomes of patients undergoing TAVI with the S3-THV to those undergoing TAVI with the XT-THV, we retrospectively identified all patients treated with TAVI at our institution with either device. Patients underwent TAVI by the transfemoral, transaortic or transapical approach according to previously described techniques[17].

A multidisciplinary heart team involving at least one interventional cardiologist and one cardiac surgeon discussed all cases and consensus was achieved regarding therapeutic strategy. All patients provided informed written consent for the procedure and data collection, and the local ethics committee approved the study.

***Pre-procedural planning***

All patients underwent TTE examination and native valve function was assessed according to the recommended guidelines[19]. In addition, pre-procedural MSCT evaluation including measurements of the aortic annulus and aortic root was systematically performed. Aortic annulus dimensions were measured according to standard procedures using dedicated software (Philips Brilliance 64-slice MDCT scanner, Philips Healthcare, Best, the Netherlands). Valve prosthesis size was selected in accordance with the manufacturer’s recommendations after taking into account other anatomic features such as the presence and location of calcification, eccentricity of the aortic annulus and dimensions of the sinuses of Valsalva and sino-tubular junction in case of borderline sizing ranges. In addition to dimensions, annulus orientation was assessed with MSCT. Implantation projection was selected so that the aortic valve would be seen coaxially, with the three cusps aligned. Cardiac catheterization and femoral angiography were performed prior to the procedure to assess for concomitant coronary artery disease and vessel narrowing or tortuosity.

***Study devices***

The SXT-THV and the S3-THV designs have been described in detail previously[15,20]. Both consist of bovine pericardium sewn to a balloon-expandable cobalt-chromium tubular frame. The XT-THV was available in the 23, 26, and 29 mm sizes and was implanted with the use of the NovaFlex catheter, which employed an 18- or 19-F introducer sheaths. The S3-THV is available in the 23, 26, and 29 mm sizes. The device’s height is about 15% greater than that of the XT-THV. It was implanted with the use of the lower-profile Commander delivery catheter, which employed 14- (sizes 23 and 26 mm) or 16-F (size 29 mm) expandable sheaths (eSheath, Edwards Lifesciences, Inc.). The S3-THV stent was designed with a frame geometry that provides greater radial force. The difference in cell geometry between the inflow and the outflow causes the valve frame to foreshorten more from the ventricular side. The device also includes an outer polyethylene terephthalate fabric seal designed to minimize PVR.

***Study procedure***

The techniques of SAPIEN XT and SAPIEN S3 valve implantation have been described in detail elsewhere[15,20]. In our center, all trans-femoral (TF) cases were performed under local anesthesia and conscious sedation in the catheterization laboratory. The selected femoral artery was “pre-closed” with two 6-Fr suture-mediated closure devices Perclose ProGlide(Abbott Laboratories, Abbot Park, Illinois). With a pigtail in the right coronary cusp, aortography was performed to correct, if necessary, the implantation projection provided by MSCT. Pre-dilatation was performed routinely in the XT-THV group, but only in cases of severe calcification in the S3-THV group. Device positioning was based on fluoroscopy using annular calcification as a landmark along with serial 12 to 15 mL supra-annular aortography to validate its position. The XT-THV was implanted by means of a 2-step inflation technique[21]. The S3-THV was deployed during one-slow inflation (5-10 s). Prosthesis position and function, and patency of the coronary ostia were evaluated by angiography and transthoracic echocardiography. Significant aortic regurgitation was treated by post-dilatation adding 1 to 3 cc of contrast in the balloon delivery system or second valve implantation if the valve was positioned too high or too low. Removal of the sheath was cautiously achieved with serial contralateral angiograms to detect ilio-femoral complications. In the absence of any conduction abnormality, the pacing lead was removed at the end of the procedure. Patients were monitored in the intensive care unit for at least 24 h after valve implantation. For the transapical and transaortic cases, the SXT-THV and S3-THV were deployed with the Ascendra and Certitude delivery systems, respectively. These cases were performed in a hybrid room.

***Data collection and study endpoints***

Clinical and echocardiographic data at baseline and follow-up were collected by dedicated personnel and entered in a local database and a national registry (FRANCE-TAVI)[22]. Data from the ECG and MSCT prior to the intervention were retrospectively collected by the co-authors and entered into the local database. The co-authors also retrospectively collected implant depth and device coaxiality from procedure fluoroscopy.

The primary endpoint was 30-d mortality. Secondary endpoints consisted of 1-year mortality, stroke, myocardial infarction, annulus rupture, new PPM implantation, major vascular complication, PVR greater than mild, annulus rupture, acute kidney injury and post-procedural mean gradient. Endpoints were defined according to the VARC-2 criteria[23].

***Implant depth and device coaxiality during implant measurement***

We reviewed procedural fluoroscopy of all patients in the S3-THV group to measure valve implant depth. A post-implant aortic angiogram with the device coaxial was required for implant depth measurement. First, on a single still frame, the hinge points between the device and the sinus of Valsalva on the septal and non-septal side were identified (Figure 1). Next, a line was drawn between both hinge points. The distances between this line and the bottom of the valve frame on both the septal and non-septal sides were then recorded as implant depth. Measurements were performed using the OsiriX sorftware, version 5.9.

In addition to depth, we also measured device lack of coaxiality during deployment. This was done on a single still frame at the end of valve deployment, while still under rapid pacing. The maximal perpendicular distance between the “front” and the “back” struts of the device was measured and recorded as device lack of coaxiality during deployment (Figure 2).

***Statistical analysis***

Continuous data are reported as mean ± standard deviation (SD), and categorical variables are reported as number of patients and percentages. Categorical data were compared using Fisher’s exact test, and continuous data using Student's t-test or Mann-Whitney’s *U* test, as appropriate. Events are reported as counts of first occurrence per type of event. Event probabilities at 30 d were compared for patients treated with the XT-THV *vs* the S3-THV using logistic regression. Crude and adjusted odds ratios (with 95%CI) are reported. Odds ratios are adjusted for procedure date (to account for a potential learning effect of time) and for baseline characteristics with a univariate *P*-value < 0.10 for each individual outcome. One-year survival data was fitted in a Cox proportional hazards model and the XT-THV and S3-THV groups were compared using an adjusted hazard ratio. No adjusted analyses were performed for outcomes with less than 15 events overall. Patients with previous pacemaker implantation were excluded from analyses pertaining to the outcome of new pacemaker requirement. A *P*-value < 0.05 was considered significant for adjusted models. Statistical analyses were performed with SPSS version 23 (IBM Corp, Armonk, NY).

**RESULTS**

Between March 2010 and December 2015, 790 patients underwent TAVI with the XT-THV (*n* = 507) or the S3-THV (*n* = 283) in our center. The XT-THV was used from March 2010 to September 2014, after which the S3-THV was used routinely. Patients in the S3-THV group had lower STS scores than those in the XT-THV group (STS score: 5.3% ± 3.5% *vs* 6.4% ± 4.0% respectively, *P* < 0.0001) (Table 1). Patients in the S3-THV group were also less likely to be in NYHA functional class 3 or 4 (59.1% *vs* 75.8%, *P* < 0.0001), and less likely to have peripheral vascular disease (19.8% *vs* 28.4%, *P* = 0.01) or chronic obstructive pulmonary disease (11.7% *vs* 21.9%, *P* < 0.0001). Baseline echocardiographic characteristics were similar between groups.

The use of the transfemoral approach increased from 54% in XT-THV group to more than 80% in the S3-THV group (*P* < 0.0001) (Table 2).

Predilatation was performed routinely in the XT-THV group (86.8%), which was not the case in the S3-THV group (17.7%, *P* < 0001) (Table 2).In the S3-THV group, predilatation was reserved for patients with an extensively calcified aortic valve. The lower use of predilatation in the S3-THV group did not translate into significantly more post-dilatation (S3-THV: 15.9% *vs* XT-THV: 12.0%; *P* = 0.13). As per manufacturer recommendations, device diameter to annulus diameter (area-derived) ratio was reduced from 1.11 ± 0.05 (XT-THV) to 1.05 ± 0.05 (S3-THV; *P* < 0.0001). As a result of this reduced oversizing, smaller device sizes were used in the S3-THV group (*P* < 0.0001). However, according to ROC curve analysis, a device diameter to annulus diameter ratio below the threshold of 1.03 increased the risk of post-dilatation or PVR > mild (area under the curve: 0.68; Figure 3).

While fluoroscopy time was similar between groups, contrast use decreased by more than 15% in the S3-THV group compared to the XT-THV group (131.6 ± 60.9 mL *vs* 108.2 ± 42.7 mL; *P* < 0.0001).

***Clinical outcomes***

Thirty-day mortality was lower in the S3-THV group than the XT-THV group (3.5% *vs* 8.7%; univariate OR = 0.36; *P* = 0.01) (Figure 4 and Table 3). After adjustment for baseline characteristics, this difference was no longer statistically significant (adjusted OR = 0.44, *P* = 0.21). One-year mortality was also similar between groups (25.7% *vs* 20.1%, adjusted *P* =0.55) (Figure 4). In total, 20 deaths had occurred at 1 year in the S3-THV group. These are listed in Table 4 along with cause of death.

The rates of major vascular complication and PVR > 1 were both almost 4 times lower in the S3-THV group than the XT-THV group (major vascular complication: 2.8% *vs* 9.9%, adjusted *P* < 0.0001; PVL > 1: 2.4% *vs* 9.7%, adjusted *P* < 0.0001) (Figure 5). However, the rate of new pacemaker implantation was almost twice as high in the S3-THV group (17.3% *vs* 9.8%, adjusted *P* = 0.03) (Figure 5).

Acute kidney injury was 10 times lower in the S3-THV group than the XT-THV group (1.1% *vs* 13.6%, *P* < 0.0001). There were no statistically significant differences between groups with respect to stroke, myocardial infarction and post-procedural mean gradient > 20 mmHg.

***Predictors of new pacemaker implantation in the S3-THV group***

Electrocardiographic and angiographic characteristics of patients in the S3-THV group that required a new PPM are displayed inTables 5 and 6. Implantation depth in the S3-THV group was 5.1 ± 2.5 mm on the septal side (non-coronary cusp) and 5.2 ± 2.0 mm on the non-septal side (left coronary cusp). According to multivariate analysis, independent predictors of new permanent pacemaker implantation were pre-procedural complete right bundle branch block (RBBB) (OR = 4.9; 95%CI: 1.88-12.95; *P* = 0.001), PR duration (OR = 1.14 per 10 msec increment; 95%CI: 1.00-1.29; *P* = 0.05) and device lack of coaxiality during deployment (OR = 1.13 per 1 mm increment; 95%CI: 1.00-1.29; *P* = 0.05). Device implantation depth was not a predictor of new pacemaker implantation in our series.

**DISCUSSION**

To our knowledge, this is one of the largest observational studies to date comparing the newer balloon-expandable S3-THV to the XT-THV in an all-comer population. The major findings are as follows: (1) The S3-THV is associated with similar adjusted 30-d and one-year mortality rates compared to the XT-THV; (2) The S3-THV is associated with 4-fold lower rates of both major vascular complications and PVR compared to the XT-THV; (3) The S3-THV is associated with twice the rate of new PPM implantation compared to the XT-THV; and (4) Independent predictors of new pacemaker included pre-procedural complete RBBB and PR duration, and lack of device coaxiality during implant.

***Mortality***

In a recent study, all-cause 30-d mortality rates were reported between 0% and 17.5%, with a pooled estimate rate of 5.7% for all second-generation THVs[24]. Reported 30-d mortality rates with the S3-THV ranges from 0.5% to 4.5%[16,17,25]. We report also a low 30-d mortality of 3.5% in the S3-THV cohort that was not statistically lower than the 8.7% rate of the XT-THV group after covariates adjustment. The low 30-d mortality speaks to the advancement of TAVI in regard to valve design improvement, increased operator experience, improved patient selection and procedural pre-planning, but also the lower baseline risk profile of TAVI patients.

***Vascular complications***

One of the shortcomings of TAVI is the association of major vascular complications with mortality[10]. Sheath size, severe ilio-femoral artery calcification, sheath external diameter to minimal femoral diameter artery ratio (≥ 1.05), early site experience and early operator experience, have all been previously associated with major vascular complications[13,26,27]. The S3-THV, with the lower profiles of its 14 and 16-F sheaths and the expanding properties of its E sheath, allows TAVI to be performed in patients with smaller arteries and for it to be safer in patients with larger arteries[28]. This is reflected in our series by the significant increase in proportion of transfemoral procedures. Three studies reported rates of major vascular complications of 4.5%, 5.2% and 3.6%, reflecting increased safety compared to the XT-THV[16,17,25]. We observed a similar rate of 2.9% in our S3-THV cohort, despite seeing the number operators performing TAVI increase from 4 to 9 between 2013 and 2015.

***PVR***

Patients with more than mild PVR have lower short- and long-term survival than those with trivial or mild PVR, making this an important echocardiographic outcome[29,30]. In the PARTNER trial, moderate or severe PVR was seen in 11.8% of patients implanted with the Edwards SAPIEN valve[31]. In the France 2 Registry, it was reported in 12.2%[32]. We found similar rates of PVR in the XT-THV group. In contrast, the S3-THV group had four times less PVR. Our 2.4% > mild PVR rate in the S3-THV group is comparable to other reports that showed a PVR range between 0% and 3.8%[25,33]. The reduced rate of PVR can be explained by improved annular sealing by the external cuff. Whether the decreased PVR rate with the S3 device could translate into improved long-term outcomes should be evaluated in long-term registries.

***Permanent pacemaker implantation***

The need for new PPM implantation following TAVI may be correlated to prognosis[34-36]. As the S3-THV valve frame has greater height than the XT-THV, it may extend deeper into the LVOT after deployment[15,16]. Stent frame extension in the LVOT, *i.e.*, depth of implant, has been shown to be a predictor of PPM implantation[37].

Preliminary data on the S3-THV device from the pivotal SAPIEN 3 trial have shown an increased 30-d PPM implantation rate (13.3%), despite excluding patients with LBBB, RBBB and PR > 200 ms[38]. A study by Binder *et al*[16] also showed an increased rate of PPM (20.7%) with the S3-THV. This increased risk for PPM was driven by deep implantation of the S3-THV (valve implantation depth ≥ 8 mm). Similarly, the Swiss registry showed an increased rate of PPM with the S3-THV of 17% compared to 11% with the XT-THV valve[16]. Our study showed similar results with a rate of 17.3% in S3-THV *vs* 9.8% in XT-THV **(**Table 7). As reported by others, independent predictors of new permanent pacemaker implantation in the S3-THV group included complete right bundle branch block and PR duration[25].

However, implant depth was not a predictor of new PPM in our study. Rather, lack of coaxiality of the device during its deployment was independently associated to new PPM. These findings may be explained by flaws in the way depth is estimated before the prosthesis is deployed, and by flaws in the way depth is measured after it is deployed.

Before the prosthesis is deployed, the aortic annulus is seen in a coaxial projection, with the three cusps aligned. This projection is determined from the MSCT and confirmed during the procedure by aortography. However, the device positioned in the annulus, before deployment, is not necessarily coaxial. This may be difficult to appreciate because, unlike the Corevalve, the XT-THV and the S3-THV do not have a ring at their extremity. This lack of device coaxiality before deployment can induce flaws in the estimation of depth due to parallax error[18,39]. In our experience, lack of device coaxiality induces underestimation of implant depth. In other words, the less coaxial the device, the higher it will look, and the more the operator will want to push it deeper. This increases the true depth of implant and therefore risk of conduction disturbance and new PPM.

After the prosthesis is deployed, measurement of depth of implant can also be flawed by parallax error. As previously described, the projection in which depth is measured is not the one in which the device was deployed. Indeed, after deployment, the device is not necessarily coaxial. The projection is therefore modified to obtain device coaxiality and this is when final aortography is performed and depth is measured. In this new projection, however, the aortic annulus is no longer coaxial[18,39]. An example of this is provided in Figure 6, where two cusps are seen at different levels on the septal side. Proper localization of the hinge point between the device and sinus of Valsalva, and therefore proper implant depth measurement, can be difficult in such circumstances and prone to parallax error. To adequately measure device implantation depth, future studies should rely on post-procedural MSCT. This would allow measurement of depth all around the annulus, and not only on the septal and non-septal sides. Alternatively, computer programs that allow the operator to find the unique projection where both the device and the annulus are coaxial could be used. This would be the optimal projection to deploy the device, do the final aortography and measure depth.

The premise of this concept is that there is a slight angle between the un-deployed device and the aortic annulus. This is caused by patient anatomy and delivery catheter properties. As a result of this angle, even if the C-arm is perpendicular to the aortic annulus, it may not be perpendicular to the device. Figure 7 illustrates the coaxiality concept.

***Limitations***

This retrospective study reflects a single-center experience. Groups had significant baseline characteristics differences and adjustment for these may be incomplete or flawed by residual confounding. Although PVR was assessed by experienced echocardiographers and reported according to VARC-2 criteria, the absence of a central core lab may lead to some heterogeneity in assessment of this outcome. In addition, we did not analyze the timing of conduction disturbances. Indeed, one of the possible reasons for higher PPM in the S3-THV group may be a delayed inflammatory process caused by the skirt polymer, in addition to its immediate mechanical effect on the conduction system. To reflect contemporary practice of TAVI, we collected ECG data, depth and device coaxiality only in the S3-THV group. As it is difficult to measure device coaxiality before implant on a crimped valve, we used the device coaxiality at the end of deployment. Measurements were taken as the balloon was deflated and the patient still under rapid pacing so that measurements reflected pre-deployment status. In addition, device coaxiality measurements were only available for procedures done in the catheterization laboratory, thereby excluding patients with non-transfemoral access.

***Conclusion***

The third generation Edwards S3-THV is associated to improved outcomes with lower rates of major vascular complications and PVR but higher rates of new PPM compared to its predecessor, the XT-THV.

These results are encouraging in the endeavor to take TAVI to lower risk populations. Our findings highlight the increased importance to adequately visualize the S3-THV in relation to the aortic valvular complex during deployment, in order to improve device positioning and potentially mitigate new PPM requirements.

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No other persons have made substantial contributions to this manuscript

**COMMENTS**

***Background***

Since its introduction in 2002, transcatheter aortic valve implantation (TAVI) has evolved tremendously and is now standard of care for high risk and inoperable aortic stenosis patients. However, TAVI is still associated with a higher incidence of paravalvular regurgitation (PVR), permanent pacemaker (PPM) and vascular complications when compared to surgical aortic valve replacement. In order to justify the extension of the procedure to lower risk patients, these adverse outcomes have to be mitigated. The development of novel transcatheter heart valves and refinement of technical skills have contributed to the decrease in complications rates associated with TAVI.

***Research frontiers***

TAVI indication has now moved to intermediate and lower risk patients and it is crucial to continue careful evaluation of the newer generation devices aimed at improving patient outcomes. The study aimed to compare the different iterations between 2 valves on patient outcomes. New devices with lower profile and different designs have currently been introduced to further improve valve performance and efficacy.

***Innovations and breakthroughs***

TAVI is still associated with a higher incidence of PVR, PPM and vascular complications when compared to surgical aortic valve replacement. However, the third generation edwards SAPIEN 3 transcatheter heart valve (S3-THV) the newest approved valve have improved TAVI outcomes by lowering complication rates and have recently been associated with improved outcomes compared to surgical aortic valve replacement in high risk patients. This breakthrough technology will without a doubt become the standard care of all patients in the near future with the continue improvement in device designs.

***Applications***

The third generation Edwards S3-THV is associated to improved outcomes with lower rates of major vascular complications and PVR but higher rates of new PPM compared to its predecessor, the SAPIEN XT transcatheter heart valve (XT-THV). These results are encouraging in the endeavor to take TAVI to lower risk populations. The authors’ findings highlight the increased importance to adequately visualize the S3-THV in relation to the aortic valvular complex during deployment, in order to improve device positioning and potentially mitigate new PPM requirements. Dedicated software devices that can align the annulus and the prosthesis during deployment could help in coaxial implantation of the valve.

***Terminology***

TAVI: Transcatheter aortic valve implantation; PVR: Paravalvular regurgitation.

***Peer-review***

The paper is well written and offers a fairly large comparison of the performance of these 2 valves.

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| **Table 1 Baseline characteristics** | | | |
| **Variable** | **S3-THV**  **(*n* = 283)** | **XT-THV**  **(*n* = 507)** | ***P*-value** |
| **Age** | 82.8 ± 7.1 | 83.5 ± 7.0 | 0.14 |
| **Female sex** | 137 (48.4) | 275 (54.3) | 0.12 |
| **STS-PROM, %** | 5.3 ± 3.5 | 6.4 ± 4.0 | < 0.0001 |
| **Logistic EuroSCORE, %** | 15.7 ± 10.8 | 18.8 ± 11.5 | < 0.0001 |
| **NYHA Class 3 or 4** | 162 (59.1) | 383 (75.8) | < 0.0001 |
| **History of syncope** | 1 (0.5) | 10 (2.1) | 0.19 |
| **Atrial arrhythmia (flutter or fibrillation)** | 80 (29.5) | 135 (27.8) | 0.67 |
| **Diabetes** | 71 (25.1) | 124 (24.5) | 0.86 |
| **Hypertension** | 161 (71.6) | 344 (68.8) | 0.49 |
| **Dyslipidemia** | 99 (44.0) | 263 (52.6) | 0.04 |
| **Active smoker** | 4 (1.4) | 18 (3.6) | 0.11 |
| **Previous PPM** | 35 (12.4) | 60 (11.8) | 0.91 |
| **Previous PCI** | 81 (29.3) | 114 (22.9) | 0.06 |
| **Previous CABG** | 25 (9.0) | 51 (10.3) | 0.62 |
| **Previous SAVR** | 2 (0.7) | 7 (1.4) | 0.50 |
| **Previous stroke** | 25 (8.8) | 39 (7.7) | 0.59 |
| **Peripheral vascular disease** | 56 (19.8) | 143 (28.4) | 0.01 |
| **eGFR, mL/min per 1.73 m2** | 62.8 ± 24.6 | 61.4 ± 22.6 | 0.42 |
| **eGFR < 40 mL/min per 1.73 m2** | 82 (16.2) | 41 (14.5) | 0.61 |
| **Dialysis** | 4 (1.5) | 13 (2.6) | 0.44 |
| **Chronic obstructive pulmonary disease** | 33 (11.7) | 110 (21.9) | < 0.0001 |
| **Body mass index, kg/m2** | 26.5 ± 5.1 | 26.3 ± 4.9 | 0.61 |
| **LVEF, %** | 54.9 ± 14.8 | 53.6 ± 14.2 | 0.24 |
| **LVEF < 30%** | 55 (11.1) | 31 (11.4) | 0.91 |
| **Mean aortic gradient, mmHg** | 46.7 ± 15.3 | 46.9 ± 15.3 | 0.92 |
| **AVA, cm2** | 0.67 ± 0.17 | 0.65 ± 0.14 | 0.31 |
| **Pulmonary artery systolic pressure, mmHg** | 44.5 ± 13.0 | 46.5 ± 12.9 | 0.06 |
| **Pulmonary artery systolic pressure > 50 mmHg** | 64 (28.3) | 123 (28.5) | 1 |
| Values are mean ± SD or *n* (%). AVA: Aortic valve area; CABG: Coronary artery bypass graft; eGFR: Glomerular filtration rate estimated by the MDRD formula; EuroSCORE: European System for Cardiac Operative Risk Evaluation; LVEF: Left ventricular ejection fraction; NYHA: New York Heart Association functional class; PPM: Permanent pacemaker; PCI: Percutaneous coronary intervention; SAVR: Surgical aortic valve replacement; STS-PROM: Society of Thoracic Surgeons Predicted Risk of Mortality; S3-THV: SAPIEN 3 transcatheter heart valve; XT-THV: SAPIEN XT transcatheter heart valve. | | | |

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| **Table 2 Procedural characteristics** | | | |
| **Procedural characteristic** | **S3-THV**  **(*n* = 283)** | **XT-THV**  **(*n* = 507)** | ***P*-value** |
| **Transfemoral approach** | 232 (82.6) | 273 (53.8) | < 0.0001 |
| **Local anesthesia** | 232 (82.6) | 271 (54.2) | < 0.0001 |
| **Predilatation** | 50 (17.7) | 440 (86.8) | < 0.0001 |
| **Postdilatation** | 45 (15.9) | 61 (12.0) | 0.13 |
| **Implanted device size**  **23 mm**  **26 mm**  **29 mm** | 111 (39.8)  101 (36.2)  67 (24.0) | 127 (25.1)  270 (53.4)  109 (21.5) | < 0.0001 |
| **Valve area oversizing, %** | 11.5 ± 9.8 | 22.9 ± 11.2 | < 0.0001 |
| **Device diameter /annulus diameter**  **(area-derived)** | 1.05 ± 0.05 | 1.11 ± 0.05 | < 0.0001 |
| **Need for seconde valve implantation** | 7 (2.5) | 8 (1.6) | 0.42 |
| **Annulus rupture** | 0 (0) | 13 (2.6) | 0.01 |
| **Conversion to SAVR** | 2 (0.7) | 14 (2.8) | 0.06 |
| **Contrast use (mL)** | 108.2 ± 42.7 | 131.6 ± 60.9 | < 0.0001 |
| **Fluoroscopy time (min)** | 17.4 ± 9.9 | 16.5 ± 9.8 | 0.28 |
| Values are mean ± SD or *n* (%). SAVR: Surgical aortic valve replacement; S3-THV: SAPIEN 3 transcatheter heart valve; XT-THV: SAPIEN XT transcatheter heart valve. | | | |

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| **Table 3 Thirty-day and 1-year outcomes** | | | | | | |
| **30-d outcomes** | **S3-THV**  **(*n* =283)** | **XT-THV**  **(*n* = 507)** | **Odds ratio**  **(95%CI)** | ***P*-value** | **Adjusted odds ratio (95%CI)** | **Adjusted *P*-value** |
| **Death** | 8 (3.5) | 42 (8.7) | 0.36 (0.16-0.81) | 0.01 | 0.44 (0.12-1.56) | 0.21 |
| **Stroke** | 4 (1.4) | 13 (2.8) | 0.51 (0.16-1.58) | 0.24 | 0.59 (0.08-4.33) | 0.60 |
| **Myocardial infarction** | 0 (0) | 2 (0.4) | 0 (0-∞) | 1 |  |  |
| **New pacemaker implantation1** | 43 (17.3) | 44 (9.8) | 1.88 (1.19-2.97) | 0.007 | 1.68 (1.05-2.69) | 0.03 |
| **Major vascular complication** | 8 (2.8) | 50 (9.9) | 0.27 (0.13-0.57) | 0.001 | 0.20 (0.09-0.44) | < 0.0001 |
| **Paravalvular regurgitation > mild** | 6 (2.4) | 47 (9.7) | 0.23 (0.10-0.55) | 0.001 | 0.20 (0.08-0.47) | < 0.0001 |
| **Acute kidney injury** | 3 (1.1) | 69 (13.6) | 0.07 (0.02-0.22) | < 0.0001 | 0.12 (0.04-0.39) | < 0.0001 |
| **Mean gradient > 20 mmHg** | 7 (2.8) | 6 (1.3) | 2.48 (0.78-7.89) | 0.13 |  |  |
| **Mean gradient, mmHg** | 11.8 ± 5.8 | 10.0 ± 5.0 |  | < 0.0001 |  |  |
| **Total hospital length of stay, d [median (IQR)]** | 8 [5-13] | 9 [7-14] |  | < 0.0001 |  |  |
|  |  |  |  |  |  |  |
| **1-yr outcomes** |  |  |  | ***P*-value** | **Adjusted hazard ratio (95%CI)** | **Adjusted *P*-value** |
| **Death** | 20 (25.7) | 87 (20.1) |  | 0.24 | 0.86 (0.52-1.42) | 0.55 |
| Values are mean ± SD or *n* (%) unless specified otherwise. 1Patients with previous permanent pacemaker were excluded from this analysis. No adjusted analyses were performed for outcomes with less than 15 events overall. IQR: Inter-quartile range; S3-THV: SAPIEN 3 transcatheter heart valve; XT-THV: SAPIEN XT transcatheter heart valve. | | | | | | |

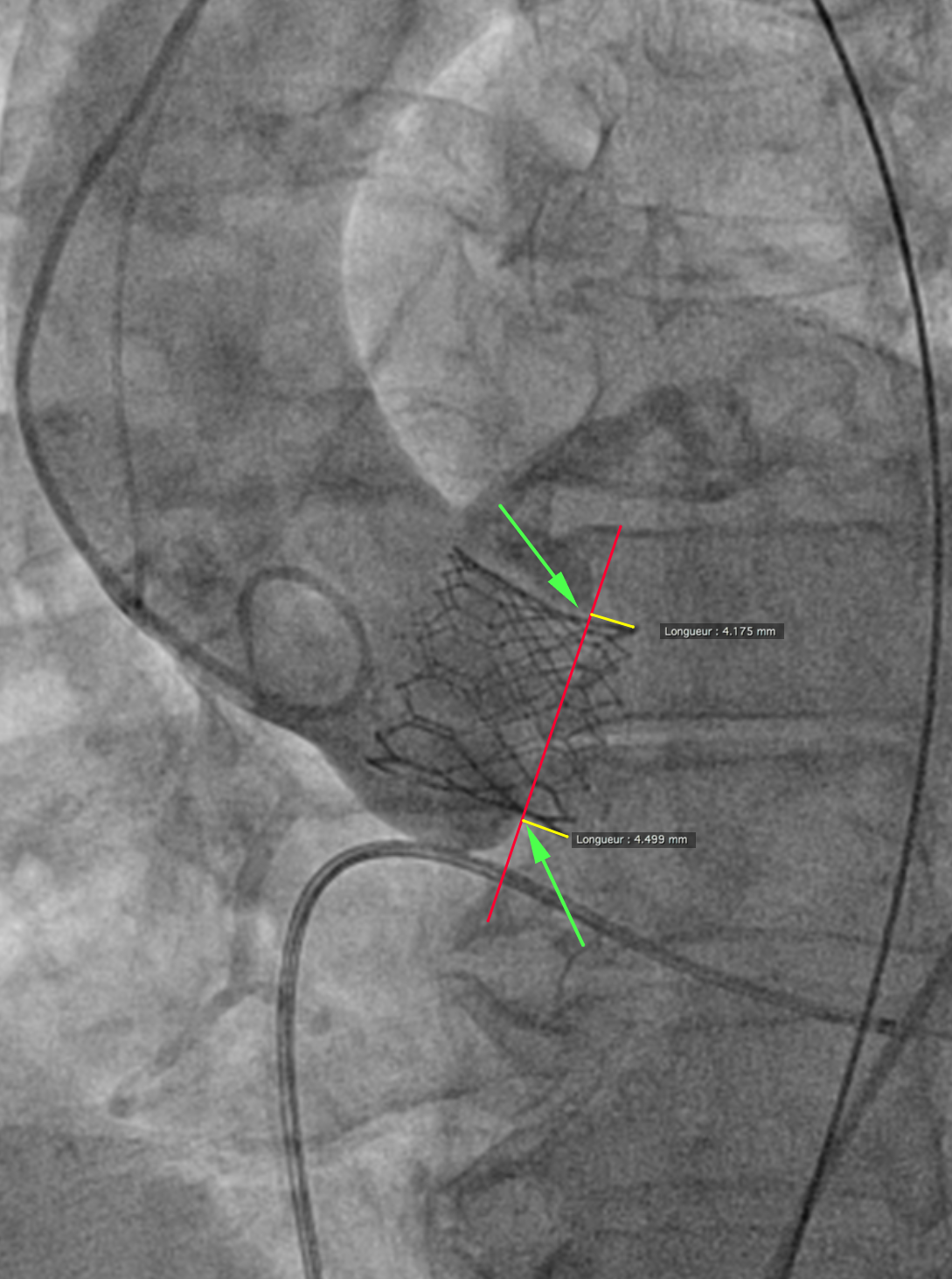
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| **Table 4 Causes of death at 1 year in the SAPIEN 3 transcatheter heart valve group** | | |
| **Patient** | **Days to death** | **Cause of death** |
| 1 | 0 | Dissection of ascending aorta |
| 2 | 2 | Left main compression/cardiogenic shock |
| 3 | 3 | Iliac rupture |
| 4 | 5 | Sudden cardiac death |
| 5 | 10 | Cardiogenic shock |
| 6 | 22 | Heart failure |
| 7 | 24 | Subdural hematoma |
| 8 | 25 | Unknown |
| 9 | 31 | Stroke |
| 10 | 36 | Acute renal failure |
| 11 | 62 | Unknown |
| 12 | 87 | Heart failure |
| 13 | 96 | Heart failure |
| 14 | 133 | Unknown |
| 15 | 200 | Sudden cardiac death |
| 16 | 202 | Cancer |
| 17 | 247 | Myocardial infarction |
| 18 | 268 | Septic shock |
| 19 | 305 | Chronic obstructive pulmonary disease acute exacerbation |
| 20 | 326 | Major Stroke |
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| **Table 5 Electrocardiographic and angiographic characteristics according to new permanent pacemaker requirement in the SAPIEN 3 transcatheter heart valve group** | | | |
| **Variable** | **New PPM**  **(n=43)** | **No PPM**  **(n=201)** | **p-value** |
| **Complete RBBB** | 12 (32.4) | 17 (9.5) | 0.001 |
| **Complete LBBB** | 0 (0) | 14 (7.8) | 0.14 |
| **Fascicular block** | 12 (32.4) | 33 (18.4) | 0.07 |
| **QRS duration, ms** | 108 ± 26 | 101 ± 23 | 0.10 |
| **PR duration, ms** | 196 ± 37 | 183 ± 30 | 0.04 |
| **Implant depth (septal), mm** | 5.3 ± 2.4 | 5.0 ± 2.6 | 0.67 |
| **Implant depth (non-septal), mm** | 4.9 ± 2.4 | 5.2 ± 1.9 | 0.64 |
| **Device lack of coaxiality during deployment, mm** | 4.0 ± 3.6 | 2.9 ± 2.5 | 0.06 |
| Values are mean ± SD or *n* (%). LBBB: Left bundle branch block; RBBB: Right bundle branch block; PPM: Permanent pacemaker. | | | |

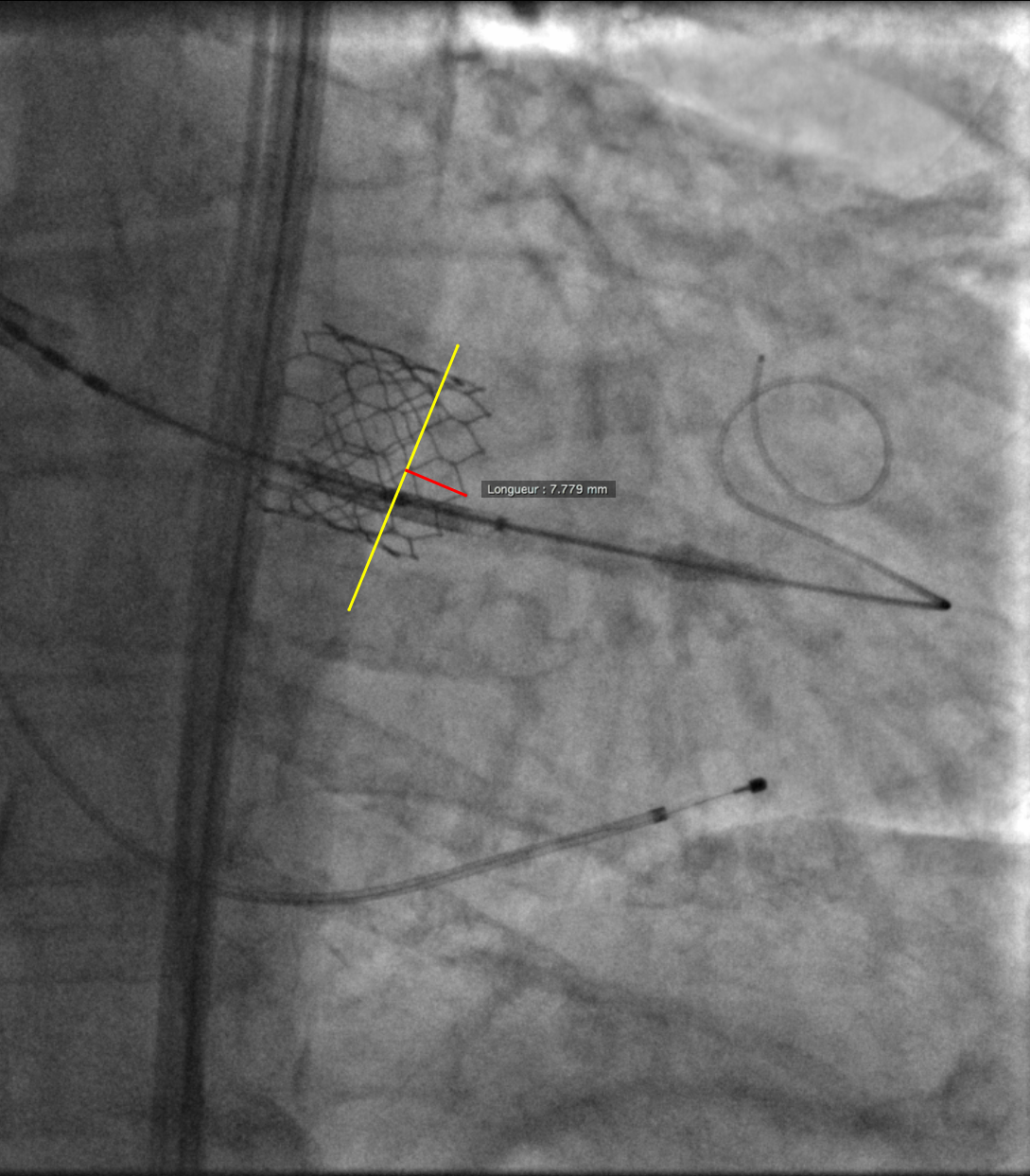
|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Table 6 Predictors of new pacemaker implantation in the S3 group** | | | | | |
| Parameter | Univariate analysis | | Multivariate analysis | | |
| OR | *P*-value | OR | 95%CI | *P*-value |
| **Complete RBBB** | 4.60 | < 0.001 | 4.90 | 1.88-12.95 | 0.001 |
| **Complete LBBB** | 1 | 1 | - | - | - |
| **Fascicular block** | 2.12 | 0.06 | 1.88 | 0.71-5.00 | 0.20 |
| **QRS duration (per 10 ms increment)** | 1.12 | 0.10 | 0.87 | 0.65-2.72 | 0.345 |
| **PR duration (per 10 msec increment)** | 1.14 | 0.05 | 1.14 | 1.00-1.29 | 0.05 |
| **Implant depth (septal, per 1 mm increment)** | 1.05 | 0.66 | - | - | - |
| **Implant depth (non-septal, per 1 mm increment)** | 0.94 | 0.63 | - | - | - |
| **Device lack of coaxiality during implant (per 1 mm increment)** | 1.13 | 0.07 | 1.13 | 1.00-1.29 | 0.049 |
| LBBB: Left bundle branch block; RBBB: Right bundle branch block. | | | | | |

**Table 7 Summary of studies comparing the rate of permanent pacemaker between the S3 and XT device**

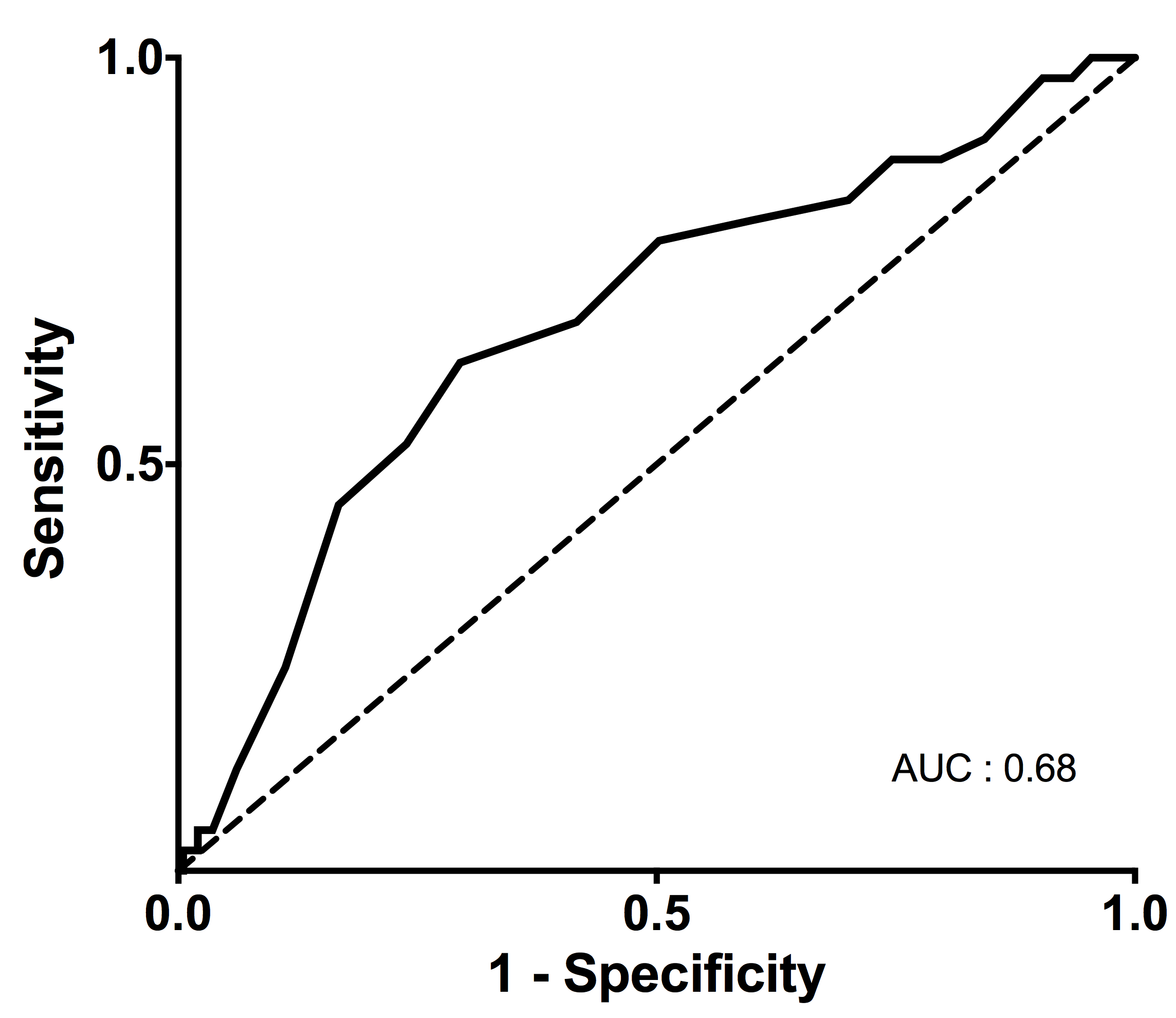
|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **PPM** | **S3** | **XT** | ***P* value** | **Predictor/comments** |
| **Binder *et al*[16]**  **2015**  **Circulation**  **Interventions** | **17%** | **13%** | **0.01** | **Predictors: Depth, RBBB** |
| **Binder *et al*[14]**  **2013**  **JACC**  **Interventions** | **13.3%** |  |  | **Excluded patient with LBBB, PR > 200 ms**  **No predictors studied** |
| **Husser *et al*[25]**  **2015**  **JACC Interventions** | **15.2%** |  |  | **Predictors not studied** |
| **Binder *et al*[16]**  **2015**  **EuroIntervention** | **20.7%** |  |  | **Predictor > 8 mm depth of implants** |
| **Nijhoff *et al*[17]**  **2015**  **Circulation**  **Interventions** | **9.8%** | **8.8%** | **0.94** | **High implants: 80/20 in aorta as mentioned by authors** |

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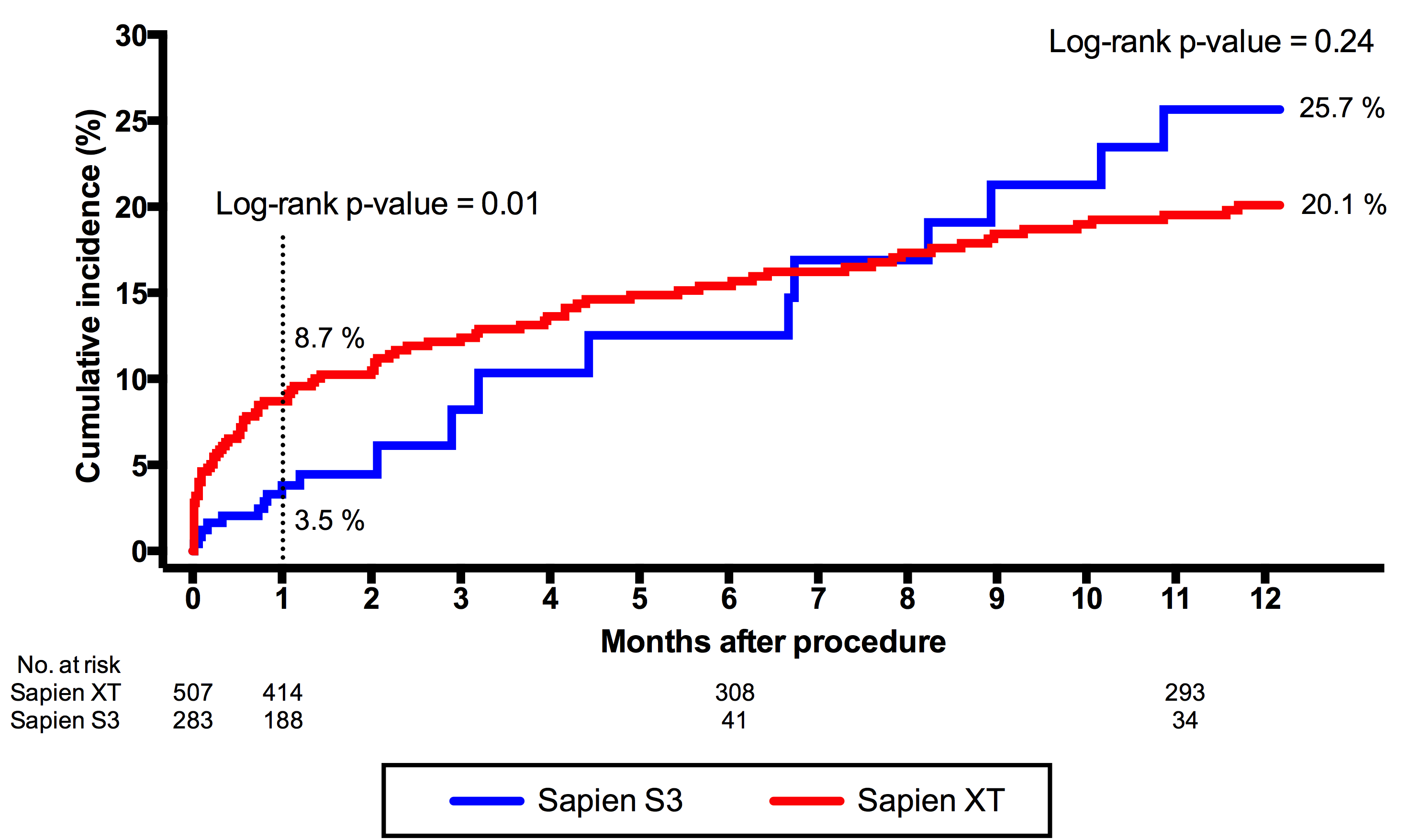
**Figure 1 Depth of implant measurement.** The arrows show the hinge points between the device and neighboring sinuses of Valsalva. Next, the red line is drawn from the septal to the non-septal hinge point. The yellow lines, drawn perpendicularly from the red line to the extremity of the device frame, represent depth on the septal side (left) and the non-septal side (right).



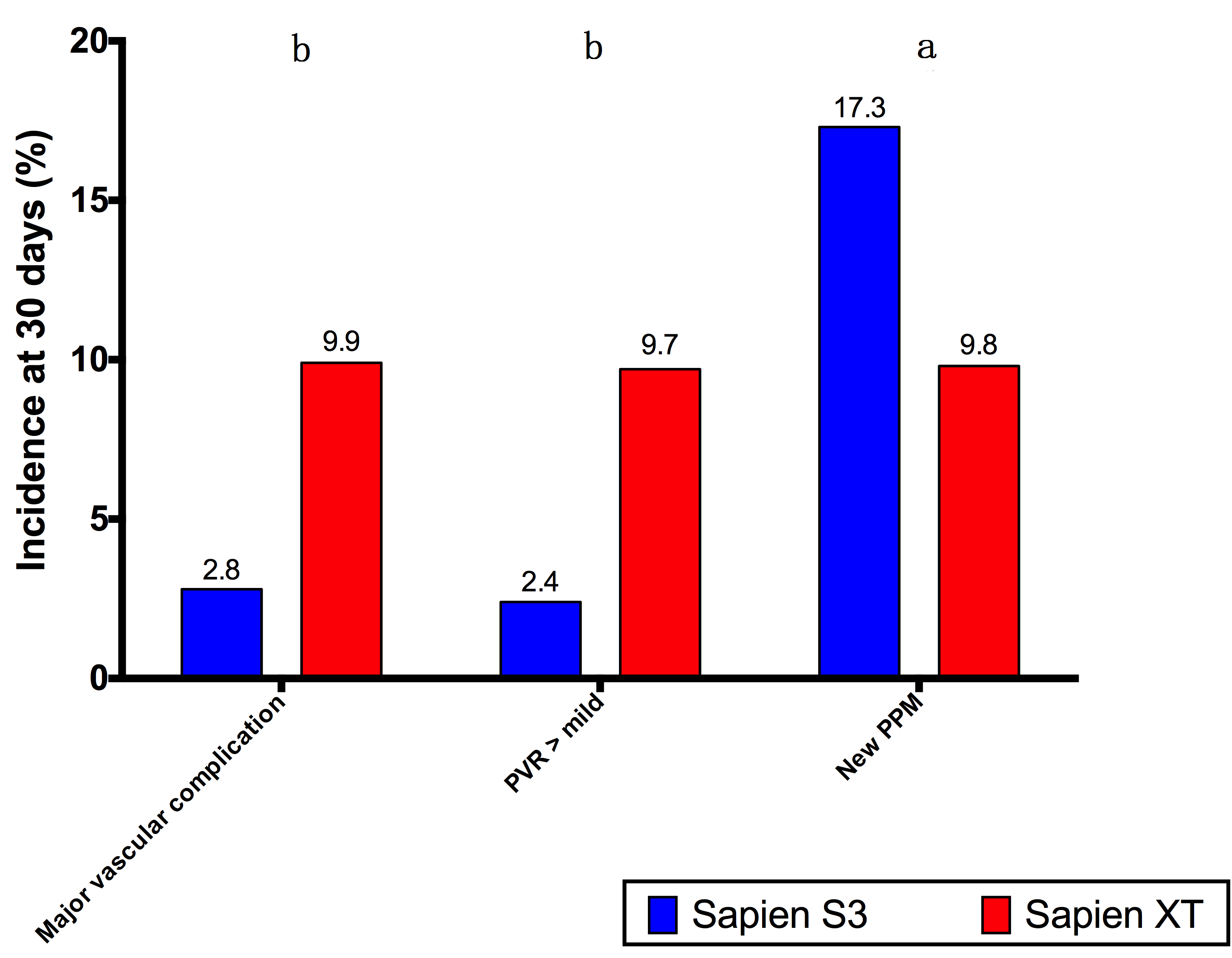
**Figure 2 Device coaxiality measurement.** On a still frame, immediately after deployment while still under rapid pacing, a line is drawn connecting neighboring valve struts on the ventricular side of the device (yellow line). Next, a perpendicular line is drawn from the yellow line to the tip of the strut that appears the deepest (red line). The length of this red line is recorded as device lack of coaxiality.

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**Figure 3 ROC curve analysis of device diameter to annulus diameter ratio.** ROC curve analysis of device diameter to annulus diameter ratio below the threshold of 1.03 increased the risk of post-dilatation or PVR > mild (area under the curve: 0.68). PVR: Paravalvular regurgitation.



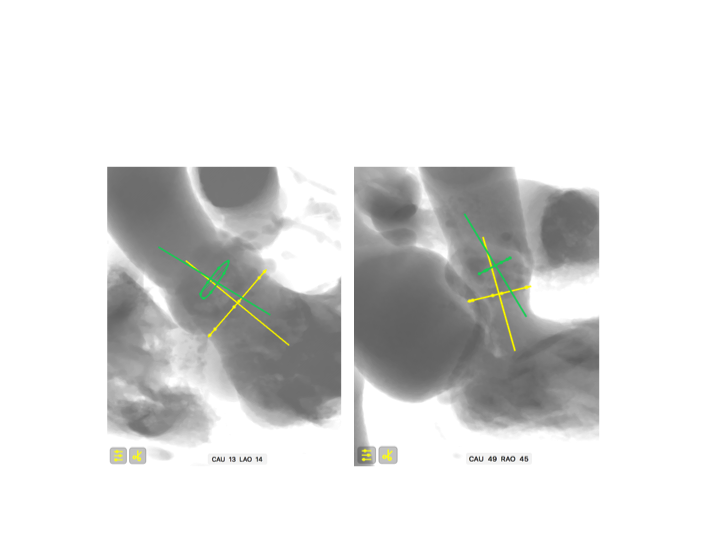
**Figure 4 Cumulative incidence of all-cause mortality.** Cumulative incidence (%) of all-cause 1-year mortality in the S3-THV group (blue line) and the XT-THV group (red line). S3-THV: SAPIEN 3 transcatheter heart valve; XT-THV: SAPIEN XT transcatheter heart valve.

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**Figure 5 Incidence of major vascular complication, > mild para-valvular regurgitation and new permanent pacemaker.** Thirty-day incidence (%) of major vascular complication, > mild PVR and new PPM in the S3-THV group (blue bars) and the XT-THV group (red bars). a*P* < 0.05; b*P* < 0.0001.XT-THV: SAPIEN XT transcatheter heart valve; PPM: Permanent pacemaker; PVR: Paravalvular regurgitation.



**Figure 6 Example of difficult depth measurement.** In this case, the projection has been modified after implant so the device appears coaxial. However, the annulus is no longer coaxial: Two aortic cusps are seen at different levels on the septal side (arrows), making difficult the localization of the hinge point and therefore the measurement depth of implant.

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**Figure 7 Coaxiality concept.** In this example, the aortic annulus is drawn in yellow and the device is in green. Two different C-arm angulations of the same structures are shown. If the operator selects the angulation on the left for deployment, estimation of implant depth will be more difficult as one of the structures (the device) is not coaxial. Notice that in both angulations, the annulus (yellow) is coaxial.