European Journal of Cardio-Thoracic Surgery

Pacemaker Implant after Sutureless or Stented Valve: Results From a Controlled Randomized Trial

--Manuscript Draft--

Manuscript Number:	EJCTS-2021-101959R2
Full Title:	Pacemaker Implant after Sutureless or Stented Valve: Results From a Controlled Randomized Trial
Article Type:	Original Article
Order of Authors:	Roberto Lorusso
	Justine Mafalda Ravaux
	Francesco Pollari
	Thierry A Folliguet
	Utz Kappert
	Bart Meuris
	Malakh L Shrestha
	Eric E Roselli
	Nikolaos Bonaros
	Olivier Fabre
	Pierre Corbi
	Giovanni Troise
	Martin Andreas
	Frederic Pinaud
	Steffen Pfeiffer
	Sami Kueri
	Erwin Tan
	Pierre Voisine
	Evaldas Girdauskas
	Filip Rega
	Julio Garcia-Puente
	Theodor Fischlein
Corresponding Author:	Justine Mafalda Ravaux MUMC Maastricht , NETHERLANDS
Corresponding Author E-Mail:	jmravaux@hotmail.com
Section/Category:	Valves
Manuscript Classifications:	Valve disease; Arrhythmias; Electrophysiology; Pacemaker/ICD/Device
Author Comments:	To the kind attention of: Matthias Siepe European Journal of Cardiothoracic Surgery Maastricht, 21th October 2021 Object: Request of consideration for publication of the manuscript titled “Pacemaker

	Implant after Sutureless or Stented Valve: Results From a Controlled Randomized Trial” Dear Dr. Siepe, By this letter, I would like to have your opinion about the submission of a manuscript, as an Original Article, titled “Pacemaker Implant after Sutureless or Stented Valve: Results From a Controlled Randomized Trial”. Our research addressed an important issue in the area of cardiac surgery, namely the occurrence of unplanned permanent pacemaker implantation (PPI) after sutureless Perceval aortic valve implantation. This paper provides a unique experience from a prospective, randomized, adaptive, open label trial comparing sutureless Perceval aortic valve with conventional stented valves, involving 914 patients across 47 sites around the world. Our findings showed an increased PPI rate for Perceval valves being size-dependent, with a higher rate for size XL. Additionally, these trial confirmed the negative impact of pre-operative conduction disorders on post-operative conduction disturbances leading to PPI. These evidences, in our opinion, appear critical to further stimulate the scientific and cardiological/cardiac surgical communities to investigate this important aspect of post-operative outcome. This study was furthermore presented at the poster session of the 57th Annual Meeting of the Society of Thoracic Surgeon in Austin, Texas, United States (online session). Furthermore, the paper respects the following criteria: - All authors have participated in the work and have reviewed and agree with the content of the article. -No portion of the text has been copied from other material in the literature (unless in quotation marks, with citation). -I am aware that it is the authors responsibility to obtain permission for any figures or tables reproduced from any prior publications, and to cover fully any costs involved. Such permission must be obtained prior to final acceptance. By the way, authors ensure that the manuscript adheres to European Journal of Cardiothoracic surgery’s instructions to authors. Thank you in advance for considering our request. Sincerely, and on behalf of all office, Justine Ravaux M.D. Roberto Lorusso, M.D. Ph.D. Corresponding Author: Justine Mafalda Ravaux Department of Cardio-Thoracic Surgery Heart& Vascular Centre Maastricht University Medical Centre (MUMC+) Cardiovascular Research Institute Maastricht (CARIM) Maastricht University Maastricht, The Netherlands P. Debyelaan, 25 6202 AZ Maastricht – The Netherlands Tel: +32(0)472597359 E: jmravaux@hotmail.com
Abstract:	Objectives Sutureless aortic valves demonstrated non-inferiority to standard stented valves for major cardiovascular and cerebral events at 1 year after aortic valve replacement (AVR). We aim to assess the factors correlating with permanent pacemaker implant (PPI) in both cohorts. Methods PERSIST-AVR is a prospective, randomized, open-label trial. Patients undergoing AVR were randomized to receive a sutureless (Su-AVR) or stented sutured bioprosthesis (SAVR). Multivariable analysis was performed to identify possible independent risk factors associated with PPI. A logistic regression analysis was performed to estimate the risk of PPI associated to different valve size. Results

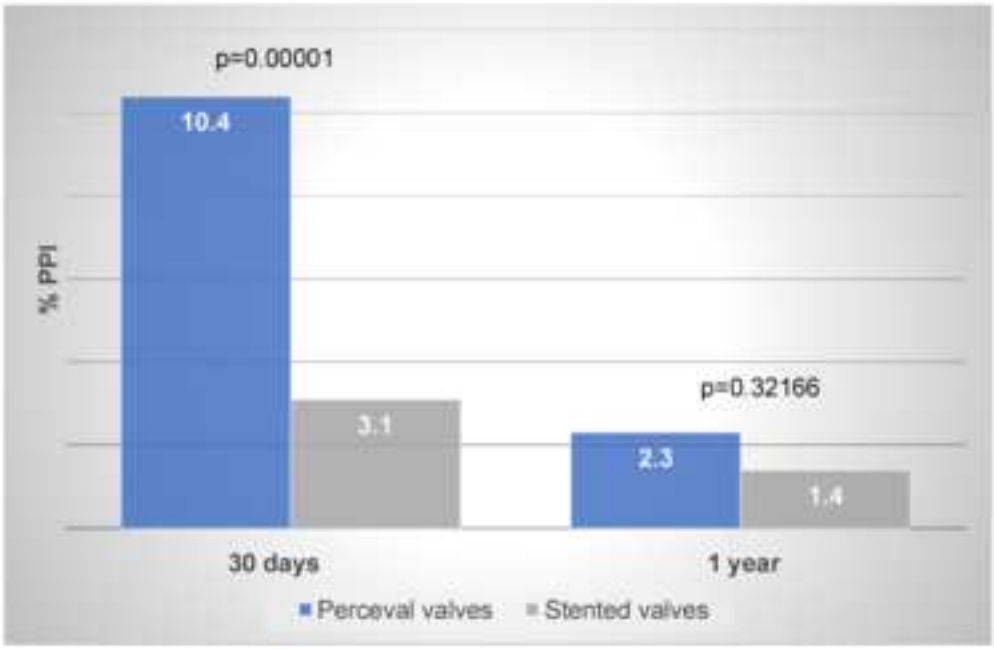
	The two groups (Su-AVR; n= 450, SAVR n=446) were well balanced in terms of preoperative risk factors. Early PPI rates were 10.4% in Su-AVR and 3.1% in SAVR groups. PPI prevalence correlated with valve size XL (p=0.0119) and preoperative conduction disturbances (p=0.0079) in the Su-AVR group. No predictors were found in the SAVR cohort. Logistic regression analysis showed a significantly higher risk for PPI with size XL compared to each individual sutureless valve sizes (OR 0.272 vs size S (95%confidence interval 0.07-0.95), 0.334 vs size M (95%CI 0,16-0;68), 0.408 vs size L (95%CI 0,21-0.81)) but equivalent risk of PPI rates for all other combination of valve sizes. Conclusions Su-AVR is associated with higher PPI rate as compared to SAVR. However, the increased PPI rate appears to be size-dependent with significant higher rate only for size XL. The combination of preoperative conduction disorder and a size XL can lead to a higher probability of early PPI in Su-AVR.
Response to Reviewers:	Associate Editor 1.We appreciate the authors efforts to address our comments. Thank you. Reply : Thank you for this positive comment. Changes : None 2.However, using the word "non-inferiority" (line 92 page 5; line 213; page 9; line 235 page 10), which is a well-defined statistical entity, mandating prespecified sample sizes and a predefined hazard risk, is not entirely appropriate, since this information is missing. Reply : Thank you for this helpful comment. The expression “non-inferiority” was used in the manuscript when referring to the PERSIST-AVR randomized trial (Fischlein T et al. Sutureless versus conventional bioprosthesis for aortic valve replacement in severe symptomatic aortic valve stenosis. J Thorac Cardiovasc Surg 2021; 161:920-932) which was designed to demonstrate the noninferiority of Perceval sutureless prosthesis compared with standard aortic valves, using a conventional or minimally invasive approach, in patients with severe symptomatic aortic valve stenosis. In this post-hoc analysis you are right we cannot claim “non-inferiority”. We deleted the expression “non-inferiority” in line 235 page 10. No changes have been applied to line 93 page 5 and line 159 page 7 as we were referring to the PESRSIT AVR trial. Changes : See manuscript, line 235 page 10. 3.Having discussed this topic with our statistician he suggests "harmonization of the authors' text and a deletion of the term "non-inferiority". Reply : Thank you for this important comment. The text had been harmonized and the term “non-inferiority” has been deleted when necessary, as mentioned by the reviewer’s suggestion. Changes : See previous comment and improvement of the manuscript, line 235, page 10. Reviewer 2 The authors answered all questions and comments of reviewers. The text is interesting and will be helpful to surgeons who care for these patients. Reply : Thank you for your positive comments and you support to improve the manuscript. Changes : None. Reviewer 3 The requested changes have been made, I have no other comments. Reply : Thank you for your positive comments. Change : None.

	Reviewer 4 First of all, I would like to thank the authors for considering all my comments. All of them were sufficiently addressed and I have no new comments anymore. Reply : Thank you for your positive and pertinent comments. Change : None.
Order of Authors (with Contributor Roles):	Roberto Lorusso (Conceptualization; Data curation; Funding acquisition; Investigation; Methodology; Project administration; Resources; Supervision; Validation; Visualization)
	Justine Mafalda Ravaux (Conceptualization; Data curation; Methodology; Validation; Visualization; Writing – original draft; Writing – review & editing)
	Francesco Pollari (Conceptualization; Funding acquisition; Investigation; Resources; Validation; Visualization)
	Thierry A Folliguet (Conceptualization; Methodology; Resources; Validation; Visualization)
	Utz Kappert (Conceptualization; Funding acquisition; Methodology; Validation; Visualization)
	Bart Meuris (Conceptualization; Funding acquisition; Methodology; Validation; Visualization)
	Malakh L Shrestha (Conceptualization; Funding acquisition; Methodology; Validation; Visualization)
	Eric E Roselli (Conceptualization; Funding acquisition; Methodology; Validation; Visualization)
	Nikolaos Bonaros (Conceptualization; Funding acquisition; Methodology; Validation; Visualization)
	Olivier Fabre (Conceptualization; Funding acquisition; Methodology; Validation; Visualization)
	Pierre Corbi (Conceptualization; Funding acquisition; Methodology; Validation; Visualization)
	Giovanni Troise (Conceptualization; Funding acquisition; Investigation; Methodology; Validation; Visualization)
	Martin Andreas (Conceptualization; Funding acquisition; Investigation; Methodology; Validation; Visualization; Writing – review & editing)
	Frederic Pinaud (Conceptualization; Funding acquisition; Methodology; Project administration; Validation; Visualization)
	Steffen Pfeiffer (Conceptualization; Methodology; Project administration; Validation; Visualization)
	Sami Kueri (Conceptualization; Methodology; Resources; Validation; Visualization)
	Erwin Tan (Conceptualization; Investigation; Methodology; Validation; Visualization)
	Pierre Voisine (Conceptualization; Funding acquisition; Methodology; Project administration; Validation; Visualization)
	Evaldas Girdauskas (Conceptualization; Data curation; Methodology; Validation; Visualization)
	Filip Rega (Conceptualization; Funding acquisition; Methodology; Project administration; Resources; Validation; Visualization)
	Julio Garcia-Puente (Conceptualization; Funding acquisition; Investigation; Methodology; Validation; Visualization)
	Theodor Fischlein (Conceptualization; Data curation; Funding acquisition; Investigation; Methodology; Project administration; Resources; Supervision; Validation; Visualization)

Central illustration

Graphical Abstract

Rate of early (0-30 days from surgery) and late (1 year follow-up) permanent pacemaker implant (PPI) in both groups.



PPI= Permanent Pacemaker Implant

TITLE PAGE

Pacemaker Implant after Sutureless or Stented Valve: Results From a Controlled Randomized Trial

Running Head/Short title: Pacemaker Implant in the PERSIST-Trial

Roberto Lorusso[1,2], MD, PhD, Justine M Ravaux[1,2], MD, Francesco Pollari[3], MD, PhD, Thierry A Folliguet[4], MD, PhD, Utz Kappert[5], MD, PhD, Bart Meuris[6], MD, PhD, Malakh L Shrestha[7], MD, Eric E Roselli[8], MD, Nikolaos Bonaros[9], MD, PhD, Olivier Fabre[10,11], MD, PhD, Pierre Corbi[12], MD, PhD, Giovanni Troise[13], MD, Martin Andreas[14], MD, PhD, Frederic Pinaud[15], MD, Steffen Pfeiffer[3], MD, Sami Kueri[16,17], MD, Erwin Tan[18], MD, PhD, Pierre Voisine[19,20], MD, Evaldas Girdauskas[21], MD, Filip Rega[6,22], MD, PhD, Julio Garcia-Puente[23], MD, Theodor Fischlein[3], MD, PhD, on behalf the PERSIST-AVR Investigators

[1] Cardio-Thoracic Surgery Department, Heart & Vascular Centre, Maastricht University Medical Center + (MUMC+), Maastricht, The Netherlands

[2] Cardiovascular Research Institute Maastricht (CARIM), Maastricht, The Netherlands

[3] Cardiac Surgery, Cardiovascular Center, Paracelsus Medical University-Klinikum Nürnberg, Nuremberg, Germany

[4] Department of Cardiac Surgery & Transplantation, Assistance Publique, Höpital Henri Mondor, Université Paris 12 UPEC, France

[5] Department of Cardiac Surgery, Dresden Heart Centre University Hospital, Dresden University of Technology, Dresden, Germany

[6] Cardiac Surgery Department, Universitaire Ziekenhuizen Leuven, Leuven, Belgium

[7] Department of Thoracic and Cardiovascular Surgery, Hannover Medical School, Hannover, Germany

[8] Thoracic and Cardiovascular Surgery, Cleveland Clinic, Cleveland, Ohio, United States

[9] Department of Cardiac Surgery, Innsbruck Medical University, Innsbruck, Austria

[10] Department of Cardiac Surgery of Artois, Hospital Center of Lens, Lens, France

[11] Private Hospital of Bois-Bernard, Ramsay Santé, France

[12] Department of Thoracic and Cardiovascular Surgery, Cardio-Vascular Center, University Hospital of Poitiers, Poitiers, France

[13] Division of Cardiac Surgery, Poliambulanza Foundation, Brescia, Italy

[14] Department of Cardiac Surgery, Medical University of Vienna, Vienna, Austria

[15] Department of Cardiac Surgery, CHU d'Angers, University Hospital Angers, Angers, France

[16] Department of Cardiovascular Surgery, University Heart Center Freiburg Bad Krozingen, Bad Krozingen, Germany

[17] Medical Faculty, Albert-Ludwigs-University Freiburg, Freiburg, Germany

[18] Department of Cardiothoracic Surgery, Catharina Hospital, Eindhoven, The Netherlands

[19] Department of Surgery, Université Laval, Québec City, Québec, Canada

[20] Division of Cardiac Surgery, Department of Cardiology, Institut Universitaire de Cardiologie et de Pneumologie de Québec (IUCPQ), Québec City, Québec, Canada

[21] Department of Cardiovascular Surgery, University Heart and Vascular Center Hamburg, Hamburg, Germany

[22] Division of Experimental Cardiac Surgery, Department of Cardiovascular Sciences, University of Leuven, Leuven, Belgium

[23] Department of Cardiac Surgery, Hospital Universitario Virgen de la Arraixaca, Murcia, Spain.

Meeting Presentation: e-poster at the Society of Thoracic Surgeons
57th Annual Meeting
Austin, Texas, The United States

Classification: Original article

Total Word count: 4463 words

Corresponding author: Justine Mafalda Ravaux, MD

Cardio-Thoracic Surgery Department, Heart & Vascular Center

Maastricht University Medical Centre (MUMC+)

Cardio vascular Research Institute Maastricht (CARIM)

P. Debyelaan, 25 – 6202 AZ - Maastricht – The Netherlands

Tel. +31 43 3995636 – Fax: +31 43 3995004 – Email: jmravaux@hotmail.com

VISUAL ABSTRACT

Key question

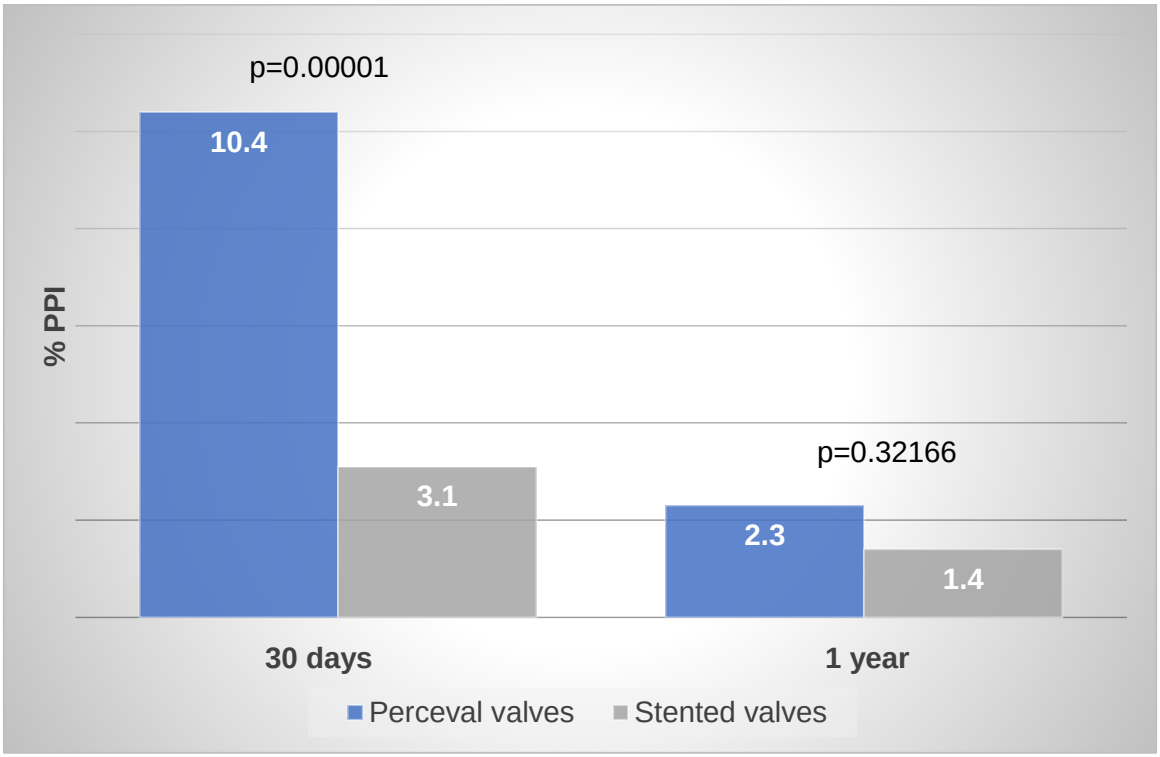
Is permanent pacemaker implantation (PPI) more frequent after sutureless aortic valve replacement (Su-AVR)?

Key Finding(s)

The increased PPI rate after Su-AVR group correlated with valve size XL and preoperative conduction disorder.

Take-home message

PPI is a frequent complication post-Su-AVR. Patients with larger valve size and preoperative arrhythmias should be monitored carefully.



PPI= Permanent Pacemaker Implant

STRUCTURED ABSTRACT

Objectives

Sutureless aortic valves demonstrated non-inferiority to standard stented valves for major cardiovascular and cerebral events at 1 year after aortic valve replacement (AVR). We aim to assess the factors correlating with permanent pacemaker implant (PPI) in both cohorts.

Methods

PERSIST-AVR is a prospective, randomized, open-label trial. Patients undergoing AVR were randomized to receive a sutureless (Su-AVR) or stented sutured bioprosthesis (SAVR). Multivariable analysis was performed to identify possible independent risk factors associated with PPI. A logistic regression analysis was performed to estimate the risk of PPI associated to different valve size.

Results

The two groups (Su-AVR; n= 450, SAVR n=446) were well balanced in terms of preoperative risk factors. Early PPI rates were 10.4% in Su-AVR and 3.1% in SAVR groups. PPI prevalence correlated with valve size XL (p=0.0119) and preoperative conduction disturbances (p=0.0079) in the Su-AVR group. No predictors were found in the SAVR cohort. Logistic regression analysis showed a significantly higher risk for PPI with size XL compared to each individual sutureless valve sizes (OR 0.272 vs size S (95%confidence interval 0.07-0.95), 0.334 vs size M (95%CI 0,16-0;68), 0.408 vs size L (95%CI 0,21-0.81)) but equivalent risk of PPI rates for all other combination of valve sizes.

Conclusions

Su-AVR is associated with higher PPI rate as compared to SAVR. However, the increased PPI rate appears to be size-dependent with significant higher rate only for size XL. The combination of preoperative conduction disorder and a size XL can lead to a higher probability of early PPI in Su-AVR.

Abstract words count: 250

ClinicalTrials.gov: NCT02673697

Keywords: aortic valve replacement – pacemaker – sutureless valves

TEXT

Introduction

The comparison between sutureless valves and standard stented valves has been investigated in previous studies, demonstrating decreased cross-clamp time using the Perceval prosthesis and similar results for major cardiovascular and cerebral events over the short to mid-term follow-up (1-3). The Perceval sutureless aortic valve (CORCYM, Saluggia, Italy) is a bovine pericardial valve nitinol-stent mounted offering an alternative to traditional flexible prostheses (4). Higher permanent pacemaker implantation (PPI) rate after sutureless valve has been already highlighted although with a wide range of occurrence of such perioperative event (5-7) Indeed, recent studies report a PPI rate after sutureless aortic valve replacement (Su-AVR) from 3% to 13.3% (5-7), while the incidence of conduction disorders leading to PPI after aortic valve replacement with a stented valves (SAVR) varies between 3 and 7% (8-10). However, the identification of predictive factors associated with PPI remains still controversial (11). A recent meta-analysis demonstrated a twofold greater risk of PPI after rapid deployment prosthesis (including Su-AVR) than in a SAVR cohort (12), independently of the type of the valve used. The impact of post-operative PPI on late morality after Su-AVR is still under investigation (13) and the matter of PPI after Su-ARV might represent a limitation for an extended use of sutureless valves despite shorter operative times, and enhancement of minimally-invasive procedures (14). Nevertheless, data from international registry as "Sutureless and Rapid Deployment International Registry" show a temporal decreasing trend in PPI after Su-AVR (15). However, dedicated, objective, and in-depth analysis of such an issue has been lacking. The aim of the present study was, therefore, to assess the incidence and related factors correlated with PPI after either Su-AVR and SAVR in a prospective, randomized study.

Methods

Ethical Statement

Ethical approval was provided by the local ethics committee before patient recruitment (Medical Ethics Research Committee, 151138). The study was registered at clinical-trials.gov (NCT02673697) and performed in accordance with the declaration of Helsinki. All subjects gave written informed consent.

Patients and methods

PERSIST-AVR is a multicenter, prospective, randomized, open label, interventional post-market trial, with a parallel assignment schema. The design of the study has been previously published (16). For the record, 910 patients underwent randomization (1:1 blocked randomization). The choice of the surgical bioprosthesis in the stented valve arm was left to the discretion of the surgeon. Patients were enrolled 47 sites in in Europe, Canada, United States, Chile, and Israel from March 2016 to September 2018. Clinical, echocardiographic and blood test outcomes were collected preoperatively, at discharge and at each follow up (1 year follow up completed).

Statistical Analyses

Categorical variables are presented as absolute number and percentages. Continuous variables are described by the mean (± standard deviation). The actual treatment population was the analysed population. Cumulative freedom from events have been evaluated using the method of Kaplan-Meier. Comparison of curves among arms has been performed with the log-rank test. Multivariable analysis on Perceval and Stented cohorts was run to identify possible independent risk factors associated with occurrence of PPI. Selection of analyzed variables were based on previous literature reporting on potentials factors influencing PPI rate (12-13). The following variables were considered potential predictors of PPI: valve size (M, L, XL), age, female sex, surgical approach by full sternotomy, concomitant procedure and pre-operative

conduction disorder. Multiple logistic regression models with simultaneous consideration of all clinically relevant variables (covariates) that influence the PPI rates was used. After four steps, the Backward selection reached a model fit with p=0.994 (higher better) leading to the inclusion of only 2 covariates of interest into the final model (valve size and preoperative conduction). Every covariate with a cut off p-values >0.1 were excluded from the final model by the Backward selection. Valve size S were use as reference and corresponded to the intercept.

Results

A total of 914 patients were enrolled, and 910 underwent randomization, at 47 international centers. The actual treatment population consists of 450 patients with Perceval valve implanted and 446 with a traditional stented valve implanted. The population in the primary outcome analysis (per protocol) involved 819 patients, 407 in the sutureless group and 412 in the stented group (17). The actual treatment population consists of 450 patients with a Perceval valve implanted and 446 with a traditional stented valve implanted.

Preoperative patient profiles are reported in **Table 1**, demonstrating no significant differences in pre-operative risk (Euroscore II/ STS Score) and baseline characteristics between Perceval and stented valve cohorts. Operative data are summarized in **Table 2**. A mini-sternotomy approach was used in almost 50% of the patients in both groups. The number of concomitant procedures was also well balanced between the two cohorts. Most patients were successfully implanted at the first attempt in both groups. In the stented valves group, there were 10 cases where the valve was not successfully implanted, due to valve deficiency discovered after implant, sizing, positioning difficulties, anatomical patient features. In the Perceval group, there were 5 cases of valves not successfully implanted due to valve deficiency observed at first attempt in 4 patients and one sizing issue.

The incidence of early PPI was significantly higher in the Su-AVR group in the perioperative phase (10,4%, 47 patients in the Su-AVR group versus 3,1%, 14 patients in the stented group), while the rate after hospital discharge, up to 1-year follow-up, showed no difference (2,3%, 10 patients in the Su-AVR group versus 1,4%, 6 patients in the stented

group). The incidence of early PPI in the Perceval group was higher according to the prosthesis size (4.9% in size S; 6.8% in size M; 7.3% in size L; 21.6% in size XL). The logistic regression analysis in the Perceval group showed significantly higher risk of PPI with size XL compared to each individual valve sizes (OR 0.272 vs size S, 0.334 vs size M, 0.408 vs size L), but equivalent risk of PPI rates for all other combination of valve sizes (**Figure 1**). The multivariable analysis (**Tables 3, 4**) showed that PPI prevalence correlated with valve size XL (p=0.0119) and preoperative conduction disturbances (p=0.0179) in the Perceval group. No relevant PPI predictors were found in the SAVR cohort (**Tables 5, 6**).

Discussion

We report the results of a prospective, randomized, open-label, non-inferiority trial comparing patients with severe symptomatic aortic valve stenosis undergoing surgical aortic valve replacement, with or without concomitant procedures treated with conventional stented tissue valves versus Perceval sutureless valves, with respect to post-operative conduction disturbances requiring PPI. The findings of the present study can be summarized as followed: (i) Perioperative PPI rate was significantly higher in the Su-AVR, (ii) no difference was found for PPI in the post-hospital discharge period up to 1-year follow-up, (iii), pre-operative conduction disturbances and valve size XL were independent predictors of post-operative PPI in the Su-AVR group, (iv) the others combinations of valve size did not show statistical difference for PPI rates in the Su-AVR group.

In our cohort, the rate of PPI after Su-AVR was in accordance with previously published experiences (18-19). Notwithstanding, in the SAVR cohort, post-operative PPI was rather low, if compared with available data in the literature (10, 20-21). Recently, Beretta and colleagues (22), in their comparison of 243 patients undergoing rapid-deployment valve replacement versus conventional SAVR, showed that the rate of PPI was more than four-fold higher in the rapid-deployment group (10.5% versus 2.1%). The mechanisms of atrio-ventricular conduction disturbances after Su-AVR leading to PPI is not definitively elucidated yet. Lam and colleagues (23) investigated a potential learning-curve effect leading to more PPI after Su-AVR. However,

231 the recent serie of Mikus et al (24), emphasized the role of the surgeon's experience in the
232 post-operative need for PPI after Perceval implant.

233 Pre-operative conduction disorders have already been shown as important predictive
234 factors for PPI after Su-AVR. Specifically, Coti and colleagues identified a right bundle branch
235 block as a risk factor for post-operative PPI in patients receiving a rapid-deployment aortic
236 valve (25). In the present trial, preoperative conduction disturbances were predictive factors
237 for post-operative PPI in the Su-AVR group. Also, in the recent retrospective serie of Szecel
238 and colleagues (26), involving 468 patients receiving Perceval valve, the PPI rate was 7.9% in
239 the overall population while it was only 3.9% in the subgroup of patients without preexisting
240 conduction or rhythm disorders. Additionally, Paparella and colleagues (27), in their analysis
241 of a centralized database involving 11 centers from Italy, found no increased risk of PPI in the
242 Perceval group with respect to the conventional SAVR after adjustment for the presence of
243 pre-operative rhythm disturbances. This emphasizes the potential key role of baseline
244 conduction disturbances in developing further atrio-ventricular conduction defects leading to
245 PPI.

246 In our study, the use of a valve size XL in the Su-AVR group was an independent
247 predictor of post-operative PPI, while the other valve sizes in the Su-AVR group did not show
248 statistical difference for PPI rates compared to stented valves. This finding is in accordance
249 with the findings by Toledano and colleagues (18), who observed, in their analysis of 140
250 patients receiving a Perceval implant, a trend towards higher new-onset atrio-ventricular block
251 with greater sutureless prosthesis size. Indeed, larger valves sizes may have larger sealing
252 collars compared to smaller size, leading to more post-operative PPI (28). Moreover, the depth
253 of the guiding suture for placing the valve may have a negative impact on post-SuAVR PPI, as
254 a recent modified insertion of the guiding suture at the base of the aortic annulus has shown
255 to confer lower PPI when using a Perceval valve (29). Indeed, the greatest sub-annular
256 protrusion when using a Perceval valve size XL with respect to smaller valve sizes may explain
257 the compression of the conduction systems during deployment of such valve size and the
258 consequent post-operative need for PPI (28,29). Additionally, results from a European

multicenter experience (30) showed a lower incidence of PPI after Su-AVR when using a Perceval valve size S. As the increased PPI rate for sutureless appears to be size-dependent with a higher rate for XL size (showing the greatest sub-annular protrusion), the next generation design (Perceval PLUS), with adapted design to reduce sub-annular valve collar protrusion, should be able to address this crucial aspect. Further clinical investigations are therefore required to evaluate the influence of the new Perceval valve design on this peculiar aspect.

Limitations

Several limitations of this study have to be underlined. This study was performed in a selected, non-consecutive study population, leading to potentials bias. The statistical regression was performed on the two separated cohorts, and not on the entire population, as the "same valve size" is hardly comparable in the two cohorts. The decision about valve size was left to the discretion of the performing surgeon and the indication for PPI was decided by the treating physician from each centers, without consensus across centers. Also, the surgical technique may differ across involved centers and surgeons.

Conclusions

In conclusion, the increased PPI rate for Su-AVR appears to be size-dependent with a higher rate for size XL. The combination of preoperative conduction disorder and a size XL can lead to a higher probability of early PPI in Su-AVR.

Funding statement

This research project was funded by CORCYM S.r.l.

Conflict of interest statement

Dr. Roberto Lorusso is a consultant for Medtronic, Getinge and LivaNova and an Advisory Board Member of Eurosets; all honoraria are paid to the University for research support.

Martin Andreas has received institutional research funding (Edwards, Abbott, Medtronic, LSI), and has served as a proctor/speaker/consultant (Edwards, Abbott, Medtronic).

Data Availability Statement

The data underlying this article are available in the article.

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Table 1. Baseline characteristics

Table 2. Operative data characteristics

Table 3. Predictors of PPI in the Perceval group **:** Multivariable logistic regression after Backward selection in all variables.

Table 4. Predictors of PPI in the Perceval group : Multivariable logistic regression after Backward selection in valves sizes.

Table 5. Predictors of PPI in the stented valve group: Multivariable logistic regression after Backward selection in all variables.

Table 6. Predictors of PPI in the stented valve group: Multivariable logistic regression after Backward selection in valves sizes.

Figures Legend

Figure 1. Forest plot. Odds ratio PPI early event by valve size (Perceval).

414 **Table 1**. Baseline characteristics
415

	PERCEVAL (n=450)	**STENTED (n=446)**
Age	75.5 ± 5.7	75.0 ± 6.2
Female sex	234 (52.0%)	189 (42.4%)
STS score	2.4 ± 1.8	2.1 ± 1.3
STS score High (>8)	12 (2.7)	1 (0.2)
STS Intermediate (4-8)	33 (7.3)	30 (6.7)
STS Low (<4)	395 (87.8)	407 (91.3)
EuroSCORE II	2.2 ± 1.9	2.0 ± 1.4
NYHA Class		
NYHA I	0	0
NYHA II	290 (64.4)	284 (63.7)
NYHA III	152 (33.8)	158 (35.4)
NYHA IV	7 (1.6)	2 (0.4)
Comorbid conditions		
Systemic Hypertension	370 (82.2%)	360 (80.7%)
Dyslipidemia	251 (55.8%)	283 (63.5%)
Diabetes	125 (27.8%)	123 (27.6%)
Tobacco User	98 (21.8%)	130 (29.1%)
Coronary Artery Disease	181 (40.2%)	162 (36.3%)
Chronic Lung Disease	54 (12.0%)	45 (10.1%)
Neoplasia	37 (8.2%)	38 (8.5%)
Pulmonary Hypertension	33 (7.3%)	41 (9.2%)
Peripheral Vascular Disease	34 (7.6%)	34 (7.6%)
Angina	68 (15.1%)	54 (12.1%)
Carotid Artery disease	50 (11.1%)	55 (12.3%)

Heart Failure	23 (5.1%)	26 (5.8%)
Transient Ischemic Attack (TIA)	21 (4.7%)	6 (1.3%)
Stroke	22 (4.9%)	13 (2.9%)
Myocardial Infarction	19 (4.2%)	17 (3.8%)
Endocarditis	1 (0.2%)	1 (0.2%)
Previous cardiovascular procedures	50 (11.1%)	61 (13.7%)
CABG	1 (0.2%)	2 (0.4%)
PCI	40 (8.9%)	52 (11.7%)
Pulse generator implant	9 (2.0%)	10 (2.2%)
Arrhythmia treatment	1 (0.2%)	3 (0.7%)
Site-reported pre-operative hemodynamic data		
Mean pressure gradient (mmHg)	52.1 ± 15.2	46.6 ± 11.3
Peak pressure gradient (mmHg)	82.7 ± 24.9	75.8 ± 17.5
Effective orifice area (cm^2)	0.7 ± 0.2	0.7 ± 0.2

Values are mean ± standard deviation, n (%).

CABG : coronary artery bypass grafting; PCI : percutaneous coronary intervention

Table 2. Operative data characteristics

	PERCEVAL (n=450)	STENTED (n=446)
Operative characteristics		
Surgical approach		
Full sternotomy	222 (49.3%)	236 (52.9%)
Mini-sternotomy	228 (50.7%)	210 (47.1%)
Bicuspid aortic valve†	47 (10.4%)	54 (12.1%)
Valve size		
S (21 mm)	41 (9.1%)	NA
M (23 mm)	147 (32.7%)	NA
L (25 mm)	151 (33.6%)	NA
XL (27 mm)	111 (24.7%)	NA
19 mm	NA	22 (4.9%)
21 mm	NA	125 (28.0%)
23 mm	NA	183 (41.0%)
25 mm	NA	104 (23.3%)
27 mm	NA	11 (2.5%)
29 mm	NA	1 (0.2%)
Concomitant procedures	136 (30.2%)	127 (28.5%)
CABG	108 (24.0%)	98 (22.0%)
Septal myectomy	17 (3.8%)	14 (3.1%)
Aortic annulus enlargment	0 (0.0%)	4 (0.9%)
Other	18 (4.0%)	24 (5.4%)

†Sievers type 1 only allowed per protocol..

CABG: coronary artery bypass graft. NA: not applicable

Table 3. Predictors of PPI in the Perceval group **:** Multivariable logistic regression after Backward selection in all variables.

	Intercept	Valve size S (reference)	Valve size M	Valve size L	Valve size XL	Age	Female sex	Surgical Approach Full Sternotomy	No Concomittant Procedure	No Preoperative Conduction Disorders
Estimate	-2.6485	0	-0.2945	-0.0971	0.7762	0.0119	0.1153	0.1561	0.1288	-0.5999
Standard Error	2.0229	.	0.2964	0.2775	0.3079	0.0263	0.1913	0.1759	0.1922	0.1705
p-values	0.1904	.	0.3203	0.7264	0.0117	0.6497	0.5465	0.3749	0.5028	0.0004

PPI = Permanent Pacemaker Implant

Table 4. Predictors of PPI in the Perceval group : Multivariable logistic regression after Backward selection in valves sizes.

	Intercept	Valve size reference (S)	Valve size XL	No preoperative conduction disorders
Estimate	-1.4105	0	0.9499	-1.0846
Standard error	0.4379	.	0.3778	0.4084
p-value	0.0013	.	0.0119	0.0079

PPI = Permanent Pacemaker Implant

Table 5. Predictors of PPI in the stented valve group: Multivariable logistic regression after Backward selection in all variables.

	Intercept	Valve size 19 (mm)	Valve size 21 (mm)	Valve size 23 (mm)	Valve size 25 (mm)	Valve size 27 (mm)	Age	Female sex	Surgical Approach Full Sternotomy	No Concomittant Procedure	No Preoperative Conduction Disorders
Estimate	-4.5532	4.6357	3.7638	3.4448	3.816	-7.2384	-0.0357	-0.1852	0.882	0.5488	-0.241
Standard Error	201.8187	201.8006	201.7997	201.7995	201.7997	321.9024	0.0374	0.3153	0.2976	0.3014	0.2773
p-values	0.982	0.9817	0.9851	0.9864	0.9849	0.9821	0.3401	0.5571	0.003	0.0686	0.3848

PPI = Permanent Pacemaker Implant

Table 6. Predictors of PPI in the stented valve group: Multivariable logistic regression after Backward selection in valves sizes.

	Intercept	Surgical Approach Full Sternotomy	No Concomittant Procedure
Estimate	-5.0826	1.7254	1.175
Standard Error	0.7693	0.5865	0.5896
p-values	0	0.0033	0.0463

PPI = Permanent Pacemaker Implant

TITLE PAGE

Pacemaker Implant after Sutureless or Stented Valve: Results From a Controlled Randomized Trial

Running Head/Short title: Pacemaker Implant in the PERSIST-Trial

Roberto Lorusso[1,2]*, MD, PhD, Justine M Ravaux[1,2]*, MD, Francesco Pollari[3], MD, PhD, Thierry A Folliguet[4], MD, PhD, Utz Kappert[5], MD, PhD, Bart Meuris[6], MD, PhD, Malakh L Shrestha[7], MD, Eric E Roselli[8], MD, Nikolaos Bonaros[9], MD, PhD, Olivier Fabre[10,11], MD, PhD, Pierre Corbi[12], MD, PhD, Giovanni Troise[13], MD, Martin Andreas[14], MD, PhD, Frederic Pinaud[15], MD, Steffen Pfeiffer[3], MD, Sami Kueri[16,17], MD, Erwin Tan[18], MD, PhD, Pierre Voisine[19,20], MD, Evaldas Girdauskas[21], MD, Filip Rega[6,22], MD, PhD, Julio Garcia-Puente[23], MD, Theodor Fischlein[3], MD, PhD, on behalf the PERSIST-AVR Investigators

*Equally contributors

[1] Cardio-Thoracic Surgery Department, Heart & Vascular Centre, Maastricht University Medical Center + (MUMC+), Maastricht, The Netherlands

[2] Cardiovascular Research Institute Maastricht (CARIM), Maastricht, The Netherlands

[3] Cardiac Surgery, Cardiovascular Center, Paracelsus Medical University-Klinikum Nürnberg, Nuremberg, Germany

[4] Department of Cardiac Surgery & Transplantation, Assistance Publique, Höpital Henri Mondor, Université Paris 12 UPEC, France

[5] Department of Cardiac Surgery, Dresden Heart Centre University Hospital, Dresden University of Technology, Dresden, Germany

[6] Cardiac Surgery Department, Universitaire Ziekenhuizen Leuven, Leuven, Belgium

[7] Department of Thoracic and Cardiovascular Surgery, Hannover Medical School, Hannover, Germany

[8] Thoracic and Cardiovascular Surgery, Cleveland Clinic, Cleveland, Ohio, United States

[9] Department of Cardiac Surgery, Innsbruck Medical University, Innsbruck, Austria

[10] Department of Cardiac Surgery of Artois, Hospital Center of Lens, Lens, France

[11] Private Hospital of Bois-Bernard, Ramsay Santé, France

[12] Department of Thoracic and Cardiovascular Surgery, Cardio-Vascular Center, University Hospital of Poitiers, Poitiers, France

[13] Division of Cardiac Surgery, Poliambulanza Foundation, Brescia, Italy

[14] Department of Cardiac Surgery, Medical University of Vienna, Vienna, Austria

[15] Department of Cardiac Surgery, CHU d'Angers, University Hospital Angers, Angers, France

[16] Department of Cardiovascular Surgery, University Heart Center Freiburg Bad Krozingen, Bad Krozingen, Germany

[17] Medical Faculty, Albert-Ludwigs-University Freiburg, Freiburg, Germany

[18] Department of Cardiothoracic Surgery, Catharina Hospital, Eindhoven, The Netherlands

[19] Department of Surgery, Université Laval, Québec City, Québec, Canada

[20] Division of Cardiac Surgery, Department of Cardiology, Institut Universitaire de Cardiologie et de Pneumologie de Québec (IUCPQ), Québec City, Québec, Canada

[21] Department of Cardiovascular Surgery, University Heart and Vascular Center Hamburg, Hamburg, Germany

[22] Division of Experimental Cardiac Surgery, Department of Cardiovascular Sciences, University of Leuven, Leuven, Belgium

[23] Department of Cardiac Surgery, Hospital Universitario Virgen de la Arraixaca, Murcia, Spain.

Meeting Presentation: e-poster at the Society of Thoracic Surgeons
57th Annual Meeting
Austin, Texas, The United States

Classification: Original article

Total Word count: 4463 words

Corresponding author: Justine Mafalda Ravaux, MD

Cardio-Thoracic Surgery Department, Heart & Vascular Center

Maastricht University Medical Centre (MUMC+)

Cardio vascular Research Institute Maastricht (CARIM)

P. Debyelaan, 25 – 6202 AZ - Maastricht – The Netherlands

Tel. +31 43 3995636 – Fax: +31 43 3995004 – Email: jmravaux@hotmail.com

VISUAL ABSTRACT

Key question

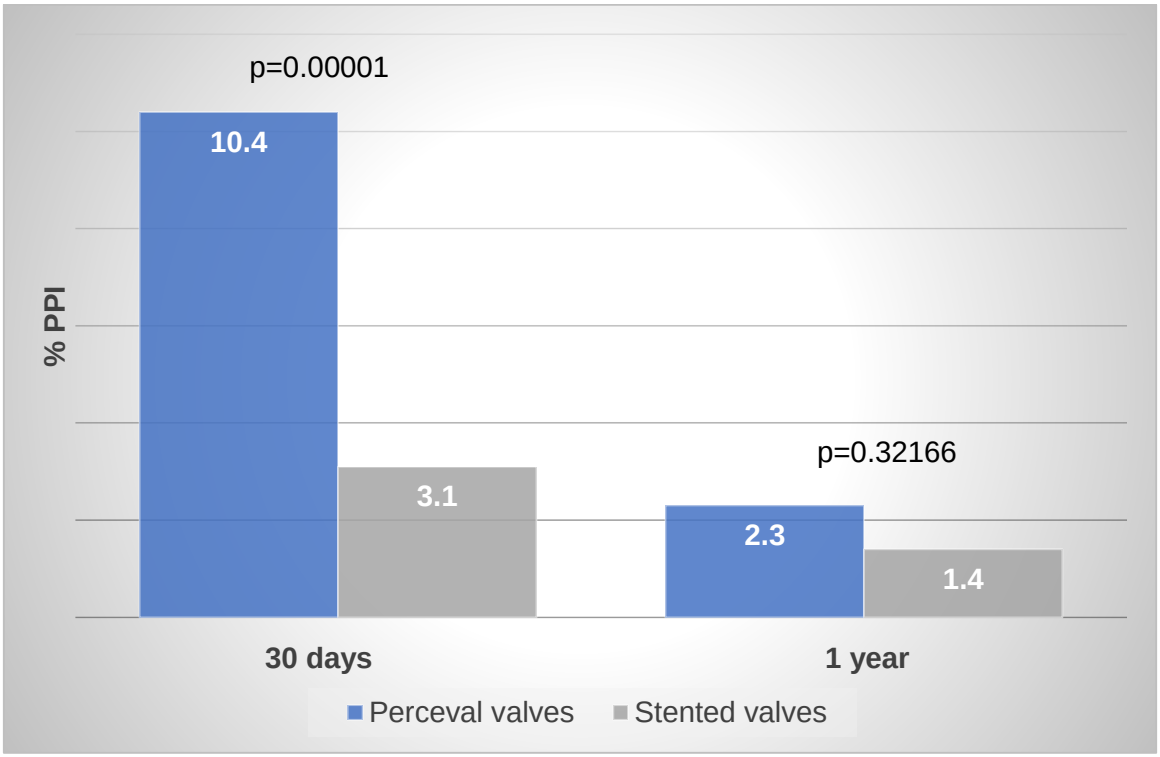
Is permanent pacemaker implantation (PPI) more frequent after sutureless aortic valve replacement (Su-AVR)?

Key Finding(s)

The increased PPI rate after Su-AVR group correlated with valve size XL and preoperative conduction disorder.

Take-home message

PPI is a frequent complication post-Su-AVR. Patients with larger valve size and preoperative arrhythmias should be monitored carefully.



PPI= Permanent Pacemaker Implant

STRUCTURED ABSTRACT

Objectives

Sutureless aortic valves demonstrated non-inferiority to standard stented valves for major cardiovascular and cerebral events at 1 year after aortic valve replacement (AVR). We aim to assess the factors correlating with permanent pacemaker implant (PPI) in both cohorts.

Methods

PERSIST-AVR is a prospective, randomized, open-label trial. Patients undergoing AVR were randomized to receive a sutureless (Su-AVR) or stented sutured bioprosthesis (SAVR). Multivariable analysis was performed to identify possible independent risk factors associated with PPI. A logistic regression analysis was performed to estimate the risk of PPI associated to different valve size.

Results

The two groups (Su-AVR; n= 450, SAVR n=446) were well balanced in terms of preoperative risk factors. Early PPI rates were 10.4% in Su-AVR and 3.1% in SAVR groups. PPI prevalence correlated with valve size XL (p=0.0119) and preoperative conduction disturbances (p=0.0079) in the Su-AVR group. No predictors were found in the SAVR cohort. Logistic regression analysis showed a significantly higher risk for PPI with size XL compared to each individual sutureless valve sizes (OR 0.272 vs size S (95%confidence interval 0.07-0.95), 0.334 vs size M (95%CI 0,16-0;68), 0.408 vs size L (95%CI 0,21-0.81)) but equivalent risk of PPI rates for all other combination of valve sizes.

Conclusions

Su-AVR is associated with higher PPI rate as compared to SAVR. However, the increased PPI rate appears to be size-dependent with significant higher rate only for size XL. The combination of preoperative conduction disorder and a size XL can lead to a higher probability of early PPI in Su-AVR.

Abstract words count: 250

ClinicalTrials.gov: NCT02673697

Keywords: aortic valve replacement – pacemaker – sutureless valves

TEXT

Introduction

The comparison between sutureless valves and standard stented valves has been investigated in previous studies, demonstrating decreased cross-clamp time using the Perceval prosthesis and similar results for major cardiovascular and cerebral events over the short to mid-term follow-up (1-3). The Perceval sutureless aortic valve (CORCYM, Saluggia, Italy) is a bovine pericardial valve nitinol-stent mounted offering an alternative to traditional flexible prostheses (4). Higher permanent pacemaker implantation (PPI) rate after sutureless valve has been already highlighted although with a wide range of occurrence of such perioperative event (5-7) Indeed, recent studies report a PPI rate after sutureless aortic valve replacement (Su-AVR) from 3% to 13.3% (5-7), while the incidence of conduction disorders leading to PPI after aortic valve replacement with a stented valves (SAVR) varies between 3 and 7% (8-10). However, the identification of predictive factors associated with PPI remains still controversial (11). A recent meta-analysis demonstrated a twofold greater risk of PPI after rapid deployment prosthesis (including Su-AVR) than in a SAVR cohort (12), independently of the type of the valve used. The impact of post-operative PPI on late morality after Su-AVR is still under investigation (13) and the matter of PPI after Su-ARV might represent a limitation for an extended use of sutureless valves despite shorter operative times, and enhancement of minimally-invasive procedures (14). Nevertheless, data from international registry as "Sutureless and Rapid Deployment International Registry" show a temporal decreasing trend in PPI after Su-AVR (15). However, dedicated, objective, and in-depth analysis of such an issue has been lacking. The aim of the present study was, therefore, to assess the incidence and related factors correlated with PPI after either Su-AVR and SAVR in a prospective, randomized study.

Methods

Ethical Statement

Ethical approval was provided by the local ethics committee before patient recruitment (Medical Ethics Research Committee, 151138). The study was registered at clinical-trials.gov (NCT02673697) and performed in accordance with the declaration of Helsinki. All subjects gave written informed consent.

Patients and methods

PERSIST-AVR is a multicenter, prospective, randomized, open label, interventional post-market trial, with an adaptative design. The design of the study has been previously published (16). The trial was conceived to demonstrate the non-inferiority of the Perceval sutureless prosthesis compared with standard aortic valves, using a conventional or minimally invasive approach, in patients with severe symptomatic aortic valve stenosis. Details about the organization of the trial and a list of participating centers are provided in the supplementary Appendix 1. The protocol was developed in collaboration with the Steering Committee and was approved by the institutional review board or medical ethic committee at each center. All patients provided written inform consent. CORCYM S.r.l. funded all trial-related activities, participated in site selection, and supported data monitoring, trial management, and statistical analysis. An independent clinical events committee adjudicated all clinical events related to the primary and secondary outcomes. For the record, 910 patients underwent randomization (1:1 blocked randomization). Additional information on the methods is provided in the supplementary Appendix 2. The choice of the surgical bioprosthesis in the stented valve arm was left to the discretion of the surgeon. Patients were enrolled 47 sites in in Europe, Canada, United States, Chile, and Israel from March 2016 to September 2018. Clinical, echocardiographic and blood test outcomes were collected preoperatively, at discharge and at each follow up (1 year follow up completed). This study is a sub-study of the PERSIST-AVR trial, especially focusing on the issue of post-operative PPI.

Statistical Analyses

Categorical variables are presented as absolute number and percentages. Continuous variables are described by the mean (± standard deviation). The actual treatment population, defined as all randomized and implanted patients according to the "as-treated' principle, was the analysed population. Multivariable analysis on Perceval and Stented cohorts was run to identify possible independent risk factors associated with occurrence of PPI. Selection of analyzed variables were based on previous literature reporting on potentials factors influencing PPI rate (12-13). The following variables were considered potential predictors of PPI: valve size (M, L, XL), age, female sex, surgical approach by full sternotomy, concomitant procedure and pre-operative conduction disorder. Pre-operative conduction disorders were identified in the presence of sinus dysfunction, atrio-ventricular blocks and intra-ventricular blocks (e.g. left and/or right bundle branch block) at the pre-operative electrocardiogram. A pooled modeling was considered not appropriate due to the different sizes of the two groups (sutureless and stented valves). Multiple logistic regression models with simultaneous consideration of all clinically relevant variables (covariates) that influence the PPI rates was used. After four steps, the Backward selection reached a model fit with p=0.994 (higher better) leading to the inclusion of only 2 covariates of interest into the final model (valve size and preoperative conduction). Every covariate with a cut off p-values >0.1 were excluded from the final model by the Backward selection. Valve size S were use as reference and corresponded to the intercept.

Results

A total of 914 patients were enrolled, and 910 underwent randomization; 453 patients were assigned to the sutureless group and 457 to the stented group. After randomization, 12 patients were not implanted, two were implanted with a non-study valve and 59 patients (28 patients in the sutureless and 31 patients in the stented group) crossed over to the other study arm. Supplementary tables report, respectively, the reasons for not implanting the valve (table S1) and the reasons for crossovers (table S2). The actual treatment population therefor

consists of 450 patients with Perceval valve implanted and 446 with a traditional stented valve implanted, while the population in the primary outcome analysis (per protocol) involved 819 patients, 407 in the sutureless group and 412 in the stented group (17). The actual treatment population consists of 450 patients with a Perceval valve implanted and 446 with a traditional stented valve implanted.

Preoperative patient profiles are reported in **Table 1**, demonstrating no significant differences in pre-operative risk (Euroscore II/ STS Score) and baseline characteristics between Perceval and stented valve cohorts. Operative data are summarized in **Table 2**. A mini-sternotomy approach was used in almost 50% of the patients in both groups. The number of concomitant procedures was also well balanced between the two cohorts. Most patients were successfully implanted at the first attempt in both groups. In the stented valves group, there were 10 cases where the valve was not successfully implanted, due to valve deficiency discovered after implant, sizing, positioning difficulties, anatomical patient features. In the Perceval group, there were 5 cases of valves not successfully implanted due to valve deficiency observed at first attempt in 4 patients and one sizing issue.

The incidence of early PPI was significantly higher in the Su-AVR group in the perioperative phase (10,4%, 47 patients in the Su-AVR group versus 3,1%, 14 patients in the stented group), while the rate after hospital discharge, up to 1-year follow-up, showed no difference (2,3%, 10 patients in the Su-AVR group versus 1,4%, 6 patients in the stented group) (**Central Image**). The incidence of early PPI in the Perceval group was higher according to the prosthesis size (4.9% in size S; 6.8% in size M; 7.3% in size L; 21.6% in size XL). The main indication for PPI was atrio-ventricular block III for both stented (7/14) and Perceval (29/47) groups. Other reasons are reported in the table S3. The logistic regression analysis in the Perceval group showed significantly higher risk of PPI with size XL compared to each individual valve sizes (OR 0.272 vs size S, 0.334 vs size M, 0.408 vs size L), but equivalent risk of PPI rates for all other combination of valve sizes (**Figure 1**). The multivariable analysis (**Tables 3, 4**) showed that PPI prevalence correlated with valve size XL (p=0.0119) and

preoperative conduction disturbances (p=0.0179) in the Perceval group. No relevant PPI predictors were found in the SAVR cohort (**Tables 5, 6**).

Discussion

We report the results of a post-hoc analysis of a prospective, randomized, open-label trial comparing patients with severe symptomatic aortic valve stenosis undergoing surgical aortic valve replacement, with or without concomitant procedures treated with conventional stented tissue valves versus Perceval sutureless valves, with respect to post-operative conduction disturbances requiring PPI. The findings of the present study can be summarized as followed: (i) Perioperative PPI rate was significantly higher in the Su-AVR, (ii) no difference was found for PPI in the post-hospital discharge period up to 1-year follow-up, (iii), pre-operative conduction disturbances and valve size XL were independent predictors of post-operative PPI in the Su-AVR group, (iv) the others combinations of valve size did not show statistical difference for PPI rates in the Su-AVR group.

In our cohort, the rate of PPI after Su-AVR was in accordance with previously published experiences (18-19). Notwithstanding, in the SAVR cohort, post-operative PPI was rather low, if compared with available data in the literature (10, 20-21). Recently, Beretta and colleagues (22), in their comparison of 243 patients undergoing rapid-deployment valve replacement versus conventional SAVR, showed that the rate of PPI was more than four-fold higher in the rapid-deployment group (10.5% versus 2.1%). The mechanisms of atrio-ventricular conduction disturbances after Su-AVR leading to PPI is not definitively elucidated yet. Lam and colleagues (23) investigated a potential learning-curve effect leading to more PPI after Su-AVR. However, the recent serie of Mikus et al (24), emphasized the role of the surgeon's experience in the post-operative need for PPI after Perceval implant.

Pre-operative conduction disorders have already been shown as important predictive factors for PPI after Su-AVR. Specifically, Coti and colleagues identified a right bundle branch block as a risk factor for post-operative PPI in patients receiving a rapid-deployment aortic valve (25). In the present trial, preoperative conduction disturbances were predictive factors

for post-operative PPI in the Su-AVR group. Also, in the recent retrospective serie of Szecel and colleagues (26), involving 468 patients receiving Perceval valve, the PPI rate was 7.9% in the overall population while it was only 3.9% in the subgroup of patients without preexisting conduction or rhythm disorders. Additionally, Paparella and colleagues (27), in their analysis of a centralized database involving 11 centers from Italy, found no increased risk of PPI in the Perceval group with respect to the conventional SAVR after adjustment for the presence of pre-operative rhythm disturbances. This emphasizes the potential key role of baseline conduction disturbances in developing further atrio-ventricular conduction defects leading to PPI. In the conventional SAVR group, full sternotomy surgical approach and concomitant procedure were identified as potentials predictors for PPI. However, the number of PPI in the conventional SAVR group (20/446) was too low to reach a powerful clinically analysis.

In our study, the use of a valve size XL in the Su-AVR group was an independent predictor of post-operative PPI, while the other valve sizes in the Su-AVR group did not show statistical difference for PPI rates compared to stented valves. This finding is in accordance with the findings by Toledano and colleagues (18), who observed, in their analysis of 140 patients receiving a Perceval implant, a trend towards higher new-onset atrio-ventricular block with greater sutureless prosthesis size. Indeed, larger valves sizes may have larger sealing collars compared to smaller size, leading to more post-operative PPI (28). Moreover, the depth of the guiding suture for placing the valve may have a negative impact on post-SuAVR PPI, as a recent modified insertion of the guiding suture at the base of the aortic annulus has shown to confer lower PPI when using a Perceval valve (29). Indeed, the greatest sub-annular protrusion when using a Perceval valve size XL with respect to smaller valve sizes may explain the compression of the conduction systems during deployment of such valve size and the consequent post-operative need for PPI (28,29). Additionally, results from a European multicenter experience (30) showed a lower incidence of PPI after Su-AVR when using a Perceval valve size S. As the increased PPI rate for sutureless appears to be size-dependent with a higher rate for XL size (showing the greatest sub-annular protrusion), the next generation design (Perceval PLUS), with adapted design to reduce sub-annular valve collar

protrusion, should be able to address this crucial aspect. Further clinical investigations are therefore required to evaluate the influence of the new Perceval valve design on this peculiar aspect.

Also, post-operative PPI has been shown to be associated with prolonged hospital stay and intensive care unit admission; generating thereby higher cost-related outcomes. The previous work of Robich et al (21) demonstrates from the Nationwide Inpatient Sample Database that mortality rate may be lower in patient receiving post-SAVR PPI but at the costs of higher financial resources and longer hospital length of stay. Reducing post-operative PPI rate may relieve the costs for the care system.

Limitations

Several limitations of this study have to be underlined. This study was performed in a selected, non-consecutive study population, leading to potentials bias. The statistical regression was performed on the two separated cohorts, and not on the entire population, as the “same valve size” is hardly comparable in the two cohorts. The decision about valve size was left to the discretion of the performing surgeon and the indication for PPI was decided by the treating physician from each centers, without consensus across centers. Also, the surgical technique may differ across involved centers and surgeons. Additionally, it would have been interesting to analyze the pacemaker dependency one year after implantation but this information was not collected.

Conclusions

In conclusion, the increased PPI rate for Su-AVR appears to be size-dependent with a higher rate for size XL. The combination of preoperative conduction disorder and a size XL can lead to a higher probability of early PPI in Su-AVR.

Funding statement

This research project was funded by CORCYM S.r.l.

Conflict of interest statement

Dr. Roberto Lorusso is a consultant for Medtronic, Getinge and LivaNova and an Advisory Board Member of Eurosets; all honoraria are paid to the University for research support.

Martin Andreas has received institutional research funding (Edwards, Abbott, Medtronic, LSI), and has served as a proctor/speaker/consultant (Edwards, Abbott, Medtronic).

Data Availability Statement

The data underlying this article are available in the article.

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Tables Legends

Table 1. Baseline characteristics

Table 2. Operative data characteristics

Table 3. Predictors of PPI in the Perceval group **:** Multivariable logistic regression after Backward selection in all variables.

Table 4. Predictors of PPI in the Perceval group : Multivariable logistic regression after Backward selection in valves sizes.

Table 5. Predictors of PPI in the stented valve group: Multivariable logistic regression after Backward selection in all variables.

Table 6. Predictors of PPI in the stented valve group: Multivariable logistic regression after Backward selection in valves sizes.

Figures Legends

Central Image. Rate of early (0-30 days from surgery) and late (1 year follow-up) permanent pacemaker implant (PPI) in both group.

Figure 1. Forest plot. Odds ratio PPI early event by valve size (Perceval).

447 **Table 1**. Baseline characteristics
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	PERCEVAL (n=450)	**STENTED (n=446)**
Age	75.5 ± 5.7	75.0 ± 6.2
Female sex	234 (52.0%)	189 (42.4%)
STS score	2.4 ± 1.8	2.1 ± 1.3
STS score High (>8)	12 (2.7)	1 (0.2)
STS Intermediate (4-8)	33 (7.3)	30 (6.7)
STS Low (<4)	395 (87.8)	407 (91.3)
EuroSCORE II	2.2 ± 1.9	2.0 ± 1.4
NYHA Class		
NYHA I	0	0
NYHA II	290 (64.4)	284 (63.7)
NYHA III	152 (33.8)	158 (35.4)
NYHA IV	7 (1.6)	2 (0.4)
Comorbid conditions		
Systemic Hypertension	370 (82.2%)	360 (80.7%)
Dyslipidemia	251 (55.8%)	283 (63.5%)
Diabetes	125 (27.8%)	123 (27.6%)
Tobacco User	98 (21.8%)	130 (29.1%)
Coronary Artery Disease	181 (40.2%)	162 (36.3%)
Chronic Lung Disease	54 (12.0%)	45 (10.1%)
Neoplasia	37 (8.2%)	38 (8.5%)
Pulmonary Hypertension	33 (7.3%)	41 (9.2%)
Peripheral Vascular Disease	34 (7.6%)	34 (7.6%)
Angina	68 (15.1%)	54 (12.1%)
Carotid Artery disease	50 (11.1%)	55 (12.3%)

Heart Failure	23 (5.1%)	26 (5.8%)
Transient Ischemic Attack (TIA)	21 (4.7%)	6 (1.3%)
Stroke	22 (4.9%)	13 (2.9%)
Myocardial Infarction	19 (4.2%)	17 (3.8%)
Endocarditis	1 (0.2%)	1 (0.2%)
Previous cardiovascular procedures	50 (11.1%)	61 (13.7%)
CABG	1 (0.2%)	2 (0.4%)
PCI	40 (8.9%)	52 (11.7%)
Pulse generator implant	9 (2.0%)	10 (2.2%)
Arrhythmia treatment	1 (0.2%)	3 (0.7%)
Site-reported pre-operative hemodynamic data		
Mean pressure gradient (mmHg)	52.1 ± 15.2	46.6 ± 11.3
Peak pressure gradient (mmHg)	82.7 ± 24.9	75.8 ± 17.5
Effective orifice area (cm^2)	0.7 ± 0.2	0.7 ± 0.2

Values are mean ± standard deviation, n (%).

CABG : coronary artery bypass grafting; PCI : percutaneous coronary intervention

Table 2. Operative data characteristics

	PERCEVAL (n=450)	STENTED (n=446)
Operative characteristics		
Surgical approach		
Full sternotomy	222 (49.3%)	236 (52.9%)
Mini-sternotomy	228 (50.7%)	210 (47.1%)
Bicuspid aortic valve†	47 (10.4%)	54 (12.1%)
Valve size		
S (21 mm)	41 (9.1%)	NA
M (23 mm)	147 (32.7%)	NA
L (25 mm)	151 (33.6%)	NA
XL (27 mm)	111 (24.7%)	NA
19 mm	NA	22 (4.9%)
21 mm	NA	125 (28.0%)
23 mm	NA	183 (41.0%)
25 mm	NA	104 (23.3%)
27 mm	NA	11 (2.5%)
29 mm	NA	1 (0.2%)
Concomitant procedures	136 (30.2%)	127 (28.5%)
CABG	108 (24.0%)	98 (22.0%)
Septal myectomy	17 (3.8%)	14 (3.1%)
Aortic annulus enlargment	0 (0.0%)	4 (0.9%)
Other	18 (4.0%)	24 (5.4%)

†Sievers type 1 only allowed per protocol..

CABG: coronary artery bypass graft. NA: not applicable

Table 3. Predictors of PPI in the Perceval group **:** Multivariable logistic regression after Backward selection in all variables.

	Intercept	Valve size S (reference)	Valve size M	Valve size L	Valve size XL	Age	Female sex	Surgical Approach Full Sternotomy	No Concomittant Procedure	No Preoperative Conduction Disorders
Estimate	-2.6485	0	-0.2945	-0.0971	0.7762	0.0119	0.1153	0.1561	0.1288	-0.5999
Standard Error	2.0229	.	0.2964	0.2775	0.3079	0.0263	0.1913	0.1759	0.1922	0.1705
p-values	0.1904	.	0.3203	0.7264	0.0117	0.6497	0.5465	0.3749	0.5028	0.0004

PPI = Permanent Pacemaker Implant

Table 4. Predictors of PPI in the Perceval group : Multivariable logistic regression after Backward selection in valves sizes.

	Intercept	Valve size reference (S)	Valve size XL	No preoperative conduction disorders
Estimate	-1.4105	0	0.9499	-1.0846
Standard error	0.4379	.	0.3778	0.4084
p-value	0.0013	.	0.0119	0.0079

PPI = Permanent Pacemaker Implant

Table 5. Predictors of PPI in the stented valve group: Multivariable logistic regression after Backward selection in all variables.

	Intercept	Valve size 19 (mm)	Valve size 21 (mm)	Valve size 23 (mm)	Valve size 25 (mm)	Valve size 27 (mm)	Age	Female sex	Surgical Approach Full Sternotomy	No Concomittant Procedure	No Preoperative Conduction Disorders
Estimate	-4.5532	4.6357	3.7638	3.4448	3.816	-7.2384	-0.0357	-0.1852	0.882	0.5488	-0.241
Standard Error	201.8187	201.8006	201.7997	201.7995	201.7997	321.9024	0.0374	0.3153	0.2976	0.3014	0.2773
p-values	0.982	0.9817	0.9851	0.9864	0.9849	0.9821	0.3401	0.5571	0.003	0.0686	0.3848

PPI = Permanent Pacemaker Implant

Table 6. Predictors of PPI in the stented valve group: Multivariable logistic regression after Backward selection in valves sizes.

	Intercept	Surgical Approach Full Sternotomy	No Concomittant Procedure
Estimate	-5.0826	1.7254	1.175
Standard Error	0.7693	0.5865	0.5896
p-values	0	0.0033	0.0463

PPI = Permanent Pacemaker Implant

Figure 1

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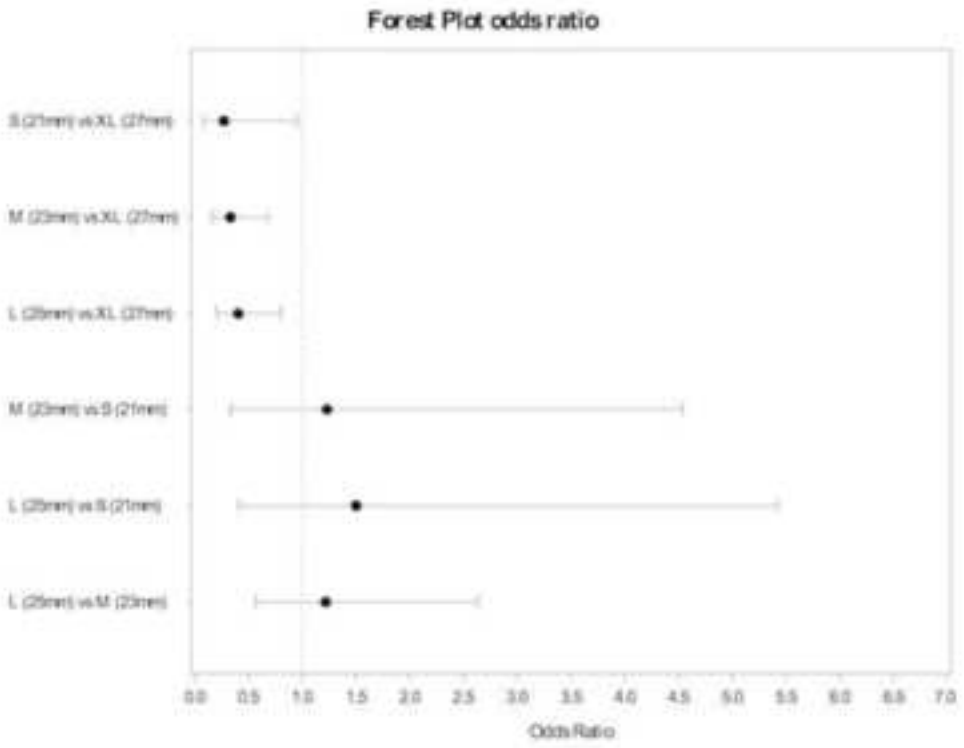

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