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Effectiveness of the new generation transcatheter aortic valve in the real life studies. Review and meta-analysis

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Abstract. – OBJECTIVE: The aim of the meta-analysis was to assess post-procedural outcome of the new generation of transcatheter aortic valve implantation (TAVI) devices, focusing on the transfemoral and balloon-expandable SAPIEN 3 (Edwards Lifesciences Inc., Irvine, CA, USA), the self-expanding CoreValve™ Evolut series R and PRO (R/PRO)™ (Medtronic Inc., Minneapolis, MN, USA) and ACURATE *neo*™ transcatheter aortic valve (Symetis SA, a Boston Scientific company, Ecublens, Switzerland).

MATERIALS AND METHODS: All observational studies were retrieved through PubMed computerized database from January 2014 until June 30th, 2019. The risk difference (RD) with the 95% confidence interval (CI) was used to assess the effectiveness of the intervention under comparison. The primary end point was 30-day mortality. Safety end points included: (i) stroke, (ii) moderate/severe paravalvular leak, and (iii) the need for new permanent pacemaker implantation.

RESULTS: Meta-analysis demonstrated no significant differences as regards to either 30-day mortality or stroke for all the groups of prostheses under comparison. ACURATE *neo* was associated with significantly less new permanent pacemaker implantation compared to SAPIEN 3 (RD: -0.06; 95% CI -0.08 to -0.03; $p<0.0001$; $I^2=0\%$) or to EVOLUT R/PRO (RD: -0.06; 95% CI -0.09 to -0.02; $p=0.0009$; $I^2=0\%$). A significant reduction of new permanent pacemaker need was observed in the group of patients implanted with SAPIEN 3 compared to EVOLUT R/PRO (RD: -0.07; 95% CI -0.09 to -0.04; $p<0.00001$; $I^2=7\%$). The occurrence of moderate/severe leak was significantly increased in the group of patients implanted with ACURATE *neo vs.* SAPIEN 3 (RD: 0.04; 95% CI 0.02 to 0.05; $p<0.00001$; $I^2=0\%$). No significant differences were found between ACURATE *neo vs.* EVOLUT R/PRO (RD: -0.01; 95% CI -0.04 to 0.02; $p=0.69$; $I^2=0\%$) and between SAPIEN 3 *vs.* EVOLUT R/PRO (RD: -0.01; 95% CI -0.04 to 0.01; $p=0.28$; $I^2=73\%$).

CONCLUSIONS: The results of the meta-analysis show that: (1) ACURATE *neo* was associated with significantly less new permanent pacemaker implantation than SAPIEN 3 and EVOLUT R/PRO; (2) SAPIEN 3 had significantly lower occurrence of moderate/severe valvular leak than ACURATE *neo*.

Key Words:
Transcatheter Aortic Valve Implantation, TAVI, TAVR, Aortic stenosis, Prosthetic aortic valves, Meta-analysis.

Introduction

Transcatheter aortic valve implantation (TAVI) is recognized as an effective therapy for the treatment of aortic stenosis in high, intermediate, and even low-risk operable patients[1,2].

Recent randomized trials of TAVI showed that, in patients who were at intermediate or high risk for death with surgery, TAVI was either superior or noninferior to standard therapies, including SAVR[3-14].

As a result of continuous TAVI evolution, several new generation transcatheter heart valves have been developed incorporating features (i.e., lower profile, easier positioning, repositionability, and recoverability) addressed to minimize proce-

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dural complications such as paravalvular regurgitation, valve malpositioning, vascular complications, and conduction disorders and to improve clinical outcomes[15-17].

The aim of the meta-analysis was to compare the clinical outcome of the new generation transcatheter aortic valves, focusing on real life studies, either as a complement to Randomized Controlled Trials (RCTs), and to provide new insight on the "effectiveness" of the treatments administered in everyday clinical practice in patients with severe aortic stenosis, undergoing transfemoral TAVI.

Materials and Methods

This review and meta-analysis were performed in accordance with the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) statement[18].

Study Definition

We searched through PubMed computerized database for observational studies (Obs.) performing a direct comparison of almost two of the newest heart valves: the balloon-expandable SAPIEN 3 (Edwards Lifesciences Inc., Irvine, CA, USA), the self-expanding CoreValve™ Evolut series R, and PRO (R/PRO)™ (Medtronic Inc., Minneapolis, MN, USA) and ACURATE *neo*™ transcatheter aortic prosthesis (Symetis SA, a Boston Scientific company, Ecublens, Switzerland) in patients with severe aortic stenosis undergoing transfemoral TAVI. The reference lists of the retrieved full-text articles were also examined to identify potentially relevant studies not selected by the electronic search. The search was restricted to English-language journals. Studies on patients undergoing direct aortic or transapical TAVI were excluded. The search was performed from January 2014 to June 30th, 2019. Two investigators independently performed the eligibility screening with the aim to include only studies that report 30-day mortality and/or at least one of the safety endpoints under evaluation. In case of disagreement, consensus was obtained after consulting a third reviewer.

Outcomes

The primary end point was 30-day mortality. Safety end points included: (i) stroke, (ii) moderate/severe paravalvular leak, and (iii) the need for new permanent pacemaker implantation. Indeed, to avoid risk of bias, due to unobserved or inaccurately measured confounders, we included in the meta-analysis the data related to the overall population of patients from the selected studies.

Statistical Analysis

The meta-analysis was performed using Review Manager (RevMan) [Computer program] Version 5.3. (Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014) using the risk difference (RD) with the 95% Confidence Interval (CI), and the absolute risk reductions were calculated using the Mantel-Haenszel random-effect model to take into account possible heterogeneity among studies. We performed the analysis using the risk difference instead of the relative risk because the differences between the absolute risks give a better representation of the effectiveness of the interventions under comparison.

We evaluated the effectiveness of the prosthetic implanted valves by comparing the following groups of patients: (i) ACURATE *neo vs.* SAPIEN 3, (ii) ACURATE *neo vs.* EVOLUT R/PRO, and (iii) SAPIEN 3 *vs.* EVOLUT R/PRO.

A Forest plot was used for a graphical presentation of the results. The selected studies were examined to assess the homogeneity/heterogeneity of the results by visually inspecting the CIs of the risk estimates in the different studies and computing the Cochran's Q test and I^2 statistics[19]. A bidirectional α error of ≤ 0.05 was defined as statistically significant.

Results

Of 1,686 studies identified for screening, the systematic review selected 15 Obs.[20-34] that meet the inclusion criteria and were included in the meta-analysis (Figure 1). The selected studies included 9,100 patients. Specifically, ACURATE *neo* was implanted in 2,294 patients, EVOLUT R/PRO in 2,742 patients and SAPIEN 3 in 4,064 patients (Table I). Six studies compared the ACURATE *neo vs.* SAPIEN 3[20-24] and/or EVOLUT R/PRO[21,24,25], and 11 studies SAPIEN 3 *vs.* EVOLUT R/PRO[21,24,26-34]. Two studies included all the TAVI valves under evaluation[21-24]. The characteristics of the selected studies are reported in Table I.

Meta-analysis demonstrated no significant differences as regards to either 30-day mortality and stroke for all the groups of prostheses under comparison. In particular:

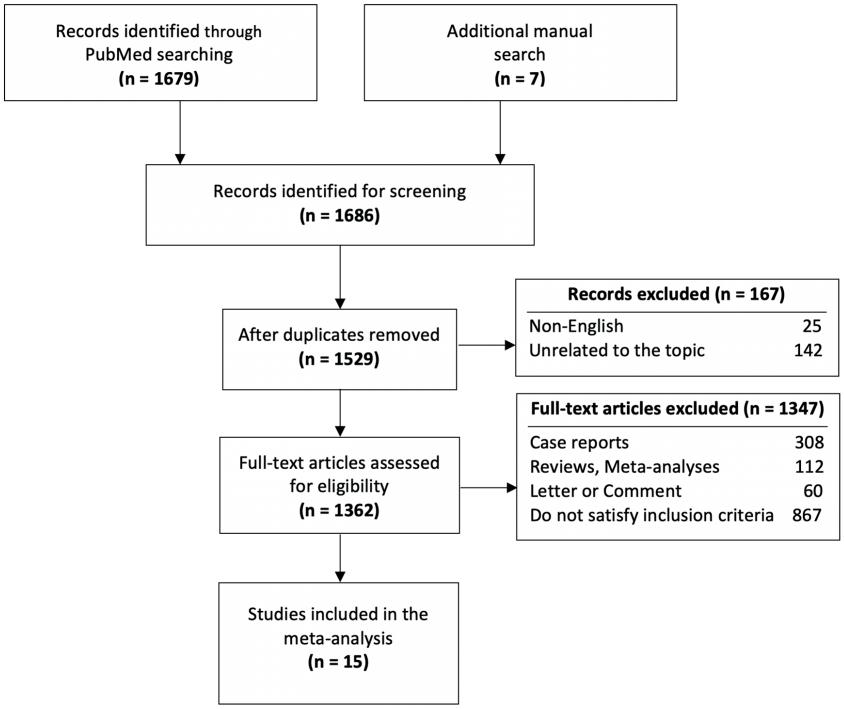

Figure 1. Flow-chart of the study selection process.

- *30-day mortality* was lower, non-significantly, in the comparison between SAPIEN 3 (RD: 0.01; 95% CI -0.01 to 0.02; p=0.31; I^2=0%) or EVOLUT R/PRO (RD: 0.01; 95% CI -0.00 to 0.03; p=0.12; I^2=0%) *vs*. the ACURATE *neo* (Figure 2). Again, a lower mortality, not significant, was observed in the comparison between SAPIEN 3 *vs*. EVOLUT R/PRO (RD -0.00; 95% CI -0.01 to 0.01; p=0.59; I^2=0%) (Figure 2).
- *the occurrence of stroke* was similar in all the comparisons (Figure 3).

Indeed, the need for new permanent pacemaker implantation was significantly reduced in the patients implanted with ACURATE *neo* with respect to SAPIEN 3 (RD: -0.06; 95% CI -0.08 to -0.03; p<0.0001; I^2=0%) and EVOLUT R/PRO (RD: -0.06; 95% CI -0.09 to -0.02; p=0.0009; I^2=0%). A significant lower need for new permanent pacemaker was observed also in patients implanted with SAPIEN 3 compared to EVOLUT R/PRO (RD: -0.07; 95% CI -0.09 to -0.04; p<0.00001; I^2=7%) (Figure 4).

On the contrary, the occurrence of moderate/severe postprocedural leak increased significantly in the comparison between ACURATE *neo vs*. SAPIEN 3 (RD: 0.04; 95% CI 0.02 to 0.05; p<0.00001; I^2=0%) (Figure 5). While the occurrence of postprocedural leak in the comparison between ACURATE *neo vs*. EVOLUT R/PRO was similar (RD: -0.01; 95% CI -0.04 to 0.02; p=0.69; I^2=0%). Also, the comparison between SAPIEN 3 *vs*. EVOLUT R/PRO, did not show significant differences, but high heterogeneity (I^2=73%) values were observed (Figure 5).

Discussion

The technological progress and the most accurate indications to TAVI have not completely solved the post-procedural adverse events, such as the need for new permanent pacemaker implantation[35], the periprosthetic leak[31,36], and stroke[37]. New generation of TAVI devices have been designed to reduce the profile of the delivery catheter, enable repositioning and the ability to recover, facilitate the technical procedure, and reduce TAVI-related complications[17]. However, Evidence-Based Medicine and Clinical Research on their safety and

Table I. Characteristics of the selected studies.

Study	Period	Country	Centre (n)	Design	Transcatheter heart valves				
					Self-expandable			Balloon-expandable	Pts included in the meta-analysis
					ACURATE *neo*	EVOLUT		SAPIEN 3	
						R	PRO		
Ben-Shoshan et al, 2017[27]	December 2014-April 2016	Israel	Single-centre	Retrospective study comparing short-term outcome of pts undergoing TF-TAVI with SAPIEN 3 and EVOLUT R valves.	==	108	==	124	232
Husser et al, 2017[20]	January 2014-January 2016	Germany	Multicentre	A registry-based study comparing THVs, SE ACURATE *neo vs*. BE SAPIEN 3, in terms of device failure and early safety at 30 days.	311	==	==	810	1121
Kim et al, 2017[21]	January 2011-May 2017	Germany	Single-centre	Retrospective study comparing SE *vs*. BE THVs according to the degree of aortic valve calcification.	425	15	==	379	819
Schaefer et al, 2017[23]	2012-2016	Germany	Single-centre	Retrospective study aimed to compare acute 30-day outcomes of ACURATE *neo vs*. SAPIEN 3 THVs.	104	==	==	104	208
Abdelghani et al, 2018[26] (CHOICE-Extend registry)	March 2014 - November 2017	Germany	Single-centre	A registry comparing new generation SE and BE THVs in large *vs*. small aortic valve annulus.	==	100	==	334	434
Eitan et al, 2018[28]	February 2014-August 2017	Germany	Single-centre	Short-term outcome in consecutive pts undergoing TF-TAVI with aortic annulus $\geq$ 26 mm.	==	37	==	55	92
Enríquez-Rodríguez et al, 2018[29]	Non reported	Spain	Two-centre	A case-matched cohort comparing the hemodynamic performance of SAPIEN 3 *vs*. EVOLUT R THVs.	==	64	==	80	144
Gonska et al, 2018[30]	February 2014-September 2016	Germany	Single-centre	The influence of new permanent pacemaker implantation on one year outcome in consecutive pts treated with new generation devices.	==	27	==	360	387
Mauri et al, 2018[22]	February 2014-August 2016	Germany	Multicentre	Retrospective study to identify predictors of paravalvular regurgitation and new permanent pacemaker implantation following TAVI with new generation THVs.	92	==	==	92	184
Costa et al, 2019[24]	June 2007-February 2018	Italy	Single-centre	Retrospective study designed to determine the appropriateness of new permanent pacemaker implantation after TAVI.	99	269	16	177	561
Finkelstain et al, 2019[31]	February 2012-December 2016	Israel	Multicentre	A retrospective analysis on a large multicenter registry.	==	512	==	223	735
Pagnesi et al, 2019[25] (NEOPRO registry)	January 2012-March 2018	Europe, Canada, USA	Multicentre	A retrospective multicenter registry comparing ACURATE *neo vs*. EVOLUT PRO THVs.	1263	==	288	==	1551
Stundl et al, 2019[32]	February 2008-September 2016	Germany	Single-centre	The degree of paravalvular aortic regurgitation in consecutive pts treated with "early" *vs*. "newer generation" of THVs.	==	114	==	101	215
Veulemans et al, 2019[33]	January 2014-September 2016	Germany	Single-centre	Retrospective analysis comparing quality, success rate, and costs between SAPIEN 3 and EVOLUT R.	==	101	==	103	204
Vlastra et al, 2019[34]	2007-2018	USA, Brazil, Israel, Europe	Multicentre	Data from 10 studies, selected through a systematic search, included in a combined dataset, pooled and analyzed in order to compare BE with SE valves.	==	1091		1122	2213
Total number of implanted THVs					2294	2742		4064	9100

BE: Balloon-expandable; SE: Self-expandable; THVs: Transcatheter Heart Valves; TAVI: Transcatheter Aortic Valve Implantation; TF: Transfemoral; pts: patients.

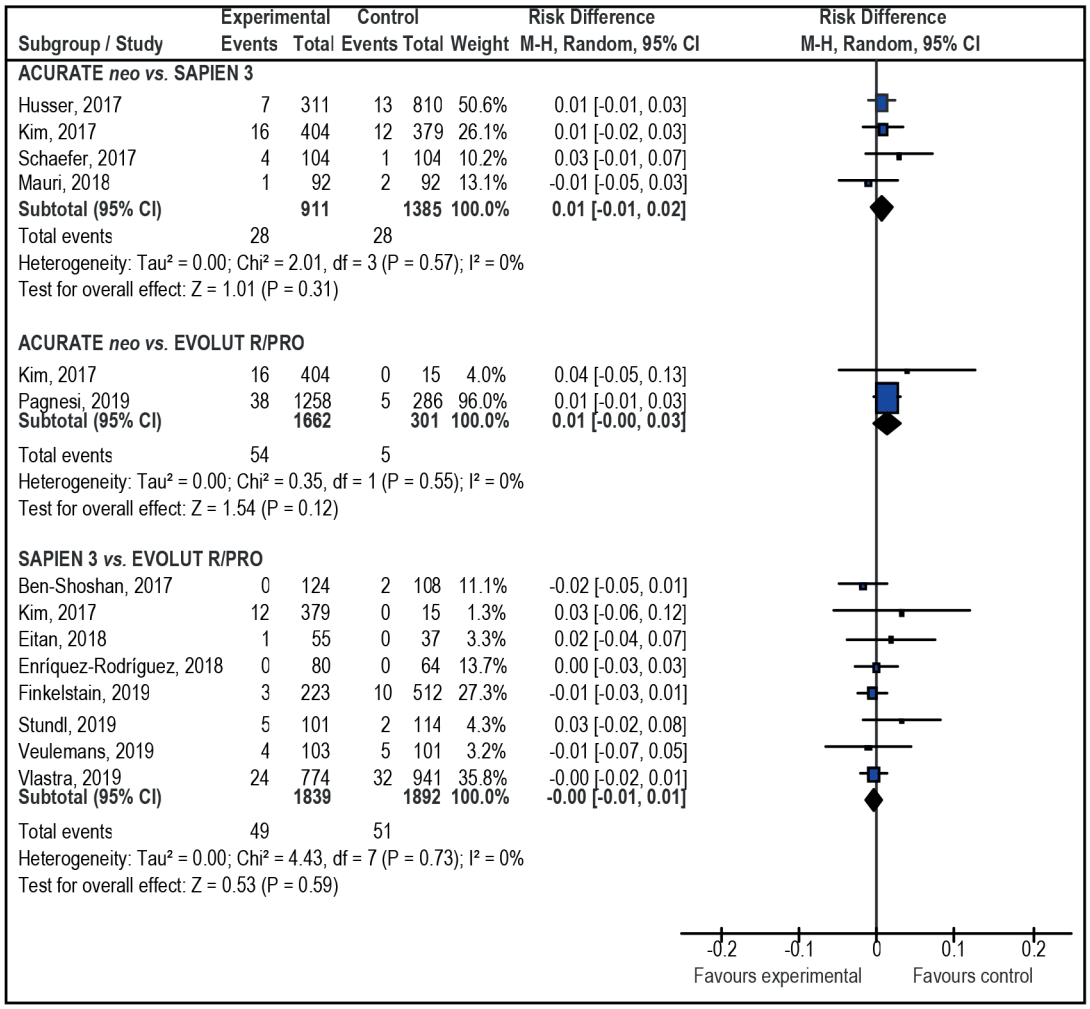

Figure 2. Mortality at 30-day. ACURATE *neo vs.* (*i*) SAPIEN 3, (*ii*) EVOLUT R/PRO. SAPIEN 3 *vs.* EVOLUT R/PRO.

effectiveness are limited and studies are mainly designed to compare the balloon-expandable *vs.* self-expandable valves without making a head-to-head comparison of the latest generation of prostheses[26,34]. Three trials, the SCOPE I (ClinicalTrial.gov Identifier: NCT03011346), SCOPE II (ClinicalTrial.gov Identifier: NCT03192813), designed to perform an head-to-head comparison of the latest valve prostheses (ACURATE *neo vs.* SAPIEN 3 and ACURATE *neo vs.* EVOLUT R/PRO, respectively) and the ACURATE IDE (ClinicalTrial.gov Identifier: NCT03735667) designed to compare the ACURATE *neo* with Edwards SAPIEN 3 and Medtronic CoreValve Evolut R or Evolut PRO are still ongoing (see: https://clinicaltrials.gov). Therefore, due to the lack of RCTs, we designed our meta-analysis to evaluate 30-day mortality and postprocedural adverse events in some new TAVI devices as SAPIEN 3, EVOLUT series (R/PRO) and the ACURATE *neo* from the real world observational data. Indeed Obs. can provide information on the daily clinical practice in the overall population undergoing transfemoral TAVI without rigorous exclusion criteria.

The main finding from our meta-analysis comes from: (i) a significant lower need for new pacemaker implantation in the group of patients implanted with ACURATE *neo* compared to SAPIEN 3 ($p<0.0001$) and EVOLUT R/PRO ($p=0.0009$) and, (ii) a significant higher postprocedural leak in the group of patients implanted with ACURATE *neo* compared to SAPIEN 3 ($p<0.00001$).

SAPIEN 3 and EVOLUT R/PRO heart valves did not show differences in the incidence of leak after TAVI (Figure 5). However, a higher occur-

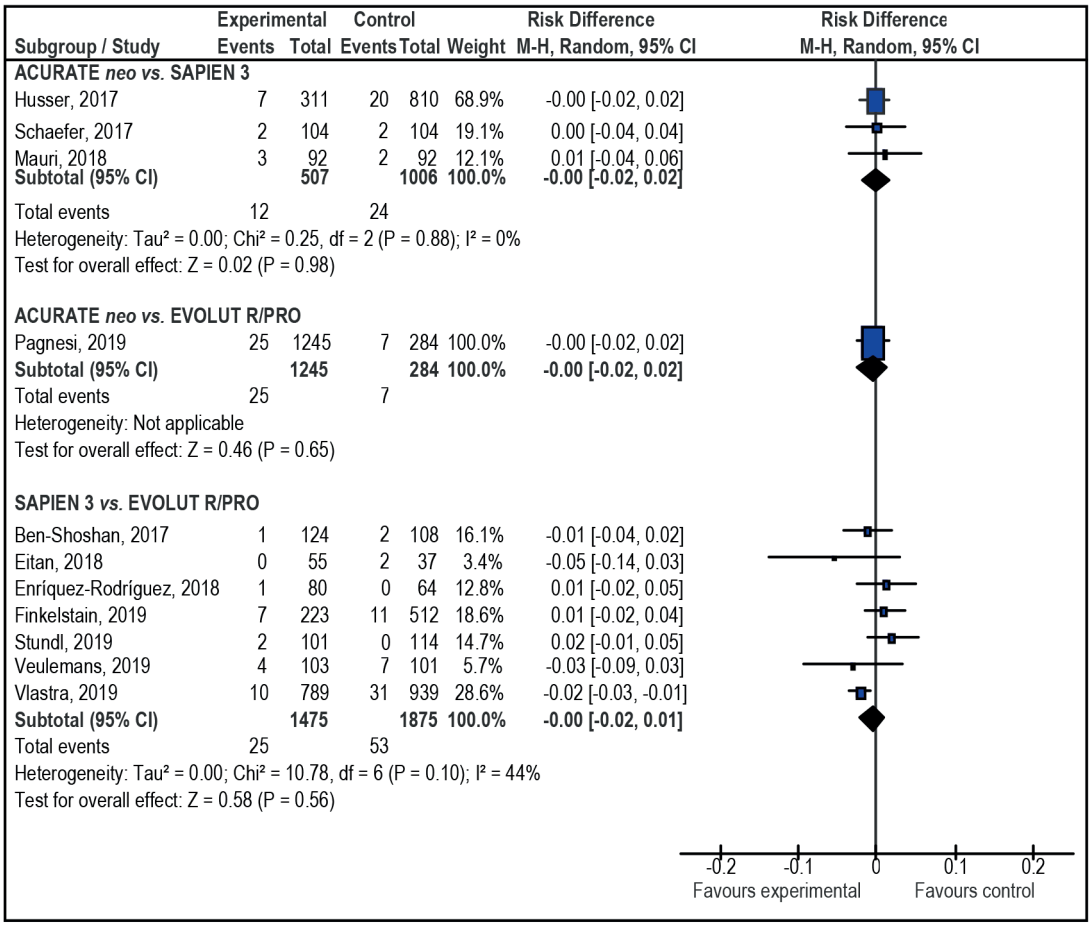

Figure 3. Incidence of stroke.

rence of new permanent pacemaker implantation was observed in the group of patients implanted with the EVOLUT R/PRO valve (p<0.00001) (Figure 4).

Moreover, we have to emphasize that: (i) we included in the meta-analysis all data available from Obs., (ii) patient population were homogeneous each other, as demonstrated by the I^2 statistics equal to 0 in many comparisons (Figure 2-5).

Indeed, despite the risks of bias due to unmeasured confounders, Obs. often provide the best available evidence of treatment effectiveness[38]. Anglemyer et al[39], analyzing the impact of the study design, Obs. *vs.* RCTs, on the estimate of the measure of effect, found that there was increasing evidence that in most cases RCTs and non-randomized studies yielded similar findings, when the studies had homogeneous data.

Furthermore, we can witness the evolution of clinical research every day. Thus, it can be observed that the acceptance of observational data occurs more and more frequently, both through the use of the registry and through the implementation of capillary networks that record the daily clinical practice[40].

In conclusion our findings, showing adverse outcomes related to the need for new permanent pacemaker implantation and the occurrence of postprocedural moderate/severe aortic insufficiency, could be related to the structural diversity of valve prostheses. However, the issue seems to remain unresolved and warrants further investigations.

Our meta-analysis, based on data from Obs., could overestimate the treatments effect due to the lack of randomization[41,42]. RCTs on efficacy of the new generation of TAVI devices, considered a key tool for comparative effectiveness research, are still recruiting. Their findings may help provide answers to the limitations of Obs.

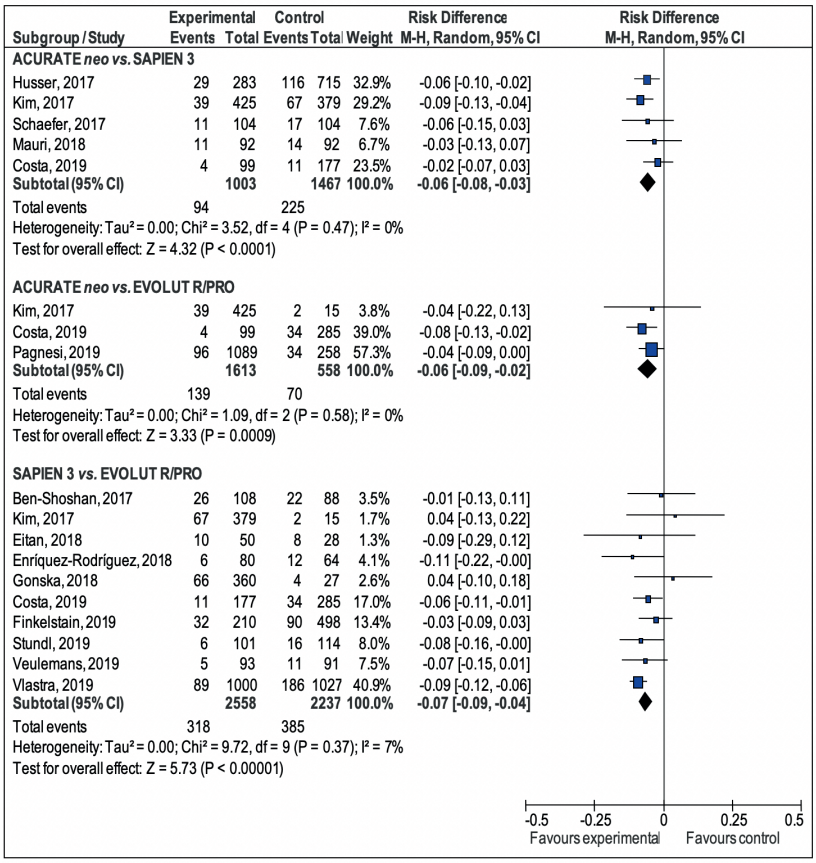

Figure 4. The need for new permanent pacemaker implantation.

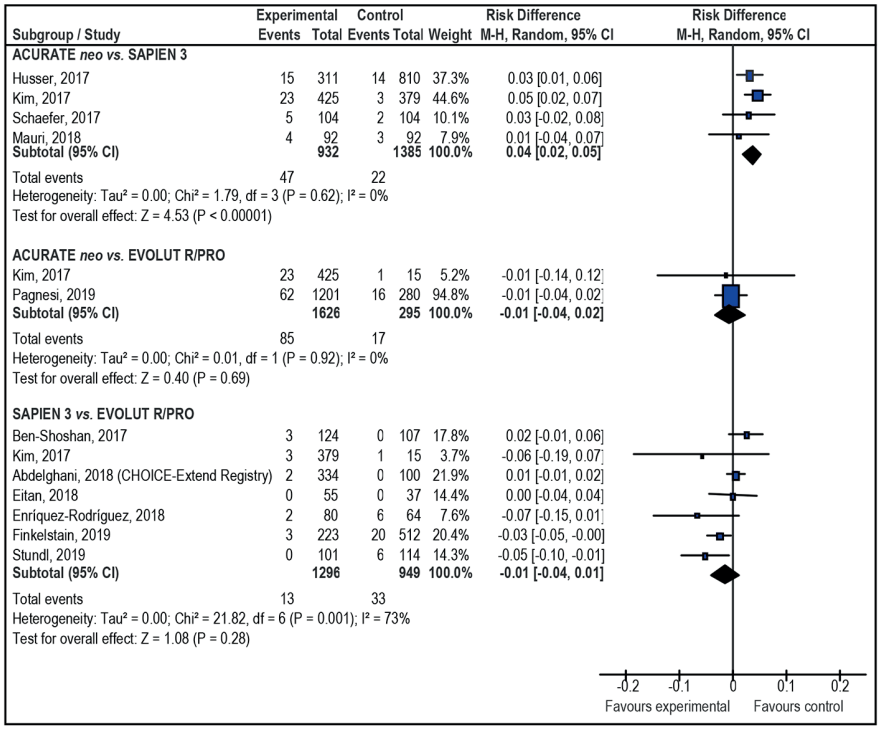

Figure 5. Incidence of moderate/severe paravalvular leak.

Conclusions

The meta-analysis shows that: (*i*) ACURATE *neo* required significant less new permanent post-procedural pacemaker implantation than SAPIEN 3 and EVOLUT R/PRO, (*ii*) SAPIEN 3 had significant lower occurrence of moderate/severe valvular leak than ACURATE *neo*.

Conflict of interest

The authors declare no conflicts of interest.

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