Clinical Research in Cardiology (2019) 108:430–437
https://doi.org/10.1007/s00392-018-1372-6

ORIGINAL PAPER

Efficacy and safety of new-generation transcatheter aortic valves: insights from the Israeli transcatheter aortic valve replacement registry

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Received: 2 May 2018 / Accepted: 13 September 2018 / Published online: 20 September 2018

Abstract

Aim To compare procedural outcomes of transcatheter aortic valve replacement (TAVR) patients treated with new-generation valves.

Methods We performed a retrospective analysis on an Israeli multicenter registry comprised of four tertiary centers, comparing patient outcomes implanted with the Edwards SAPIEN S3 (ES3) vs. the Medtronic Evolut R (MER) valves.

Results The study population included 735 patients (ES3 $n=223$; MER $n=512$). The use of MER was significantly associated ($p<0.05$) with higher rates of post-dilatation (35% vs. 10%), and the need for a second valve (2.7% vs. 0.5%). Procedural device success was comparable between groups (97% vs. 98%, $p=0.76$); however, moderate angiographic paravalvular leak was higher (3.3% vs. 0.5%, $p=0.027$) for MER vs. ES3, respectively. As compared to MER, 1 month echocardiography revealed higher peak and mean aortic valve gradients for ES3 (12/6 vs. 17/10 mmHg, $p<0.001$, respectively). While the safety outcome at 1 month was lower for MER (8.8% vs. 13.9%, $p=0.035$), similar 1-month, 1-year, and 3-year all-cause mortality were observed (1.9% vs. 1.3%; 8% vs. 8.5%, and 9.7 vs. 10.3%, for MER vs. ES3, respectively). In a propensity score matching analysis, there was no difference in major outcomes between the groups, including device success and the 1 month safety outcome.

Conclusion Although favorable efficacy and safety clinical outcomes were observed in this large contemporary registry for both new-generation devices used, some procedural and post-procedural outcomes differ significantly between the two valves.

Keywords TAVR · New generation · Outcomes · Multicenter registry

Introduction

Transcatheter aortic valve replacement (TAVR) is recommended for patients with symptomatic severe aortic stenosis (AS) who are at intermediate to high surgical risk [1]. The two most common prosthetic transcatheter aortic valve devices in current practice are the self-expandable

Ariel Finkelstein and Arie Steinvil contributed equally to this paper.

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s00392-018-1372-6) contains supplementary material, which is available to authorized users.

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Medtronic (Medtronic, Minneapolis, Minnesota) [2] and the balloon-expandable Edward SAPIEN (Edwards Lifesciences, Irvine, California) [3] series of valves. The newer generations of both valve and delivery systems, namely, the Edwards SAPIEN S3 (ES3) [4] and the Medtronic Evolut R (MER) [5, 6], have been designed to reduce the rate of procedural complications, and have demonstrated favorable safety outcomes, along with high procedural success rates. Previous small-scale retrospective cohorts evaluated and compared the short-term outcomes of patients undergoing TAVR with the two new-generation valves [7, 8]. However, a direct head-to-head comparison in a clinical trial has never been performed. It is therefore essential to compare their efficacy and safety in large real-life contemporary cohorts. Our aim was to compare the procedural outcomes of TAVR patients treated with new-generation valves enrolled in a large multicenter registry.

Methods

Study design and setting

We performed a retrospective analysis on an Israeli multicenter registry [9–11] comprised of four tertiary centers, comparing patients outcomes implanted with the ES3 vs. the MER valves between February 2012 and December 2016. The study was approved by the institutional review board at each of the participating centers.

Study population

All patients had severe aortic stenosis, which was defined by echocardiography and practice guidelines (valvular orifice area < 1.0 cm^2 or < 0.6 cm^2/m^2 and/or a mean transaortic valvular gradient > 40 mmHg and/or jet velocity > 4.0 m/s) [1]. Patients who were included underwent a thorough baseline assessment process. Data regarding laboratory tests, and the Society of Thoracic Surgeons (STS) score predicted risk of mortality (STS-PROM) were collected, in addition to history taking, physical examination, and a comprehensive echocardiographic assessment. All the collected data were pooled into a dedicated multicenter database.

Outcome measures

Outcome measures were defined according to the Valve Academic Research Consortium-2 (VARC-2) [12] consensus definitions. In brief, device success was defined according to procedural mortality, correct positioning of the valve, mean aortic valve gradient < 20 mm Hg or peak velocity < 3 m/s, and no moderate or severe prosthetic valve regurgitation. The safety outcome at 30 days was defined as a composite of all-cause mortality, stroke, life-threatening bleeding, acute kidney injury stage 2 or 3, coronary artery obstruction requiring intervention, major vascular complication, and valve-related dysfunction requiring repeat procedure. Other complications during hospitalization were noted.

Valve selection and procedural definitions

All procedural aspects including valve selection, anesthesia, and access site were determined by operator discretion and were based on clinical, anatomical and angiographic characteristics. Access routes for TAVR included trans-femoral, trans-apical, or trans-axillary approaches. By default, the trans-femoral access was preferred in all centers, providing anatomic limitations were not present.

Statistical methods

Categorical variables were reported as numbers and percentages, and continuous variables were reported as mean and standard deviation (SD) or as medians and interquartile range (IQR). Continuous variables were tested for normal distribution using histograms and Q–Q Plots. Continuous variables were compared between groups using independent samples *T* test or Mann–Whitney test and categorical variables were compared using Pearson's Chi test or Fisher's exact test. Univariable logistics regressions were used for binary outcomes. Multivariable logistic regression models were adjusted for age, gender, and baseline characteristics with a p value < 0.1 (obesity, ischemic heart disease, hyperlipidemia, renal dysfunction, STS score, and systolic dysfunction) according and adjusted to multiple confounders. Odds ratio (OR) and 95% confidence interval (CI) were reported. In addition to multivariable analyses, analyses of outcomes were performed using propensity score matching. Propensity scores were matched with a caliper range of ± 0.05 to obtain matched pairs of patients. Age, gender and variables with a p value < 0.15 in Table 1 were included in the propensity score. Subsequently, balance of matching was assessed by statistical comparison using Student's *t* test or Mann–Whitney test for continuous and Pearson's Chi test or Fisher's exact test for categorical variables. A p value of > 0.1 was considered as evidence for non-significant differences between both groups. Baseline and procedural characteristics using the propensity score matching are presented in the supplemental tables (1–3). A two-tailed p value less than 0.05 was considered as statistically significant. All statistical analyses were performed with SPSS (IBM Corp. Released 2013. IBM SPSS Statistics for Windows, Version 22.0. Armonk, NY: IBM Corp.).

Table 1 Baseline characteristics according to valve type

	Edwards SAPIEN S3 $n=223$	Medtronic Evolut R $n=512$	p value
Age	81(77–85)	83(79–87)	<0.001
Female gender, %	33	65	<0.001
Obesity (BMI > 25), %	71	64	0.087
Prior to thoracotomy, %	15	12	0.351
Ischemic heart disease, %	61	46	<0.001
Systolic dysfunction, %	26.4	13.9	<0.001
Atrial fibrillation, %	28	29	0.709
Pacemaker/ICD, %	13	14	0.632
Diabetes mellitus, %	40	40	0.983
Hyperlipidemia, %	65	74	0.007
Hypertension, %	82	87	0.118
Smoking, %	5	6	0.834
CVA/TIA	18	14	0.161
Peripheral vascular disease, %	11	10	0.624
Porcelain aorta, %	5	3	0.384
COPD, %	12	8	0.118
Renal dysfunction (eGFR < 60 ml/min/1.73 m^2), %	54	68	<0.001
Dialysis, %	3	2	0.531
Liver disease, %	0.5	0.7	0.809
Prior malignancy, %	18	16	0.497
Frailty	33.8	36.5	0.536
STS mortality, %	3.1 (2.5–4.6)	3.5 (2.6–5.2)	0.003
NYHA class	3 (±0.7)	2.8 (±0.7)	<0.001

Results

Patients' characteristics

The study population included 735 patients (ES3 $n=223$; MER $n=512$). Patients implanted with MER were more likely to be older (83 vs. 81 years, $p<0.001$) and of female gender (65% vs. 33%, $p<0.001$). Ischemic heart disease was less prevalent (46% vs. 61%, $p<0.001$) in patients implanted with MER, in contrast to renal failure (68% vs. 54%, respectively; $p<0.001$) and hyperlipidemia (74% vs. 65%, respectively; $p=0.007$). In addition, patients implanted with MER had higher STS scores (3.5% vs. 3.1%, $p=0.003$) as compared to ES3. The mean STS score along the study period dropped significantly from 7.4 (±6.8) in 2009 to 4.1 (±3.1) in 2017 ($p<0.001$ for trend). Other baseline characteristics are described in Table 1.

Echocardiographic characteristics at baseline

Echocardiography variables are presented in Table 2. Pre-procedural aortic valve peak/mean pressure gradients were comparable (71/44 mmHg for MER vs. 70/44 mmHg for ES3). Ejection fraction was lower in patients implanted with ES3 (54% vs. 57%, $p=0.012$) with the left ventricular dimensions being larger. Concomitant mitral regurgitation was present in 10% and 15% of patients implanted with ES3 and MER, respectively ($p=0.12$). There were no differences in baseline diastolic dysfunction, tricuspid regurgitation or right ventricle dysfunction.

	Edwards SAPIEN S3 $n=53$	Medtronic Evolut R $n=231$	p value
Echocardiography at 1 month			
Aortic valve peak pressure, mmHg	17 (13–23)	12 (9–16)	<0.001
Aortic valve mean pressure, mmHg	10 (7–13)	6 (5–9)	<0.001
Ejection fraction, %	54 (±10)	57 (±9)	0.033
Systolic pulmonary artery pressure, mmHg	33 (23–41)	33 (27–43)	0.375

Table 2 Echocardiographic characteristics according to valve type at baseline and 1 month

	Edwards SAPIEN S3 $n=223$	Medtronic Evolut R $n=512$	p value
Baseline echocardiography			
Aortic valve peak pressure, mmHg	70 (55–85)	71 (57–86)	0.333
Aortic valve mean pressure, mmHg	44 (35–53)	44 (35–54)	0.787
Aortic valve area, cm^2	0.7 (0.6–0.9)	0.7 (0.6–0.8)	0.004
Ejection fraction, %	54 (±12)	57 (±11)	0.012
Diastolic dysfunction grade ≥ 2, %	12	21	0.09
Mitral regurgitation ≥ moderate, %	10	15	0.12
Tricuspid regurgitation ≥ moderate, %	13	12	0.77
Right ventricle dysfunction ≥ moderate, %	7	4	0.227
Systolic pulmonary artery pressure, mmHg	37 (29–49)	39 (30–48)	0.371
Left ventricle end -diastolic diameter, mm	49 (44–53)	45 (41–50)	< 0.001
Left ventricle end-systolic diameter, mm	31 (27–38)	28 (24–32)	< 0.001
Interventricular septal diameter, mm	13 (11–14)	13 (12–14)	0.387
Left atrial area, cm^2	25 (21–29)	24 (21–28)	0.564
Left ventricle end-diastolic diameter, mm	48 (42–50)	45 (41–49)	0.043
Left ventricle end-systolic diameter, mm	30 (24–34)	28 (24–32)	0.017
Left atrial area, cm^2	23 (21–29)	23 (20–28)	0.32

Procedural characteristics

Table 3 summarizes key procedural variables. The transfemoral approach was used in most patients (MER 95%; ES3 92%; $p=0.176$). The use of MER was significantly associated with higher rates of post-dilatation (35% vs. 10%, $p<0.001$), moderate to severe paravalvular leak (PVL) per angiography (3.3% vs. 0.5%, $p=0.027$), and the need for a second valve (2.7% vs. 0.5%, $p=0.048$), however, it was associated with lower rates of pre-dilatation (21% vs. 63%, $p<0.001$), for MER vs. ES3 respectively. Rates of permanent pacemaker implantation (PPI) were 17.5% vs. 14.4% ($p=0.303$).

Procedural and clinical outcomes

Procedural and clinical outcomes were comparable between the two groups (Table 3). Procedural device success was comparable between groups (97% vs. 98%, $p=0.76$); however, moderate paravalvular leak per echocardiography was only numerically higher (4% vs. 1.4%, $p=0.176$) for MER vs. ES3, respectively. The 1-month, 1-year, and 3-year all-cause mortality rates during follow-up were similar between groups (1.9% vs. 1.3%, $p=0.764$; 8% vs. 8.5%, $p=0.804$; and 9.7 vs. 10.3%, $p=0.807$ for MER vs. ES3, respectively). In spite of the similar efficacy outcomes, the composite safety outcome at 1-month follow-up was higher in patients who underwent ES3 implantation (13.9%) compared to MER (8.8%, $p=0.035$). Among components of the safety outcome at 1 month, acute kidney injury stage 2 or higher was more prevalent among patients implanted with ES3 compared to MER (7.2% vs. 2.7%, $p=0.005$), while valve-related dysfunction requiring repeat procedure was more prevalent among patients implanted with MER compared to ES3 (2.7% vs. 0.5%, $p=0.048$). Other components of the safety outcome at 1 month did not differ between the two groups (Table 3). Outcomes with low rates (< 2.5%) were comparable between the groups and include conversion to surgery, septal perforation, mitral apparatus damage, tamponade, annular rapture, procedure CPR, peri-procedural (72 h) myocardial infarction, and dialysis (data not presented in a table).

In multivariable analyses (Table 4) adjusted for age, gender, and marginally significantly different baseline characteristics (p value < 0.1), there was no difference in device success (OR 1, 95% CI 0.3–3.5, $p=0.985$), safety outcome at 1 month (OR 0.7, 95% CI 0.3–1.3, $p=0.233$), as well as in-hospital permanent pacemaker implantation (OR 1.4, 95% CI 0.8–2.7, $p=0.253$). Patients implanted with MER were less likely to suffer from acute kidney injury of any stage (OR 0.5, 95% CI 0.3–0.9, $p=0.02$). A propensity score matching analyses of the two valves is presented in Table 4.

Table 3 Procedural characteristics, outcomes and complications according to valve type

	Edwards SAPIEN S3 $n=223$	Medtronic Evolut R $n=512$	p value
Procedural characteristics			
General anesthesia, %	9	7	0.534
Femoral access, %	92	95	0.176
Pre-dilatation, %	63	21	< 0.001
Post-dilatation, %	10	35	< 0.001
Paravalvular leak ≥ moderate per angiography, %	0.5	3.3	0.027
Mean valve size, mm, *n*			
23	57	54	< 0.001
26	88	216	
29	78	242	
Device success, %	98	97	0.76
Valve malposition, %	0	1.7	0.184
Procedural mortality, %	0	1	0.33
Mean aortic valve gradient < 20 mmHg or peak velocity < 3 m/s, %	93	95	0.306
Paravalvular leak ≥ moderate per echo post procedure, %	1.4	4	0.176
Safety outcome at 1 month, %	13.9	8.8	0.035
Mortality, %	1.3	1.9	0.764
Stroke, %	3.1	2.2	0.37
Life-threatening bleeding, %	2.7	1.6	0.378
Acute kidney injury stage 2 or 3, %	7.2	2.7	0.005
Coronary artery obstruction requiring intervention, %	0.6	0.5	> 0.999
Major vascular complication	4.6	3.3	0.422
Valve-related dysfunction requiring repeat procedure, %	0.5	2.7	0.048
Other in-hospital complications			
New post-procedure left bundle branch block, %	22.2	28.6	0.093
Permanent pacemaker implantation, %	14.4	17.5	0.303
New atrial fibrillation, %	6.6	3.4	0.094
Heart failure post procedure, %	6.5	3.8	0.115
Long-term mortality			
1 year mortality, %	8.5	8	0.804
3 year mortality, %	10.3	9.7	0.807

Table 4 Multivariable and propensity score matching of outcomes of Evolut R compared to Sapien S3

	Univariable		Multivariable[a]		Propensity score matching[b]	
	OR (95% CI)	p value	OR (95% CI)	p value	OR (95% CI)	p value
Acute kidney injury (any stage)	0.5 (0.3–0.9)	0.023	0.5 (0.3–0.9)	0.02	0.3 (0.1–0.7)	0.005
In-hospital bleeding (any)	0.8 (0.2–2.8)	0.73	1.5 (0.3–6.9)	0.614	0.6 (0.1–3.8)	0.564
In-hospital stroke	0.7 (0.2–2.7)	0.583	0.7 (0.1–3.3)	0.644	0.7 (0.1–3.9)	0.625
In-hospital permanent pacemaker implantation	1.4 (0.8–2.5)	0.226	1.4 (0.8–2.7)	0.253	1.38 (0.7–2.8)	0.374
Device success	1.1 (0.3–3.2)	0.988	1 (0.3–3.5)	0.985	0.4 (0.2–1.2)	0.094
Safety outcome at 1 month	0.7 (0.3–1.2)	0.187	0.7 (0.3–1.3)	0.233	0.5 (0.2–1.1)	0.096

[a]Adjusted for age, gender, obesity, ischemic heart disease, hyperlipidemia, renal dysfunction, STS mortality, systolic dysfunction

[b]Adjusted for age, gender, obesity, ischemic heart disease, hyperlipidemia, renal dysfunction, STS mortality, systolic dysfunction, hypertension, COPD

Outcomes according to propensity score matching

Propensity score matching enabled a comparison of 126 patients in each group. Analyses of the groups demonstrated no differences in device success (96% for ES3 vs. 90.5% for MER, $p=0.079$) and its components, or the safety outcome at 1 month (12.7% for ES3 vs. 6.3% for MER, $p=0.086$). Similar to the univariable analyses, higher rates of acute kidney injury were shown in patients who were implanted with ES3 (7.6%) compared to MER (1.6%, $p=0.026$). The differences remained significant after adjustment for the propensity score (OR 0.3, 95% CI 0.1–0.7, $p=0.005$). There were no differences in other measured outcomes including rates of PPI and mortality (Table 4 and Supplemental table 3).

Echocardiographic characteristics at 1 month

Echocardiography was available for 284 patients. At 1 month aortic valve pressure gradients were higher in patients implanted with ES3 compared with patients implanted with MER (17/10 vs. 12/6 mmHg, $p<0.001$). Ejection fraction was not significantly different between the groups at baseline and at 1-month follow-up. The above-mentioned baseline differences in left ventricle dimensions remained larger in patients implanted with ES3. Other echocardiographic variables are presented in Table 2.

Discussion

The present cohort demonstrates comparable rates of VARC-2 defined efficacy and safety outcome measures in both new-generation TAVR valves, as well as other specified short- and long-term complications. High device success rates were demonstrated with both valves. The results of the present registry data provide additional evidentiary support for the ongoing improvement of the safety outcomes of this technology. Our results indicate enhanced safety and maturation of this technology, as compared to early experience reports [13], including lower reported rates in 30 day mortality (1.7% vs. 6.5%), 1 year mortality (8.1% vs. 26.8%), neurological events (2.4 vs. 5.5%), major vascular complications (3.3% vs. 4.6%), PPI (16.5% vs. 3.8%), and moderate PVL (3.3% vs. 11.8%), respectively.

A previous randomized comparison of older generation of TAVR valves (Medtronic CoreValve vs. Edwards SAPIEN XT) demonstrated higher frequencies of PVL according to angiography, and valve malpositioning among patients implanted with CoreValve [14]. The ES3 and MER valves were designed to improve device success and safety. Development of the ES3 was aimed to reduce PVL of earlier generations, a known predictor of adverse outcome among patients undergoing TAVR [15], by incorporating a paravalvular sealing system [4]. However, an increase in the rate of post-procedural permanent pacemaker implantations was demonstrated along with this alteration [16]. As expected, this additional skirt aimed to reduce the PVL, resulted in higher local trauma delivered to the conduction system, with a tradeoff of higher post-procedural need for permanent pacemaker implantation [17]. Thus, an inverse trajectory of PVL (11.8–3.7%) and PPI (3.8–8.5%) rates had occurred from the earlier Sapien XT experience [13] to current ES3 device.

A higher rate of post-procedure moderate and/or severe PVL was shown in our cohort for the MER valve. This difference was significant for the angiographic outcome and only numerically higher for the echocardiography outcome. Moreover, patients implanted with MER were more likely to have VARC-2 defined valve-related dysfunction requiring repeat procedure, as compared to ES3 (2.7% vs. 0.5%, $p=0.048$, respectively). This increased risk should be viewed carefully and needs further investigation focused on anatomical and procedural characteristics. There is a wide variety of differences between the MER and ES3 implantation itself, the most robust the accurate positioning of the valve is during implantation. MER positioning during implantation is extremely variable. Implantation depth is one of the leading causes for post-procedural PVL. This may explain the higher rate of second valve implantations for MER as compared to ES3, for which the implantation is a "one shot" step, with valve positioning determined just prior to balloon inflation and valve deployment. After positioning of the valve at the annular level, pacing and starting the inflation, little can be done for valve position, and therefore the main reason for PVL for ES3 is either a very calcified native valve, or an undersized prosthetic valve. On the other hand, the higher observed 1-month gradients for ES3 are expected as well, since the MER is supra-annular in its native design, unlike the ES3, which is annular. This has been shown in valve-in-valve procedures, in bench testing as well as in registries [18].

Predictors of AV block post-procedure include advanced age [19], post-dilatation [20], higher mean aortic valve gradient prior to implantation [20], and calcium load [20] (which was not available in our study). Although differences in the above parameters were noted, our data demonstrated similar rates of new post-procedure LBBB or permanent pacemaker implantation, in contrast to the previously demonstrated rise in post-procedural permanent pacemaker implantation [21].

Device migration and major vascular complication were previously shown to be predictors of early mortality [22]. The ES3 system includes a 14-F expandable sheath and an active three-dimensional coaxial positioning catheter, and the MER's 14-F equivalent repositionable system was incorporated for the purpose of diminishing vascular

complications and optimizing valve positioning [16]. In the present cohort, vascular complications and valve malposition rates did not differ between patients implanted with the two valves. In fact, device success and all of its separate parameters were not significantly different between the compared valves. The safety outcome at 1 month, however, was better in patients implanted with ES3, most probably due to acute kidney injury. In a previous study [6], rates of acute kidney injury stage 2 or 3 (1.2%) were lower than currently reported in both valves, especially compared to ES3. A possible explanation may be the lower baseline kidney function among patients with ES3. However, these low rates may also be explained by an improved experience of the operators as compared to previous studies that translated to a lower amount of contrast media used. Nevertheless, rates of acute kidney injury stage 2 or 3 vary in other studies [23].

A high proportion of low-risk TAVI patients was observed in the present analysis. As clinical real-life practice often exceeds practice guidelines based on delay from trial data to guidelines' publication, physician experience and patient's choice, a clear trend toward treatment of lower STS populations was observed in our cohort. Similar trends have been seen in previous real-life reports [24, 25] even before intermediate-risk trials have been published [2], or the eventual publication of the clinical studies which include lower risk patients [26, 27].

Several limitations in the present study should be regarded. First, while data was collected prospectively, the analysis was conducted retrospectively. A retrospective analysis incorporates an inherent bias. Second, the two study groups were not of equal size. Less than a third of the patients in the cohort were implanted with ES3. A larger group is less influenced by cases in the extremes of both sides of the data. In addition, a larger group of patients is accompanied by more operator experience, which may lower complication rates and increase success rates. Finally, it also should be noted, that more patients with ischemic heart disease were selected to be implanted with the ES3. This may have biased our results as well, since the possible need for future coronary interventions directed several operators to prefer ES3 implantation over MER.

Compliance with ethical standards

Conflict of interest Dr. Ariel Finkelstein receives proctor fees from Medtronic and Edwards Lifesciences. None of the other authors have a conflict of interest to declare.

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