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Comparison of balloon-expandable vs. self-expandable valves in patients undergoing transfemoral transcatheter aortic valve implantation: from the CENTER-collaboration

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Aims The aim of this study was to compare clinical outcomes of patients undergoing transfemoral transcatheter aortic valve implantation (TAVI) with balloon-expandable (BE) valves vs. self-expandable (SE) valves. Transcatheter aortic valve implantation is a minimally invasive and lifesaving treatment in patients with aortic valve stenosis. Even though BE-valves and SE-valves are both commonly used on a large scale, adequately sized trials comparing clinical outcomes in patients with severe aortic valve stenosis treated with BE-valves compared with SE-valves are lacking.

Methods and results In this CENTER-collaboration, data from 10 registries or clinical trials, selected through a systematic search, were pooled and analysed. Propensity score methodology was used to reduce treatment selection bias and potential confounding. The primary endpoints were mortality and stroke at 30 days follow-up in patients treated with BE-valves compared with SE-valves. Secondary endpoints included clinical outcomes, e.g. bleeding during hospital admission. All outcomes were split for early-generation BE-valves compared with early-generation SE-valves and new-generation BE-valves with new-generation SE-valves. The overall patient population ($N = 12\,381$) included 6239 patients undergoing TAVI with BE-valves and 6142 patients with SE-valves. The propensity matched population had a mean age of 81 ± 7 years and a median STS-PROM score or 6.5% [interquartile range (IQR) 4.0–13.0%].

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At 30-day follow-up, the mortality rate was not statistically different in patients undergoing TAVI with BE-valves compared with SE-valves [BE: 5.3% vs. SE: 6.2%, relative risk (RR) 0.9; 95% confidence interval (CI) 0.7–1.0, $P = 0.10$]. Stroke occurred less frequently in patients treated with BE-valves (BE: 1.9% vs. SE: 2.6%, RR 0.7; 95% CI 0.5–1.0, $P = 0.03$). Also, patients treated with BE-valves had a three-fold lower risk of requiring pacemaker implantation (BE: 7.8% vs. SE: 20.3%, RR 0.4; 95% CI 0.3–0.4, $P < 0.001$). In contrast, patients treated with new-generation BE-valves more frequently experienced major and life-threatening bleedings compared with new-generation SE-valves (BE: 4.8% vs. SE: 2.1%, RR 2.3; 95% CI 1.6–3.3, $P < 0.001$).

Conclusion In this study, which is the largest study to compare valve types in TAVI, we demonstrated that the incidence of stroke and pacemaker implantation was lower in patients undergoing transfemoral TAVI with BE-valves compared with SE-valves. In contrast, patients treated with new-generation BE-valves more often suffered from major or life-threatening bleedings than patients with new-generation SE-valves. Mortality at 30-days was not statistically different in patients treated with BE-valves compared with SE-valves. This study was a propensity-matched analysis generated from observational data, accordingly current outcomes will have to be confirmed in a large scale randomized controlled trial.

Keywords Transcatheter aortic valve implantation • Transcatheter aortic valve replacement • Balloon-expandable valve • Self-expandable valve • Medtronic CoreValve • Edwards Sapien • Stroke

Introduction

Transcatheter aortic valve implantation (TAVI) is a minimally invasive and life-saving treatment in patients with severe aortic valve stenosis.[1] Even though this treatment was originally developed for patients who were considered inoperable, during the last years TAVI has expanded from high- to intermediate-risk patients.[2] Since the introduction of TAVI, two valves in particular have been widely used; the balloon-expendable (BE) Edwards SAPIEN valve (Edwards lifesciences Inc., Irvine, CA, USA) and the self-expandable (SE) Medtronic CoreValve (Medtronic Inc. Minneapolis, MN, USA).

The Edwards SAPIEN XT and consecutive Edwards SAPIEN 3 (first in human in 2009 and 2012, respectively) valves are both composed of three bovine pericardium leaflets mounted on a cobalt chromium frame.[3,4] These Edwards SAPIEN valves are expanded by inflation of a balloon during rapid-pacing.[5] The CoreValve system and the CoreValve Evolut R system (first in human in 2004 and 2013, respectively) consist of three porcine pericardial leaflets, mounted on a self-expanding nitinol frame. Both devices have shown to be efficacious at treating aortic valve stenosis with relatively low rates of long-term complications such as paravalvular regurgitation.[6,7]

Accordingly, the current challenge is to further decrease the rates in mortality, stroke, bleeding, new-onset atrial fibrillation, and need for permanent pacemaker implantation. Even though BE and SE valves are commonly used on a large scale, patient-level data evaluating adverse outcomes in patients treated with BE-valves compared with SE-valves is lacking. The current available evidence includes two modestly sized randomized controlled trials ($n = 240$ and $n = 447$) and one propensity-matched analysis ($n = 408$).[8–10] However, as a consequence of the relatively low incidence of short-term complications, these studies are considered underpowered to compare individual clinical endpoints. Therefore, in the absence of adequately powered large randomized controlled trials, the aim of this collaborative propensity-matched analysis was to compare 30-day stroke and mortality in patients undergoing transfemoral TAVI with BE-valves vs. SE-valves, split for early vs. new-generation valve types, in a large study population.

Methods

Study design and population

The CENTER-trial is an international collaboration, including patients with severe aortic valve stenosis undergoing transfemoral TAVI. The patient population of the CENTER-trial was selected through a systematic search. Registries or trials including patients undergoing transfemoral TAVI with either Edwards SAPIEN valves (Edwards lifesciences Inc., Irvine, CA, USA) or Medtronic CoreValves (Medtronic Inc. Minneapolis, MN, USA) were invited to participate in the CENTER-collaboration. Patients undergoing TAVI with other valve types or different access routes than the transfemoral approach were not eligible for inclusion. All patients provided written informed consent for the procedure and data collection according to the policy of each participating hospital. The CENTER-trial is registered at clinicaltrials.gov (NCT03139968).

Search strategy and study selection

We searched PubMed, Medline, and Embase for studies reporting stroke rates in patients undergoing TAVI, published between January 2002 and June 2017 (keywords used in the search are provided in Supplementary material online, *S1*). Moreover, we identified additional articles through the references of reviews. Studies were eligible for inclusion if they complied with the following requirements: original studies, including patients with aortic valve stenosis treated with transfemoral TAVI and reporting of 30-day stroke outcomes. Moreover, in order to ensure ample operator experience in the implantation of BE- and SE-valves, the included studies had to report on both the use of the self-expandable Medtronic CoreValve (MCV) prosthesis and the balloon-expandable Edwards SAPIEN (ES) valve in more than 50 patients per arm. Studies were excluded if they only addressed patients undergoing valve-in-valve and re-do procedures or bicuspid valves or addressed overlapping study population.

During the systematic search, a total of 903 individual studies were screened by two independent reviewers (R.D. and J.v.H.). After

screening, 28 studies matched the inclusion and exclusion criteria (Supplementary material online, *S2*), and the principle investigators of these studies were contacted for collaboration. Of these 28 principle investigators, 10 consented to collaboration and were included in the CENTER-collaboration (Supplementary material online, *S3*). The CENTER-collaboration consists of three national registries, two multicentre registries, four single-centre registries, and one randomized controlled trial. Accordingly, the CENTER-collaboration includes a global patient population with patients treated in the United States, Brazil, Israel, and several European countries. All collaborators provided a dedicated database with baseline patient characteristics, echocardiographic data, procedural information, and follow-up data. The combined dataset was checked for duplicate subjects, consequently, 47 duplicate patients were removed from the final dataset. Accordingly, a total of 12 381 patients undergoing transfemoral TAVI between 2007 and 2018 with BE- or SE-valves were included in the current patient pooled analyses.

Study endpoints

The primary endpoints of this analysis were death from any cause and stroke in patients with BE-valves compared with SE-valves occurring within the first 30 days after TAVI, as defined by the standardized definitions from the Valve Academic Research Consortium (VARC).[11–19] The OBSERVANT trial defined stroke as a neurological deficit lasting more than 24 h, or less than 24 h in case of positive neuroimaging, which is equivalent to the VARC-definition for stroke.[20] Secondary outcomes included in-hospital mortality, stroke, myocardial infarction, and major or life-threatening bleeding, as defined by the VARC-criteria, as well as implantation of permanent pacemakers and new-onset atrial fibrillation. Secondary outcomes compared early-generation valve types (Edwards SAPIEN and SAPIEN XT vs. Medtronic CoreValve) and new-generation valve-types (SAPIEN 3 vs. Evolut).

Statistical analysis

The study population was divided into two groups: patients treated with BE- vs. SE-valves. Baseline categorical variables were presented as frequencies and percentages, values of continuous variables were tested for normal distribution and reported as mean ± standard deviation or median (25th–75th percentile) where applicable. We applied multiple imputation methods to estimate missing data. The imputation procedure and subsequent multivariable regression models were performed according to the Rubin's protocol under the assumption that missing data are missing at random. Propensity score methodology was used to reduce treatment selection bias and potential confounding. The propensity score was calculated using logistic regression. Baseline patient characteristics that either significantly predicted the used valve-type (BE or SE), or that correlated with the occurrence of the primary endpoints of this study (mortality and stroke) were included in the propensity score model. Accordingly, the propensity score included the following 12 variables: age, gender, body mass index, logistic EuroSCORE, previous myocardial infarction, previous percutaneous coronary intervention (PCI), previous stroke or transient ischaemic attack (TIA), history of peripheral artery disease, history of atrial fibrillation, history of coronary artery disease, dyslipidaemia, and a glomerular filtration rate (GFR) of less than 30 mL/min/1.73 m^2. For each patient with a BE-valve, a corresponding comparison patient with SE-valve was selected (1:1 ratio) on the basis of the nearest propensity score using the one-to-one nearest neighbour method (with a caliper of 0.2 of the standard deviation of the propensity score on the logit scale) and no replacement. We assessed the distributions of demographic data and comorbidities in the BE-valve and SE-valve with standardized mean differences, which were calculated as a difference in means or proportions of a variable divided by a pooled estimate of the standard deviation of that variable. A standardized mean difference of 0.1 or less indicated a negligible difference between the means of the two cohorts. For the primary and secondary outcomes analysis, in both the total and the matched cohort, the incidence of the primary and secondary outcomes between BE-valve and SE-valve at 30 days was estimated, with stratification by time period, using Mantel–Haenszel weighting. The corresponding asymptotic two-sided 95% confidence interval (CI) of the relative risk (RR) was reported. The stratification per time period (three time periods: 2007–2010, 2011–2014, 2015–2018) was performed since SE-valves were relatively more frequently used in the early years of TAVI, whereas BE-valves were relatively more frequently used in the recent years of TAVI (Supplementary material online, *S4*). All statistical tests were two-tailed, and a *P*-value of <0.05 was considered statistically significant. Calculations were generated by SPSS software (version 24.0 for Windows, SPSS, Inc., Chicago, IL, USA).

Results

Baseline characteristics of the overall study population

A total of 12 381 patients with severe aortic valve stenosis who underwent transfemoral TAVI with a BE-valve ($n = 6239$) or SE-valve ($n = 6142$) were included in the CENTER-collaboration (*Table 1*). The mean patient age was 82 ± 7 years and 58% were women. The median STS-PROM score was 6.4% (IQR 4.0–13.0%). Patients treated with SE-valves more frequently had a history of prior PCI and patients with BE-valves more frequently had a prior history of peripheral artery disease.

Clinical outcomes in the overall population

Patients treated with BE-valves less often required conversion to open heart surgery during the TAVI procedure compared with patients treated with SE-valves (BE: 0.8% vs. SE: 1.2%, RR 0.7; 95% CI 0.5–1.0, $P = 0.04$) (Supplementary material online, *S5*). Moreover, patients treated with BE-valves less frequently required permanent pacemaker implantation (BE: 7.5% vs. SE: 20.3%, RR 0.4; 95% CI 0.3–0.4, $P < 0.001$). On contrary, in-hospital major or life-threatening bleedings were more frequently reported in patients treated with BE-valves compared with SE-valves (BE: 6.3% vs. SE: 5.2%, RR 1.2; 95% CI 1.0–1.4, $P = 0.02$). The occurrence of in-hospital mortality (BE: 4.8% vs. SE: 5.2%, RR 0.9; 95% CI 0.8–1.1, $P = 0.30$), stroke (BE: 1.8% vs. SE: 2.2%, RR 0.8; 95% CI 0.6–1.1, $P = 0.10$), myocardial infarction (BE: 0.7% vs. SE: 0.8%, RR 0.8; 95% CI 0.6–1.3, $P = 0.42$), and new-onset atrial fibrillation (BE: 5.3% vs. SE: 5.6%, RR 1.0; 95% CI 0.8–1.2, $P = 0.67$) were comparable among both valve types. At 30-days of follow-up, mortality (BE: 5.6% vs. SE: 5.9%, RR 1.0; 95% CI 0.8–1.1, $P = 0.61$) and likewise the stroke rate was comparable (BE: 2.2% vs. SE: 2.6%, RR 0.8; 95% CI 0.7–1.1, $P = 0.15$) among both valve-types.

Baseline characteristics of the propensity-matched analysis

From the total CENTER patient population, a total of 4096 pairs of patients who underwent transfemoral TAVI with a SE-valve or BE-valve, with similar baseline demographic and clinical characteristics, were obtained using the propensity score method (*Table 1*). The use of the propensity score method generated a matched population with a mean age of 81 ± 7 years and 57% were women. The median STS-PROM score was 6.5% (IQR 4.0–13.0%).

Table 1 Baseline patient characteristics of the overall population and propensity matched cohort

	Overall patient population			Propensity matched population		
	BE ($n = 6239$)	SE ($n = 6142$)	SMD	BE ($n = 4096$)	SE ($n = 4096$)	SMD
Demographics						
Age (years)	81.7 ± 6.9	81.2 ± 7.1	0.071	81.5 ± 7.1	81.3 ± 7.1	0.028
Female gender	3700 (59)	3420 (56)	0.081	2364 (58)	2336 (57)	0.015
Body mass index (kg/m^2)	27.0 ± 4.8	27.3 ± 4.9	0.062	27.2 ± 4.8	27.1 ± 4.8	0.021
Medical history						
Previous CVA or TIA	660 (11)	631 (10)	0.018	420 (10)	436 (11)	0.023
Previous MI	815 (13)	855 (14)	0.041	558 (14)	574 (14)	0.018
Previous PCI	1239 (20)	1421 (23)	0.107	883 (22)	886 (22)	0.002
Previous CABG	728 (12)	745 (12)	0.024	497 (12)	511 (13)	0.018
Diabetes mellitus	1952 (31)	1924 (31)	0.043	1298 (32)	1293 (32)	0.003
Hypertension	4920 (79)	4815 (78)	0.015	3223 (79)	3231 (79)	0.006
Dyslipidaemia	3383 (54)	3410 (56)	0.029	2236 (55)	2247 (55)	0.007
Peripheral artery disease	992 (16)	816 (13)	0.116	588 (14)	599 (15)	0.012
Coronary artery disease	2552 (41)	2530 (41)	0.007	1668 (41)	1682 (41)	0.009
Atrial fibrillation	1764 (28)	1590 (26)	0.071	1087 (27)	1115 (27)	0.019
GFR<30 mL/min	855 (14)	827 (14)	0.011	565 (14)	574 (14)	0.011
Logistic EuroSCORE (%)	15.2 (10.0–23.1)	14.6 (9.0–22.7)	0.055	15.0 (9.7–23.0)	15.0 (9.3–23.3)	0.018
STS-PROM (%)	6.4 (4.0–13.9)	6.4 (3.9–12.3)	0.082	6.3 (4.0–14.4)	6.6 (4.0–12.8)	0.051
Aortic mean gradient	51.1 ± 17.5	51.0 ± 17.2	0.006	51.0 ± 17.6	51.1 ± 17.4	0.006
Implanted valves[a]	$n = 5739$	$n = 5910$		$n = 3764$	$n = 3937$	
Edwards Sapien	474 (8)			313 (8)		
Sapien XT	3552 (62)			2329 (62)		
Sapien 3	1713 (30)			1122 (30)		
CoreValve		4240 (72)			2846 (72)	
Evolut		1670 (28)			1091 (28)	

A standardized mean difference of 0.1 or less indicated a negligible difference between the means of the two cohorts.
GFR: glomerular filtration rate; SMD, standardized mean difference; TIA: transient ischaemic attack.
[a]The exact valve type was unknown for patients included in the BRAVO3 study (6%).

Clinical outcomes for the matched population

In the matched population, patients treated with BE-valves less frequently experienced in-hospital stroke (BE: 1.5% vs. SE: 2.3%, RR 0.6; 95% CI 0.5–0.9, $P = 0.008$), and likewise in-hospital mortality was lower among patients treated with a BE-valves compared with SE-valves (BE: 4.3% vs. SE: 5.7%, RR 0.8; 95% CI 0.6–0.9, $P = 0.009$) (*Table 2*, *Figure 1*). Moreover, patients treated with BE-valves had a three-fold lower risk of permanent pacemaker implantation (BE: 7.8% vs. SE: 20.3%, RR 0.4; 95% CI 0.3–0.4, $P < 0.001$). On contrary, there was a trend to in-hospital major or life-threatening bleedings more frequently occurring in patients treated with BE-valves compared with SE-valves (BE: 6.6% vs. SE: 5.5%, RR 1.2; 95% CI 1.0–1.4, $P = 0.07$). Rates of conversion to open heart surgery (BE: 0.6% vs. SE: 1.2%, RR 0.7; 95% CI 0.4–1.1, $P = 0.10$), in-hospital myocardial infarction (BE: 0.6% vs. SE: 0.7%, RR 0.9; 95% CI 0.5–1.6, $P = 0.72$), and new-onset atrial fibrillation (BE: 5.6% vs. SE: 5.5%, RR 1.0; 95% CI 1.3–0.8, $P = 0.97$) were not different among the two valve types. At 30-days follow-up, the stroke rate remained significantly lower in patients treated with BE valves (BE: 1.9% vs. SE: 2.6%, RR 0.7; 95% CI 0.5–1.0, $P = 0.03$). The lower rate of stroke in patients treated with BE-valves compared with SE-valves was consistent among procedures performed in the early years of TAVI and those in more recent years (Supplementary material online, *S4*) and likewise among nine out of ten collaborating studies (Supplementary material online, *S6*). Of patients treated with a BE-valve who suffered from stroke after TAVI, 13.7% died during hospital admission, compared with 26.3% of the patients treated with SE-valves suffering from stroke ($P = 0.09$). In-hospital mortality was considerably higher in stroke patients (odds ratio 5.5, 95% CI 3.6–8.5). Mortality at 30 days follow-up was comparable among both valve types (BE: 5.3% vs. SE: 6.2%, RR 0.9; 95% CI 0.7–1.0, $P = 0.10$).

Clinical outcomes split for early-generation valves and new-generation valves

Clinical outcomes were compared between patients undergoing transfemoral TAVI with early-generation Edwards SAPIEN (ES) and SAPIEN XT (XT) BE-valves vs. early-generation Medtronic CoreValve (MCV) SE-valves, and likewise new-generation SAPIEN 3

Table 2 Outcomes in the propensity matched population (*N* = 8192)

	BE (*n* = 4096)	SE (*n* = 4096)	Relative risk (95% CI)	*P*-value
Procedural				
Conversion to open heart surgery	21 (0.6%)	47 (1.2%)	0.7 (0.4–1.1)	0.10
During hospital admission				
Mortality	150 (4.3%)	206 (5.7%)	0.8 (0.6–0.9)	0.009
Stroke	56 (1.5%)	89 (2.3%)	0.6 (0.5–0.9)	0.008
Myocardial infarction	24 (0.6%)	27 (0.7%)	0.9 (0.5–1.6)	0.72
Major or life-threatening bleeding	232 (6.6%)	197 (5.5%)	1.2 (1.0–1.4)	0.07
New-onset atrial fibrillation	116 (5.6%)	73 (5.5%)	1.0 (0.8–1.3)	0.97
Permanent pacemaker implantation	270 (7.8%)	753 (20.3%)	0.4 (0.3–0.4)	<0.001
At 30 days				
Mortality	184 (5.3%)	237 (6.2%)	0.9 (0.7–1.0)	0.10
Stroke	65 (1.9%)	98 (2.6%)	0.7 (0.5–1.0)	0.03

Incidence and relative risk (95% confidence interval) of clinical outcomes in patients treated with BE-valves compared with SE-valves, stratified by time period, analysed using the Mantel–Haenszel method. Reporting of secondary outcomes was not an inclusion criteria, and accordingly was not always documented by collaborating studies. Conversion to open heart surgery was complete in 92%, in-hospital mortality in 87%, stroke in 94%, myocardial infarction in 94%, major or life-threatening bleeding in 87%, new-onset atrial fibrillation in 42%, and permanent pacemaker implantation in 88%.

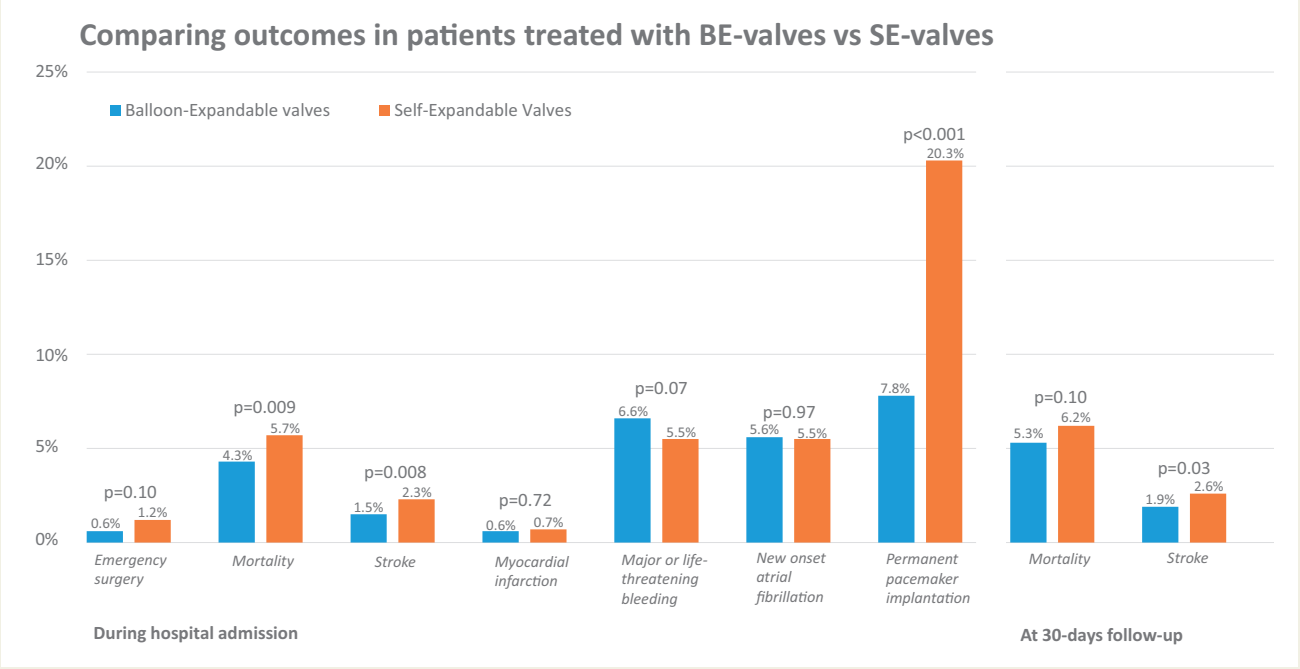

Figure 1 Clinical outcomes in patients treated with balloon-expandable valves compared with self-expandable valves.

(S3) BE-valves vs. new-generation SE-valves (Evolut series) (*Table 3*, *Figure 2*). Patients treated with new-generation BE-valves had a four-fold lower risk of conversion to open heart surgery during the TAVI procedure than patients treated with new-generation SE-valves (S3: 0.7% vs. Evolut: 2.6%, RR 0.3; 95% CI 0.2–0.4, $P < 0.001$). Moreover, in-hospital mortality was lower in patients treated with early-generation BE-valves compared with early-generation SE-valves (ES: 6.8 and XT: 5.1% vs. MCV: 6.8%, RR 0.8; 95% CI 0.7–0.9, $P = 0.003$). In contrast, the rate of 30-day mortality was comparable in patients treated with early-generation BE-valves and early-generation SE-valves (ES: 9.1% and XT: 5.9% vs. MCV: 7.1%, RR 0.9; 95% CI 0.8–1.0, $P = 0.11$). Mortality in new-generation valves was comparable both during hospital admission (S3: 2.4% vs. Evolut: 3.1%, RR 0.8; 95% CI 0.5–1.1, $P = 0.14$) and at 30-day follow-up (S3: 3.1% vs. Evolut: 3.4%, RR 0.9; 95% CI 0.6–1.3, $P = 0.73$). Patients treated with new-generation BE-valves less frequently suffered from stroke both during hospital-admission (S3: 0.8% vs. Evolut: 2.8%, RR 0.3; 95% CI 0.2–0.5, $P < 0.001$) and at 30-days of follow-up (S3: 1.3% vs. Evolut: 3.3%, RR

Table 3 Outcomes split for early-generation and new-generation valves

	BE ($n = 3764$)	SE ($n = 3937$)	Relative risk (95% CI)	*P*-value
Procedural				
Conversion to open heart surgery	Total: 31 (0.9%)	Total: 47 (1.2%)	0.7 (0.4–1.1)	0.10
	ES: 2 (0.6%)/XT: 22 (1.0%)	MCV: 20 (0.7%)	1.3 (0.9–2.0)	0.21
	S3: 7 (0.7%)	Evolut: 27 (2.6%)	0.3 (0.2–0.4)	<0.001
During hospital admission				
	Total: 142 (4.4%)	Total: 206 (5.7%)	0.8 (0.6–1.0)	0.02
Mortality	ES: 21 (6.8%)/XT: 98 (5.1%)	MCV: 163 (6.8%)	0.8 (0.7–0.9)	0.003
	S3: 23 (2.4%)	Evolut: 32 (3.1%)	0.8 (0.5–1.1)	0.14
Stroke	Total: 50 (1.4%)	Total: 85 (2.3%)	0.6 (0.5–0.9)	0.008
	ES: 5 (1.6%)/XT: 37 (1.7%)	MCV: 56 (2.1%)	0.8 (0.6–1.1)	0.15
	S3: 8 (0.8%)	Evolut: 29 (2.8%)	0.3 (0.2–0.5)	<0.001
Myocardial infarction	Total: 23 (0.7%)	Total: 25 (0.7%)	1.0 (0.6–1.7)	0.97
	ES: 2 (0.6%)/SXT: 17 (0.8%)	MCV: 20 (0.7%)	1.0 (0.6–1.6)	0.90
	S3: 4 (0.4%)	Evolut: 5 (0.5%)	0.8 (0.3–2.1)	0.69
Major or life-threatening bleeding	Total: 154 (4.8%)	Total: 147 (4.3%)	1.1 (0.9–1.4)	0.34
	ES: 8 (2.6%)/XT: 102 (5.1%)	MCV: 126 (5.2%)	0.9 (0.8–1.1)	0.35
	S3: 44 (4.8%)	Evolut: 21 (2.1%)	2.3 (1.6–3.3)	<0.001
New onset atrial fibrillation	Total: 103 (5.5%)	Total: 63 (5.4%)	1.1 (0.8–1.5)	0.52
	ES: 15 (7.0%)/XT: 73 (6.0%)	MCV: 59 (5.6%)	1.1 (0.8–1.4)	0.42
	S3: 15 (4.4%)	Evolut: 4 (3.7%)	1.2 (0.6–2.5)	0.67
Permanent pacemaker implantation	Total: 270 (7.8%)	Total: 753 (20.3%)	0.4 (0.3–0.4)	<0.001
	ES: 19 (6.1%)/XT: 162 (7.5%)	MCV: 567 (21.2%)	0.3 (0.3–0.4)	<0.001
	S3: 89 (8.9%)	Evolut: 186 (18.1%)	0.5 (0.4–0.6)	<0.001
At 30 days				
Mortality	Total: 175 (5.6%)	Total: 223 (6.2%)	0.9 (0.7–1.1)	0.24
	ES: 27 (9.1%)/XT: 124 (5.9%)	MCV: 191 (7.1%)	0.9 (0.8–1.0)	0.11
	S3: 24 (3.1%)	Evolut: 32 (3.4%)	0.9 (0.6–1.3)	0.73
Stroke	Total: 58 (1.8%)	Total: 93 (2.6%)	0.7 (0.5–1.0)	0.04
	ES: 5 (1.7%)/XT: 43 (2.1%)	MCV: 62 (2.3%)	0.9 (0.7–1.1)	0.30
	S3: 10 (1.3%)	Evolut: 31 (3.3%)	0.4 (0.2–0.6)	<0.001

Incidence and relative risk (95% confidence interval). Early generation valves: Edwards SAPIEN (ES), SAPIEN XT (XT) vs. Medtronic CoreValve (MCV). New-generation valves: SAPIEN 3 valve (S3) vs. Evolut series (Evolut). In the BRAVO-3 study, the exact valve type was not recorded, these patients are excluded from the current analysis.

0.4; 95% CI 0.2–0.6, $P < 0.001$) compared with patients treated with new-generation BE-valves. The stroke rate in early-generation valves was comparable during hospital admission (ES: 1.6% and XT: 1.7% vs. MCV: 2.1%, RR 0.8; 95% CI 0.6–1.1, $P = 0.15$) and at 30-day follow-up (ES: 1.7% and XT: 2.1% vs. MCV: 2.3%, RR 0.9; 95% CI 0.7–1.1, $P = 0.30$). Patients undergoing TAVI with new-generation BE-valves more frequently encountered major or life-threatening bleedings compared with patients treated with new-generation SE-valves (S3: 4.8% vs. Evolut: 2.1%, RR 2.3; 95% CI 1.6–3.3, $P < 0.001$). On contrary, the rate of major and life-threatening bleeding in early-generation valves was comparable (ES: 2.6% and XT: 5.1% vs. MCV: 5.2%, RR 0.9; 95% CI 0.8–1.1, $P = 0.35$). Patients undergoing TAVI with new-generation BE-valves less frequently required permanent pacemaker implantation compared with patients treated with new-generation SE-valves (S3: 8.9% vs. Evolut: 18.1%, RR 0.5; 95% CI 0.4–0.6, $P < 0.001$), this difference was larger in patients treated with early-generation valves (ES: 6.1% and XT: 7.5% vs. MCV: 21.2%, RR 0.3; 95% CI 0.3–0.4, $P < 0.001$).

Discussion

The main finding of the current large scale, propensity-matched study was that the stroke rate was lower in patients undergoing transfemoral TAVI with BE-valves compared with SE-valves. Additionally, patients treated with a BE-valve had a three-fold lower risk of requiring permanent pacemaker implantation. There was no difference in 30-day mortality rates between both valve types. In contrast, patients treated with new-generation BE-valves more often suffered from major or life-threatening bleedings than patients with new-generation SE-valves.

Description of the study results

Patients treated with early-generation SE-valves frequently needed pacemaker implantation in 21.2% of the cases, this rate reduced in new-generation SE-valves to 18.1%, but remained considerably higher compared with new-generation BE-valves (8.9%, $P < 0.001$). The high rate of permanent pacemaker implantation in patients

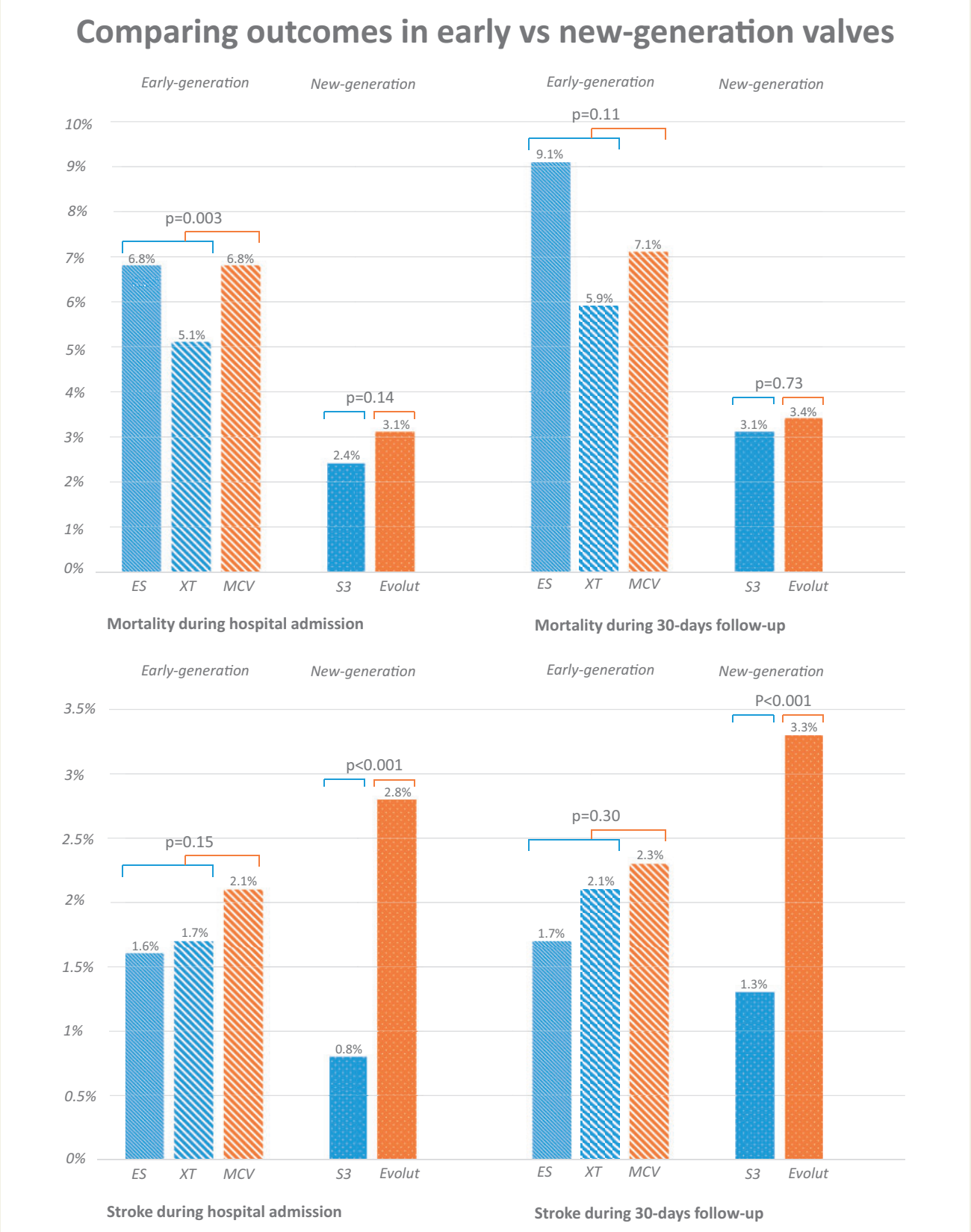

Figure 2 Clinical outcomes in patients treated with early-generation balloon-expandable valves compared with early-generation self-expandable valves, and new-generation balloon-expandable valves compared with new-generation self-expandable valves.

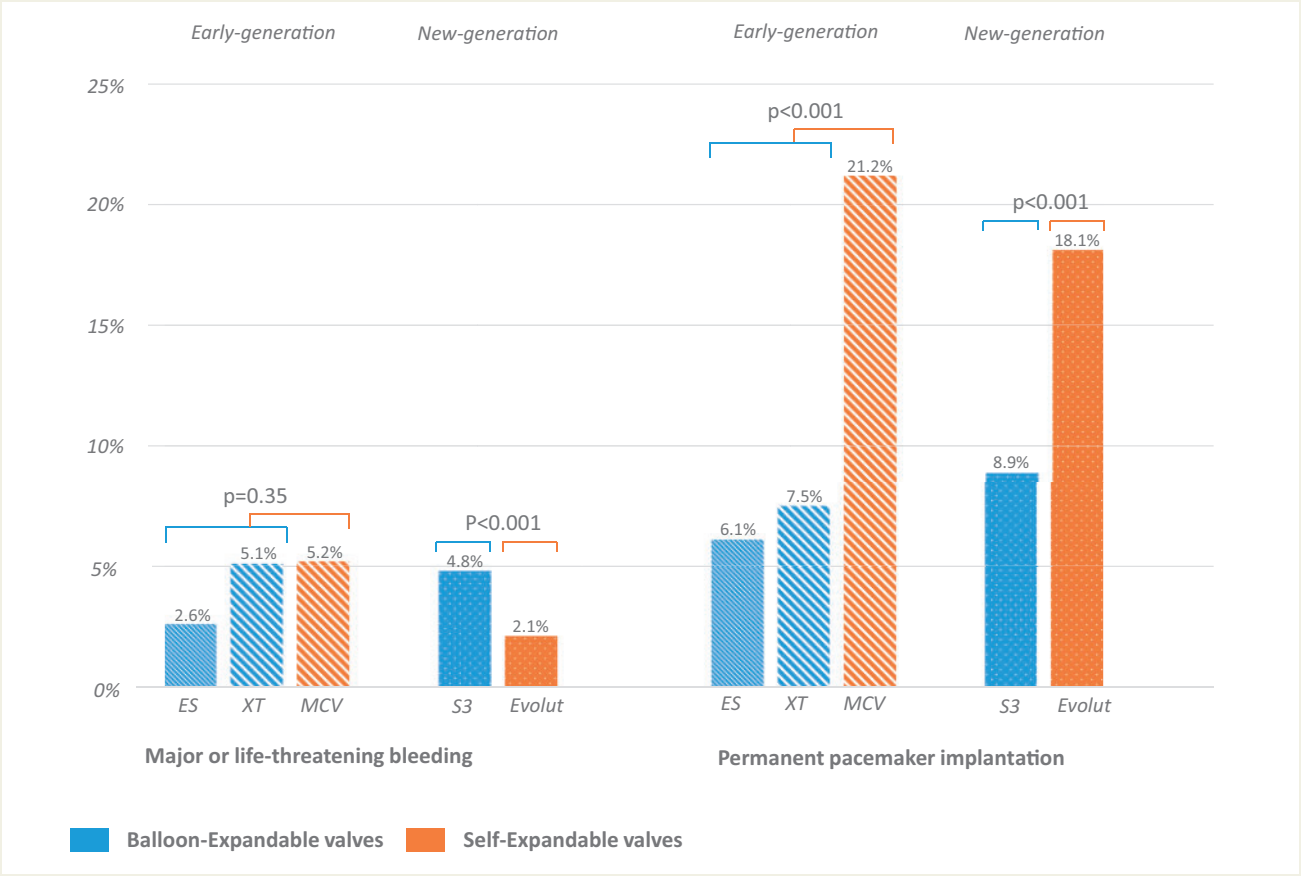

Figure 2 Continued

treated with SE-valves has previously been documented.[21] However, in our study population we also found higher rates of in-hospital mortality as well as 30-day stroke in patients who underwent TAVI with a SE-valve. The higher stroke rate in SE-valves compared with BE-valves was mainly powered by the new-generation valves, which highlights the importance of this finding. We hypothesize that the working mechanism of the implantation of SE-valves may generate the higher observed procedural stroke rate. SE-valves are implanted slowly, and stepwise and have the option to reposition the prosthesis before final implantation, accordingly the longer implantation time may increase the likelihood of embolization of particles of the native calcified valve, when compared with the rather rapid positioning of BE-valves. Also the surface of the SE-valve systems is larger compared with BE-valves, this may generate more extensive manipulation of the often calcified aortic arch. This is in accordance with a study from Erdoes *et al.*,[22] which quantified the amount of cerebral embolization during TAVI, by performing transcranial Doppler recordings during 44 TAVI procedures. There was a 41% higher rate of high-intensity transient signals, representing cerebral embolization, in patients treated with SE-valves compared with BE-valves ($P = 0.02$). Cerebral embolization was higher both during and after valve-deployment in patients treated with SE-valves. Likewise, a recent histopathologic assessment of captured debris derived from cerebral protection devices from 246 TAVI procedures, showed that in patients treated with SE-valves, more frequently larger particles were captured compared with those treated with BE-valves.[23] The higher in-hospital mortality rate in patients treated with SE-valves may be the consequence of this higher procedural stroke rate. Patients with stroke after TAVI had a 5.5-fold higher chance to die during hospital admission. Also, the mortality rate in patients treated with SE-valves suffering from stroke was higher compared with patients treated with BE-valves suffering from stroke. Moreover, the trend to a higher rate of emergency surgery in patients treated with SE-valves may also have contributed to the higher in-hospital mortality rate among patients treated with SE-valves. Lastly, in this study patients treated with new-generation BE-valves more frequently experienced in-hospital major or life-threatening bleedings compared with patients treated with new-generation SE-valves. The early-generation Edwards SAPIEN valve required large sheath sizes (22F/24F), however, the new-generation SAPIEN 3 requires smaller sheath sizes (14F/16F), this is similar to the Evolut-series. Accordingly, this finding is subject to further research.

Comparison with the literature

To our knowledge, there are three earlier clinical studies providing a head-to-head comparison of patients treated with BE-valves compared with SE-valves. The PRAGMATIC collaboration was also an international propensity-matched analysis, including patients from multiple centres ($n = 408$).[9] In the PRAGMATIC collaboration, the rate of pacemaker implantation was also higher in patients treated

with SE-valves (RR 4.6; 95% CI 2.4–9.1, $P < 0.001$). Similar to this study, rates of 30-day mortality (SE: 8.8% vs. BE: 6.4%, RR 1.4; 95% CI 0.7–3.0, $P = 0.35$) and stroke (SE: 2.9% vs. BE: 1.0%, RR 3.1; 95% CI 0.6–15.4, $P = 0.17$) were numerically slightly higher in patients treated with SE-valves. However, due to the modest sample size of the PRAGMATIC study, the study was underpowered to detect statistical significant differences in these relatively rare outcomes. Moreover, in the PRAGMATIC collaboration studies were not selected through a systematic review, accordingly it is unclear if collaborating centres had experience with both valve types, this may have resulted in a comparison of clinical outcomes between centres rather than valve-types.

The CHOICE-trial ($n = 240$) was a randomized study that concluded there was a lower rate of device success in SE-valves compared with BE-valves (78% vs. 96%, $P < 0.001$), as a consequence of more frequent aortic regurgitation in patients treated with SE-valves.[8] Aortic regurgitation, even when defined as mild, is associated with a three-fold higher mortality risk.[24,25] The CHOICE-trial also found that pacemaker implantation occurred more frequently in patients treated with SE-valves. The SOLVE-TAVI ($n = 447$) was a recent randomized controlled trial evaluating BE vs. SE-valves.[10] The combined primary endpoint of mortality, stroke, regurgitation and permanent pacemaker implantation was comparable in both arms (BE: 26.1% vs. SE: 27.2%, $P_{equivalence} = 0.02$). However, this combined endpoint was mainly powered by the rate of pacemaker implantation, which was high in both arms (BE: 19.0% vs. SE: 22.9%, $P = 0.34$), suggesting a possible learning curve in the implantation of the SAPIEN 3 valve. In contrast to this study, there was a higher number of stroke in the patients treated with BE-valves (BE: 4.7% vs. SE: 0.5%, $P = 0.01$). However, due to the relative low incidence of stroke and mortality, all three trials were underpowered to assess these individual endpoints.

Current device developments and future perspectives

Both Edwards Lifesciences and Medtronic Cardiovascular continue to develop new valves in order to further reduce clinical complications. First results suggest that implantation of these new devices are associated to a lower pacemaker implantation rate. The self-expanding Evolut series (now joined by the EVOLUT-R and the EVOLUT-Pro valves) are the newest developments of Medtronic Cardiovascular. Pacemaker implantation in patients treated with the EVOLUT-R was lower (16.4%) compared with earlier self-expanding valves.[7] The CENTERA is a new, self-expanding valve from Edwards Lifesciences that allows repositionability of the valve prior to the final implantation. In the pivotal trial in high-risk patients ($n = 203$), new pacemaker implantation was required in a mere 4.5%.[26] Accordingly, in this first trial, this novel self-expanding valve showed four-fold lower pacemaker implantation rate compared with the self-expandable valves in this study, and also a two-fold lower pacemaker implantation rate compared with balloon-expandable valves. With the expansion of TAVI to low-risk patients, the reduction of stroke and mortality will become even more important. Currently, the newest devices of both Edwards Lifesciences (PARTNER 3, NCT02675114) and Medtronic Cardiovascular (NCT02701283) are both studied in low-risk patients in large scale randomized controlled trials. The results of these trials will tell us more about clinical outcomes of the newest generation of valves. However, we believe this study warrants a dedicated large scale randomized trial.

Study limitations

This study was a propensity-matched analysis, generated from real-world observational data. However, even though the populations of the current collaboration were selected through a systematic-search, the willingness of principle investigators to collaborate may be the result of preconceived beliefs about the optimal therapy and this may have influenced the final study population. Moreover, due to the non-randomized nature of this study, the results are subject to selection bias and confounding. Even though propensity-score matching was performed in an aim to minimize these biases, hidden bias may remain due to the influences of unmeasured confounders. Moreover, propensity matching may increase the heterogeneity due to strengthening of unmeasured confounders. Furthermore, in this collaboration, many participating studies did not have independent adjudication committees, which may have resulted in potential reporting bias, however we do not expect this to have a relation with a certain valve type. Also, in this study, aortic regurgitation after TAVI was not available as an outcome, accordingly we cannot compare differences in aortic regurgitation between different valve-types. Finally, this study focused on short-term clinical complications, accordingly, conclusions on valve durability or long-term outcomes cannot be made.

Supplementary material

Supplementary material is available at *European Heart Journal* online.

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Conflict of interest: F.S.B. is a proctor for Edwards Lifesciences and Medtronic. M.B. is consultant for Edwards Lifesciences and received speaker honoraria from Medtronic and Biotronik. A.L. is a consultant for Medtronic and has received honoraria from Abbott Vascular. A.D.O. is a proctor for Edwards Lifesciences and for Symetis. A.A. is proctor for Boston Scientific. J.B. receives an unrestricted research grant from Edwards Lifesciences and is a proctor for Edwards Lifesciences. All others have declared no conflict of interest.

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