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Evolution of transcatheter aortic valve implantation over 7 years: results of a prospective single-centre registry of 2000 patients in a large municipal hospital (TAVIK Registry)

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ABSTRACT

Objectives Use of transcatheter aortic valve implantation (TAVI) to treat severe aortic stenosis (AS) has gained popularity, accompanied by an evolution of patient and clinical factors. We aimed to characterise changes and evaluate their impact on outcomes.

Setting In this single-centre, German TAVIK registry patients undergoing TAVI between 2008 and 2015 were documented prospectively.

Participants/interventions 2000 consecutive patients with AS undergoing TAVI were divided in four cohorts. 500 patients underwent TAVI in each of the following time bins: April 2008 to July 2010 (cohort I), July 2010 to April 2013 (cohort II), April 2012 to October 2013 (cohort III) and October 2013 to March 2015 (cohort IV).

Results The mean age was 81.8 years, without significant variation across cohorts. Compared with cohort I, prior MI (5.4%vs11.0%; p<0.001) and New York Heart Association class IV (10.0%vs3.6%; p<0.001) were less common in cohort IV. Across cohorts, there was a fall in EuroSCORE (24.3%–18.7%), frailty (48.4%–17.0%) and use of transapical access (43.6%–29.0%), while transfemoral access increased (56.4%–71.0%; p<0.001 for each). Periprocedurally, there was a fall in moderate/severe aortic regurgitation (3.2%–0.0%) and rate of unplanned cardiopulmonary bypass (4.0%–1.0%; both p<0.001). A similar trend applied to 30-day rate of major vascular complications (5.2%–1.8%; p=0.006), life-threatening bleeding (7.0%–3.0%; p<0.001) and cardiovascular mortality (4.4%–1.8%; p=0.020). One-year post-TAVI, mortality and stroke rates did not differ.

Conclusions Evolution of TAVI between 2008 and 2015 saw a trend towards its usage in lower risk patients and rapid progression towards improved safety. Evaluation and refinement should now continue to further lessen stroke and pacemaker rates.

Strengths and limitations of this study

► This large-scale cohort study including 2000 patients with severe aortic stenosis undergoing transcatheter aortic valve implantation (TAVI) provides valuable insight in patient characteristics, device usage and clinical outcomes of TAVI between 2008 and 2015.

► The large sample size provides robustness and strong statistical power for the reported outcomes.

► Given the time span covered by the study and the rapid evolution of TAVI, it was not initially possible to predict all of the factors which would be necessary for meaningful comparisons in later cohorts.

Indeed, a 20-fold increase was reported in Germany between 2008 and 2014,[2 3] with similar trends documented for other populations.[4 5]

This rapid increase in popularity has been accompanied by a range of technical and clinical advancements. First, valves themselves have been modified to facilitate better apposition and delivery to a wider range of patients. For example, the Edwards SAPIEN valve has seen a reduction in the size of delivery apparatus and sheath diameter, the addition of a skirt to reduce regurgitation and a greater range of prosthesis sizes to minimise prosthesis–patient mismatch.[6 7] Second, the procedure itself has come under scrutiny, with a number of alternative access routes developed[8 9] and the merit of balloon predilatation carefully evaluated.[10 11] Third, mounting TAVI experience means that surgeons and their teams are rapidly acquiring the necessary operator skill and expertise to minimise complications. Such experience has also led to the greater appropriacy of patient

INTRODUCTION

Transcatheter aortic valve implantation (TAVI) is becoming ever more prominent in the treatment of severe aortic stenosis (AS).[1]

selection by multidisciplinary Heart Teams. Finally, evidence from more recent clinical trials has supported the suitability of TAVI for patients at lower surgical risk, resulting in the performance of the procedure in individuals also eligible for surgical aortic valve replacement (SAVR).[12–15] It is logical to assume that these cumulative evolutionary steps have had considerable impact on procedural and longer term outcomes. However, robust evidence outlining the nature and degree of this impact does not appear to have been published.

In the present cohort study, data for 2000 patients who underwent transapical (TA) or transfemoral (TF) TAVI procedures at a single centre in Germany between 2008 and 2015 were analysed. We aimed to fully characterise the changes to TAVI over time, and to gain insight into their effect on parameters such as patient selection, periprocedural outcomes and early safety endpoints.

METHODS

Study design
The prospective TAVIK registry documented consecutive patients undergoing TAVI between May 2008 and March 2015 with the TAVIK team Karlsruhe, Germany.[16–18]

Patients
Patients were consecutively enrolled if they were diagnosed with severe AS (aortic valve area (AVA) of $<1\,cm^2$, an indexed AVA of $<0.6\,cm^2/m^2$, a maximum jet velocity of >4 m/s or a mean transvalvular gradient of $>40\,mm$ Hg) or a severe defect of an aortic bioprosthesis and had been assigned to undergo TAVI by the Karlsruhe Heart Team, which included cardiologists and cardiac surgeons. During the duration of data collection for this analysis, 1039 isolated SAVRs were performed which are not reported for the current analysis. The two principal criteria used to determine suitability for TAVI were a logistic EuroSCORE of ≥15 or age ≥75 years with a logistic EuroSCORE of <15. The presence of additional comorbidities not considered in the EuroSCORE, such as malignancy (but with a life expectancy greater than 1 year), liver cirrhosis, severe pulmonary disease with long-term provision of oxygen, frailty and porcelain aorta were also evaluated. Patients who were unwilling to undergo SAVR were also considered for TAVI. An unsuitable native aortic valve annulus was considered a contraindication for TAVI, as was a life expectancy or quality of life that was seriously affected by comorbidities (such as dementia with disability, a prior major stroke, uncontrolled congestive heart failure or cardiogenic shock).

Patient involvement
No patients were asked for input in the creation of this article.

Intervention
All TAVI (TF and TA) procedures were performed under general anaesthesia by a multidisciplinary team comprised an interventional cardiologist, cardiac surgeon and anaesthesiologist specialised in cardiac surgery that were trained together with catheterisation laboratory and operating room personnel to perform transcatheter procedures. The team was composed of essentially the same people over the study period.

Prior to the TAVI procedure, patients were evaluated using angiographic CT, transoesophageal echocardiography (TEE) and coronary angiography. The most appropriate transcatheter heart valve (THV) size was determined by measuring the diameter of the native annulus using CT combined with TEE in the long-axis view at the level of leaflet insertion.

The THVs implanted included the balloon-expandable SAPIEN, SAPIEN XT or SAPIEN 3 (Edwards Lifesciences); and the self-expanding CoreValve (Medtronic), ACURATE (Symetis), Portico Valve (St Jude Medical) and Jena Valve (Jena Valve Technology).

Documentation
Patient characteristics were documented at baseline and details of the TAVI procedure recorded. These included access route, type of THV implanted and periprocedural complications. Device success was defined according to the Valve Academic Research Consortium (VARC)-2 criteria[19] as no procedural mortality, correct positioning of a single valve, a mean valve gradient of <20 mm Hg and no moderate/severe aortic valve regurgitation. Early safety was also determined according to VARC-2 parameters at 30 days. Patients being enrolled before the VARC criteria were published were recoded to enable the analysis. Patients were followed up at outpatient visits or by telephone interview over the year following TAVI. No audits or external adjudication was performed.

Statistics
Patients were divided into four cohorts of 500 consecutive implantations: cohort I: April 2008 to July 2010; cohort II: July 2010 to April 2012; cohort III: April 2012 to October 2013; cohort IV: October 2013 to March 2015. Categorical variables were compared using the χ^2 test, while continuous variables were compared using the Student's t-test or Wilcoxon rank-sum test, as appropriate. Statistical significance across cohorts was calculated using the χ^2 method, adjusting the p values after the Bonferroni method for the proportions. Pairwise results were corrected using the Bonferroni-Holm-Shaffer procedure for multiple comparisons. An analysis of variance was employed for multiple comparisons of continuous variables among the four groups, using the Games-Howell as a post hoc test. One-year cumulative mortality was assessed using Kaplan-Meier estimates and compared using pairwise log-rank tests.

Data analysis was conducted using SPSS V.20 (IBM). A p<0.05 was considered statistically significant.

RESULTS
Patients
The mean age of the 2000 patients included in the study was 81.8±5.5 years, with no significant difference across cohorts (p=0.389) (figure 1A). However, the proportion of females was higher for cohort I (62.8%) than for the latter three cohorts (p<0.001 across groups), with the proportion of patients who were considered to be frail falling over time (48.4%, 42.8%, 25.2% and 17.0% for cohorts I–IV, respectively; p<0.01 across groups) (figure 1A). Myocardial infarction within the 90 days prior to study inclusion was notably less common in cohort IV (5.4% vs 11.0%, 14.8% and 13.8% for cohorts I–III, respectively; p<0.0001 across cohorts) (table 1). The proportion of patients undergoing TAVI as an emergency procedure was also lower in latter cohorts (2.0%, 2.8%, 0.2% and 0.2% for cohorts I–IV, respectively; p=0.001 across groups). There were no significant differences in BMI or prior cardiovascular interventions across groups. The mean logistic EuroSCORE decreased from cohort I (24.3±16.7) through cohorts II (21.7±15.6), III (19.6±14.3) and IV (18.7%±13.7) (p<0.001 across groups) (figure 1B)

There was no significant difference in left ventricular ejection fraction across cohorts. While similar proportions of cohorts I and II were in New York Heart Association (NYHA) class IV prior to TAVI (10.0% and 10.8%, respectively), these numbers had fallen significantly by cohorts III (5.0%) and IV (3.6%; p<0.001 across cohorts) (table 1). Though no time-dependent trend was seen in the proportions of patients in NYHA class III or with a porcelain aorta, significant differences were found between cohorts, with lower frequencies in cohorts II and III (p<0.001 across groups in both cases).

Procedural characteristics
While TA access fell across cohorts from 43.6% in cohort I to 29.0% in cohort IV (p<0.001), TF access rose from 56.4% to 71.0%, respectively (p<0.001) (table 2). Balloon-expandable valves were more common than the self-expandable valve (CoreValve, Medtronic) in all cohorts, though a trend towards a decrease in the former and an increase in the latter was evident from cohorts I to III, followed by a sharp 13.2% shift back towards use of the balloon-expandable valves in cohort IV (table 2). SAPIEN models were most commonly used in each cohort, with progression from the SAPIEN through the SAPIEN XT and SAPIEN 3generations correlating with availability. The more recently developed ACURATE (Symetis), Portico (St Jude Medical) and JenaValve (JenaValve Technology; now discontinued) valves were used more frequently in the latter two cohorts, though proportions only reached 7.8%, 2.8% and 0.6%, respectively.

Device success and periprocedural complications
Device success increased slightly from cohort I to II (86.2%–91.4%; p=0.012) (table 2) with no further increase thereafter (89.6% and 90.2% for cohorts III and IV, respectively). There was nominal trend towards reduced procedural mortality (3.0%, 2.2, 2.2% and 1.2%

for consecutive cohorts, respectively; overall p=0.275), though this did not reach significance. Moderate/severe valve regurgitation fell overall, despite small fluctuations (3.2%, 0.6%, 1.8% and 0.0%, respectively; p<0.001). A similar, non-significant pattern was notable for incorrect positioning (1.4%, 0.6%, 0.2% and 0.6%, respectively; p=0.141). There was a decrease in the rate of unplanned cardiopulmonary bypass (CPB) from 4.0% in cohort I to 2.8%, 0.4% and 1.0% for the subsequent three cohorts (p<0.001). A particularly high proportion of patients with mean AV gradients ≥20 mm Hg was seen in cohort IV (5.6% vs 3.2%, 1.6% and 1.8% for cohorts I–III, respectively; overall p=0.001).

The proportion of patients with mean AV gradients ≥20 mm Hg was higher in isolated SAPIEN 3 implantations (5%, 15/323) compare to SAPIEN XT (1.3%, 11/840) and SAPIEN (3.0, 10/326). This was potentially due to the more frequent use of 23 mm S3 (10.9%) compared with the XT (3.5%) or SAPIEN valve (4.2%). Patients undergoing CoreValve or ACCURATE implantations had mean AV gradients ≥20 mm Hg in 0.8% (3/350) or 11.4% (9/79).

Early safety (30 days)
The proportion of patients meeting the VARC-2 early safety composite endpoint during the first 30 days post-TAVI decreased through subsequent cohorts (from 16.2% in cohort I to 11.8% in cohort IV), with overall borderline significance seen (p=0.068) (table 2). This was mainly driven by a fall in the proportion of patients experiencing major vascular complications (5.2%, 3.4%, 2.0% and 1.8% for cohorts I to IV; p=0.002) and life-threatening bleeding (7.0%, 5.4%, 2.0% and 3.0%, respectively; p=0.004). There were no significant differences in all-cause mortality between the four cohorts, though cardiovascular mortality decreased from 4.4% in cohort I to 1.8% in cohort IV, with a small peak of 5.4% in cohort II (overall p=0.018). Rates of stroke and acute kidney injury stage 2/3 did not show any particular trends over time, though clear peaks occurred in cohorts IV (4.0%) and III (5.3%), respectively. The former peak was driven by a rise in non-disabling stroke.

One-year outcomes
The cumulative 1-year mortality rate was statistically different across cohorts (83.4%, 78.8%, 86.6% and 84.8% for cohorts I–IV, respectively; p=0.013) (figure 2A), which was because of a significant difference between cohorts II and III (p=0.001). The same was true of the proportions of patients experiencing at least one stroke during this period (2.6%, 1.8%, 1.8% and 4.0%, respectively; p=0.090) (figure 2B). Conversely, the proportions of patients experiencing at least one life-threatening/major bleeding event varied significantly across cohorts (7.4%, 4.2%, 1.8% and 3.2%, respectively; p<0.001) (figure 2C). The proportion of patients experiencing at least one major vascular complication fell across cohorts (5.2%, 3.4%, 2.0% and 1.8%, respectively; p=0.002) (figure 2D).
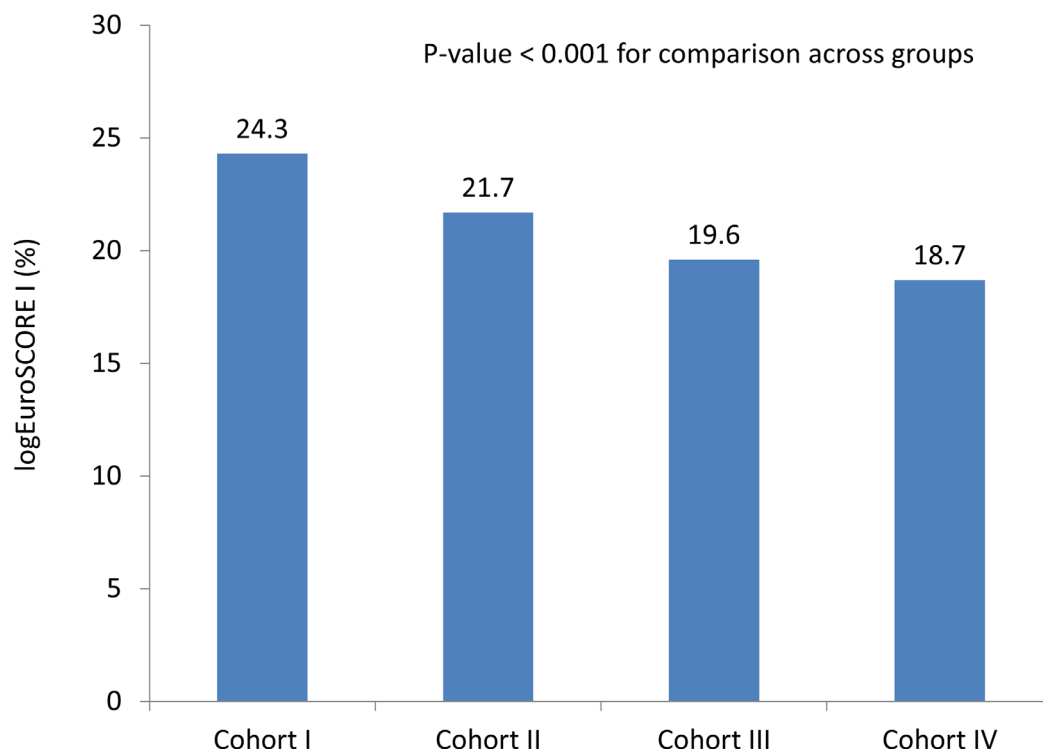
Age, gender and frailty
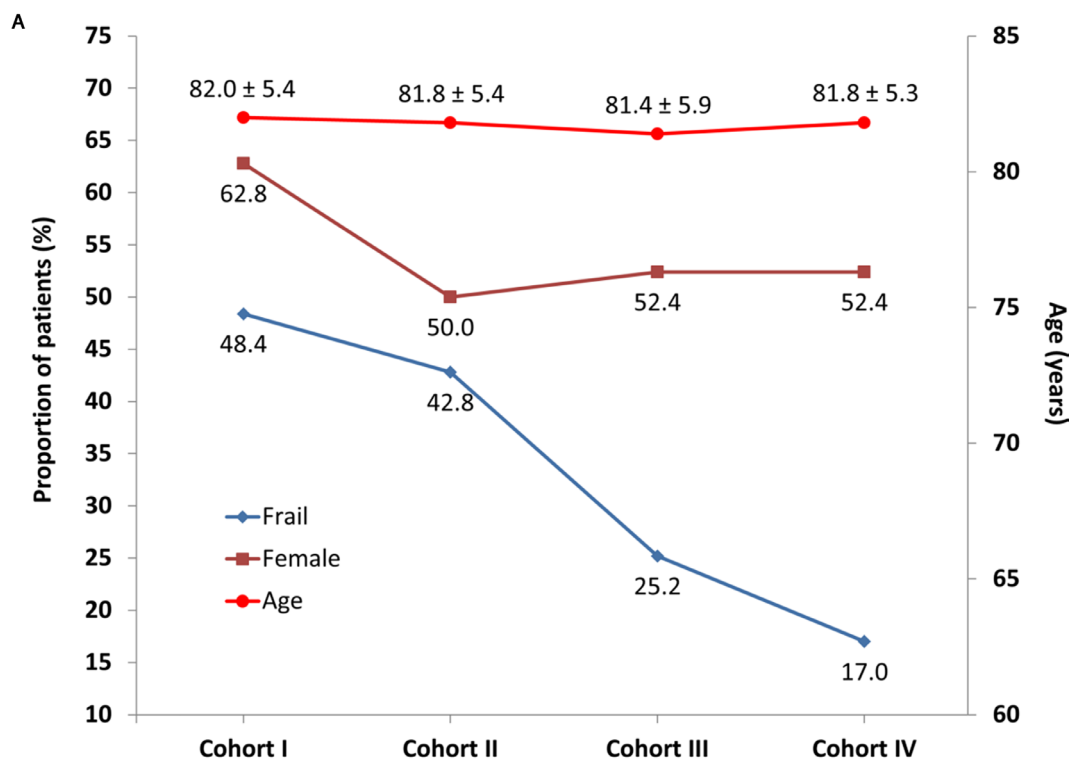
Figure 1 Changes in TAVI patient characteristics across cohorts. (A) Mean age ±SD (p=0.389 across groups), proportions of female patients (p<0.001 across groups) and frail patients (based on mental weakness, poor mobility, incontinence and self-care; p<0.001 across groups). (B) Mean logistic EuroSCORE (p<0.001 across groups). TAVI, transcatheter aortic valve implantation.

Table 1 Patient characteristics

	Cohort I (n=500) Mean±SD/%	Cohort II (n=500) Mean±SD/%	Cohort III (n=500) Mean±SD/%	Cohort IV (n=500) Mean±SD/%	Overall P values
Age (years)	82.0±5.4	81.8±5.4	81.4±5.9	81.8±5.3	0.389
BMI (kg/m^2)	26.4±4.6	26.7±4.8	26.9±4.9	27.1±5.0	0.097
Comorbidities					
CAD	59.6	60.6	62.6	60.6	0.802
History of MI (<90 days)	11.0	14.8	13.8	5.4	<0.001
Mitral disease ≥II°	12.0	14.6	13.4	12.0	0.555
Diabetes mellitus (%)	28.8	28.4	28.4	23.0	0.120
PAD (%)	17.0	14.0	14.0	18.2	0.202
Previous cardiac intervention					
PCI	27.6	30.2	33.6	32.2	0.190
CABG	20.8	16.8	16.2	14.6	0.062
Valve surgery	4.8	3.2	2.0	3.0	0.093
Pacemaker implantation	9.8	12.4	12.4	11.4	0.528
Frailty					
Mental status	10.4	7.2	7.4	7.8	0.220
Incontinence	10.6	8.0	7.2	1.6	<0.001
Poor mobility	42.0	33.4	17.2	12.4	<0.001
Activities of daily living	33.0	30.6	14.8	4.6	<0.001
LVEF (%)	57.0±14.4	56.7±14.1	56.6±12.6	57.1±12.8	0.938
NHYA class III	81.8	75.6	76.8	92.4	<0.001
NYHA class IV	10.0	10.8	5.0	3.6	<0.001
Porcelain aorta	9.2	1.4	3.2	11.8	<0.001
Emergency indication	2.0	2.8	0.2	0.2	0.001

BMI, body mass index; CABG, coronary artery bypass graft; CAD, coronary artery disease; LVEF, left ventricular ejection fraction; MI, myocardial infarction; NYHY, New York Heart Association; PAD, peripheral artery disease; PCI, percutaneous coronary intervention.

DISCUSSION

This large-scale cohort study provides valuable insight into the changes in patient characteristics, device usage and clinical outcomes of TAVI between 2008 and 2015. A reduction in patient frailty, surgical risk and functional impairment was observed over cohorts, alongside an increase in the number of procedures performed via the TF route. Several improvements in periprocedural outcomes were also seen, such as a fall in moderate/severe valve regurgitation and rate of unplanned CPB. Early safety composite outcomes improved slightly across cohorts, predominantly driven by a reduction in the rates of major vascular complications and life-threatening bleeding. The latter parameters followed the same trend at 1 year, though no difference in cumulative mortality or stroke was evident. Overall, data suggest a rapid and constructive evolution of TAVI.

Changes in patient characteristics

Patient frailty and severity of functional impairment at baseline fell across cohorts, as did surgical risk score (as determined by EuroSCORE I). In addition, the proportion

of patients with prior MI had fallen considerably by cohort IV, with the TAVI procedure less commonly performed in the emergency setting. This reflects the initial use of TAVI in inoperable or high-risk patients only,[20] and the trend towards more intermediate and lower risk patients undergoing the procedure over time.[13 21 22] This may also explain the greater proportion of women who underwent TAVI in cohort I, as females with AS have been noted to present with more advanced disease[23] and at a greater surgical risk.[24]

The extension of TAVI to lower risk patients is supported by a growing body of evidence demonstrating its similar safety and reduced invasiveness compared with SAVR. For example, a multicentre, propensity score-matched, observational study of 266 patients with a mean logistic EuroSCORE of <10 found similar, low rates of early mortality, MI and stroke between SAVR and TAVI patients.[25] These results were echoed by a study of 362 patients with a mean logistic EuroSCORE of 7.0, which reported similar rates of cerebrovascular events and in-hospital/1-year mortality.[26] Furthermore, a recent analysis of 20 340 patients found no

Table 2 Procedural characteristics, procedural outcomes and early safety (30 days)

	Cohort I (n=500) %	Cohort II (n=500) %	Cohort III (n=500) %	Cohort IV (n=500) %	Overall P values
Access route (%)					<0.001
TA	43.6	39.0	30.0	29.0	
TF	56.4	61.0	70.0	71.0	
Valve expansion mechanism (%)					<0.001
Balloon-expandable	85.4	77.8	75.8	89.0	
Self-expandable	14.6	22.2	24.2	11.0	
Valve implanted (%)					<0.001
SAPIEN	70.0	0.8	0.0	0.2	
SAPIEN XT	15.6	75.0	67.4	13.2	
SAPIEN 3	0.0	0.0	1.0	64.4	
CoreValve*	14.4	22.2	24.2	11.0	
ACURATE	0.0	2.2	7.0	7.8	
Portico	0.0	0.0	0.4	2.8	
JenaValve	0.0	0.0	0.0	0.6	
Device success (%)	86.2	91.4	89.6	90.2	0.050
Reason for device failure (%)					
Procedural mortality	3.0	2.2	2.2	1.2	0.275
Mean AV gradient ≥20 mm Hg	3.2	1.6	1.8	5.6	0.001
Moderate/severe prosthetic valve regurgitation	3.2	0.6	1.8	0.0	<0.001
Incorrect positioning	1.4	0.6	0.2	0.6	0.141
Second valve required	3.0	3.6	4.4	2.4	0.336
Other complications (%)					
Conversion to open surgery	2.4	2.0	0.6	1.8	0.146
Unplanned CPB	4.0	2.8	0.4	1.0	<0.001
Pericardial tamponade	1.2	0.4	0.8	1.6	0.257
New pacemaker	15.8	14.5	16.4	13.9	0.708
Early safety (30 days) composite endpoint†	16.2	15.4	12.4	11.8	0.068
All-cause mortality	5.4	7.0	4.4	4.4	0.212
Cardiovascular	4.4	5.4	3.4	1.8	0.018
Non-cardiovascular	1.0	1.6	1.0	2.6	0.113
Stroke	2.6	1.8	1.8	4.0	0.090
Disabling	2.0	1.4	1.4	2.0	0.783
Non-disabling	0.6	0.6	0.6	2.0	0.014
Life-threatening bleeding	7.0	5.4	2.0	3.0	0.004
Acute kidney injury stage 2/3	2.3	2.5	5.3	2.7	0.021
Coronary artery obstruction requiring intervention	1.2	0.4	0.0	0.6	0.077
Major vascular complication	5.2	3.4	2.0	1.8	0.002
Valve-related dysfunction requiring intervention	0	0	0	0	

VARC-2 criteria Kappetein et al.[19]

*Only CoreValve, but no Evolut or Evolut R were implanted.

†Composite of all-cause mortality, all stroke (disabling and non-disabling), 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 (BAV, TAVI or SAVR).

AV, aortic valve; BAV, balloon aortic valvuloplasty; CBP, cardiopulmonary bypass; SAVR, surgical aortic valve replacement; TA, transapical; TAVI, transcatheter aortic valve implantation; TF, transfemoral; VARC-2, Valve Academic Research Consortium-2.
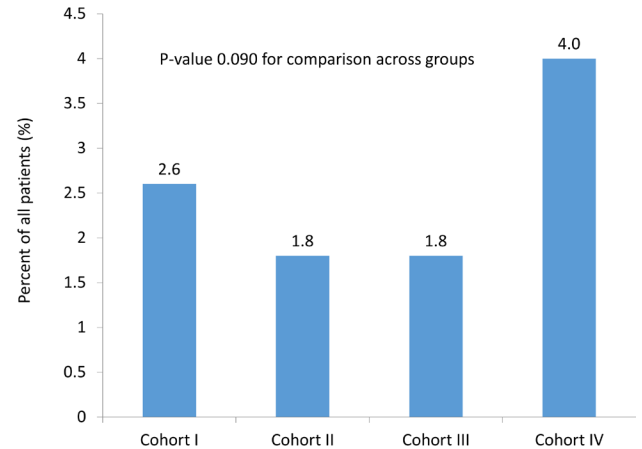
difference in in-hospital mortality rates between the two procedures for low-risk patients (EuroSCORE <10), and a lower rate for intermediate-risk patients (EuroSCORE 10–20) undergoing TAVI.[3] Though an elevated likelihood of major vascular complications and a need for permanent pacemaker implantation remain a limitation of the
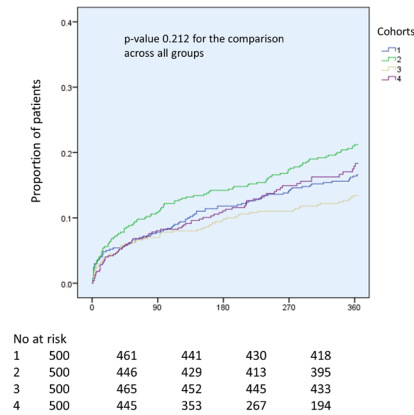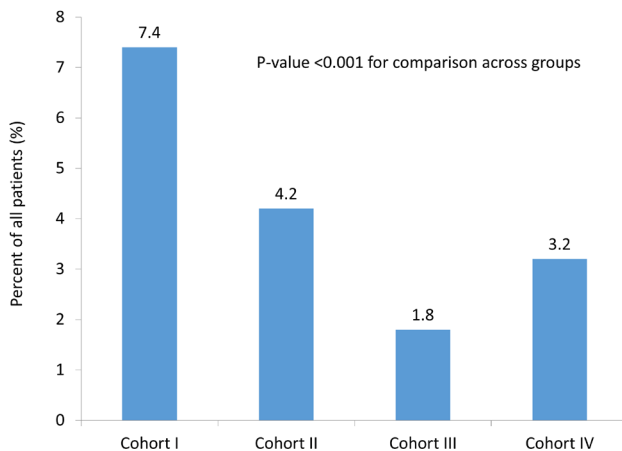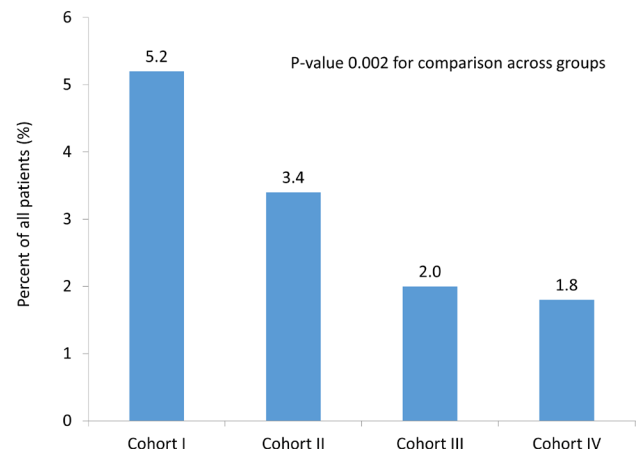
Figure 2 Mortality, stroke, bleeding and vascular complications up to 1 year after TAVI. (A) Kaplan-Meier curves for all-cause mortality during the year following TAVI; p=0.013 for comparison across cohorts, which is due to a significant difference between cohorts II and III (p=0.001), but not the other cohorts. (B) Proportion of patients experiencing at least one stroke episode during the year following TAVI; p=0.090 for comparison across cohorts. (C) Patients experiencing at least one life-threatening/major bleeding event within the year after TAVI; p<0.001 for comparison across cohorts. (D) Patients experiencing at least one major vascular complication within the year after TAVI; p=0.002 for comparison across cohorts. TAVI, transcatheter aortic valve implantation.

TAVI technique across all risk bands,[3 25 27 28] reduced rates of major bleeding, acute kidney injury, reintervention, low cardiac output postintervention and postoperative delirium compared with SAVR have all been noted in lower risk TAVI patients.[3 27 28] Considered alongside increasing physician familiarity with TAVI, the growing trend towards the performance of this procedure in lower risk patients is unsurprising. However, the long-term durability of TAVI prostheses beyond 5 years is currently unknown[29] and longer follow-up is required.

Changes in access route and valve type

The proportion of patients undergoing TAVI via the TA route has fallen over time, while the popularity of the TF route has risen. This may be partly due to the development of smaller delivery devices, which reduce limitations imposed by femoral artery diameters.[30]

The gradual increase in the use of self-expandable valves may have been partly influenced by the rise in TF-TAVI popularity, for which the CoreValve is indicated. Introduction of the new generation SAPIEN 3, which became available in Europe at the start of 2014, may explain the sharp shift towards greater use of balloon-expandable valves in cohort IV. Indeed, SAPIEN generations were used according to their availability, with the original SAPIEN predominant in cohort 1, the SAPIEN XT used mainly in cohorts II and III (following its introduction to the European market in 2010) and the SAPIEN 3 in cohort IV. Furthermore, a later increase in the use of newer alternative valves (ACURATE, Portico and Jena-Valve (now discontinued)) was seen. Taken together, this suggests that physicians are eager to keep up with the changing technology and recognise the merit of device developments.

Changes in device success and complication rates

Device success increased between cohorts I and II, with no further increment in later cohorts. This may be partly attributable to physician learning curve. However, given that previous studies have reported the learning curve to apply only to the first 35–150 patients,[4 31–34] a number vastly exceeded by the present cohorts, this is not easy to determine. Furthermore, the marked switch from the majority of patients receiving the SAPIEN valve in cohort I to the SAPIEN XT in Cohort II cannot be overlooked. The improved features of the XT valve include a greater range of sizes, addition of an inner polyethylene terephthalate (PET) fabric skirt, and a smaller, more flexible delivery system (NovaFlex).[7] The former two improvements may explain the significantly reduced degree of valve regurgitation, while the latter is likely to have made negotiation of the vascular and coronary anatomy easier, perhaps explaining the nominal reductions in incorrect positioning. Furthermore, introduction of the next generation SAPIEN 3 with an additional PET fabric cuff in the inflow portion of the valve and an even greater valve size availability[7] may partly explain further reductions in the severity of valve regurgitation in cohort IV. Indeed, multiple studies comparing the SAPIEN XT to the SAPIEN 3 have found significantly lower rates of regurgitation with the new generation valve.[35–39] Given that aortic valve regurgitation after TAVI has been associated with poor survival outcomes,[40 41] the low levels of procedural mortality in cohort IV may be directly linked. Reductions in the requirement for a second valve in cohort IV could be the result of the more flexible, tapered-tip Commander delivery system and longer stent frame, which may facilitate easier placement of the SAPIEN 3.[7] Improvements over valve generations may also explain the trend towards a reduction in the need for conversion to CPB over cohorts. However, the most commonly reported reason for device failure with the SAPIEN 3 is a mean aortic gradient ≥20 mm Hg,[42] due to use of the 23 mm valve with a smaller annulus. This is reflected in our data by a 5.0% rate of residual gradient ≥20 mm Hg as opposed to the SAPIEN (3.0%) and the XT valve (1.3%) that is accompanied by an increase in the use of the 23 mm valve (10.9% of S3, 3.5% of XT and 4.2% of SAPIEN valves). It is thus in line with the particularly high proportion of patients with AV gradients ≥20 mm Hg after TAVI in cohort IV. Consequently, changes to prosthesis design and, on the other hand, valve size selection, are likely to have played a significant role in outcome evolution.

Changes in 30-day outcomes

A nominal reduction in the proportion of patients meeting the VARC-2 early safety composite endpoint was seen through consecutive cohorts. This appears to have been primarily influenced by a fall in vascular complications and life-threatening bleeding. While the growing experience of the surgical team may have a role to play here, several other elements are likely to have contributed. The first is the size of delivery systems,[43] with progressively smaller diameters reducing the degree of vascular trauma and the serious bleeding with which it is often associated.[44] Furthermore, given that TA-TAVI has been associated with a greater incidence of life-threatening bleeding compared with TF-TAVI,[45 46] declining use of TA access may also have played a part. Surprisingly, a slight increase in non-disabling stroke was seen in cohort IV compared with all other cohorts (change in concomitant pharmacotherapy was excluded as a reason), with kidney injury peaking noticeably in cohort III. There are no obvious explanations for these findings, and it will be interesting to see whether similar frequencies are recorded in future studies.

Although the rate of 30-day all-cause mortality did not change significantly over time, a reduction in the proportion of patients who died from cardiovascular causes was apparent in later cohorts. This is likely due to the observed trend towards a fall in the proportion of patients in NYHA class IV, given that higher NYHA class has been identified as an independent predictor of cardiovascular mortality after TAVI.[47 48] Thus, it is unsurprising that the paradigm shift towards TAVI in lower risk, less symptomatic/comorbid patients is reflected in the overall rate of cardiovascular death.

Changes in 1-year outcomes

Despite fluctuations in baseline, procedural and 30-day variables, survival and stroke rates over the year following TAVI did not differ significantly across cohorts. It is interesting that both male gender, which increased over cohorts in the present study, and frailty, which fell, have been associated with a higher risk of mortality in the year after TAVI.[49 50] It is therefore possible that each of these counterbalanced the effect of the other. Furthermore, the age of patients remained stable across cohorts, meaning that natural age-related death was not an influential factor. Conversely, life-threatening/major bleeding and major vascular complications up to 1 year were less frequent in later cohorts. Again, these two factors are closely linked, and are likely reflective of valve and delivery device improvements and reduced use of the TA access.[43–46] Overall, TAVI evolution appears to have led to longer term health benefits, if not a reduction in mortality.

Limitations

Given the time span covered by the study and the rapid evolution of TAVI, it was not initially possible to predict all of the factors which would be necessary for meaningful comparisons in later cohorts. Accordingly, explanations for access route decision were not systematically recorded, and the subclavian and transaortic access routes were not accounted for. This is regrettable, as the expansion of access options is an important development in the TAVI procedure, which make it available to a larger number of patients with specific and interesting characteristics. However, the data provided herein regarding the TA and TF routes are abundant and of high quality. Second,

due to the growing popularity of TAVI, the amount of time necessary to perform the procedure on 500 consecutive patients grew shorter as the study progressed. Consequently, the time frame applicable to each cohort differed. This was unavoidable, and is reflective of real-world progress. Similarly, the variety and proportions of valve types used fluctuated throughout the study, meaning that outcomes are likely to have been influenced by the distributions within any one particular cohort. However, again, this provides an interesting snapshot of trends in TAVI over time. Finally, the effect of the learning curve could not be distinguished from other factors due to the high number of patients in each cohort. However, this large sample size provides robustness and strong statistical power for most outcomes, which should be considered a strength of the study.

CONCLUSIONS

Evolution of TAVI between 2008 and 2015 saw a trend towards its usage in lower risk patients and rapid progression towards improved safety. This is especially true given the improvements in valve design, which have minimised valvular regurgitation and life-threatening bleeding rates. While mortality rates were already at a very low level throughout the evaluation period, technical refinement should now continue to further lessen stroke and pacemaker rates.

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