BMJ Open

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)

Gerhard Schymik,1 Valentin Herzberger,1 Jens Bergmann,1 Peter Bramlage,2 Lars O Conzelmann,3 Alexander Würth,4 Armin Luik,1 Holger Schröfel,5 Panagiotis Tzamalis1

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% vs 11.0%; p < 0.001) and New York Heart Association class IV (10.0% vs 3.6%; 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).

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.

INTRODUCTION

Transcatheter aortic valve implantation (TAVI) is becoming ever more prominent in the treatment of severe aortic stenosis (AS). Indeed, a 20-fold increase was reported in Germany between 2008 and 2014, and with similar trends documented for other populations.

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. 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 the merit of balloon predilatation carefully evaluated.

Second, the procedure itself has come under scrutiny, with a number of alternative access routes developed and the merit of balloon predilatation carefully evaluated. 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...
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 cm², an indexed AVA of <0.6 cm²/m², 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 of 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 (Synetis), 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 criteria19 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 chi² 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 chi² 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 XT and SAPIEN 3 generations correlating with availability. The more recently developed ACCURATE (Symetis), Portico (St Jude Medical) and JenaValve (Jena-Valve 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%–91.1%; 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) compared 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 (5.5%) 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).
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.
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, and the trend towards more intermediate and lower risk patients undergoing the procedure over time. 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 and at a greater surgical risk.

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. 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. Furthermore, a recent analysis of 20,540 patients found no

### Table 1  Patient characteristics

| 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/m²)  | 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        | 0.933 |
| 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 |
| NYHA 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; NYHA, New York Heart Association; PAD, peripheral artery disease; PCI, percutaneous coronary intervention.
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. Though an elevated likelihood of major vascular complications and a need for permanent pacemaker implantation remain a limitation of the

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

| Access route (%) | Cohort I (n=500) % | Cohort II (n=500) % | Cohort III (n=500) % | Cohort IV (n=500) % | Overall P values |
|------------------|--------------------|--------------------|--------------------|--------------------|-----------------|
| TA               | 43.6               | 39.0               | 30.0               | 29.0               | <0.001          |
| 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 (%) |                |                    |                    |                    | <0.001          |
| Procedural mortality | 3.0             | 2.2                | 2.2                | 1.2                | 0.275           |
| Mean AV gradient >20mm 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 | 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.
TAVI technique across all risk bands, 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. 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 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. 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.

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.
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,1,33–34 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 terphthalate (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 availability7 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 $\geq 20$ 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 $\geq 20$ 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 $\geq 20$ 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.37,40 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.

Author affiliations

1. Department of Cardiology, Medical Clinic IV, Municipal Hospital Karlsruhe, Academic Teaching Hospital of the University of Freiburg, Karlsruhe, Germany
2. Institute for Pharmacology and Preventive Medicine, Cloppenburg, Germany
3. Helios Clinic for Cardiac Surgery, Karlsruhe, Germany
4. Department of Cardiology, Medical Clinic III, Victorius Hospital Karlsruhe, Karlsruhe, Germany
5. Department Cardiovascular Surgery, University Heart Center Freiburg, Bad Krozingen, Germany

Acknowledgements We would like to thank Helen Sims (Institute for Pharmacology and Preventive Medicine) for her help with the manuscript.

Contributors GS, VH, JB, LOC, AW, AL, HS and PT designed and established the registry and acquired the data. PB and GS outlined the analyses, PT performed the analyses and GS, PB and PT interpreted the outcomes. PB drafted the first version of the manuscript, which all other authors revised for important intellectual content. All authors approved the final version of the manuscript to be submitted. They all agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or non-for-profit sectors.

Competing interests GS and HS are proctors and Peter Bramlage consultant for Edwards Lifesciences.

Patient consent Not required.

Ethics approval The registry was performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments and received approval from the responsible local ethics committee in Stuttgart.

Provenance and peer review Not commissioned; externally peer reviewed.

Data sharing statement The data are available from the corresponding author on reasonable request.

REFERENCES

1. Gadesle L, Blumenstein J, Kim WK, et al. Trends in aortic valve replacement in Germany in 2015: transcatheter versus isolated surgical aortic valve repair. Clin Res Cardiol 2017;106:411–9.
2. Eggebrecht H, Mehta RH. Transcatheter aortic valve implantation (TAVI) in Germany 2008-2014: on its way to standard therapy for aortic valve stenosis in the elderly? Eurointervention 2016;11:1029–33.
3. Möllmann H, Bestehorn K, Bestehorn M, et al. In-hospital outcome of transcatheter vs. surgical aortic valve replacement in patients with aortic valve stenosis: complete dataset of patients treated in 2013 in Germany. Clin Res Cardiol 2016;105:553–9.
4. Holzhey DM, Hänssig M, Walther T, et al. Transapical aortic valve implantation - the leipzig experience. Ann Cardiothorac Surg 2012;1:129–37.
5. Ludman PF, Moat N, de Belder MA, et al. Transcatheter aortic valve implantation in the United Kingdom: temporal trends, predictors of outcome, and 6-year follow-up: a report from the UK Transcather Aortic Valve Implantation (TAVI) Registry, 2007 to 2012. Circulation 2015;131:1181–90.
6. Minha S, Waksman R. Evaluation of the Edwards Lifesciences SAPIEN transcatheter heart valve. Expert Rev Med Devices 2011;4:553–62.
7. Abdel-Wahab M, Jose J, Richard G. Transfemoral TAVI devices: design overview and clinical outcomes. Eurointervention 2015;11 Suppl W:W114–W118.
8. Bapat V, Khawaja MZ, Attia R, et al. Transaortic transcatheter aortic valve implantation using Edwards Sapien valve: a novel approach. Catheter Cardiovasc Interv 2012;79:733–40.
9. Ciucu C, Tarantini G, Latib A, et al. Trans-subclavian versus transapical access for transcatheter aortic valve implantation: a multicenter study. Catheter Cardiovasc Interv 2016;87:332–8.
10. Pagnesi M, Jabbour RJ, Latib A, et al. Usefulness of predilation before transcatheter aortic valve implantation. Am J Cardiol 2016;118:107–13.
11. Bagur R, Kwok CS, Nombela-Franco L, et al. Transcatheter aortic valve implantation with or without preimplantation balloon aortic valvuloplasty: a systematic review and meta-analysis. J Am Heart Assoc 2016;5:e003191.
12. Piazza N, Lange R, Martucci G, et al. Patient selection for transcatheter aortic valve implantation: patient risk profile and anatomical selection criteria. Arch Cardiovasc Dis 2012;105:165–73.
13. Wenaweser P, Stortecky S, Schwander S, et al. Clinical outcomes of patients with estimated low or intermediate surgical risk undergoing transcatheter aortic valve implantation. Eur Heart J 2013;34:1894–905.
14. Kappetein AP, Osnabruggen RL, Head SJ. Patient selection for TAVI in 2014: is there a justification for treating low- or intermediate-risk patients? The surgeon’s view. Eurointervention 2014;10:U11–U15.
15. Leon MB, Smith CR, Mack MJ, et al. Transcatheter or surgical aortic-valve replacement in intermediate-risk patients. N Engl J Med 2016;374:1609–20.
16. Schymik G, Schröfel H, Schymik JS, et al. Acute and late outcomes of Transcatheter Aortic Valve Implantation (TAVI) for the treatment of severe symptomatic aortic stenosis in patients at high- and low-surgical risk. J Interv Cardiol 2012;25:364–74.
17. Schymik G, Tzamtzis P, Bramlage P, et al. Clinical impact of a new left bundle branch block following TAVI implantation: 1-year results of the TAVIK cohort. Clin Res Cardiol 2015;104:551–62.
18. Schymik G, Tzamtzis P, Bramlage P, et al. Clinical outcomes of the European Association of Cardio-Thoracic Surgeons Transcatheter Aortic Valve Implantation-2 Consensus Document. Eur J Cardiothorac Surg 2012;42:545–560.
19. Vahanian A, Alfieri OR, Al-Attar N, et al. Transcatheter valve implantation for patients with aortic stenosis: A position statement from the European association of cardio-thoracic surgery (EACTS) and the European Society of Cardiology (ESC), in collaboration with the
European Association of Percutaneous Cardiovascular Interventions (EAPCI). *Eur J Cardiothorac Surg* 2008;34:1–8.

21. Cribier A, Durand E, Eltchaninoff H. Patient selection for TAVI in 2014: is it justified to treat low- or intermediate-risk patients? *The cardiologist’s view*. EuroIntervention 2014;10 Suppl U:U16–21.

22. Lange R, Bleiziffer S, Mazzitelli D, et al. Improvements in transcatheter aortic valve implantation outcomes in lower surgical risk patients: a glimpse into the future. *J Am Coll Cardiol* 2012;59:280–7.

23. Barbash IM, Finkelstein A, Barsheshet A, et al. Outcomes of patients at estimated low, intermediate, and high risk undergoing transcatheter aortic valve implantation for aortic stenosis. *Am J Cardiol* 2015;116:1916–22.

24. D’Errigo P, Barbanti M, Ranucci M, et al. Transcatheter aortic valve implantation versus surgical aortic valve replacement for severe aortic stenosis: results from an intermediate risk propensity-matched population of the Italian OBSERVANT study. *Int J Cardiol* 2013;167:1945–52.

25. Castrodeza J, Amat-Santos LJ, Blanco M, et al. Propensity score matched comparison of transcatheter aortic valve implantation versus conventional surgery in intermediate and low risk aortic stenosis patients: a hint of real-world. *Cardiol J* 2016;23:541–51.

26. Cao C, Liou KP, Pathan FK, et al. Transcatheter aortic valve implantation versus surgical aortic valve replacement: meta-analysis of clinical outcomes and cost-effectiveness. *Curr Pharm Des* 2016;22:1953–65.

27. Gargiulo G, Sannino A, Capodanno D, et al. Transcatheter aortic valve implantation versus surgical aortic valve replacement: a systematic review and meta-analysis. *Ann Intern Med* 2016;165:334–44.

28. Ansalan M, Walther T. Durability of prostheses for transcatheter aortic valve implantation. *Nat Rev Cardiol* 2016;13:360–7.

29. Eltchaninoff H, Durand E, Borz B, et al. Prospective analysis of 30-day safety and performance of transfemoral transcatheter aortic valve implantation with Edwards SAPIEN XT versus SAPIEN prostheses. *Arch Cardiovasc Dis* 2012;105:132–40.

30. Minha S, Waksman R, Satler LP, et al. Learning curves for transfemoral transcatheter aortic valve replacement in the PARTNER-I trial: Success and safety. *Catheter Cardiovasc Interv* 2016;87:165–75.

31. Alli O, Rihal CS, Suri RM, et al. Learning curves for transfemoral transcatheter aortic valve replacement in the PARTNER-I trial: technical performance. *Catheter Cardiovasc Interv* 2016;87:154–62.

32. Arai T, Lefèvre T, Hovasse T, et al. Evaluation of the learning curve for transcatheter aortic valve implantation via the transfemoral approach. *Int J Cardiol* 2016;203:491–7.

33. Lunardi M, Pesarini G, Zivelonghi C, et al. Clinical outcomes of transcatheter aortic valve implantation: from learning curve to proficiency. *Open Heart* 2016;3:e000420.

34. Nijhoff F, Abawi M, Agostoni P, et al. Transcatheter aortic valve implantation with the new balloon-expandable Sapien 3 versus Sapien XT valve system: a propensity score-matched single-center comparison. *Circ Cardiovasc Interv* 2015;8:e002408.

35. Ando T, Biasoulis A, Holmes AA, et al. Sapien 3 versus Sapien XT prosthetic valves in transcatheter aortic valve implantation: a meta-analysis. *Int J Cardiol* 2016;220:472–8.

36. Arai T, Lefèvre T, Hovasse T, et al. Comparison of Edwards SAPIEN 3 versus SAPIEN XT in transfemoral transcatheter aortic valve implantation: difference of valve selection in the real world. *J Cardiol* 2017;69:565–9.

37. Kazun Y, Maeno Y, Kawamori H, et al. Comparison of SAPIEN 3 and SAPIEN XT transcatheter heart valve stent-frame expansion: evaluation using multi-slice computed thoromrphography. *Eur Heart J Cardiovasc Imaging* 2016;17:1054–62.

38. Yang TH, Webb JG, Blanke P, et al. Incidence and severity of paravalvular aortic regurgitation with multidetector computed tomography nominal area oversizing or undersizing after transcatheter aortic valve implantation with the Sapien 3: a comparison with the Sapien XT. *JACC Cardiovasc Interv* 2015;8:462–71.

39. Takagi H, Uremoto T. Impact of paravalvular aortic regurgitation after transcatheter aortic valve implantation on survival. *Int J Cardiol* 2016;221:48–51.

40. de Brito FS, Carvalho LA, Sarmento-Leite R, et al. Outcomes and predictors of mortality after transcatheter aortic valve implantation: results of the Brazilian registry. *Catheter Cardiovasc Interv* 2015;85:659–63.

41. Wohrle J, Gonska B, Rodewald C, et al. Transfemoral aortic valve implantation with the new Edwards sapien 3 valve for treatment of severe aortic stenosis-impact of valve size in a single center experience. *PLoS One* 2016;11:e0151247.

42. Van Mieghem I, Snellinck G, et al. Incidence, predictors, and implications of access site complications with transfemoral transcatheter aortic valve implantation. *Am J Cardiol* 2012;110:1361–7.

43. Mwipatayi BP, Ricardo A, Maslonyane-Jones TV, et al. Incidence and prognosis of vascular complications after transcatheter aortic valve implantation. *J Vasc Surg* 2013;58:1028–36.

44. Pilgrim T, Stortecky S, Luterbacher F, et al. Transcatheter aortic valve implantation and bleeding: incidence, predictors and prognosis. *J Thromb Thrombolysis* 2013;35:456–62.

45. Borz B, Durand E, Godin M, et al. Incidence, predictors and impact of bleeding after transcatheter aortic valve implantation using the balloon-expandable Edwards prosthesis. *Heart* 2013;99:860–5.

46. Amabile N, Agostini H, Gilard M, et al. Impact of low preprocedural transvalvular gradient on cardiovascular mortality following TAVI: an analysis from the FRANCE 2 registry. *EuroIntervention* 2014;10:842–9.

47. Seifert M, Schnabel R, Conradi L, et al. Predictors and outcomes after transcatheter aortic valve implantation using different approaches according to the valve academic research consortium definitions. *Catheter Cardiovasc Interv* 2013;82:640–52.

48. Green P, Arnold SV, Cohen DJ, et al. Relation of frailty to outcomes after transcatheter aortic valve replacement (from the PARTNER trial). *Am J Cardiol* 2015;116:264–9.

49. Kodali S, Williams MR, Doshi D, et al. Sex-specific differences at presentation and outcomes among patients undergoing transcatheter aortic valve replacement: a cohort study. *Ann Intern Med* 2016;164:377–84.