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Journal:	BMJ Open
Manuscript ID	bmjopen-2017-020204
Article Type:	Research
Date Submitted by the Author:	23-Oct-2017
Complete List of Authors:	Kaier, Klaus; Medical Center-University of Freiburg, Institute for Medical Biometry and Statistics Oettinger, Vera; Heart Center Freiburg University, Department of Cardiology and Angiology I Reinecke, H; University of Muenster, Department of Cardiology and Angiology, Adult Congenital and Valvular Heart Disease Center Muenster Schmoor, Claudia; Medical Centre, University of Freiburg Frankenstein, L.; University of Heidelberg, Dpt. of Cardiology, Angiology, Pulmology Vach, Werner; Institute of Medical Biometry and Medical Informatics, Hehn, Philip; Faculty of Medicine and Medical Center – University of Freiburg von zur Mühlen, Constantin; Heart Center Freiburg University, Department of Cardiology and Angiology I Bode, Christoph; Heart Center Freiburg University, Department of Cardiology and Angiology I Zehender, Manfred; Heart Center Freiburg University, Department of Cardiology and Angiology I Reinöhl, Jochen; Heart Center Freiburg University, Department of Cardiology and Angiology I
Keywords:	Valvular heart disease < CARDIOLOGY, HEALTH ECONOMICS, CARDIOLOGY, Adult cardiology < CARDIOLOGY

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Volume-outcome relationship in transcatheter aortic valve implantations in Germany 2008-2014

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Word count excluding title page, abstract, references, figures and tables: 2838

ABSTRACT

Keywords: TAVI, volume-outcome; minimum volume standards; hospital quality; mortality

Objectives: We examine the volume-outcome relationship in isolated transcatheter aortic valve implantations (TAVI) in Germany between 2008 and 2014 (N=43,996). Our interest was whether the volume-outcome relationship for TAVI exists on the center level, whether it occurs equally for different outcomes, and how it develops over time.

Methods: The comprehensive German Federal Bureau of Statistics DRG database was queried for data on all isolated TAVI procedures performed in Germany between 2008 and 2014. Logistic and linear regression analyses were carried out for the endpoints in-hospital mortality, bleeding, stroke, probability of ventilation >48 hours, length of hospital stay, and reimbursement. Risk-adjustment was applied using a predefined set of patient characteristics to account for differences in the risk factor composition of the patient populations between centers and over time. Centers performing TAVI were stratified into groups performing <50, 50-99, and ≥100 procedures per year.

Results: Risk-adjusted in-hospital mortality steadily decreases over the years and is lower the higher the annual procedure volume at the respective center is. The magnitude of the latter effect declines over the observation period. Overall, our results indicate a ceiling effect in the volume-outcome relationship: The volume-outcome relationship is eminent in circumstances of relatively unfavorable outcomes. Alongside improving outcomes, however, the volume-outcome relationship decreases. In addition, a volume-outcome relationship seems to be absent in circumstances of constantly low event rates.

Conclusions: The hypothesized volume-outcome relationship for TAVI exists but diminishes and may disappear over time. This might be the case for other interventional procedures, too, which should be taken into account when considering mandatory minimum thresholds.

STRENGTHS AND LIMITATIONS OF THIS STUDY

- Study based on administrative data; coding errors are inevitable. However, about 20% of all cardiovascular diagnosis-related groups are reviewed by independent teams of physicians on behalf of the health insurers.
- Risk-adjustment included a number of parameters whose reliability cannot be fully secured, and we cannot guarantee that all parameters of relevance are included in the model. A major limitation is that the data source does not include information on the type of device used in individual TAVI procedures. In addition, information regarding the experience of surgeons at each centre would be highly relevant for the analysis but is unavailable.
- The dataset omits patients with a baseline diagnosis of pure aortic regurgitation, as well as those who underwent TAVI with any other concomitant cardiac procedure. This makes sense from a clinical perspective, but further complicates direct comparisons with other administrative datasets.
- The study provides comprehensive data on everyday TAVI practice in a large industrialized country over a multiyear period.

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KEY QUESTIONS

What is already known about this subject?

After their introduction, outcomes of new interventions are subject to a learning curve effect, meaning that outcomes improve over a period of time and then level off. The volume of procedures performed at an institution can influence this process, and is thought to have some effect on patient outcomes even after learning is complete (volume-outcome-hypothesis).

What does this study add?

This study tracks patient outcomes by center procedure volume in all transcatheter aortic valve implantation (TAVI) procedures performed in Germany between the procedure's introduction in 2008 and 2014, providing empirical evidence on shape and extent of the above described effects for this procedure.

How might this impact on clinical practice?

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This data is of interest to clinical practitioners, hospital administrators, and policy makers involved in the implementation of new clinical procedures.

COMPETING INTERESTS AND FUNDING

The authors declare no conflicts of interest. There was no external funding for this work.

DATA SHARING STATEMENT

No additional data available.

AUTHORSHIP STATEMENT

KK and JR developed the research question and designed the methodology. VÖ, HR, LF, CvzM, CB, MZ and JR provided the medical knowledge of German TAVI practice informing the study design. KK defined the categories, outcomes and measures and developed and implemented the formal analysis and statistical with support by WV and CS. KK and JR collected the data and evidence. KK, VÖ, and WV interpreted and contextualized the results. KK and PH wrote the initial draft of the article, with JR contributing. All authors participated in the critical revision of the article and provided final approval of the version to be published.

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INTRODUCTION

Transcatheter aortic valve implantation (TAVI) is a rapidly evolving technique for therapy of aortic stenosis, with a very early and pronounced utilization in Germany [1]. Previous studies report hospital-specific learning curves with respect to in-hospital outcomes such as procedural success, mortality and clinical complications of varying lengths and magnitudes [2–6]. In general, learning curve effects within and between centers can to some degree be explained by the volume of procedures performed at the center. This relationship can be summed up as the "practice-makes-perfect hypothesis", according to which quality of care either increases with the number of patients as a result of economies of scale, with a competing explanation of "selective-referral", according to which higher-quality hospitals attract greater demand and therefore have a greater volume of patients [7,8].

There are a number of criticisms on empirical analyses on the volume-outcome relationship: Many studies lack appropriate adjustment for differences in the risk factor composition of the patient populations between centers [9,10]. Secondly, most studies focus on in-hospital mortality only [11], which is easy to measure, but it is recommended to include additional quality measurements. Finally, most studies divided patients into groups of equal size for analyzing the volume-outcome relationship, which makes it difficult to make use of such results when justifying specific volume thresholds[6,12,13].

Although the evidence regarding the existence of an inverse relationship between the number of TAVI procedures and related outcomes is limited [14,15], medical authorities in Germany and several other countries have issued guidelines calling for minimum numbers of procedures for primary operators performing TAVI [16–19]. There however remains some question whether, firstly, the volume-outcome relationship outlined above exists on the center level regarding TAVI and, secondly, whether or not it takes place in all outcomes and complications equally, and how an existing volume-outcome relationship might change over the years.

To address these questions, we calculated annual procedure volumes for all German hospitals that performed TAVI procedures between January 2008 and December 2014. In order to account for differences in the patient population between high-, medium-, and low-volume centers and over time, we carried out baseline-adjusted regression analyses for the endpoints in-hospital mortality, bleeding, stroke, probability of ventilation >48 hours, length of hospital stay, and reimbursement.

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METHODS

Data

Since 2005, data on all hospitalizations in Germany have been available for scientific use via the Diagnosis Related Groups (DRG) statistics collected by the Research Data Center of the Federal Bureau of Statistics (DESTATIS). These hospitalization data, including diagnoses and procedures, are a valuable source of representative nationwide data on the in-hospital treatment of patients. This database represents a virtually complete collection of all hospitalizations in German hospitals that are reimbursed according to the DRG system. From this database [1], we have extracted data on 43,996 cases of isolated TAVI for our analysis.

Our study did not involve direct access by the investigators to data on individual patients but only access to summary results provided by the Research Data Center. Therefore, approval by an ethics committee and informed consent were determined not to be required, in accordance with German law. All summary results were anonymized by DESTATIS. In practice, this means that any information allowing the drawing of conclusions regarding a single patient or a specific hospital are censored by DESTATIS to guarantee data protection. Especially the use of the anonymous, persistent "institute indicator of hospitals" is highly restricted in order not to publish any information directly attributable to a single hospital.

As described previously [1,20], we were able to use the OPS codes (OPS codes: 5-35a.0 in 2007 and 5-35a.00, 5-35a.01 from 2008) to identify all TAVI procedures performed (and reimbursed) in Germany between 2008 and 2014. Patients with a baseline diagnosis of pure aortic regurgitation (main or secondary diagnosis other than I35.0, I35.2, I06.0, I06.2) and those with concomitant cardiac surgery or percutaneous coronary intervention were not included in this analysis. A complete list of procedure codes as well as a more detailed discussion of the validity of the data source may be found in a previous manuscript [1,20].

Measures

Regarding the in-hospital complications, bleeding was defined as requiring a transfusion of more than 5 units of red blood cells (RBC). For all other comorbidities and complications the existing anamnestic or acute distinctive codes were used (we have discussed OPS and ICD codes in greater detail previously [20]).

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In order to analyze possible effects of the above discussed mandatory minimum quantities, the number of procedures per year and center was categorized (i.e. n<50, 50≤n<100, n≥100) on the basis of an anonymous, persistent "institute indicator of hospitals" provided by DESTATIS. These particular thresholds are applied because the minimum number of 50 procedures is often mentioned in official TAVI-guidelines [16–19], and these thresholds are widely applied in the literature [21–23].

The primary outcome was in-hospital mortality. Secondary outcomes include post-procedural complications such as stroke and bleeding events (transfusion of >=5 RBC), as well as reimbursement, length of hospital stay and proportion of patients with ventilation >48h.

Statistical analysis

In a first step, multivariate regression analyses were carried out for the different endpoints, with all available patient and procedural characteristics (as defined by Reinöhl et al. [1]) included as covariates (all covariates listed in Table 1). In addition, an interaction term between time (in years) and the above mentioned annual volume categories was included in the regression analyses in order to investigate the volume-outcome relationship over the years.

Table 1: Baseline characteristics (2008-2014)

Ν	43,996
Female	55.87%
Age in years, mean/SD	80.95/6.11
Estimated logistic EuroSCORE ¹ , mean/SD	22.21%/13.57%
Aortic valve stenosis	68.22%
Combined aortic valve diseases	26.56%
Heart failure	
NYHA II	8.26%
NYHA III or IV	41.66%
Hypertension	62.66%
CAD	46.88%
Previous myocardial infarction	
within 4 months	1.59%
within 1 year	0.75%
after 1 year	4.35%
Previous CABG	12.75%
Previous cardiac surgery	18.06%
Peripheral vascular disease	12.39%
Carotid disease	6.17%
COPD	15.14%
Pulmonary hypertension	22.32%
Renal disease	
GFR <15ml/min	2.95%
GFR <30ml/min	4.90%
Atrial fibrillation	45.93%
Diabetes	33.30%

¹For calculation of the logistic EuroSCORE, we were able to populate all fields except for critical preoperative state and left ventricular function. In

these we assumed an inconspicuous state (i.e. no critical preoperative state and no left ventricular dysfunction) and thus calculated a best-case scenario.

Abbreviations: NYHA - New York Heart Association Functional Classification; CAD - coronary artery disease; CABG - coronary artery bypass graft; COPD – chronic obstructive pulmonary disease; GFR – glomerular filtration rate.

Please note that in comparison to the data published by Reinöhl et al., one TA-TAVI procedure (in 2010) needed to be removed from the dataset due to incomplete information.

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Logistic and linear regression analyses are applied for dichotomous and continuous endpoints, respectively. The question of how to account for patients treated in the same hospital was discussed previously [13,24,25]. As recommended in a previous study that also used data from the German DRG-statistic [13], we used cluster-robust standard errors to account for this dependency. Risk-adjusted rates and means within each year and hospital volume category were obtained by

computing the corresponding predicted probabilities or means, respectively, for an artificial subject with each confounder set to its mean value (prediction at the means, see Table 1 for mean values of all confounders).

The visualization of these risk-adjusted rates or means together with their 95% confidence intervals constitutes the main analytical approach in this paper. To assess the statistical significance of the observed volume-outcome relationship, of the time trend and a potential change of the volume-outcome relationship over time, we applied to the estimated rates or means a random effects meta regression (command metareg [26]) with time and volume as continuous covariates. A model with an interaction term was used to assess the change in the volume-outcome relationship. A model without an interaction was used to assess the main effects.

All analyses were carried out using Stata 13.1 (StataCorp, College Station, Texas, USA).

RESULTS

Between 2008 and 2014, a total of 43,996 TAVI procedures were performed in 113 different centers in Germany. The total number of TAVI procedures performed per year increased markedly over the observation period, from 1,122 in 2008 to 11,559 in 2014 (see Table 2).

Table 2: Number of procedures with regard to the performed TAVI volume of a distinct center in a given year.

TAVI Volume in Center	2008	2009	2010	2011	2012	2013	2014
<50 procedures, n (number of centers)	613 (40)	1,234 (61)	1,155 (51)	1,107 (43)	960 (36)	765 (31)	617 (30)
50-99 procedures, n (number of centers)	236 (3)	658 (10)	1,875 (26)	1,957 (27)	1,569 (20)	1,930 (25)	1,135 (16)
>=100 procedures, n (number of centers)	273 (n/a*)	707 (n/a)	1,776 (3)	3,459 (7)	5,711 (16)	6,452 (9)	9,807 (20)
Total number, n (number of centers)	1,122 (>=44)	2,599 (>=72)	4,806 (80)	6,523 (77)	8,240 (72)	9,147 (65)	11,559 (66)

Please note that the numbers of procedures performed per year at a given center were not constant over the observation period, so that it is possible for a center to fall into a different volume group in a different year. Number of centres in parentheses.

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* n/a = not available, exact number censored by DESTATIS due to data protection concerns

As reported previously [1], substantial reductions in in-hospital mortality have been achieved between 2008 and 2013, and we find this trend to continue into 2014. Regarding center-specific procedure volumes of all TAVI procedures, it appears that the differences in unadjusted in-hospital mortality between the procedure volume groups (<50, 50-99, and >=100) steadily decline over the years (see Table 3). Figure 1 A provides risk-adjusted in-hospital mortality rates allowing for comparison despite possible differences in the patient selection process and consequently the risk factor composition between hospitals in the different procedure volume groups and over time (See Table S1 for details of the process used to generate the results shown in Figure 1A). These results indicate that risk-adjusted inhospital mortality rates (1) steadily decrease over the years (annual change: -0.58 percentage points (pp), p<0.001), are (2) lower the higher the procedure volume at the hospital is (volume effect: -0.74pp, p=0.002), but that (3) this volume effect declines over the seven year observation period (p-value of interaction term: p=0.027; annual change of volume effect: 0.2pp). alige ...

Table 3: Unadjusted in-hospital outcomes with regard to the performed TAVI volume of a distinct center in a given year.

	Mortality, %	Stroke, %	Bleeding, %	Length of stay, mean in days	Reim- bursement, mean in €	Proportion of patients with ventilation >48h, %
2008						
<50 procedures	10.11%	3.26%	14.36%	19.2		9.79%
50-99 procedures	9.32%	2.12%	11.44%	21.8		6.78%
>=100 procedures	6.59%	2.56%	7.33%	14.7		4.76%
2009						
<50 procedures	9.81%	3.57%	14.18%	21.6		9.48%
50-99 procedures	8.36%	3.34%	11.25%	18.5		7.14%
>=100 procedures	6.08%	2.12%	7.21%	18.0		7.36%
2010						
<50 procedures	9.00%	2.51%	12.12%	21.0	37,071€	8.74%
50-99 procedures	8.11%	2.56%	11.41%	19.1	36,173€	8.69%
>=100 procedures	6.14%	2.20%	6.25%	17.0	35,074€	5.01%
2011						
2011	7 (90/	2 250/	0.20%	20.0	25.0046	0.040/
< 50 procedures	7.08%	2.35%	9.39%	20.0	35,984€	8.04%
50-99 procedures	8.02%	2.35%	9.04%	19.3	35,424€	8.28%
>=100 procedures	5.87%	3.01%	9.31%	17.3	35,046€	7.29%
2012						
<50 procedures	6 15%	2 20%	8 11%	18 7	35 291£	7 29%
50-99 procedures	7.07%	2.23%	8 41%	18.9	34 798£	5 48%
>=100 procedures	5.03%	2.42%	6 30%	16.7	34,733£	5 39%
	5.6576	2.10/0	0.3070	10.7	51,2550	5.5570
2013						
<50 procedures	5.49%	2.09%	9.28%	20.2	35,808€	6.93%
50-99 procedures	5.85%	2.33%	6.53%	18.2	34,650€	4.56%
>=100 procedures	5.29%	2.70%	5.98%	16.3	34,456€	5.29%
-						
2014						
<50 procedures	5.34%	2.75%	5.99%	19.9	35,993€	6.15%
50-99 procedures	4.58%	2.20%	5.73%	18.3	34,904€	4.32%
>=100 procedures	3.70%	2.28%	4.22%	15.3	34,771€	3.92%

Please note that the numbers of procedures performed per year at a given center were not constant over the observation period, so that it is possible for a center to fall into a different volume group in a different year.

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Over the seven years of data we analyzed, a slight decreasing trend was visible in the risk-adjusted inhospital stroke rate, which started out at 2-2,5% in 2008-2009 and ranged from 1,5-2% in 2013-2014 (Figure 1 B). Volume-outcome relationship was actually negative for years following 2010, with highervolume centers having higher stroke rates.

Risk-adjusted bleeding rates (Figure 1 C), in contrast, showed a clear beneficial effect of higher center procedure volumes for all years but 2011. The magnitude of the effect was distinct from 2008-2010 and decreased in the following years in parallel with an ongoing marked decrease in the general likelihood of bleeding complications, but still was present in 2013/2014.

For risk-adjusted in-hospital ventilation rate (>48h) (Figure 1 D), a pronounced beneficial effect of higher center procedure volumes persisted throughout the observation period. In addition, risk-adjusted in-hospital ventilation rates decreased substantially over the years. As for bleeding, the magnitude of the volume effect was distinct in the first years but steadily declined over the seven year period (annual change of the volume effect: 0.30pp, p=0.041).

Risk-adjusted in-hospital length of stay shows a strong beneficial effect of center procedure volume (Figure 2 A). Unlike the situation found for the endpoints mortality and bleeding, the magnitude of the effect did not decrease much over the observed timeframe. There also is a slight reduction in average length of stay over the years.

Standardized reimbursement data (Figure 2 B) is only available starting in 2010 due to a change in the reimbursement system making previous data difficult to compare. In Germany, reimbursement is based on DRGs which are defined by the patients' diagnoses, gender and age, treatment procedures, complications or comorbidities, and further attributes. Based on this data, a predetermined reimbursement rate per case is calculated. Hospitals receive additional reimbursement for long-stay outlier cases [27]. Furthermore, additional reimbursement is possible for very complex intensive care treatments, which have to be proven by documentation of illness severity and treatment effort during ICU stay [28]. As shown in Figure 2 B, there is a drop in the overall reimbursement level from 2010-2012, but reimbursement stays roughly the same thereafter. In much the same way as found for length of hospital stay, risk-adjusted amount of reimbursement decreased only slightly over time, and showed a large volume effect which did not change over the five year period.

CONCLUSIONS

Our study shows mixed results regarding a volume-outcome relationship in TAVI procedures in German hospitals. First of all, TAVI-related in-hospital mortality decreased substantially between 2008 and 2014 and was lower the higher the procedure volume at the respective hospital is. The magnitude of this volume-outcome relationship, however, declines over the observation period. Especially in later years (2012-2014) differences in mortality between low-, medium-, and high-volume centers are small.

Regarding in-hospital mortality and secondary endpoints, a volume-outcome relationship is eminent in circumstances of relatively unfavorable outcomes (see early years of mortality, bleeding, and ventilation) and decreases as outcomes improve (later years of mortality, bleeding, and ventilation), but is not present in circumstances of constantly low event rates (see stroke). In addition, in most of the cases when we observe a distinct annual decrease, we also observe a decreasing volume effect over time. Presumably, the small centers succeed in participating at the system level learning curve to a degree which allows them to catch up to some degree to the group of high-volume. Unfortunately, our data does not allow addressing the question whether this is due to exchange of expertise or to increasing cumulative experience. The group of small centers may also benefit from there being only a reduced capacity for improvement even in large volume centers some years after the introduction of a new procedure.

Interestingly, decreases in the volume effect over time were not observed for the endpoints of in-hospital length of stay and reimbursement. Presumably, this might be due to the fact that high-volume centers are at a major advantage in streamlining clinical workflows before and after the procedure.

Two recent studies showed volume-outcome relationships for TAVI procedures performed in US hospitals in 2012 [14,15]. In both studies, patients were divided into groups of equal sample size. Disregarding the accompanying problems regarding the external validity of the results [12,13], the results shown in these studies are similar to ours: Among others, inverse volume-outcome relationships were shown for the endpoints death and bleeding [14,15]. One of the two studies also included the endpoints length of stay and hospitalization costs and identified significant differences between the observed hospital volume quartiles (TAVI/year cutoffs <=5, 6-10, 11-20 and >20) [15]. The other study also included the endpoint stroke and did not show significant differences between volume groups (TAVI cutoffs: 20 or 10 cases for different access routes) [14].

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As stated before, medical authorities in several countries have issued guidelines calling for minimum numbers of procedures for primary operators performing TAVI [16–19].

In Germany, such mandatory minimums are not yet implemented, but a mandatory number of 50 TAVI procedures annually is officially recommended [19], and this number is also mentioned in guidelines from the UK, Canada and Portugal [16–18]. Our results confirm the existence of a volume-outcome relationship for TAVI procedures between 2008 and 2014, and these effects are in line with existing evidence from TAVI procedures performed in US hospitals [6,14,15]. The above discussed weakening of the volume-outcome relationship over time, however, relativizes the rationale behind mandatory minimum numbers of procedures: The volume-outcome relationship may be considerable in the years following the introduction of a new procedure when there still is a lot of room for improvement (in the two of the cited studies [14,15], i.e. 2012). After a few years, then, the association between procedure numbers and better performance may diminish (see our results regarding the year 2014 and presumably thereafter). In the worst case, the volume effect is already gone by the time mandatory minimums are finally implemented, or the implementation hinders the system to reach optimal health service without restrictions. It should be, however, noted that the average number of TAVI procedures per hospital is larger in Germany compared to most other countries, and that hence the time span until such a point is reached may be longer in other countries.

This might be especially problematic since mandatory minimum quantities on the center level are not free of further disadvantages. They are thought to lead to centralization of procedures in large hospitals, necessitating costly patient transfers and potentially worse aftercare. In addition, it is unclear how an optimal threshold could be set (and adjusted yearly) and by whom, how effects of physician volume and hospital volume should be combined, whether low-volume hospitals and their surgeons perceive the thresholds as new incentives to operate, and how new and innovative hospitals might be able to enter the market [29]. The latter question is especially relevant for TAVI since a recent study showed that between 2010 and 2015 a new center entering the TAVI market needed to perform 54 procedures to achieve clinical outcomes comparable to those reported in high-volume centers [30]. According to the authors of the study, this represents more than 2 years of continuous activity [30].

In addition, the question remains how to integrate the observed volume effects into the existing theory. The "practice-makes-perfect hypothesis" implies a contrary causal relationship than the theory of

"selective-referral" [7,8], and we cannot answer the question whether volume generates quality (practice makes perfect), quality generates volume (selective referral), or both.

Furthermore, Gandjour et al. differentiated the "practice-makes-perfect hypothesis" into learning curve effects, economies of scope, and the concept of a focused factory [31]. Improved outcomes may result from economies of scale: every time doctors perform a procedure, they gain experience. Economies of scope, in contrast, would occur from the simultaneous performance of dissimilar procedures. In the TAVI context, this means that a high-volume center might see improved TAVI outcomes as a result of the performance of high numbers of other procedures. Accordingly, Epstein already raised the question whether similar procedures should also be counted towards a set volume threshold [29]. The focused factory concept, in contrast, assumes that focusing on a small number of procedures could also be favorable [31]. Unfortunately, none of the existing approaches analyzed whether the volume-outcome relationship differs in accordance to the number of other (closely related) procedures conducted in the respective center.

We conclude that the hypothesized volume-outcome relationship for TAVI exists but diminishes and may disappear over time. This might be the case for other interventional procedures, too, which should be taken into account when considering mandatory minimum thresholds.

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Table 1: Baseline characteristics (2008-2014)

2	Ν	43,996
3	Female	55 87%
4	Age in years mean/SD	80.95/6.11
5	Estimated logistic EuroSCORE ¹ mean/SD	22 21%/13 57%
6	Aortic valve stenosis	68 22%
7	Combined aortic valve diseases	26 56%
8	Heart failure	
9	NYHA II	8 26%
10		41 66%
11	Hypertension	62.66%
12	CAD	46.88%
13	Previous myocardial infarction	
14	within 4 months	1 59%
15	within 1 year	0.75%
16	after 1 year	4 35%
17	Previous CABG	12 75%
18	Previous cardiac surgery	18.06%
19	Peripheral vascular disease	12 39%
20	Carotid disease	6.17%
21	COPD	15 14%
22	Pulmonary hypertension	22 32%
23	Renal disease	
24	GER <15ml/min	2 95%
25	GER <30ml/min	4 90%
26	Atrial fibrillation	45.93%
27	Diabatas	
28	Diabetes	33.30%
29	¹ For calculation of the logistic EuroSCORE, we w	ere able to populate all fields except for critical preoperative state and left ventricular function. In
30	these we assumed an inconspicuous state (i.e. r	no critical preoperative state and no left ventricular dysfunction) and thus calculated a best-case
31	Abbreviations: NYHA – New York Heart Associa	tion Functional Classification: CAD - coronary artery disease: CABG - coronary artery bypass graft: COPD - chronic
32	obstructive pulmonary disease; GFR – glomerul	ar filtration rate.
33	Please note that in comparison to the data put	blished by Reinöhl et al., one TA-TAVI procedure (in 2010) needed to be removed from the dataset due to
34	incomplete information.	
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Table 2: Number of procedures with regard to the performed TAVI volume of a distinct center in a given year.

TAVI Volume in Center	2008	2009	2010	2011	2012	2013	2014
<50 procedures, n (number of centers)	613 (40)	1,234 (61)	1,155 (51)	1,107 (43)	960 (36)	765 (31)	617 (30)
50-99 procedures, n (number of centers)	236 (3)	658 (10)	1,875 (26)	1,957 (27)	1,569 (20)	1,930 (25)	1,135 (16)
>=100 procedures, n (number of centers)	273 (n/a*)	707 (n/a)	1,776 (3)	3,459 (7)	5,711 (16)	6,452 (9)	9,807 (20)
Total number, n (number of centers)	1,122 (>=44)	2,599 (>=72)	4,806 (80)	6,523 (77)	8,240 (72)	9,147 (65)	11,559 (66)

Please note that the numbers of procedures performed per year at a given center were not constant over the observation period, so that it is possible for a center to fall into a different volume group in a different year. Number of centers in parentheses.

* n/a = not available, exact number censored by DESTATIS due to data protection concerns

<text><text><text><text>

Table 3: Unadjusted in-hospital outcomes with regard to the performed TAVI volume of a distinct center in a given year.

	Mortality, %	Stroke, %	Bleeding, %	Length of stay, mean in days	Reim- bursement, mean in €	Proportion of patients with ventilation >48h, %
2008						
<50 procedures	10.11%	3.26%	14.36%	19.2		9.79%
50-99 procedures	9.32%	2.12%	11.44%	21.8		6.78%
>=100 procedures	6.59%	2.56%	7.33%	14.7		4.76%
2009						
<50 procedures	9.81%	3.57%	14.18%	21.6		9.48%
50-99 procedures	8.36%	3.34%	11.25%	18.5		7.14%
>=100 procedures	6.08%	2.12%	7.21%	18.0		7.36%
2010						
<50 procedures	9.00%	2.51%	12.12%	21.0	37,071€	8.74%
50-99 procedures	8.11%	2.56%	11.41%	19.1	36,173€	8.69%
>=100 procedures	6.14%	2.20%	6.25%	17.0	35,074€	5.01%
2011						
2011	7 600/	2 250/	0.20%	20.0		Q 0.10/
< 50 procedures	7.00% 8.02%	2.55%	9.59%	20.0	35,904t	0.04%
>=100 procedures	0.UZ%	2.55%	9.04%	19.5	35,424t	0.20%
>=100 procedures	5.07 /6	5.01%	9.51%	17.5	55,040€	1.29/0
2012						
<50 procedures	6.15%	2,29%	8.44%	18.7	35.294€	7.29%
50-99 procedures	7.07%	2.42%	8.41%	18.9	34.798€	5.48%
>=100 procedures	5.03%	2.10%	6.30%	16.7	34.233€	5.39%
2013						
<50 procedures	5.49%	2.09%	9.28%	20.2	35,808€	6.93%
50-99 procedures	5.85%	2.33%	6.53%	18.2	34,650€	4.56%
>=100 procedures	5.29%	2.70%	5.98%	16.3	34,456€	5.29%
2014						
<50 procedures	5.34%	2.75%	5.99%	19.9	35,993€	6.15%
50-99 procedures	4.58%	2.20%	5.73%	18.3	34,904€	4.32%
>=100 procedures	3.70%	2.28%	4.22%	15.3	34,771€	3.92%

Please note that the numbers of procedures performed per year at a given center were not constant over the observation period, so that it is possible for a center to fall into a different volume group in a different year.

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Figure 1: Risk-adjusted in-hospital mortality, stroke, bleeding and ventilation rates and their association with center-specific procedure volumes in a given year.

Estimates are based on risk-adjusted logistic regression analysis including all available patient characteristics as confounders (see Table 1). Predicted probabilities are calculated by setting each confounder to its mean value (prediction at the means, see Table 1 for means). Annual and volume effects were calculated using random effects meta regression based on the estimated rates. A separate model with an interaction term was used to assess the change in the volume-outcome relationship. pp= percentage points

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 Estimates are based on risk-adjusted linear regression analyses including all available patient characteristics as confounders (see Table 1). Predicted probabilities are calculated by setting each confounder to its mean value (prediction at the means, see Table 1 for means). Annual and volume effects were calculated using random effects meta regression based on the estimated means. A separate a model with an interaction term was used to assess the change in the volume-outcome relationship.

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. Table S1: Results of the logistic regression model, transformation into discrete event probabilities and subsequent meta regressions

3 First step: Logistic regression model on 43,996 TAVI cases with in-hospital mortality as dependent variable,

4 an interaction term (n_ik_year_50_100#year) between categorical time (in years) and volume categories and

22 predefined patient and procedural characteristics as potential confounder. 5

n ik year 5	0 100	OR	p-value	95% CI]					
	procedure volume <50	1.000	•							
	procedure volume 50-99	0.989	0.98	0.437 - 2.241						
	procedure volume >=100	0.668	0.004	0.506 - 0.882					Third step: A random effects	
									meta regression (using	
year						n_ik_year_50_100#year Prob.	p-value	95% CI	Stata's sommand matavag)	
~	2008	1.000				procedure volume <50 # 2008 0.090	0.000	0.068 - 0.113	Stata's command metaregy	
0	2009	0.929	0.6/1	0.661 - 1.305		procedure volume <50 # 2009 0.085	0.000	0.0/1 - 0.098	with time and volume as	
1	2010	0.844	0.376	0.579 - 1.229		procedure volume <50 # 2010 0.077	0.000	0.059 - 0.095	continuous covariates was	volu
	2011	0.686	0.032	0.486 - 0.968	Second step: Predicted probabilities are	procedure volume <50 # 2011 0.064	0.000	0.048 - 0.08	applied to the estimated	Annu
2	2012	0.525	0.004	0.340 - 0.812	calculated by setting each confounder to	procedure volume $<50 \# 2012 = 0.050$	0.000	0.033 - 0.066	rates	
3	2013	0.405	0.001	0.302 - 0.718 0.288 - 0.712	its mean value (prediction at the means)	procedure volume $<50 \ \# \ 2013 \ 0.044$	0.000	0.029 - 0.059	Tutes.	
5	2014	0.455	0.001	0.288 - 0.712	using State's marging command with	procedure volume 50-99 # 2014 0.045	0.000	0.027 - 0.033		
4 n ik vear F) 100#vear				using stata sinal gins command with	procedure volume 50-99 # 2008 0.090	0.000	0.020 - 0.133		
5 proce	$\frac{1}{2}$	0 929	0 874	0 376 - 2 298	application of the atmeans option.	procedure volume 50-99 # 2009 0.070	0.000	0.050 - 0.082		
Droce	dure volume 50-99 # 2010	0.909	0.828	0.384 - 2.151		procedure volume 50-99 # 2010 0.070	0.000	0.057 - 0.082		
6 proce	dure volume 50-99 # 2011	1.105	0.822	0.464 - 2.631		procedure volume 50-99 # 2012 0.062	0.000	0.049 - 0.076		
7 proce	dure volume 50-99 # 2012	1.280	0.597	0.512 - 3.202		procedure volume 50-99 # 2013 0.050	0.000	0.038 - 0.061		
proce	dure volume 50-99 # 2013	1.141	0.781	0.452 - 2.877	_	procedure volume 50-99 # 2014 0.039	0.000	0.026 - 0.052		
8 proce	dure volume 50-99 # 2014	0.908	0.845	0.346 - 2.385		procedure volume >=100 # 2008 0.062	0.000	0.06 - 0.064	Fourth sten: A second	
proce	lure volume >=100 # 2009	1.007	0.981	0.583 - 1.740		procedure volume >=100 # 2009 0.058	0.000	0.034 - 0.083		
9 proce	lure volume >=100 # 2010	1.120	0.598	0.735 - 1.705		procedure volume >=100 # 2010 0.059	0.000	0.044 - 0.074	random effects meta	
proce	lure volume >=100 # 2011	1.260	0.223	0.869 - 1.827		procedure volume >=100 # 2011 0.054	0.000	0.047 - 0.061	regression model was applied	
proce	lure volume >=100 # 2012	1.399	0.164	0.872 - 2.244		procedure volume >=100 # 2012 0.047	0.000	0.039 - 0.054	including also an interaction	
1 proce	lure volume >=100 # 2013	1.606	0.046	1.009 - 2.558		procedure volume >=100 # 2013 0.047	0.000	0.040 - 0.055	term.	Volume effe
proce	lure volume >=100 # 2014	1.100	0.687	0.692 - 1.749		procedure volume >=100 # 2014 0.032	0.000	0.028 - 0.036		Annual chan
~									Annual cha	ange of volume e
3 Female		0.902	0.045	0.815 - 0.998						
Age in years		1.009	0.155	0.997 - 1.022						
+ Estimated lo	gistic EuroSCORE	1.022	0.000	1.015 - 1.029						
Aortic valve	stenosis	0.030	0.000	0.504 - 0.802						
Combined a	ortic valve diseases	0.553	0.000	0.447 - 0.085						
	1	1 550	0.000	1 264 - 1 900						
	1	1 034	0.517	0 934 - 1 1//						
Hypertensic		0.698	0.000	0 612 - 0 797						
Previoue MI	within 4 months)	0.683	0.048	0.467 - 0.997						
Previous MI	within 1 year)	1.042	0.881	0.608 - 1.785						
Previous MI	after 1 year)	0.979	0.816	0.821 - 1.169						
Previous CA	G	1.017	0.884	0.809 - 1.278						
Previous car	liac surgery	0.808	0.117	0.619 - 1.055						
Peripheral v	iscular disease	1.118	0.140	0.964 - 1.295						
Carotid dise	se	0.896	0.165	0.768 - 1.046						
COPD		0.979	0.744	0.863 - 1.111						
Pulmonary ł	ypertension	0.852	0.021	0.744 - 0.976						
GFR <15%		1.770	0.000	1.443 - 2.170						
GFR <30%		1.414	0.000	1.167 - 1.714						
Atrial fibrilla	ion	1.211	0.000	1.115 - 1.315						
Diabetes		1.024	0.640	0.926 - 1.133						

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Volume-outcome relationship in transcatheter aortic valve implantations in Germany 2008-2014: A secondary data analysis of electronic health records

Journal:	BMJ Open
Manuscript ID	bmjopen-2017-020204.R1
Article Type:	Research
Date Submitted by the Author:	05-Mar-2018
Complete List of Authors:	Kaier, Klaus; Medical Center-University of Freiburg, Institute for Medical Biometry and Statistics Oettinger, Vera; Heart Center Freiburg University, Department of Cardiology and Angiology I Reinecke, H; University of Muenster, Department of Cardiology and Angiology, Adult Congenital and Valvular Heart Disease Center Muenster Schmoor, Claudia; Medical Centre, University of Freiburg Frankenstein, L.; University of Heidelberg, Dpt. of Cardiology, Angiology, Pulmology Vach, Werner; Institute of Medical Biometry and Medical Informatics, Hehn, Philip; Faculty of Medicine and Medical Center – University of Freiburg von zur Mühlen, Constantin; Heart Center Freiburg University, Department of Cardiology and Angiology I Bode, Christoph; Heart Center Freiburg University, Department of Cardiology and Angiology I Zehender, Manfred; Heart Center Freiburg University, Department of Cardiology and Angiology I Reinöhl, Jochen; Heart Center Freiburg University, Department of Cardiology and Angiology I
Primary Subject Heading :	Cardiovascular medicine
Secondary Subject Heading:	Health economics
Keywords:	Valvular heart disease < CARDIOLOGY, HEALTH ECONOMICS, CARDIOLOGY, Adult cardiology < CARDIOLOGY

SCHOLARONE[™] Manuscripts

Volume-outcome relationship in transcatheter aortic valve implantations in Germany 2008-2014: A secondary data analysis of electronic health records

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Word count excluding title page, abstract, references, figures and tables: 2947

ABSTRACT

Keywords: TAVI, volume-outcome; minimum volume standards; hospital quality; mortality

Objectives: We examine the volume-outcome relationship in isolated transcatheter aortic valve implantations (TAVI). Our interest was whether the volume-outcome relationship for TAVI exists on the center level, whether it occurs equally for different outcomes, and how it develops over time.

Design: Secondary data analysis of electronic health records. The comprehensive German Federal Bureau of Statistics DRG database was queried for data on all isolated TAVI procedures performed in Germany between 2008 and 2014. Logistic and linear regression analyses were carried out. Risk-adjustment was applied using a predefined set of patient characteristics to account for differences in the risk factor composition of the patient populations between centers and over time. Centers performing TAVI were stratified into groups performing <50, 50-99, and ≥100 procedures per year.

Setting: Germany 2008 - 2014.

Participants: All patients undergoing isolated TAVI in the observation period.

Interventions: none.

Primary and secondary outcome measures: In-hospital mortality, bleeding, stroke, probability of ventilation >48 hours, length of hospital stay, and reimbursement.

Results: Between 2008 and 2014, a total of 43,996 TAVI procedures were performed in 113 different centers in Germany with a total of 2,532 cases of in-hospital mortality. Risk-adjusted in-hospital mortality decreases over the years and is lower the higher the annual procedure volume at the center is. The magnitude of the latter effect declines over the observation period. Our results indicate a ceiling effect in the volume-outcome relationship: The volume-outcome relationship is eminent in circumstances of relatively unfavorable outcomes. Alongside improving outcomes, however, the volume-outcome relationship decreases. Also, a volume-outcome relationship seems to be absent in circumstances of constantly low event rates.

Conclusions: The hypothesized volume-outcome relationship for TAVI exists but diminishes and may disappear over time. This might be the case for other interventional procedures, too, which should be taken into account when considering mandatory minimum thresholds.

STRENGTHS AND LIMITATIONS OF THIS STUDY

- Study based on administrative data; coding errors are inevitable. However, about 20% of all cardiovascular diagnosis-related groups are reviewed by independent teams of physicians on behalf of the health insurers.
- Risk-adjustment included a number of parameters whose reliability cannot be fully secured, and we cannot guarantee that all parameters of relevance are included in the model. A major limitation is that the data source does not include information on the type of device used in individual TAVI procedures. In addition, information regarding the experience of surgeons at each centre would be highly relevant for the analysis but is unavailable.
- Hospital volume was classified into three fixed categories (<50, 50-99, >=100), which is in line with thresholds mentioned in official guidelines and previously applied in the literature. Possible effects related to very high volumes, however, might be hidden in the analyzed group of patients treated in hospitals with >=100 cases per year.
- The dataset omits patients with a baseline diagnosis of pure aortic regurgitation, as well as those who underwent TAVI with any other concomitant cardiac procedure. This makes sense from a clinical perspective, but further complicates direct comparisons with other administrative datasets.
- The study provides comprehensive data on everyday TAVI practice in a large industrialized country over a multiyear period.

KEY QUESTIONS

What is already known about this subject?

After their introduction, outcomes of new interventions are subject to a learning curve effect, meaning that outcomes improve over a period of time and then level off. The volume of procedures performed at an institution can influence this process, and is thought to have some effect on patient outcomes even after learning is complete (volume-outcome-hypothesis).

What does this study add?

This study tracks patient outcomes by center procedure volume in all transcatheter aortic valve implantation (TAVI) procedures performed in Germany between the procedure's introduction in 2008 and 2014, providing empirical evidence on shape and extent of the above described effects for this procedure.

How might this impact on clinical practice?

This data is of interest to clinical practitioners, hospital administrators, and policy makers involved in the implementation of new clinical procedures.

COMPETING INTERESTS AND FUNDING

The authors declare no conflicts of interest. There was no external funding for this work.

DATA SHARING STATEMENT

No additional data available.

AUTHORSHIP STATEMENT

KK and JR developed the research question and designed the methodology. VÖ, HR, LF, CvzM, CB, MZ and JR provided the medical knowledge of German TAVI practice informing the study design. KK defined the categories, outcomes and measures and developed and implemented the formal analysis and statistical with support by WV and CS. KK and JR collected the data and evidence. KK, VÖ, and WV interpreted and contextualized the results. KK and PH wrote the initial draft of the article, with JR contributing. All authors participated in the critical revision of the article and provided final approval of the version to be published.

INTRODUCTION

Transcatheter aortic valve implantation (TAVI) is a rapidly evolving technique for therapy of aortic stenosis, with a very early and pronounced utilization in Germany [1]. Previous studies report hospital-specific learning curves with respect to in-hospital outcomes such as procedural success, mortality and clinical complications of varying lengths and magnitudes [2–6]. In general, learning curve effects within and between centers can to some degree be explained by the volume of procedures performed at the center. This relationship can be summed up as the "practice-makes-perfect hypothesis", according to which quality of care either increases with the number of patients as a result of economies of scale, with a competing explanation of "selective-referral", according to which higher-quality hospitals attract greater demand and therefore have a greater volume of patients [7,8].

There are a number of criticisms on empirical analyses on the volume-outcome relationship: Many studies lack appropriate adjustment for differences in the risk factor composition of the patient populations between centers [9,10]. Secondly, most studies focus on in-hospital mortality only [11], which is easy to measure, but it is recommended to include additional quality measurements. Finally, most studies divided patients into groups of equal size for analyzing the volume-outcome relationship, which makes it difficult to make use of such results when justifying specific volume thresholds [6,12–14].

Although the evidence regarding the existence of an inverse relationship between the number of TAVI procedures and related outcomes is limited [15,16], medical authorities in Germany and several other countries have issued guidelines calling for minimum numbers of procedures for primary operators performing TAVI [17–20]. There however remains some question whether, firstly, the volume-outcome relationship outlined above exists on the center level regarding TAVI and, secondly, whether or not it takes place in all outcomes and complications equally, and how an existing volume-outcome relationship might change over the years.

To address these questions, we calculated annual procedure volumes for all German hospitals that performed TAVI procedures between January 2008 and December 2014. In order to account for differences in the patient population between high-, medium-, and low-volume centers and over time, we carried out baseline-adjusted regression analyses for the endpoints in-hospital mortality, bleeding, stroke, probability of ventilation >48 hours, length of hospital stay, and reimbursement.

METHODS

Data

Since 2005, data on all hospitalizations in Germany have been available for scientific use via the Diagnosis Related Groups (DRG) statistics collected by the Research Data Center of the Federal Bureau of Statistics (DESTATIS). These hospitalization data, including diagnoses and procedures, are a valuable source of representative nationwide data on the in-hospital treatment of patients. This database represents a virtually complete collection of all hospitalizations in German hospitals that are reimbursed according to the DRG system. From this database [1], we have extracted data on 43,996 cases of isolated TAVI for our analysis.

Our study did not involve direct access by the investigators to data on individual patients but only access to summary results provided by the Research Data Center. Therefore, approval by an ethics committee and informed consent were determined not to be required, in accordance with German law. All summary results were anonymized by DESTATIS. In practice, this means that any information allowing the drawing of conclusions regarding a single patient or a specific hospital are censored by DESTATIS to guarantee data protection. Especially the use of the anonymous, persistent "institute indicator of hospitals" is highly restricted in order not to publish any information directly attributable to a single hospital.

As described previously [1,21], we were able to use the OPS codes (OPS codes: 5-35a.0 in 2007 and 5-35a.00, 5-35a.01 from 2008) to identify all TAVI procedures performed (and reimbursed) in Germany between 2008 and 2014. Patients with a baseline diagnosis of pure aortic regurgitation (main or secondary diagnosis other than 135.0, 135.2, 106.0, 106.2) and those with concomitant cardiac surgery or percutaneous coronary intervention were not included in this analysis. Although some concomitant procedures might be informative (a cardiac surgery procedure during the same hospital stay as TAVI might likely represent a complication following a TAVI procedure), these cases cannot be consistently identified in our dataset as, in many cases, concomitant procedures might have taken place in another center. A complete list of procedure codes can be found in Table S1, a more detailed discussion of the data source may be found in a previous manuscript [1,21].

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Patient and Public Involvement

The development of the research question was guided by the intention to provide hospitals and policymakers with empirical evidence that enables them to structure the infrastructure in such a way as to deliver the best possible outcomes to patients. The selected outcome measures represent the most severe complications to the procedure and are of high significance to patient quality of life after the intervention. There was, however, no direct involvement of patients in the design, the recruitment and conduct of the study, nor will the results be disseminated to study participants as the study was based on anonymized administrative data.

Measures

Regarding the in-hospital complications, bleeding was defined as requiring a transfusion of more than 5 units of red blood cells (RBC). For all other comorbidities and complications the existing anamnestic or acute distinctive codes were used (we have discussed OPS and ICD codes in greater detail previously [21]).

In order to analyze possible effects of the above discussed mandatory minimum quantities, the number of procedures per year and center was categorized (i.e. n<50, 50≤n<100, n≥100) on the basis of an anonymous, persistent "institute indicator of hospitals" provided by DESTATIS. These particular thresholds are applied because the minimum number of 50 procedures is often mentioned in official TAVI-guidelines [17–20], and these thresholds are widely applied in the literature [22–24].

The primary outcome was in-hospital mortality. Secondary outcomes include post-procedural complications such as stroke and bleeding events (transfusion of >=5 RBC), as well as reimbursement, length of hospital stay and proportion of patients with ventilation >48h.

Statistical analysis

In a first step, multivariate regression analyses were carried out for the different endpoints. In a previous study, Reinöhl et al. [1] identified 21 baseline patient characteristics to describe risk profiles between procedural groups. For risk adjustment, all of these 21 baseline patient characteristics were included as covariates (all covariates listed in Table 1) in the respective regression analyses. In addition, an interaction term between time (in years) and the above mentioned annual volume categories was

included in the regression analyses in order to investigate the volume-outcome relationship over the years.

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Table 1: Baseline	characteristics	(2008-2014)
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Ν	43,996
Female	55.87%
Age in years, mean/SD	80.95/6.11
Estimated logistic EuroSCORE ¹ , mean/SD	22.21%/13.57%
Aortic valve stenosis as main diagnosis	68.22%
Combined aortic valve diseases as main diagnosis	26.56%
Heart failure	
NYHA II	8.26%
NYHA III or IV	41.66%
Hypertension	62.66%
CAD	46.88%
Previous myocardial infarction	
within 4 months	1.59%
within 1 year	0.75%
after 1 year	4.35%
Previous CABG	12.75%
Previous cardiac surgery	18.06%
Peripheral vascular disease	12.39%
Carotid disease	6.17%
COPD	15.14%
Pulmonary hypertension	22.32%
Renal disease	
GFR <15ml/min	2.95%
GFR <30ml/min	4.90%
Atrial fibrillation	45.93%
Diabetes	33.30%

¹For calculation of the logistic EuroSCORE, we were able to populate all fields except for critical preoperative state and left ventricular function.

these we assumed an inconspicuous state (i.e. no critical preoperative state and no left ventricular dysfunction) and thus calculated a best-case scenario.

Abbreviations: NYHA – New York Heart Association Functional Classification; CAD – coronary artery disease; CABG – coronary artery bypass graft; COPD – chronic obstructive pulmonary disease; GFR – glomerular filtration rate.

Please note that in comparison to the data published by Reinöhl et al., one TA-TAVI procedure (in 2010) needed to be removed from the dataset due to incomplete information.

Logistic and linear regression analyses are applied for dichotomous and continuous endpoints, respectively. The question of how to account for patients treated in the same hospital was discussed previously [13,25,26]. As recommended in a previous study that also used data from the German DRG-statistic [13], we used cluster-robust standard errors to account for this dependency.

Risk-adjusted rates and means within each year and hospital volume category were obtained by computing the corresponding predicted probabilities or means, respectively, for an artificial subject with each confounder set to its mean value (prediction at the means, see Table 1 for mean values of all confounders). Thereby, risk-adjusted rates and means are taking two aspects into account: (1) change in the patients risk factors compositions over the years, and (2) differences in the patients risk factors compositions within different hospital volume categories. Risk-adjusted rates and means are therefore interpreted as the 'true' procedure-related outcomes independent of changes in the patient population over the years and differences between low, medium, and high-volume centers. Please note that this implies the assumption that all outcome relevant parameters are used for risk-adjustment. Unfortunately, we cannot guarantee that all parameters of relevance are included in the model. In fact, the administrative dataset lacks relevant clinical information (such as echocardiographic findings or anatomical characteristics).

The visualization of these risk-adjusted rates or means together with their 95% confidence intervals constitutes the main analytical approach in this paper. To assess the statistical significance of the observed volume-outcome relationship, of the time trend and a potential change of the volume-outcome relationship over time, we applied to the estimated rates or means a random effects meta regression (command metareg [27]) with time and volume as continuous covariates. A model with an interaction term was used to assess the change in the volume-outcome relationship. A model without an interaction was used to assess the main effects.

Standardized reimbursement data is only available starting in 2010 due to a change in the reimbursement system making previous data difficult to compare. In Germany, reimbursement is based on DRGs which are defined by the patients' diagnoses, gender and age, treatment procedures, complications or comorbidities, and further attributes. Based on this data, a predetermined reimbursement rate per case is calculated. Hospitals receive additional reimbursement for long-stay outlier cases [28]. Furthermore,

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additional reimbursement is possible for very complex intensive care treatments, which have to be proven by documentation of illness severity and treatment effort during ICU stay [29].

All analyses were carried out using Stata 13.1 (StataCorp, College Station, Texas, USA).

RESULTS

 J.

 of 43,996 TAVI procedure.

 of TAVI procedures performed.

 J2 to 2008 to 11,559 in 2014 (see Table.)

 Between 2008 and 2014, a total of 43,996 TAVI procedures were performed in 113 different centers in Germany. The total number of TAVI procedures performed per year increased markedly over the observation period, from 1,122 in 2008 to 11,559 in 2014 (see Table 2).

Table 2: Number of procedures with regard to the performed TAVI volume of a distinct center in a given year.

TAVI Volume in Center	2008	2009	2010	2011	2012	2013	2014
<50 procedures, n (number of centers)	613 (40)	1,234 (61)	1,155 (51)	1,107 (43)	960 (36)	765 (31)	617 (30)
50-99 procedures, n (number of centers)	236 (3)	658 (10)	1,875 (26)	1,957 (27)	1,569 (20)	1,930 (25)	1,135 (16)
>=100 procedures, n (number of centers)	273 (n/a*)	707 (n/a)	1,776 (3)	3,459 (7)	5,711 (16)	6,452 (9)	9,807 (20)
Total number, n (number of centers)	1,122 (>=44)	2,599 (>=72)	4,806 (80)	6,523 (77)	8,240 (72)	9,147 (65)	11,559 (66)

Please note that the numbers of procedures performed per year at a given center were not constant over the observation period, so that it is possible for a center to fall into a different volume group in a different year. Number of centres in parentheses.

* n/a = not available, exact number censored by DESTATIS due to data protection concerns

As reported previously [1], substantial reductions in in-hospital mortality have been achieved between 2008 and 2013, and we find this trend to continue into 2014. Regarding center-specific procedure volumes of all TAVI procedures, it appears that the differences in unadjusted in-hospital mortality between the procedure volume groups (<50, 50-99, and >=100) steadily decline over the years (see Table 3). Figure 1 A provides risk-adjusted in-hospital mortality rates allowing for comparison despite possible differences in the patient selection process and consequently the risk factor composition between hospitals in the different procedure volume groups and over time (See Table S2 –Table S7 for details of the process used to generate the results shown in Figure 1A). These results indicate that risk-adjusted in-hospital mortality rates (1) steadily decrease over the years (annual change: -0.58 percentage points (pp), p<0.001), are (2) lower the higher the procedure volume at the hospital is (volume effect: -0.74pp, p=0.002), but that (3) this volume effect declines over the seven year observation period (p-value of interaction term: p=0.027; annual change of volume effect: 0.2pp).

Table 3: Unadjusted in-hospital outcomes with regard to the performed TAVI volume of a distinct center in a given year.

	Mortality, %	Stroke, %	Bleeding, %	Length of stay, mean in days	Reim- bursement, mean in €	Proportion of patients with ventilation >48h, %
2008						
<50 procedures	10.11%	3.26%	14.36%	19.2		9.79%
50-99 procedures	9.32%	2.12%	11.44%	21.8		6.78%
>=100 procedures	6.59%	2.56%	7.33%	14.7		4.76%
2009						
<50 procedures	9.81%	3.57%	14.18%	21.6		9.48%
50-99 procedures	8.36%	3.34%	11.25%	18.5		7.14%
>=100 procedures	6.08%	2.12%	7.21%	18.0		7.36%
2010						
<50 procedures	9.00%	2.51%	12.12%	21.0	37,071€	8.74%
50-99 procedures	8.11%	2.56%	11.41%	19.1	36,173€	8.69%
>=100 procedures	6.14%	2.20%	6.25%	17.0	35,074€	5.01%
2011						
<50 procedures	7 68%	2 25%	0.30%	20.0	25 08/F	8 0/1%
50-99 procedures	8.02%	2.33%	9.59%	10.2	35,304£	8.04%
>=100 procedures	6.02% E 97%	2.55%	9.04%	17.2	35,424€ 25.046£	7 20%
>=100 procedures	5.07 /0	5.01%	9.31/0	17.5	55,040€	7.29%
2012						
<50 procedures	6.15%	2,29%	8.44%	18.7	35,294€	7,29%
50-99 procedures	7.07%	2.42%	8.41%	18.9	34.798€	5.48%
>=100 procedures	5.03%	2.10%	6.30%	16.7	34.233€	5.39%
•						
2013						
<50 procedures	5.49%	2.09%	9.28%	20.2	35,808€	6.93%
50-99 procedures	5.85%	2.33%	6.53%	18.2	34,650€	4.56%
>=100 procedures	5.29%	2.70%	5.98%	16.3	34,456€	5.29%
2014						
<50 procedures	5.34%	2.75%	5.99%	19.9	35,993€	6.15%
50-99 procedures	4.58%	2.20%	5.73%	18.3	34,904€	4.32%
>=100 procedures	3.70%	2.28%	4.22%	15.3	34,771€	3.92%

Please note that the numbers of procedures performed per year at a given center were not constant over the observation period, so that it is possible for a center to fall into a different volume group in a different year.

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Over the seven years of data we analyzed, a slight decreasing trend was visible in the risk-adjusted inhospital stroke rate, which started out at 2-2,5% in 2008-2009 and ranged from 1,5-2% in 2013-2014 (Figure 1 B). Volume-outcome relationship was actually negative for years following 2010, with highervolume centers having higher stroke rates.

Risk-adjusted bleeding rates (Figure 1 C), in contrast, showed a clear beneficial effect of higher center procedure volumes for all years but 2011. The magnitude of the effect was distinct from 2008-2010 and decreased in the following years in parallel with an ongoing marked decrease in the general likelihood of bleeding complications, but still was present in 2013/2014.

For risk-adjusted in-hospital ventilation rate (>48h) (Figure 1 D), a pronounced beneficial effect of higher center procedure volumes persisted throughout the observation period. In addition, risk-adjusted in-hospital ventilation rates decreased substantially over the years. As for bleeding, the magnitude of the volume effect was distinct in the first years but steadily declined over the seven year period (annual change of the volume effect: 0.30pp, p=0.041).

Risk-adjusted in-hospital length of stay shows a strong beneficial effect of center procedure volume (Figure 2 A). Unlike the situation found for the endpoints mortality and bleeding, the magnitude of the effect did not decrease much over the observed timeframe. There also is a slight reduction in average length of stay over the years.

As shown in Figure 2 B, there is a drop in the overall reimbursement level from 2010-2012, but reimbursement stays roughly the same thereafter. In much the same way as found for length of hospital stay, risk-adjusted amount of reimbursement decreased only slightly over time, and showed a large volume effect which did not change over the five year period.

CONCLUSIONS

Our study shows mixed results regarding a volume-outcome relationship in TAVI procedures in German hospitals. First of all, TAVI-related in-hospital mortality decreased substantially between 2008 and 2014 and was lower the higher the procedure volume at the respective hospital is. The magnitude of this volume-outcome relationship, however, declines over the observation period. Especially in later years (2012-2014) differences in mortality between low-, medium-, and high-volume centers are small.

Regarding in-hospital mortality and secondary endpoints, a volume-outcome relationship is eminent in circumstances of relatively unfavorable outcomes (see early years of mortality, bleeding, and ventilation) and decreases as outcomes improve (later years of mortality, bleeding, and ventilation), but is not present in circumstances of constantly low event rates (see stroke). In addition, in most of the cases when we observe a distinct annual decrease, we also observe a decreasing volume effect over time. Presumably, the small centers succeed in participating at the system level learning curve to a degree which allows them to catch up to some degree to the group of high-volume. Unfortunately, our data does not allow addressing the question whether this is due to exchange of expertise or to increasing cumulative experience. The group of small centers may also benefit from there being only a reduced capacity for improvement even in large volume centers some years after the introduction of a new procedure.

Interestingly, decreases in the volume effect over time were not observed for the endpoints of in-hospital length of stay and reimbursement. Presumably, this might be due to the fact that high-volume centers are at a major advantage in streamlining clinical workflows before and after the procedure.

Two recent studies showed volume-outcome relationships for TAVI procedures performed in US hospitals in 2012 [15,16]. In both studies, patients were divided into groups of equal sample size. Disregarding the accompanying problems regarding the external validity of the results [12,13], the results shown in these studies are similar to ours: Among others, inverse volume-outcome relationships were shown for the endpoints death and bleeding [15,16]. One of the two studies also included the endpoints length of stay and hospitalization costs and identified significant differences between the observed hospital volume quartiles (TAVI/year cutoffs <=5, 6-10, 11-20 and >20) [16]. The other study also included the endpoint stroke and did not show significant differences between volume groups (TAVI cutoffs: 20 or 10 cases for different access routes) [15].

As stated before, medical authorities in several countries have issued guidelines calling for minimum numbers of procedures for primary operators performing TAVI [17–20]. In Germany, such mandatory minimums are not yet implemented, but a mandatory number of 50 TAVI procedures annually is officially recommended [20], and this number is also mentioned in guidelines from the UK, Canada and Portugal [17–19]. Our results confirm the existence of a volume-outcome relationship for TAVI procedures between 2008 and 2014, and these effects are in line with existing evidence from TAVI procedures performed in US hospitals [6,15,16]. The above discussed weakening of the volume-outcome relationship

over time, however, relativizes the rationale behind mandatory minimum numbers of procedures: The volume-outcome relationship may be considerable in the years following the introduction of a new procedure when there still is a lot of room for improvement (in the two of the cited studies [15,16], i.e. 2012). After a few years, then, the association between procedure numbers and better performance may diminish (see our results regarding the year 2014 and presumably thereafter). In the worst case, the volume effect is already gone by the time mandatory minimums are finally implemented, or the implementation hinders the system to reach optimal health service without restrictions. It should be, however, noted that the average number of TAVI procedures per hospital is larger in Germany compared to most other countries, and that hence the time span until such a point is reached may be longer in other countries.

This might be especially problematic since mandatory minimum quantities on the center level are not free of further disadvantages. They are thought to lead to centralization of procedures in large hospitals, necessitating costly patient transfers and potentially worse aftercare. In addition, it is unclear how an optimal threshold could be set (and adjusted yearly) and by whom, how effects of physician volume and hospital volume should be combined, whether low-volume hospitals and their surgeons perceive the thresholds as new incentives to operate, and how new and innovative hospitals might be able to enter the market [30]. The latter question is especially relevant for TAVI since a recent study showed that between 2010 and 2015 a new center entering the TAVI market needed to perform 54 procedures to achieve clinical outcomes comparable to those reported in high-volume centers [31]. According to the authors of the study, this represents more than 2 years of continuous activity [31].

In addition, the question remains how to integrate the observed volume effects into the existing theory. The "practice-makes-perfect hypothesis" implies a contrary causal relationship than the theory of "selective-referral" [7,8], and we cannot answer the question whether volume generates quality (practice makes perfect), quality generates volume (selective referral), or both.

Furthermore, Gandjour et al. differentiated the "practice-makes-perfect hypothesis" into learning curve effects, economies of scope, and the concept of a focused factory [32]. Improved outcomes may result from economies of scale: every time doctors perform a procedure, they gain experience. Economies of scope, in contrast, would occur from the simultaneous performance of dissimilar procedures. In the TAVI context, this means that a high-volume center might see improved TAVI outcomes as a result of the

performance of high numbers of other procedures. Accordingly, Epstein already raised the question whether similar procedures should also be counted towards a set volume threshold [30]. The focused factory concept, in contrast, assumes that focusing on a small number of procedures could also be favorable [32]. Unfortunately, none of the existing approaches analyzed whether the volume-outcome relationship differs in accordance to the number of other (closely related) procedures conducted in the respective center.

<text> We conclude that the hypothesized volume-outcome relationship for TAVI exists but diminishes and may disappear over time. This might be the case for other interventional procedures, too, which should be taken into account when considering mandatory minimum thresholds.

Figure Legends

Figure 1: Risk-adjusted in-hospital mortality, stroke, bleeding and ventilation rates and their association

with center-specific procedure volumes in a given year.

Estimates are based on risk-adjusted logistic regression analysis including all available patient characteristics as confounders (see Table 1). Predicted probabilities are calculated by setting each confounder to its mean value (prediction at the means, see Table 1 for means). Annual and volume effects were calculated using random effects meta regression based on the estimated rates. A separate model with an interaction term was used to assess the change in the volume-outcome relationship. pp= percentage points.

Figure 2: Risk-adjusted in-hospital length of stay and reimbursement and their association with center-

specific procedure volumes in a given year.

Estimates are based on risk-adjusted linear regression analyses including all available patient characteristics as confounders (see Table 1). Predicted probabilities are calculated by setting each confounder to its mean value (prediction at the means, see Table 1 for means). Annual and volume effects were calculated using random effects meta regression based on the estimated means. A separate a model with an interaction term was used to assess the change in the volume-outcome relationship.

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Caption : Figure 1: Risk-adjusted in-hospital mortality, stroke, bleeding and ventilation rates and their association with center-specific procedure volumes in a given year. # + Estimates are based on risk-adjusted logistic regression analysis including all available patient characteristics as confounders (see Table 1).
 Predicted probabilities are calculated by setting each confounder to its mean value (prediction at the means, see Table 1 for means). Annual and volume effects were calculated using random effects meta regression based on the estimated rates. A separate model with an interaction term was used to assess the change in the volume-outcome relationship. pp= percentage points.

111x83mm (600 x 600 DPI)



Figure 2: Risk-adjusted in-hospital length of stay and reimbursement and their association with centerspecific procedure volumes in a given year.

Estimates are based on risk-adjusted linear regression analyses including all available patient characteristics as confounders (see Table 1). Predicted probabilities are calculated by setting each confounder to its mean value (prediction at the means, see Table 1 for means). Annual and volume effects were calculated using random effects meta regression based on the estimated means. A separate a model with an interaction term was used to assess the change in the volume-outcome relationship.

81x32mm (600 x 600 DPI)

5-351 0*	Surgical aortic valve replacement
5-352.0*	Transcathatar aortic valve replacement
	Coronany arteny hypacs graft
2-202.°, 2-202.°, 2-	Coronary artery bypass grait
303.",	Curried without we have any loss of an anti-
5-351.1*, 5-351.2*, 5-	Surgical mitral valve replacement/reconstruction
353.1, 5-353.2	
5-351 4*	Surgical tricuspid valve replacement
5-377 0 et sega	Permanent pacemaker implantation
9 900 7*	
0-000.7 since 2010:	
0-000.c	
Diagnosis	
135.0, 106.0	Aortic valve stenosis (degenerative/rneumatic)
135.2.106.2	Combined aortic valve diseases (degenerative/rheumatic)
,	
150.1*	Left ventricular congestive heart failure (according to NYHA classes)
110*	Arterial Hypertension
125.11, 125.12, 125.13	Coronary artery disease
125.20, 125.21, 125.22	Previous myocardial infarction (within 4 months/1 year/after 1 year)
Z95.1	Previous coronary artery bypass graft
Z95.1 – Z95.4	Previous cardiac surgery
170 20-170 25 170 8	Perinheral vascular disease
170 0 172 0	
1/0.3, 1/3.3	
100.Z	
I∠⊥ [*]	Acute myocardial infarction (within the last 28 days)
J44*	Chronic obstructive pulmonary disease
127*	Pulmonary hypertension
N18*	Renal disease
N17*	Acute kidney injury
148.1*	Atrial fibrillation
E10* - E14*	Diabetes
163*, 164	Stroke or cerebral infarction incl. occlusion and stenosis of cerebral and precerebral arteri
	resulting in cerebral infarction

2 Table S2: Results of the logistic regression model, transformation into discrete event probabilities and subsequent meta regressions

3 First step: Logistic regression model on 43,996 TAVI cases with in-hospital mortality as dependent variable, an

interaction term (n_ik_year_50_100#year) between categorical time (in years) and volume categories and 22 $\,$

predefined patient and procedural characteristics as potential confounder.

6	n_ik_year_50_100	OR	p-value	95% CI					
7	procedure volume <50	1	0.00	0.407 0.044					
/	procedure volume 50-99	0.989	0.98	0.437 - 2.241					
8	procedure volume >=100	0.668	0.004	0.506 - 0.882					Third step: A random effects
~	vear					n ik year 50 100#year Prob	n-value	95% CI	meta regression (using Stata's
9	2008	1				procedure volume <50 # 2008 0.090	0.000	0.068 - 0.113	command metareg) with
10	2009	0 929	0 671	0 661 - 1 305		procedure volume <50 # 2009 0.085	0.000	0.071 - 0.098	time and volume as Coeff p-value 95% Cl
	2010	0.844	0.376	0.579 - 1.229		procedure volume <50 # 2010 0.077	0.000	0.059 - 0.095	continuous covariates was Volume effect -0.007 0.002 -0.0120.003
11	2011	0.686	0.032	0.486 - 0.968	Second step: Predicted probabilities are	procedure volume <50 # 2011 0.064	0.000	0.048 - 0.08	Annual change -0.006 0.000 -0.0080.004
12	2012	0.525	0.004	0.340 - 0.812	selected by acting each confounder to	procedure volume <50 # 2012 0.050	0.000	0.033 - 0.066	
12	2013	0.465	0.001	0.302 - 0.718	calculated by setting each confounder to	procedure volume <50 # 2013 0.044	0.000	0.029 - 0.059	rates.
13	2014	0.453	0.001	0.288 - 0.712	its mean value (prediction at the means)	procedure volume <50 # 2014 0.043	0.000	0.027 - 0.059	
14					using Stata's margins command with	procedure volume 50-99 # 2008 0.090	0.006	0.026 - 0.153	
17	n_ik_year_50_100#year				application of the atmeans option.	procedure volume 50-99 # 2009 0.078	0.000	0.058 - 0.098	\leq
15	procedure volume 50-99 # 2009	0.929	0.874	0.376 - 2.298		procedure volume 50-99 # 2010 0.070	0.000	0.059 - 0.082	
16	procedure volume 50-99 # 2010	0.909	0.828	0.384 - 2.151		procedure volume 50-99 # 2011 0.069	0.000	0.057 - 0.082	
10	procedure volume 50-99 # 2011	1.105	0.822	0.464 - 2.631		procedure volume 50-99 # 2012 0.062	0.000	0.049 - 0.076	
17	procedure volume 50-99 # 2012	1.280	0.597	0.512 - 3.202		procedure volume 50-99 # 2013 0.050	0.000	0.038 - 0.061	
10	procedure volume 50-99 # 2013	1.141	0.781	0.452 - 2.877		procedure volume >-100 # 2014 0.039	0.000	0.026 - 0.052	
10	procedure volume $>-100 \# 2014$	1 007	0.845	0.540 - 2.585		procedure volume >=100 # 2008 0.002	0.000	0.034 - 0.083	Fourth step: A second
19	procedure volume $\geq 100 \# 2009$	1 1 2 0	0.598	0 735 - 1 705		procedure volume >=100 $\#$ 2000 0.050	0.000	0.044 - 0.074	random effects meta
20	procedure volume >=100 # 2011	1.260	0.223	0.869 - 1.827		procedure volume >=100 # 2011 0.054	0.000	0.047 - 0.061	regression model was applied
20	procedure volume >=100 # 2012	1.399	0.164	0.872 - 2.244		procedure volume >=100 # 2012 0.047	0.000	0.039 - 0.054	including also an interaction Coeff p-value 95% CI
21	procedure volume >=100 # 2013	1.606	0.046	1.009 - 2.558		procedure volume >=100 # 2013 0.047	0.000	0.040 - 0.055	term. Volume effect -4.536 0.026 -8.4730.600
22	procedure volume >=100 # 2014	1.100	0.687	0.692 - 1.749		procedure volume >=100 # 2014 0.032	0.000	0.028 - 0.036	Annual change -0.011 0.000 -0.0160.006
22									Annual change of volume effect 0.002 0.027 0.000 - 0.004
23	Female	0.902	0.045	0.815 - 0.998					
24	Age in years	1.009	0.155	0.997 - 1.022					
24	Estimated logistic EuroSCORE	1.022	0.000	1.015 - 1.029					
25	Aortic valve stenosis	0.030	0.000	0.504 - 0.802					
26	Lombined aortic valve diseases	0.555	0.000	0.447 - 0.085					
20	NYHA III or IV	1.550	0.000	1.264 - 1.900					
27	CAD	1.034	0.517	0.934 - 1.144					
20	Hypertension	0.698	0.000	0.612 - 0.797					
20	Previous MI (within 4 months)	0.683	0.048	0.467 - 0.997					
29	Previous MI (within 1 year)	1.042	0.881	0.608 - 1.785					
20	Previous MI (after 1 year)	0.979	0.816	0.821 - 1.169					
30	Previous CABG	1.017	0.884	0.809 - 1.278					
31	Previous cardiac surgery	0.808	0.117	0.619 - 1.055					
22	Peripheral vascular disease	1.118	0.140	0.964 - 1.295					
32	Carotid disease	0.896	0.165	0.768 - 1.046					
33	LOPD Dulmonomi humortonoion	0.979	0.744	0.803 - 1.111					
24	CER <16%	1 770	0.021	1 1/13 - 2 170					
54	GER <30%	1.414	0.000	1.167 - 1.714					
35	Atrial fibrillation	1.211	0.000	1.115 - 1.315					
26	Diabetes	1.024	0.640	0.926 - 1.133					
30									
37									

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Table S3: Results of the logistic regression model, transformation into discrete event probabilities and subsequent meta regressions

3 First step: Logistic regression model on 43,996 TAVI cases with stroke as dependent variable, an interaction

term (n_ik_year_50_100#year) between categorical time (in years) and volume categories and 22 predefined

term (n_ik_year_50_100#year) between categorical time (in years patient and procedural characteristics as potential confounder.

5	n ik year 50,100	OP	n-value	95% CI							
6	nrocedure volume <50	1	p-value	55% CI							
7	procedure volume 50-99	0 929	0.886	0 339 - 2 5473							
/	procedure volume >=100	0.969	0.945	0 398 - 2 3631				Third stern A readout offers			
8	procedure fordine + 100	0.000	010 10	0.000 2.0001				inira step: A random enects			
~	vear					n ik vear 50 100#vear Prob. p-value	95% CI	meta regression (using Stata's			
9	2008	1				procedure volume <50 # 2008 0.022 0.000	0.012 - 0.031	command metareg) with			
10	2009	1.140	0.643	0.654 - 1.989		procedure volume <50 # 2009 0.025 0.000	0.017 - 0.032	time and volume as	Coef	p-value	95% CI
10	2010	0.732	0.308	0.401 - 1.335		procedure volume <50 # 2010 0.016 0.000	0.010 - 0.022	continuous covariates was	Volume effect 0.002	0.196	-0.001 - 0.003
11	2011	0.678	0.211	0.369 - 1.246	Second step: Predicted probabilities are	procedure volume <50 # 2011 0.015 0.000	0.009 - 0.021	applied to the estimated	Annual change -0.00	1 0.029	-0.002 - 0.000
12	2012	0.659	0.197	0.350 - 1.241	calculated by cotting each confounder to	procedure volume <50 # 2012 0.014 0.000	0.008 - 0.021	applied to the estimated			
12	2013	0.574	0.114	0.289 - 1.142	calculated by setting each combunder to	procedure volume <50 # 2013 0.013 0.000	0.006 - 0.019	rates.			
13	2014	0.759	0.426	0.385 - 1.496	its mean value (prediction at the means)	procedure volume <50 # 2014 0.016 0.000	0.008 - 0.025				
1 /					using Stata's margins command with	procedure volume 50-99 # 2008 0.020 0.026	0.002 - 0.038				
14	n_ik_year_50_100#year				application of the atmeans option.	procedure volume 50-99 # 2009 0.025 0.000	0.014 - 0.035	\leq			
15	procedure volume 50-99 # 2009	1.079	0.896	0.344 - 3.384		procedure volume 50-99 # 2010 0.019 0.000	0.014 - 0.025				
	procedure volume 50-99 # 2010	1.310	0.637	0.428 - 4.009		procedure volume 50-99 # 2011 0.017 0.000	0.012 - 0.022				
16	procedure volume 50-99 # 2011	1.233	0./15	0.400 - 3.796		procedure volume 50-99 # 2012 0.017 0.000	0.011 - 0.022				
17	procedure volume 50-99 # 2012	1.247	0.706	0.396 - 3.921		procedure volume 50-99 # 2013 0.015 0.000	0.011 - 0.020				
17	procedure volume 50-99 # 2013	1.332	0.042	0.414 - 4.288		procedure volume $50-99 \# 2014 = 0.015 = 0.000$	0.009 - 0.021				
18	procedure volume $>-100 \# 2014$	0.957	0.942	0.290 - 3.102		procedure volume >=100 # 2008 0.021 0.009	0.003 - 0.037	Fourth step: A second			
10	procedure volume $>=100 \# 2009$	1 1 3 /	0.049	0.203 - 2.287		procedure volume $>=100 \# 2003 0.013 0.000$	0.003 - 0.028	random effects meta			
19	procedure volume $\geq 100 \# 2010$	1.134	0.331	0.606 - 4.440		procedure volume $\geq 100 \# 2010 \ 0.017 \ 0.000$	0.012 - 0.023	regression model was applied			
20	procedure volume $\geq 100 \# 2011$	1 209	0.712	0.441 - 3.312		procedure volume $\geq 100 \# 2011 = 0.023 = 0.000$	0.014 - 0.020	including also an interaction	Coef	n-value	95% CI
~	procedure volume $\geq 100 \# 2012$	1 769	0.282	0.626 - 4.995		procedure volume $\geq 100 \# 2012 = 0.017 = 0.000$	0.018 - 0.025	torm	Volume effect -1 10	3 0 307	-3 311 - 1 106
21	procedure volume >=100 # 2014	1.099	0.857	0.393 - 3.076		procedure volume >=100 # 2014 0.018 0.000	0.015 - 0.020	term.	Annual change -0.00	2 0.086	-0.005 - 0.000
22								Annual cha	inge of volume effect 0.002	0.306	-0.001 - 0.002
~~	Female	0.648	0.000	0.565 - 0.744							
23	Age in years	0.900	0.000	0.890 - 0.910							
24	Estimated logistic EuroSCORE	68461	0.000	33804 - 138650							
24	Aortic valve stenosis	1.278	0.067	0.983 - 1.663							
25	Combined aortic valve diseases	1.329	0.045	1.006 - 1.755							
26	NYHA II	0.949	0.675	0.744 - 1.211							
20	NYHA III or IV	1.096	0.166	0.962 - 1.249							
27	CAD	1.011	0.875	0.885 - 1.154							
	Hypertension	0.910	0.148	0.802 - 1.034							
28	Previous MI (within 4 months)	0.278	0.000	0.167 - 0.464							
20	Previous MI (within 1 year)	1.240	0.491	0.007 - 2.328							
29	Previous IVII (after 1 year)	1.005	0.975	0.742 - 1.300							
30	Previous CABG	0.037	0.550	0.020 - 1.104							
21	Perinheral vascular disease	0 395	0.000	0 325 - 0 480							
וכ	Carotid disease	0.461	0.000	0.362 - 0.587							
32	COPD	0.355	0.000	0.295 - 0.429							
22	Pulmonary hypertension	0.198	0.000	0.164 - 0.239							
33	GFR <15%	0.266	0.000	0.183 - 0.387							
34	GFR <30%	0.297	0.000	0.226 - 0.391							
<u>э</u> т	Atrial fibrillation	1.093	0.165	0.964 - 1.239							
35	Diabetes	1.079	0.260	0.945 - 1.231							
26											
20											

2 Table S4: Results of the logistic regression model, transformation into discrete event probabilities and subsequent meta regressions

3 First step: Logistic regression model on 43,996 TAVI cases with bleeding as dependent variable, an interaction term (n_ik_year_50_100#year) between categorical time (in years) and volume categories and 22 predefined patient and procedural characteristics as potential confounder.

6 ⁿ	_ik_year_50_100	OR	p-value	95% CI					
7	procedure volume 50-99	1 806	0 366	0 506 - 1 286					
1	procedure volume >=100	0.485	0.006	0.291 - 0.811					Third stop. A random offects
8									mind step: A failed in effects
a y	ear					n_ik_year_50_100#year Prob.	p-value	95% CI	meta regression (using stata's
9	2008	1				procedure volume <50 # 2008 0.134	0.000	0.108 - 0.161	command metareg) with
10	2009	0.942	0.677	0./11 - 1.248		procedure volume <50 # 2009 0.128	0.000	0.109 - 0.146	time and volume as Coeff p-value 95% Cl
11	2010	0.775	0.086	0.579 - 1.037	Course of the second standards and be billing on the	procedure volume $<50 \# 2010 = 0.107$	0.000	0.090 - 0.125	continuous covariates was Volume effect -0.011 0.001 -0.0160.0049
10	2011	0.502	0.000	0.363 - 0.696	Second step: Predicted probabilities are	procedure volume <50 # 2011 0.002	0.000	0.057 - 0.088	applied to the estimated
12	2013	0.559	0.001	0.399 - 0.785	calculated by setting each confounder to	procedure volume <50 # 2013 0.080	0.000	0.062 - 0.098	rates.
13	2014	0.340	0.000	0.226 - 0.511	its mean value (prediction at the means)	procedure volume <50 # 2014 0.050	0.000	0.034 - 0.066	
11					using Stata's margins command with	procedure volume 50-99 # 2008 0.111	0.000	0.071 - 0.151	
14 n	_ik_year_50_100#year	0 002	0.079	0 571 1 724	application of the atmeans option.	procedure volume 50-99 # 2009 0.105	0.000	0.082 - 0.128	
15	procedure volume 50-99 # 2009	0.992	0.978	0.571 - 1.724		procedure volume 50-99 # 2010 0.102	0.000	0.089 - 0.118	
16	procedure volume 50-99 # 2011	1.224	0.458	0.718 - 2.087	7	procedure volume 50-99 # 2012 0.077	0.000	0.064 - 0.090	
10	procedure volume 50-99 # 2012	1.321	0.321	0.762 - 2.293		procedure volume 50-99 # 2013 0.059	0.000	0.049 - 0.069	
17	procedure volume 50-99 # 2013	0.894	0.693	0.511 - 1.563		procedure volume 50-99 # 2014 0.051	0.000	0.039 - 0.063	
18	procedure volume 50-99 # 2014	1.265	0.463	0.675 - 2.374		procedure volume >=100 # 2008 0.070	0.000	0.040 - 0.100	Fourth step: A second
10	procedure volume >=100 # 2009	1.070	0.828	0.581 - 1.970		procedure volume >=100 # 2009 0.071	0.000	0.052 - 0.090	random effects meta
19	procedure volume >=100 # 2010	2 198	0.799	1 249 - 3 866		procedure volume >=100 # 2010 0.039	0.000	0.048 - 0.070	regression model was applied
20	procedure volume >=100 # 2012	1.669	0.080	0.941 - 2.960		procedure volume >=100 # 2012 0.059	0.000	0.053 - 0.066	including also an interaction Coeff p-value 95% Cl
21	procedure volume >=100 # 2013	1.371	0.286	0.768 - 2.447		procedure volume >=100 # 2013 0.055	0.000	0.049 - 0.060	term. Volume effect -4.84852 0.169 -11.97 - 2.27482
21	procedure volume >=100 # 2014	1.540	0.174	0.827 - 2.868		procedure volume >=100 # 2014 0.038	0.000	0.034 - 0.042	Annual change -0.01589 0.001 -0.0240.0076
22		1.000	0.022	1 000 1 100					Annual change of volume effect 0.0024 0.170 -0.001 - 0.00595
23	emale	1.096	0.032	1.008 - 1.193					
	timated logistic EuroSCORE	5.813	0.000	3.386 - 9.979					
24	ortic valve stenosis	0.738	0.000	0.639 - 0.852					
25 C	ombined aortic valve diseases	0.677	0.000	0.580 - 0.790					
26	YHA II	0.665	0.000	0.562 - 0.786					
20	YHA III or IV	1.313	0.000	1.216 - 1.418					
27	AD	1.062	0.137	0.981 - 1.149					
28 P	revious MI (within 4 months)	0.866	0.324	0.650 - 1.153					
20. P	revious MI (within 1 year)	1.071	0.742	0.711 - 1.614					
29 _P	revious MI (after 1 year)	0.869	0.137	0.721 - 1.046					
30 P	revious CABG	0.530	0.000	0.447 - 0.629					
21 P	revious cardiac surgery	1.275	0.005	1.0// - 1.509					
31	eripheral vascular disease	1.255	0.000	1.118 - 1.409					
32	OPD	0.998	0.969	0.896 - 1.111					
22 P	ulmonary hypertension	0.833	0.002	0.741 - 0.935					
G	FR <15%	2.045	0.000	1.725 - 2.423					
34	FR <30%	1.446	0.000	1.240 - 1.685					
35	trial fibrillation	1.418	0.000	1.310 - 1.528					
25	labetes	0.908	0.410	0.094 - 1.048					
30									
37									

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2 Table S5: Results of the logistic regression model, transformation into discrete event probabilities and subsequent meta regressions

3 First step: Linear regression model on 43,996 TAVI cases with Length of hospital stay as dependent variable,

an interaction term (n_ik_year_50_100#year) between categorical time (in years) and volume categories and

22 predefined patient and procedural characteristics as potential confounder.

2	n ik vear 50 100	Coeff	p-value	95% CI								
6	procedure volume <50	0	praiac	5576 61								
7	procedure volume 50-99	2.959	0.001	1.133 - 4.786								
<i>'</i>	procedure volume >=100	-4.148	0.000	-5.5742.721					Third sten: A random effects			
8									mate regression (using State's			
0	year					n_ik_year_50_100#year Co	eff p-value	95% CI	meta regression (using stata s			
9	2008	0				procedure volume <50 # 2008 19.3	184 0.000	18.241 - 20.13	command metareg) with			
10	2009	2.179	0.001	0.950 - 3.409		procedure volume <50 # 2009 21.3	364 0.000	20.577 - 22.15	time and volume as	Coeff	p-value	95% CI
11	2010	1.472	0.019	0.247 - 2.697		procedure volume <50 # 2010 20.0	656 0.000	19.874 - 21.44	continuous covariates was	Volume effect -1.488	0.000	-2.0210.9555
11	2011	0.507	0.422	-0./31 - 1./45	Second step: Marginal means are	procedure volume <50 # 2011 19.0	691 0.000	18.890 - 20.49	applied to the estimated	Annual change -0.269	0.029	-0.5070.0307
12	2012	-1.002	0.100	-2.197 - 0.193	calculated by setting each confounder to	procedure volume <50 # 2012 18.	182 0.000	17.448 - 18.92	means.			
1 2	2015	0.562	0.360	-0.970 - 1.754	its mean value (prediction at the means)	procedure volume <50 # 2013 15.3	124 0.000	18.333 - 20.33				
15	2014	-0.000	0.551	-1.455 - 1.512	using Stata's margins command with	procedure volume 50-99 # 2014 15.	144 0.000	20 579 - 23 71				
14	n ik vear 50 100#vear				application of the atmosphere ontion	procedure volume 50-99 # 2009 18.	578 0.000	17.650 - 19.51				
1 Г	procedure volume 50-99 # 2009	-5.745	0.000	-7.9423.547	application of the atmeans option.	procedure volume 50-99 # 2010 18.	743 0.000	18.221 - 19.27				
15	procedure volume 50-99 # 2010	-4.872	0.000	-6.9262.819		procedure volume 50-99 # 2011 19.0	095 0.000	18.554 - 19.64				
16	procedure volume 50-99 # 2011	-3.555	0.001	-5.6221.488		procedure volume 50-99 # 2012 18.9	967 0.000	18.413 - 19.52				
17	procedure volume 50-99 # 2012	-2.174	0.037	-4.2190.130		procedure volume 50-99 # 2013 18.0	074 0.000	17.576 - 18.57				
17	procedure volume 50-99 # 2013	-4.452	0.000	-6.5762.327		procedure volume 50-99 # 2014 18.	137 0.000	17.545 - 18.73				
18	procedure volume 50-99 # 2014	-3.947	0.000	-6.1101.783		procedure volume >=100 # 2008 15.0	036 0.000	13.964 - 16.11	Fourth step: A second			
10	procedure volume >=100 # 2009	1.066	0.242	-0.721 - 2.853		procedure volume >=100 # 2009 18.3	281 0.000	17.543 - 19.02	random effects meta			
19	procedure volume $>=100 \# 2010$	0.788	0.365	-0.915 - 2.490		procedure volume >=100 # 2010 17	296 0.000	16./91 - 1/.8	regression model was applied			
20	procedure volume >=100 # 2011	1.972	0.021	0.292 - 3.052		procedure volume >=100 # 2011 17.3	515 0.000	17.137 - 17.89	including also an interaction	Cooff	n value	05% CI
20	procedure volume $>=100 \# 2012$	2.929	0.000	1.302 - 4.557		procedure volume >=100 # 2012 16.3	289 0.000	16.090 - 17.23		Volumo offect 22 5075	p-value	55/ 1 500 1/6
21	procedure volume $>=100 \# 2013$	0.370	0.275	-1 358 - 2 139		procedure volume $\geq 100 \ \# \ 2013 \ 10.1$	366 0.000	15 179 - 15 55	term.	Annual change -0 23991	0.333	-0.898 - 0.41837
22		0.000	0.002	210000 21200		procedure totalle. Too il Lott 150	0.000	1011/0 10100	Annual cha	ange of volume effect -0.01193	0.931	-0.299 - 0.2748
~~	Female	-0.483	0.000	-0.7250.241						0		
23	Age in years	-0.247	0.000	-0.2760.218								
24	Estimated logistic EuroSCORE	25.503	0.000	23.345 - 27.661								
27	Aortic valve stenosis	-6.255	0.000	-6.9125.598								
25	Combined aortic valve diseases	-6.592	0.000	-7.2635.921								
26	NYHA II	0.154	0.365	-0.1/9 - 0.48/								
20	NYHA III or IV	2.59/	0.000	2.3/4 - 2.821								
27	CAD	-0.03/	0.740	-0.259 - 0.184								
20	Reviews MI (within 4 months)	-0.000	0.000	-1.1110.000								
20	Previous MI (within 1 year)	0.015	0.980	-1.172 - 1.203								
29	Previous MI (after 1 year)	-0.303	0.250	-0.819 - 0.213								
20	Previous CABG	-2.938	0.000	-3.5962.280								
30	Previous cardiac surgery	-1.710	0.000	-2.4051.015								
31	Peripheral vascular disease	-0.917	0.000	-1.3450.489								
2.	Carotid disease	-1.110	0.000	-1.6140.606								
32	COPD	-0.618	0.001	-0.9730.263								
33	Pulmonary hypertension	-2.226	0.000	-2.6241.827								
22	GFR <15%	1.941	0.000	0.958 - 2.923								
34	GFR <30%	0.725	0.034	0.054 - 1.396								
35	Atrial fibrillation	2.5/5	0.000	2.303 - 2.785								
22	Diabetes	0.952	0.000	0.702 - 1.101								
36												
37												

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² Table S6: Results of the logistic regression model, transformation into discrete event probabilities and subsequent meta regressions

3 First step: Linear regression model on 43,996 TAVI cases with reimbursement as dependent variable, an

interaction term (n_ik_year_50_100#year) between categorical time (in years) and volume categories and 22

predefined patient and procedural characteristics as potential confounder.

-	n_ik_year_50_100	Coeff	p-value	95% CI	
6	procedure volume <50	0			
-	procedure volume 50-99	-905.1	0.024	-1689.5120.7	
/	procedure volume >=100	-1792.9	0.000	-2614.4971.4	Third stop: A random offsets
0	P				This step. A failed in the city
ð	vear				In ik year 50, 100#year Coeff p-value 95% Cl meta regression (using
0	2010	0			procedure volume ≤ 50 # 2010 36999 8 0 000 36302 5 - 37697 1 Stata's command metareg)
9	2011	-1104 3	0.026	-2078 5130 1	procedure volume <50 # 2011 35895 5 0 000 35214 3 - 36576 7 with time and volume as Coeff p-value 95% C
10	2012	-1872 9	0.000	-2810 5935 4	procedure volume <50 # 2012 35126 9 0 000 34499 5 - 35754 2
	2013	-1330 7	0.007	-2316 5362 9	Contribution 250 # 2013 35560 1 0 000 30970 / 36300 7
11	2013	-12/0 5	0.007	-2310.3302.5	Second step: Marginal means are procedure volume <50 # 2014 35769 3 0.000 350407 - 36060 applied to the estimated
	2014	1240.5	0.015	2235.4 245.5	calculated by setting each confounder procedure volume 50.90 # 2010 36004.7 0.000 337381 - 36651.3 means.
12	n ik vear 50 100#vear				to its mean value (prediction at the procedure volume 50-59 # 2011 35339.9 0.000 34893.2 35707.5
1 2	procedure volume 50 99 # 2011	240 5	0 5 4 5	7026 14025	procedure volume 50.90 + 2012 - 20207 - 0.000 - 204707 - 25170.6
15	procedure volume 50.00 # 2011	545.5	0.343	-783.0 - 1482.3	Thearis) using state sinal gins procedure of using 50-57 # 2012 3420.7 0.000 34470.7 33170.0
1/	procedure volume 50-99 # 2012	167.6	0.209	-404.0 - 1001.0	command with application of the procedure volume 50-99 # 2013 34392.3 0.000 34150.2 - 34390.4
14	procedure volume 50-99 # 2013	-102.0	0.775	-1276.2 - 950.9	atmeans ontion
15	procedure volume 50-99 # 2014	-51.3	0.928	-1159.3 - 1056.7	procedure volume >=100 # 2010 35206.9 0.000 347/5.2 - 35038.7
15	procedure volume >=100 # 2011	994.4	0.082	-127.8 - 2116.7	procedure volume $\geq 100 \# 2011 35097.1 0.000 34743.3 - 35449.8$
16	procedure volume >=100 # 2012	994.3	0.063	-55.5 - 2044.2	procedure volume $\geq 100 \# 2012 \ 34328.3 \ 0.000 \ 34128.7 \ -34527.9$
	procedure volume >=100 # 2013	614.5	0.267	-4/1.3 - 1/00.4	procedure volume >=100 # 2013 34481.7 0.000 34285.1 - 346/8.4
17	procedure volume >=100 # 2014	803.0	0.150	-289.3 - 1895.4	procedure volume >=100 # 2014 34769.5 0.000 34623.4 - 34915.6 Fourth step: A second
10					random effects meta
١ð	Female	-816.4	0.000	-1022.5610.4	regression model was
10	Age in years	-134.0	0.000	-159.5108.6	
19	Estimated logistic EuroSCORE	9498.4	0.000	/514./ - 11482.1	applied including also an Coeff p-value 95% CI
20	Aortic valve stenosis	-1480.8	0.000	-2097.4864.3	interaction term. Volume effect -245427.3 0.262 -702076.0 - 211221.4
20	Combined aortic valve diseases	-1671.1	0.000	-2296.61045.6	Annual change -518.0 0.050 -1036.3 - 0.2
21	NYHA II	-420.2	0.001	-665.2 -175.3	Annual change of volume effect 121.7 0.263 -105.2 - 348.7
	NYHA III or IV	686.8	0.000	501.3 - 872.2	
22	CAD	133.6	0.153	-49.7 - 316.8	
22	Hypertension	-427.8	0.000	-614.4241.3	
23	Previous MI (within 4 months)	-1677.0	0.000	-2134.61219.4	
21	Previous MI (within 1 year)	295.6	0.574	-733.9 - 1325.2	
24	Previous MI (after 1 year)	-483.1	0.009	-843.2123.0	
25	Previous CABG	-1118.8	0.000	-1687.9549.8	
25	Previous cardiac surgery	-574.4	0.061	-1174.8 - 25.9	
26	Peripheral vascular disease	86.9	0.649	-287.8 - 461.7	
	Carotid disease	-365.0	0.106	-807.3 - 77.3	
27	COPD	-0.6	0.997	-318.6 - 317.4	
20	Pulmonary hypertension	-951.6	0.000	-1302.7600.4	
28	GER <15%	1849.2	0.000	921.0 - 2777.4	
20	GED <20%	322.0	0 258	-235 7 - 879 6	
29	Atrial fibrillation	913.0	0.000	741.8 - 1084.1	
30	Dishetes	223.8	0.020	34 7 - 412 9	
50	Diabetes	-20.0	5.020	54.7 412.5	
31					

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2 Table S7: Results of the logistic regression model, transformation into discrete event probabilities and subsequent meta regressions

3 First step: Logistic regression model on 43,996 TAVI cases with ventilation as dependent variable, an

interaction term (n_ik_year_50_100#year) between categorical time (in years) and volume categories and 22

4 predefined patient and procedural characteristics as potential confounder.

E					
2					_
-	n ik vear 50 100	OR	p-value	95% CI	
-	,		P		- I
6	procedure volume <50	1			
		-			

6	procedure volume <50	1												
7	procedure volume 50-99	0./16	0.262	0.400 - 1.283										
<i>'</i>	procedure volume >=100	0.492	0.020	0.203 = 0.918						Third step: A random effects				
8 ye	ar				1	n_ik_year_50_100#year	Prob.	p-value	95% CI	meta regression (using				
9	2008	1				procedure volume <50 # 2008	0.086	0.000	0.065 - 0.107	Stata's command metareg)	_			
	2009	0.946	0.745	0.677 - 1.322		procedure volume <50 # 2009	0.082	0.000	0.067 - 0.096	with time and volume as		Coeff	p-value	95% CI
10	2010	0.853	0.362	0.605 - 1.201		procedure volume <50 # 2010	0.074	0.000	0.060 - 0.089	continuous covariates was	Volume effect	-0.010	0.004	-0.0160.004
11	2011	0.703	0.133	0.333 - 1.080	Second step: Predicted probabilities are	procedure volume <50 # 2011	0.007	0.000	0.033 - 0.081	applied to the estimated		-0.004	0.002	-0.0070.002
	2013	0.623	0.018	0.420 - 0.923	calculated by setting each confounder to	procedure volume <50 # 2013	0.055	0.000	0.040 - 0.070	rates.				
12	2014	0.532	0.004	0.345 - 0.819	its mean value (prediction at the means)	procedure volume <50 # 2014	0.048	0.000	0.032 - 0.063					
13					using Stata's margins command with	procedure volume 50-99 # 2008	0.063	0.000	0.033 - 0.094					
1 J n	ik_year_50_100#year	1 070	0.027	0 5 4 4 2 1 4 1	application of the atmeans option.	procedure volume 50-99 # 2009	0.064	0.000	0.046 - 0.083	\sim				
14	procedure volume 50-99 # 2009	1.079	0.827	0.544 - 2.141		procedure volume 50-99 # 2010	0.074	0.000	0.062 - 0.085					
15	procedure volume 50-99 # 2010	1.43	0.277	0.751 - 2.723	>	procedure volume 50-99 # 2011	0.005	0.000	0.037 - 0.057					
	procedure volume 50-99 # 2012	1.096	0.789	0.561 - 2.142		procedure volume 50-99 # 2013	0.038	0.000	0.030 - 0.045					
16	procedure volume 50-99 # 2013	0.929	0.833	0.469 - 1.841		procedure volume 50-99 # 2014	0.035	0.000	0.025 - 0.045					
17	procedure volume 50-99 # 2014	1.016	0.967	0.489 - 2.111		procedure volume >=100 # 2008	0.044	0.000	0.020 - 0.068	Fourth step: A second				
17	procedure volume >=100 # 2009	1.732	0.131	0.848 - 3.537		procedure volume >=100 # 2009	0.070	0.000	0.052 0.089	random effects meta				
18	procedure volume >=100 # 2010	1.252	0.555	0.010 - 2.402		procedure volume $\geq 100 \# 2010$	0.048	0.000	0.057 0.056	regression model was applied				
10	procedure volume >=100 # 2011 procedure volume >=100 # 2012	1.624	0.163	0.822 - 3.210		procedure volume >=100 # 2011 procedure volume >=100 # 2012	0.003	0.000	0.042 0.053	including also an interaction		Coeff	p-value	95% CI
19	procedure volume >=100 # 2013	1.636	0.165	0.817 - 3.277		procedure volume >=100 # 2013	0.045	0.000	0.040 0.050	term.	Volume effect	-6.084	0.040	-11.8700.299
20	procedure volume >=100 # 2014	1.358	0.402	0.664 - 2.776		procedure volume >=100 # 2014	0.032	0.000	0.029 0.036		Annual change	-0.011	0.004	-0.0180.004
21										Annual cha	ange of volume effect	0.003	0.041	0.000 - 0.006
ZIFe	male	0./13	0.000	0.651 - 0.781										
22	timated logistic EuroSCOPE	13.81	0.000	7 797 - 24 464										
22 A	ortic valve stenosis	0.722	0.000	0.618 - 0.843										
23	mbined aortic valve diseases	0.663	0.000	0.561 - 0.783										
24 N	/HA II	0.498	0.000	0.404 - 0.614										
	(HA III or IV	1.485	0.000	1.364 - 1.617										
230	ND	1.094	0.044	1.002 - 1.193										
26	percension evious MI (within 4 months)	0.037	0.000	0.591 - 1.093										
27 Pi	evious MI (within 1 year)	0.796	0.358	0.490 - 1.294										
27 Pi	evious MI (after 1 year)	0.897	0.268	0.740 - 1.087										
28 Pi	evious CABG	0.675	0.000	0.557 - 0.816										
PI	evious cardiac surgery	0.848	0.091	0.701 - 1.026										
29	ripneral vascular disease	0.855	0.004	0 725 - 1 007										
30	I OLIU UISEASE	1.211	0.001	1.085 - 1.351										
	Imonary hypertension	0.758	0.000	0.669 - 0.858										
3 ا G	R <15%	1.364	0.001	1.129 - 1.647										
32 G	R <30%	1.252	0.008	1.059 - 1.479										
	rial fibrillation	1.553	0.000	1.430 - 1.687										
330	apetes	1.138	0.003	1.045 - 1.239										
34														
35														
36														
37														

Pitta and abstra	Item No.	STROBE items	Location in manuscript where items are reported	RECORD items	Location in manuscript where items are reported
<u>Title and abstra</u>	1	(a) Indicate the study's design with a commonly used term in the title or the abstract (b) Provide in the abstract an informative and balanced summary of what was done and what was found	p1-2	RECORD 1.1: The type of data used should be specified in the title or abstract. When possible, the name of the databases used should be included. RECORD 1.2: If applicable, the geographic region and timeframe within which the study took place should be reported in the title or abstract. RECORD 1.3: If linkage between databases was conducted for the study, this should be clearly stated in the title or abstract.	R(ecord)1.1: p1 R1.2: p1-2 R1.3: n/a
Introduction					
Background rationale	2	Explain the scientific background and rationale for the investigation being reported	p5	00	
Objectives	3	State specific objectives, including any prespecified hypotheses	p5	2	
Methods					
Study Design	4	Present key elements of study design early in the paper	p6-9		
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	рб		
Participants	6	(a) Cohort study - Give the eligibility criteria, and the	p6	RECORD 6.1: The methods of study population selection (such as codes or	R6.1: p6 R6.2, 6.3: n/a

The RECORD statement – checklist of items, extended from the STROBE statement, that should be reported in observational studies using routinely collected health data.

			1		1 1 1 1 1 1 1 1 1 1	
1			sources and methods of selection		algorithms used to identify subjects)	
י ר			of participants. Describe methods		should be listed in detail. If this is not	
2			of follow-up		possible, an explanation should be	
4			<i>Case-control study</i> - Give the		provided.	
+ 5			eligibility criteria and the		L	
5 6			sources and methods of case		RECORD 6 2: Any validation studies	
7			sources and methods of case		All of the and an an algorithms used to sale at	
, 8			ascertainment and control		of the codes of algorithms used to select	
9			selection. Give the rationale for		the population should be referenced. If	
10			the choice of cases and controls		validation was conducted for this study	
11			Cross-sectional study - Give the		and not published elsewhere, detailed	
12			eligibility criteria, and the		methods and results should be provided.	
13			sources and methods of selection			
14			of participants		RECORD 6.3: If the study involved	
15					linkage of databases consider use of a	
16			(b) Cohort study - For matched		flow diagram or other graphical display	
17			studies give matching criteria		to demonstrate the data linkage process	
18			studies, give matching criteria	D .	in alu ding the number of individuals	
19			and number of exposed and		including the number of individuals	
20			unexposed	h h	with linked data at each stage.	
21			<i>Case-control study</i> - For matched			
22			studies, give matching criteria			
23			and the number of controls per			
24 25			case			
25 26	Variables	7	Clearly define all outcomes,	p6-7	RECORD 7.1: A complete list of codes	p6-7
20 27			exposures predictors potential	1	and algorithms used to classify	1
28			confounders and effect		exposures outcomes confounders and	
29			modifiers Give diagnostic		effect modifiers should be provided. If	
30			aritaria if applicable		these connet be reported on explanation	
31			cinteria, il applicable.		should be provided	
32		0			should be provided.	
33	Data sources/	8	For each variable of interest, give	po-/, Supplementary		
34	measurement		sources of data and details of	tables		
35			methods of assessment			
36			(measurement).			
37			Describe comparability of			
38			assessment methods if there is			
39			more than one group			
40	Bias	9	Describe any efforts to address	n6-7 9		
41 42	1-140		notential sources of bias	P ⁰ ', '		
4∠ ⊿⊃	Study size	10	Explain how the study size was	n/a (national ashart)		
+3 4 4	Study size	10	Explain now the study size was	n/a (national conort)		

		arrived at	(p6-7)		
Quantitative	11	Explain how quantitative	p7-10		
variables		variables were handled in the	1		
		analyses. If applicable, describe			
		which groupings were chosen,			
		and why			
Statistical	12	(a) Describe all statistical	p7-10		
methods		methods, including those used to			
		control for confounding			
		(b) Describe any methods used to			
		examine subgroups and			
		interactions			
		(c) Explain how missing data			
		were addressed			
		(d) <i>Cohort study</i> - If applicable,			
		explain how loss to follow-up			
		was addressed			
		<i>Case-control study</i> - If	6		
		applicable, explain how matching			
		of cases and controls was			
		addressed			
		Cross-sectional study - If	['] N		
		applicable, describe analytical		1.	
		methods taking account of			
		sampling strategy		O _b	
		(e) Describe any sensitivity			
		analyses			
Data access and				RECORD 12.1: Authors should	p6
cleaning methods				describe the extent to which the	
				investigators had access to the database	
				population used to create the study	
				population.	
				RECORD 12 2: Authors should provide	
				information on the data cleaning	
				mothods used in the study	
Linkage				RECORD 12 3: State whether the study.	n/a
Lilikage				included person level institutional	11/ a
				menudeu person-iever, institutionai-	

				level, or other data linkage across two or more databases. The methods of linkage and methods of linkage quality evaluation should be provided.	
Results					
Participants	13	 (a) Report the numbers of individuals at each stage of the study (<i>e.g.</i>, numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed) (b) Give reasons for non- participation at each stage. (c) Consider use of a flow diagram 	n/a (national cohort, administrative data, no follow-up)	RECORD 13.1: Describe in detail the selection of the persons included in the study (<i>i.e.</i> , study population selection) including filtering based on data quality, data availability and linkage. The selection of included persons can be described in the text and/or by means of the study flow diagram.	n/a (national cohort, administrative data, no follow- up)
Descriptive data	14	 (a) Give characteristics of study participants (<i>e.g.</i>, demographic, clinical, social) and information on exposures and potential confounders (b) Indicate the number of participants with missing data for each variable of interest (c) <i>Cohort study</i> - summarise follow-up time (<i>e.g.</i>, average and total amount) 	p8	2001	
Outcome data	15	Cohort study - Report numbers of outcome events or summary measures over time Case-control study - Report numbers in each exposure category, or summary measures of exposure Cross-sectional study - Report numbers of outcome events or summary measures	p13		
Main results	16	(a) Give unadjusted estimates	p10-14		

		and, if applicable, confounder- adjusted estimates and their precision (e.g., 95% confidence interval). Make clear which confounders were adjusted for and why they were included (b) Report category boundaries when continuous variables were categorized (c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period			
Other analyses	17	Report other analyses done—e.g., analyses of subgroups and interactions, and sensitivity analyses	n/a		
Discussion					
Key results	18	Summarise key results with reference to study objectives	p14-15		
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	p3, 9-10	RECORD 19.1: Discuss the implications of using data that were not created or collected to answer the specific research question(s). Include discussion of misclassification bias, unmeasured confounding, missing data, and changing eligibility over time, as they pertain to the study being reported.	p3, 9-10
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	p 14-17		
Generalisability	21	Discuss the generalisability (external validity) of the study results	p3, 14-17		

	Other Information	n				
ן ר	Funding	22	Give the source of funding and	p4		
2 2	-		the role of the funders for the	-		
4			present study and, if applicable,			
5			for the original study on which			
5			the present article is based			
7	Accessibility of				RECORD 22.1: Authors should provide	Access to public
3	protocol, raw				information on how to access any	dataset: p6
9 10	data, and				supplemental information such as the	Further data:
11	programming		$\mathbf{\wedge}$		study protocol, raw data, or	Supplemental
12	code				programming code.	tables
13		•		•		

*Reference: Benchimol EI, Smeeth L, Guttmann A, Harron K, Moher D, Petersen I, Sørensen HT, von Elm E, Langan SM, the RECORD Working Committee. The REporting of studies Conducted using Observational Routinely-collected health Data (RECORD) Statement. PLoS Medicine 2015; in press.

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BMJ Open

Volume-outcome relationship in transcatheter aortic valve implantations in Germany 2008-2014: A secondary data analysis of electronic health records

Journal:	BMJ Open
Manuscript ID	bmjopen-2017-020204.R2
Article Type:	Research
Date Submitted by the Author:	04-Jun-2018
Complete List of Authors:	Kaier, Klaus; Medical Center-University of Freiburg, Institute for Medical Biometry and Statistics Oettinger, Vera; Heart Center Freiburg University, Department of Cardiology and Angiology I Reinecke, H; University of Muenster, Department of Cardiology and Angiology, Adult Congenital and Valvular Heart Disease Center Muenster Schmoor, Claudia; Medical Centre, University of Freiburg Frankenstein, L.; University of Heidelberg, Dpt. of Cardiology, Angiology, Pulmology Vach, Werner; Institute of Medical Biometry and Medical Informatics, Hehn, Philip; Faculty of Medicine and Medical Center – University of Freiburg von zur Mühlen, Constantin; Heart Center Freiburg University, Department of Cardiology and Angiology I Bode, Christoph; Heart Center Freiburg University, Department of Cardiology and Angiology I Zehender, Manfred; Heart Center Freiburg University, Department of Cardiology and Angiology I Reinöhl, Jochen; Heart Center Freiburg University, Department of Cardiology and Angiology I Reinöhl, Jochen; Heart Center Freiburg University, Department of Cardiology and Angiology I
Primary Subject Heading :	Cardiovascular medicine
Secondary Subject Heading:	Health economics
Keywords:	Valvular heart disease < CARDIOLOGY, HEALTH ECONOMICS, CARDIOLOGY, Adult cardiology < CARDIOLOGY

SCHOLARONE[™] Manuscripts

Volume-outcome relationship in transcatheter aortic valve implantations in Germany 2008-2014: A secondary data analysis of electronic health records

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Word count excluding title page, abstract, references, figures and tables: 2947

ABSTRACT

Keywords: TAVI, volume-outcome; minimum volume standards; hospital quality; mortality

Objectives: We examine the volume-outcome relationship in isolated transcatheter aortic valve implantations (TAVI). Our interest was whether the volume-outcome relationship for TAVI exists on the center level, whether it occurs equally for different outcomes, and how it develops over time.

Design: Secondary data analysis of electronic health records. The comprehensive German Federal Bureau of Statistics DRG database was queried for data on all isolated TAVI procedures performed in Germany between 2008 and 2014. Logistic and linear regression analyses were carried out. Risk-adjustment was applied using a predefined set of patient characteristics to account for differences in the risk factor composition of the patient populations between centers and over time. Centers performing TAVI were stratified into groups performing <50, 50-99, and ≥100 procedures per year.

Setting: Germany 2008 - 2014.

Participants: All patients undergoing isolated TAVI in the observation period.

Interventions: none.

Primary and secondary outcome measures: In-hospital mortality, bleeding, stroke, probability of ventilation >48 hours, length of hospital stay, and reimbursement.

Results: Between 2008 and 2014, a total of 43,996 TAVI procedures were performed in 113 different centers in Germany with a total of 2,532 cases of in-hospital mortality. Risk-adjusted in-hospital mortality decreases over the years and is lower the higher the annual procedure volume at the center is. The magnitude of the latter effect declines over the observation period. Our results indicate a ceiling effect in the volume-outcome relationship: The volume-outcome relationship is eminent in circumstances of relatively unfavorable outcomes. Alongside improving outcomes, however, the volume-outcome relationship decreases. Also, a volume-outcome relationship seems to be absent in circumstances of constantly low event rates.

Conclusions: The hypothesized volume-outcome relationship for TAVI exists but diminishes and may disappear over time. This should be taken into account when considering mandatory minimum thresholds.

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STRENGTHS AND LIMITATIONS OF THIS STUDY

- Study based on administrative data; coding errors are inevitable, however cardiovascular diagnosis-related groups are reviewed by independent physicians on behalf of health insurers.
- Risk-adjustment included a number of parameters whose reliability cannot be fully secured, and we cannot guarantee that all parameters of relevance are included in the model.
- Hospital volume was classified into three fixed categories, which is in line with thresholds from official guidelines and previous literature, but might hide possible effects related to very high volumes.
- The dataset omits baseline diagnoses of pure aortic regurgitation, as well as patients who underwent a concomitant cardiac procedure, which makes sense from a clinical perspective, but complicates comparisons and might cause bias.
- The study provides comprehensive data on everyday TAVI practice in a large industrialized country over a multiyear period.

KEY QUESTIONS

What is already known about this subject?

After their introduction, outcomes of new interventions are subject to a learning curve effect, meaning that outcomes improve over a period of time and then level off. The volume of procedures performed at an institution can influence this process, and is thought to have some effect on patient outcomes even after learning is complete (volume-outcome-hypothesis).

What does this study add?

This study tracks patient outcomes by center procedure volume in all transcatheter aortic valve implantation (TAVI) procedures performed in Germany between the procedure's introduction in 2008 and 2014, providing empirical evidence on shape and extent of the above described effects for this procedure.

How might this impact on clinical practice?

This data is of interest to clinical practitioners, hospital administrators, and policy makers involved in the implementation of new clinical procedures.

COMPETING INTERESTS AND FUNDING

The authors declare no conflicts of interest. There was no external funding for this work.

DATA SHARING STATEMENT

No additional data available.

AUTHORSHIP STATEMENT

KK and JR developed the research question and designed the methodology. VO, HR, LF, CvzM, CB, MZ and JR provided the medical knowledge of German TAVI practice informing the study design. KK defined the categories, outcomes and measures and developed and implemented the formal analysis and statistical with support by WV and CS. KK and JR collected the data and evidence. KK, VO, and WV interpreted and contextualized the results. KK and PH wrote the initial draft of the article, with JR contributing. All authors participated in the critical revision of the article and provided final approval of the version to be published.

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INTRODUCTION

Transcatheter aortic valve implantation (TAVI) is a rapidly evolving technique for therapy of aortic stenosis, with a very early and pronounced utilization in Germany [1]. Previous studies report hospital-specific learning curves with respect to in-hospital outcomes such as procedural success, mortality and clinical complications of varying lengths and magnitudes [2–6]. In general, learning curve effects within and between centers can to some degree be explained by the volume of procedures performed at the center. This relationship can be summed up as the "practice-makes-perfect hypothesis", according to which quality of care either increases with the number of patients as a result of economies of scale, with a competing explanation of "selective-referral", according to which higher-quality hospitals attract greater demand and therefore have a greater volume of patients [7,8].

There are a number of criticisms on empirical analyses on the volume-outcome relationship: Many studies lack appropriate adjustment for differences in the risk factor composition of the patient populations between centers [9,10]. Secondly, most studies focus on in-hospital mortality only [11], which is easy to measure, but it is recommended to include additional quality measurements. Finally, most studies divided patients into groups of equal size for analyzing the volume-outcome relationship, which makes it difficult to make use of such results when justifying specific volume thresholds [6,12–14].

Although the evidence regarding the existence of an inverse relationship between the number of TAVI procedures and related outcomes is limited [15,16], medical authorities in Germany and several other countries have issued guidelines calling for minimum numbers of procedures for primary operators performing TAVI [17–20]. There however remains some question whether, firstly, the volume-outcome relationship outlined above exists on the center level regarding TAVI and, secondly, whether or not it takes place in all outcomes and complications equally, and how an existing volume-outcome relationship might change over the years.

To address these questions, we calculated annual procedure volumes for all German hospitals that performed TAVI procedures between January 2008 and December 2014. In order to account for differences in the patient population between high-, medium-, and low-volume centers and over time, we carried out baseline-adjusted regression analyses for the endpoints in-hospital mortality, bleeding, stroke, probability of ventilation >48 hours, length of hospital stay, and reimbursement.

METHODS

Data

 Since 2005, data on all hospitalizations in Germany have been available for scientific use via the Diagnosis Related Groups (DRG) statistics collected by the Research Data Center of the Federal Bureau of Statistics (DESTATIS). These hospitalization data, including diagnoses and procedures, are a valuable source of representative nationwide data on the in-hospital treatment of patients. This database represents a virtually complete collection of all hospitalizations in German hospitals that are reimbursed according to the DRG system. From this database [1], we have extracted data on 43,996 cases of isolated TAVI for our analysis.

Our study did not involve direct access by the investigators to data on individual patients but only access to summary results provided by the Research Data Center. Therefore, approval by an ethics committee and informed consent were determined not to be required, in accordance with German law. All summary results were anonymized by DESTATIS. In practice, this means that any information allowing the drawing of conclusions regarding a single patient or a specific hospital are censored by DESTATIS to guarantee data protection. Especially the use of the anonymous, persistent "institute indicator of hospitals" is highly restricted in order not to publish any information directly attributable to a single hospital.

As described previously [1,21], we were able to use the OPS codes (OPS codes: 5-35a.0 in 2007 and 5-35a.00, 5-35a.01 and 5-35a.02 from 2008) to identify all TAVI procedures performed (and reimbursed) in Germany between 2008 and 2014. Patients with a baseline diagnosis of pure aortic regurgitation (main or secondary diagnosis other than 135.0, 135.2, 106.0, 106.2) and those with concomitant cardiac surgery or percutaneous coronary intervention were not included in this analysis. Although some concomitant procedures might be informative (a cardiac surgery procedure during the same hospital stay as TAVI might likely represent a complication following a TAVI procedure), these cases cannot be consistently identified in our dataset as, in many cases, concomitant procedures might have taken place in another center. A complete list of procedure codes can be found in Table S1, a more detailed discussion of the data source may be found in a previous manuscript [1,21].

Patient and Public Involvement
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The development of the research question was guided by the intention to provide hospitals and policymakers with empirical evidence that enables them to structure the infrastructure in such a way as to deliver the best possible outcomes to patients. The selected outcome measures represent the most severe complications to the procedure and are of high significance to patient quality of life after the intervention. There was, however, no direct involvement of patients in the design, the recruitment and conduct of the study, nor will the results be disseminated to study participants as the study was based on anonymized administrative data.

Measures

Regarding the in-hospital complications, bleeding was defined as requiring a transfusion of more than 5 units of red blood cells (RBC). For all other comorbidities and complications the existing anamnestic or acute distinctive codes were used (we have discussed OPS and ICD codes in greater detail previously [21]).

In order to analyze possible effects of the above discussed mandatory minimum quantities, the number of procedures per year and center was categorized (i.e. n<50, 50≤n<100, n≥100) on the basis of an anonymous, persistent "institute indicator of hospitals" provided by DESTATIS. These particular thresholds are applied because the minimum number of 50 procedures is often mentioned in official TAVI-guidelines [17–20], and these thresholds are widely applied in the literature [22–24].

The primary outcome was in-hospital mortality. Secondary outcomes include post-procedural complications such as stroke and bleeding events (transfusion of >=5 RBC), as well as reimbursement, length of hospital stay and proportion of patients with ventilation >48h.

Statistical analysis

In a first step, multivariate regression analyses were carried out for the different endpoints. In a previous study, Reinöhl et al. [1] identified 21 baseline patient characteristics to describe risk profiles between procedural groups. For risk adjustment, all of these 21 baseline patient characteristics were included as covariates (all covariates listed in Table 1) in the respective regression analyses. In addition, an interaction term between time (in years) and the above mentioned annual volume categories was included in the regression analyses in order to investigate the volume-outcome relationship over the years.

Table 1: Baseline	characteristics	(2008-2014)
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Ν	43,996
Female	55.87%
Age in years, mean/SD	80.95/6.11
Estimated logistic EuroSCORE ¹ , mean/SD	22.21%/13.57%
Aortic valve stenosis as main diagnosis	68.22%
Combined aortic valve diseases as main diagnosis	26.56%
Heart failure	
NYHA II	8.26%
NYHA III or IV	41.66%
Hypertension	62.66%
CAD	46.88%
Previous myocardial infarction	
within 4 months	1.59%
within 1 year	0.75%
after 1 year	4.35%
Previous CABG	12.75%
Previous cardiac surgery	18.06%
Peripheral vascular disease	12.39%
Carotid disease	6.17%
COPD	15.14%
Pulmonary hypertension	22.32%
Renal disease	
GFR <15ml/min	2.95%
GFR <30ml/min	4.90%
Atrial fibrillation	45.93%
Diabetes	33.30%

¹For calculation of the logistic EuroSCORE, we were able to populate all fields except for critical preoperative state and left ventricular function.

these we assumed an inconspicuous state (i.e. no critical preoperative state and no left ventricular dysfunction) and thus calculated a best-case scenario.

Abbreviations: NYHA – New York Heart Association Functional Classification; CAD – coronary artery disease; CABG – coronary artery bypass graft; COPD – chronic obstructive pulmonary disease; GFR – glomerular filtration rate.

Please note that in comparison to the data published by Reinöhl et al., one TA-TAVI procedure (in 2010) needed to be removed from the dataset due to incomplete information.

Logistic and linear regression analyses are applied for dichotomous and continuous endpoints, respectively. The question of how to account for patients treated in the same hospital was discussed previously [13,25,26]. As recommended in a previous study that also used data from the German DRG-statistic [13], we used cluster-robust standard errors to account for this dependency.

Risk-adjusted rates and means within each year and hospital volume category were obtained by computing the corresponding predicted probabilities or means, respectively, for an artificial subject with each confounder set to its mean value (prediction at the means, see Table 1 for mean values of all confounders). Thereby, risk-adjusted rates and means are taking two aspects into account: (1) change in the patients risk factors compositions over the years, and (2) differences in the patients risk factors compositions over the years, and (2) differences in the patients risk factors compositions within different hospital volume categories. Risk-adjusted rates and means are therefore interpreted as the 'true' procedure-related outcomes independent of changes in the patient population over the years and differences between low, medium, and high-volume centers. Please note that this implies the assumption that all outcome relevant parameters are used for risk-adjustment. Unfortunately, we cannot guarantee that all parameters of relevance are included in the model. In fact, the administrative dataset lacks relevant clinical information (such as echocardiographic findings or anatomical characteristics).

The visualization of these risk-adjusted rates or means together with their 95% confidence intervals constitutes the main analytical approach in this paper. To assess the statistical significance of the observed volume-outcome relationship, of the time trend and a potential change of the volume-outcome relationship over time, we applied to the estimated rates or means a random effects meta regression (command metareg [27]) with time and volume as continuous covariates. A model with an interaction term was used to assess the change in the volume-outcome relationship. A model without an interaction was used to assess the main effects.

Standardized reimbursement data is only available starting in 2010 due to a change in the reimbursement system making previous data difficult to compare. In Germany, reimbursement is based on DRGs which are defined by the patients' diagnoses, gender and age, treatment procedures, complications or comorbidities, and further attributes. Based on this data, a predetermined reimbursement rate per case is calculated. Hospitals receive additional reimbursement for long-stay outlier cases [28]. Furthermore,

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additional reimbursement is possible for very complex intensive care treatments, which have to be proven by documentation of illness severity and treatment effort during ICU stay [29].

All analyses were carried out using Stata 13.1 (StataCorp, College Station, Texas, USA).

RESULTS

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 of 43,996 TAVI procedure.

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 .2 to 2008 to 11,559 in 2014 (see Table .

 Between 2008 and 2014, a total of 43,996 TAVI procedures were performed in 113 different centers in Germany. The total number of TAVI procedures performed per year increased markedly over the observation period, from 1,122 in 2008 to 11,559 in 2014 (see Table 2).

Table 2: Number of procedures with regard to the performed TAVI volume of a distinct center in a given year.

TAVI Volume in Center	2008	2009	2010	2011	2012	2013	2014
<50 procedures, n (number of centers)	613 (40)	1,234 (61)	1,155 (51)	1,107 (43)	960 (36)	765 (31)	617 (30)
50-99 procedures, n (number of centers)	236 (3)	658 (10)	1,875 (26)	1,957 (27)	1,569 (20)	1,930 (25)	1,135 (16)
>=100 procedures, n (number of centers)	273 (n/a*)	707 (n/a)	1,776 (3)	3,459 (7)	5,711 (16)	6,452 (9)	9,807 (20)
Total number, n (number of centers)	1,122 (>=44)	2,599 (>=72)	4,806 (80)	6,523 (77)	8,240 (72)	9,147 (65)	11,559 (66)

Please note that the numbers of procedures performed per year at a given center were not constant over the observation period, so that it is possible for a center to fall into a different volume group in a different year. Number of centres in parentheses.

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* n/a = not available, exact number censored by DESTATIS due to data protection concerns

As reported previously [1], substantial reductions in in-hospital mortality have been achieved between 2008 and 2013, and we find this trend to continue into 2014. Regarding center-specific procedure volumes of all TAVI procedures, it appears that the differences in unadjusted in-hospital mortality between the procedure volume groups (<50, 50-99, and >=100) steadily decline over the years (see Table 3). Figure 1 A provides risk-adjusted in-hospital mortality rates allowing for comparison despite possible differences in the patient selection process and consequently the risk factor composition between hospitals in the different procedure volume groups and over time (See Table S2 -Table S7 for details of the process used to generate the results shown in Figure 1 A). These results indicate that risk-.ea. .t. declines over th. .d volume effect: 0.2pp). adjusted in-hospital mortality rates (1) steadily decrease over the years (annual change: -0.58 percentage points (pp), p<0.001), are (2) lower the higher the procedure volume at the hospital is (volume effect: -0.74pp, p=0.002), but that (3) this volume effect declines over the seven year observation period (p-value of interaction term: p=0.027; annual change of volume effect: 0.2pp).

Table 3: Unadjusted in-hospital outcomes with regard to the performed TAVI volume of a distinct center in a given year.

	Mortality, %	Stroke, %	Bleeding, %	Length of stay, mean in days	Reim- bursement, mean in €	Proportion of patients with ventilation >48h, %
2008						
<50 procedures	10.11%	3.26%	14.36%	19.2		9.79%
50-99 procedures	9.32%	2.12%	11.44%	21.8		6.78%
>=100 procedures	6.59%	2.56%	7.33%	14.7		4.76%
2009						
<50 procedures	9.81%	3.57%	14.18%	21.6		9.48%
50-99 procedures	8.36%	3.34%	11.25%	18.5		7.14%
>=100 procedures	6.08%	2.12%	7.21%	18.0		7.36%
2010						
<50 procedures	9.00%	2.51%	12.12%	21.0	37,071€	8.74%
50-99 procedures	8.11%	2.56%	11.41%	19.1	36,173€	8.69%
>=100 procedures	6.14%	2.20%	6.25%	17.0	35,074€	5.01%
2011						
<50 procedures	7 68%	2 25%	0.30%	20.0	25 08/F	8 0/1%
50-99 procedures	8.02%	2.33%	9.59%	10.2	35,304£	8.04%
>=100 procedures	6.02% E 97%	2.55%	9.04%	17.2	35,424€ 25.046£	7 20%
>=100 procedures	5.07 /0	5.01%	9.31/0	17.5	55,040€	7.29%
2012						
<50 procedures	6.15%	2,29%	8.44%	18.7	35,294€	7,29%
50-99 procedures	7.07%	2.42%	8.41%	18.9	34.798€	5.48%
>=100 procedures	5.03%	2.10%	6.30%	16.7	34.233€	5.39%
•						
2013						
<50 procedures	5.49%	2.09%	9.28%	20.2	35,808€	6.93%
50-99 procedures	5.85%	2.33%	6.53%	18.2	34,650€	4.56%
>=100 procedures	5.29%	2.70%	5.98%	16.3	34,456€	5.29%
2014						
<50 procedures	5.34%	2.75%	5.99%	19.9	35,993€	6.15%
50-99 procedures	4.58%	2.20%	5.73%	18.3	34,904€	4.32%
>=100 procedures	3.70%	2.28%	4.22%	15.3	34,771€	3.92%

Please note that the numbers of procedures performed per year at a given center were not constant over the observation period, so that it is possible for a center to fall into a different volume group in a different year.

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Over the seven years of data we analyzed, a slight decreasing trend was visible in the risk-adjusted inhospital stroke rate, which started out at 2-2,5% in 2008-2009 and ranged from 1,5-2% in 2013-2014 (Figure 1 B). Volume-outcome relationship was actually negative for years following 2010, with highervolume centers having higher stroke rates.

Risk-adjusted bleeding rates (Figure 1 C), in contrast, showed a clear beneficial effect of higher center procedure volumes for all years but 2011. The magnitude of the effect was distinct from 2008-2010 and decreased in the following years in parallel with an ongoing marked decrease in the general likelihood of bleeding complications, but still was present in 2013/2014.

For risk-adjusted in-hospital ventilation rate (>48h) (Figure 1 D), a pronounced beneficial effect of higher center procedure volumes persisted throughout the observation period. In addition, risk-adjusted in-hospital ventilation rates decreased substantially over the years. As for bleeding, the magnitude of the volume effect was distinct in the first years but steadily declined over the seven year period (annual change of the volume effect: 0.30pp, p=0.041).

Risk-adjusted in-hospital length of stay shows a strong beneficial effect of center procedure volume (Figure 2 A). Unlike the situation found for the endpoints mortality and bleeding, the magnitude of the effect did not decrease much over the observed timeframe. There also is a slight reduction in average length of stay over the years.

As shown in Figure 2 B, there is a drop in the overall reimbursement level from 2010-2012, but reimbursement stays roughly the same thereafter. In much the same way as found for length of hospital stay, risk-adjusted amount of reimbursement decreased only slightly over time, and showed a large volume effect which did not change over the five year period.

CONCLUSIONS

Our study shows mixed results regarding a volume-outcome relationship in TAVI procedures in German hospitals. First of all, TAVI-related in-hospital mortality decreased substantially between 2008 and 2014 and was lower the higher the procedure volume at the respective hospital is. The magnitude of this volume-outcome relationship, however, declines over the observation period. Especially in later years (2012-2014) differences in mortality between low-, medium-, and high-volume centers are small.

Regarding in-hospital mortality and secondary endpoints, a volume-outcome relationship is eminent in circumstances of relatively unfavorable outcomes (see early years of mortality, bleeding, and ventilation) and decreases as outcomes improve (later years of mortality, bleeding, and ventilation), but is not present in circumstances of constantly low event rates (see stroke). In addition, in most of the cases when we observe a distinct annual decrease, we also observe a decreasing volume effect over time. Presumably, the small centers succeed in participating at the system level learning curve to a degree which allows them to catch up to some degree to the group of high-volume. Unfortunately, our data does not allow addressing the question whether this is due to exchange of expertise or to increasing cumulative experience. The group of small centers may also benefit from there being only a reduced capacity for improvement even in large volume centers some years after the introduction of a new procedure.

Interestingly, decreases in the volume effect over time were not observed for the endpoints of in-hospital length of stay and reimbursement. Presumably, this might be due to the fact that high-volume centers are at a major advantage in streamlining clinical workflows before and after the procedure.

Two recent studies showed volume-outcome relationships for TAVI procedures performed in US hospitals in 2012 [15,16]. In both studies, patients were divided into groups of equal sample size. Disregarding the accompanying problems regarding the external validity of the results [12,13], the results shown in these studies are similar to ours: Among others, inverse volume-outcome relationships were shown for the endpoints death and bleeding [15,16]. One of the two studies also included the endpoints length of stay and hospitalization costs and identified significant differences between the observed hospital volume quartiles (TAVI/year cutoffs <=5, 6-10, 11-20 and >20) [16]. The other study also included the endpoint stroke and did not show significant differences between volume groups (TAVI cutoffs: 20 or 10 cases for different access routes) [15].

As stated before, medical authorities in several countries have issued guidelines calling for minimum numbers of procedures for primary operators performing TAVI [17–20]. In Germany, such mandatory minimums are not yet implemented, but a mandatory number of 50 TAVI procedures annually is officially recommended [20], and this number is also mentioned in guidelines from the UK, Canada and Portugal [17–19]. Our results confirm the existence of a volume-outcome relationship for TAVI procedures between 2008 and 2014, and these effects are in line with existing evidence from TAVI procedures performed in US hospitals [6,15,16]. The above discussed weakening of the volume-outcome relationship

over time, however, relativizes the rationale behind mandatory minimum numbers of procedures: The volume-outcome relationship may be considerable in the years following the introduction of a new procedure when there still is a lot of room for improvement (in the two of the cited studies [15,16], i.e. 2012). After a few years, then, the association between procedure numbers and better performance may diminish (see our results regarding the year 2014 and presumably thereafter). In the worst case, the volume effect is already gone by the time mandatory minimums are finally implemented, or the implementation hinders the system to reach optimal health service without restrictions. It should be, however, noted that the average number of TAVI procedures per hospital is larger in Germany compared to most other countries, and that hence the time span until such a point is reached may be longer in other countries.

This might be especially problematic since mandatory minimum quantities on the center level are not free of further disadvantages. They are thought to lead to centralization of procedures in large hospitals, necessitating costly patient transfers and potentially worse aftercare. In addition, it is unclear how an optimal threshold could be set (and adjusted yearly) and by whom, how effects of physician volume and hospital volume should be combined, whether low-volume hospitals and their surgeons perceive the thresholds as new incentives to operate, and how new and innovative hospitals might be able to enter the market [30]. The latter question is especially relevant for TAVI since a recent study showed that between 2010 and 2015 a new center entering the TAVI market needed to perform 54 procedures to achieve clinical outcomes comparable to those reported in high-volume centers [31]. According to the authors of the study, this represents more than 2 years of continuous activity [31].

In addition, the question remains how to integrate the observed volume effects into the existing theory. The "practice-makes-perfect hypothesis" implies a contrary causal relationship than the theory of "selective-referral" [7,8], and we cannot answer the question whether volume generates quality (practice makes perfect), quality generates volume (selective referral), or both.

Furthermore, Gandjour et al. differentiated the "practice-makes-perfect hypothesis" into learning curve effects, economies of scope, and the concept of a focused factory [32]. Improved outcomes may result from economies of scale: every time doctors perform a procedure, they gain experience. Economies of scope, in contrast, would occur from the simultaneous performance of dissimilar procedures. In the TAVI context, this means that a high-volume center might see improved TAVI outcomes as a result of the

performance of high numbers of other procedures. Accordingly, Epstein already raised the question whether similar procedures should also be counted towards a set volume threshold [30]. The focused factory concept, in contrast, assumes that focusing on a small number of procedures could also be favorable [32]. Unfortunately, none of the existing approaches analyzed whether the volume-outcome relationship differs in accordance to the number of other (closely related) procedures conducted in the respective center.

Our study has several strengths and limitations: First of all, it is based on administrative data, and coding errors are inevitable. However, about 20% of all cardiovascular diagnosis–related groups are reviewed by independent teams of physicians on behalf of the health insurers, which should ensure a generally good reliability of the data.

Second, our risk-adjustment included a number of parameters whose reliability cannot be fully secured, and we cannot guarantee that all parameters of relevance are included in the model. A major limitation is that the data source does not include information on the type of device used in individual TAVI procedures. Therefore, information regarding the type of device and access route was not used for risk adjustment. In addition, information regarding the experience of surgeons at each centre would be highly relevant for the analysis but is also unavailable.

Thirdly, in terms of the categories used, hospital volume was classified into three fixed categories (<50, 50-99, >=100), which is in line with thresholds mentioned in official guidelines and previously applied in the literature, but might result in possible effects related to very high volumes being hidden in the analyzed group of patients treated in hospitals with >=100 cases per year.

Lastly, the dataset omits patients with a baseline diagnosis of pure aortic regurgitation, as well as those who underwent TAVI with any other concomitant cardiac procedure. This makes sense from a clinical perspective, but further complicates direct comparisons with other administrative datasets and possibly caused bias in the measurement of hospital volume and outcome.

A major strength of the study is that it provides comprehensive data on everyday TAVI practice in a large industrialized country over a multiyear period.

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We conclude that the hypothesized volume-outcome relationship for TAVI exists but diminishes and may disappear over time. This should be taken into account when considering mandatory minimum thresholds.

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Figure Legends

Figure 1: Risk-adjusted in-hospital mortality, stroke, bleeding and ventilation rates and their association

with center-specific procedure volumes in a given year.

Estimates are based on risk-adjusted logistic regression analysis including all available patient characteristics as confounders (see Table 1). Predicted probabilities are calculated by setting each confounder to its mean value (prediction at the means, see Table 1 for means). Annual and volume effects were calculated using random effects meta regression based on the estimated rates. A separate model with an interaction term was used to assess the change in the volume-outcome relationship. pp= percentage points.

Figure 2: Risk-adjusted in-hospital length of stay and reimbursement and their association with center-

specific procedure volumes in a given year.

Estimates are based on risk-adjusted linear regression analyses including all available patient characteristics as confounders (see Table 1). Predicted probabilities are calculated by setting each confounder to its mean value (prediction at the means, see Table 1 for means). Annual and volume effects were calculated using random effects meta regression based on the estimated means. A separate a model with an interaction term was used to assess the change in the volume-outcome relationship.

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Caption : Figure 1: Risk-adjusted in-hospital mortality, stroke, bleeding and ventilation rates and their association with center-specific procedure volumes in a given year.!! + Estimates are based on risk-adjusted logistic regression analysis including all available patient characteristics as confounders (see Table 1). Predicted probabilities are calculated by setting each confounder to its mean value (prediction at the means, see Table 1 for means). Annual and volume effects were calculated using random effects meta regression based on the estimated rates. A separate model with an interaction term was used to assess the change in the volume-outcome relationship. pp= percentage points.

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Figure 2: Risk-adjusted in-hospital length of stay and reimbursement and their association with centerspecific procedure volumes in a given year.

Estimates are based on risk-adjusted linear regression analyses including all available patient characteristics as confounders (see Table 1). Predicted probabilities are calculated by setting each confounder to its mean value (prediction at the means, see Table 1 for means). Annual and volume effects were calculated using random effects meta regression based on the estimated means. A separate a model with an interaction term was used to assess the change in the volume-outcome relationship.

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Table S1: Diagnosis and procedure codes used for this analysis

OPS codes	
5-351.0*	Surgical aortic valve replacement
5-35a.0*	Transcatheter aortic valve replacement
5-361.*, 5-362.*, 5-	Coronary artery bypass graft
363.*,	
5-351.1*, 5-351.2*, 5-	Surgical mitral valve replacement/reconstruction
353.1, 5-353.2	
5-351.4*	Surgical tricuspid valve replacement
5-377.0 et seqq.	Permanent pacemaker implantation
8-800.7*	Transfusion of RBC
since 2010:	
8-800.c*	
1	
Diagnosis	
135.0, 106.0	Aortic valve stenosis (degenerative/rheumatic)
135.2, 106.2	Combined aortic valve diseases (degenerative/rheumatic)
150.1*	Left ventricular congestive heart failure (according to NYHA classes)
110*	Arterial Hypertension
125.11, 125.12, 125.13	Coronary artery disease
125.20, 125.21, 125.22	Previous myocardial infarction (within 4 months/1 year/after 1 year)
Z95.1	Previous coronary artery bypass graft
Z95.1 – Z95.4	Previous cardiac surgery
170.20-170.25, 170.8,	Peripheral vascular disease
170.9, 173.9	
165.2	Carotid disease
121*	Acute myocardial infarction (within the last 28 days)
J44*	Chronic obstructive pulmonary disease 🕥
127*	Pulmonary hypertension
N18*	Renal disease
N17*	Acute kidney injury
148.1*	Atrial fibrillation
E10* - E14*	Diabetes
163*, 164	Stroke or cerebral infarction incl. occlusion and stenosis of cerebral and precerebral arterie
	resulting in cerebral infarction

2 Table S2: Results of the logistic regression model, transformation into discrete event probabilities and subsequent meta regressions

3 First step: Logistic regression model on 43,996 TAVI cases with in-hospital mortality as dependent variable, an

interaction term (n_ik_year_50_100#year) between categorical time (in years) and volume categories and 22

predefined patient and procedural characteristics as potential confounder.

6	n_ik_year_50_100	OR	p-value	95% CI									
7	procedure volume <50	1	0.00	0 427 2 241									
/	procedure volume 50-99	0.989	0.98	0.437 - 2.241									
8	procedure volume >=100	0.000	0.004	0.500 - 0.662					Third step: A random effects				
0	vear					n ik vear 50 100#vear Prob.	p-value	95% CI	meta regression (using Stata's				
9	2008	1				procedure volume <50 # 2008 0.090	0.000	0.068 - 0.113	command metareg) with				
10	2009	0.929	0.671	0.661 - 1.305		procedure volume <50 # 2009 0.085	0.000	0.071 - 0.098	time and volume as		Coeff	p-value 9	5% CI
1 1	2010	0.844	0.376	0.579 - 1.229		procedure volume <50 # 2010 0.077	0.000	0.059 - 0.095	continuous covariates was	Volume effect	-0.007	0.002 -0.01	20.003
11	2011	0.686	0.032	0.486 - 0.968	Second step: Predicted probabilities are	procedure volume <50 # 2011 0.064	0.000	0.048 - 0.08	applied to the estimated	Annual change	-0.006	0.000 -0.00	30.004
12	2012	0.525	0.004	0.340 - 0.812	calculated by setting each confounder to	procedure volume <50 # 2012 0.050	0.000	0.033 - 0.066	applied to the estimated	\rightarrow	-		
1 2	2013	0.465	0.001	0.302 - 0.718	its mean value (mediation at the means)	procedure volume <50 # 2013 0.044	0.000	0.029 - 0.059	rates.				
13	2014	0.453	0.001	0.288 - 0.712	its mean value (prediction at the means)	procedure volume <50 # 2014 0.043	0.000	0.027 - 0.059					
14					using Stata's margins command with	procedure volume 50-99 # 2008 0.090	0.006	0.026 - 0.153					
	n_ik_year_50_100#year	0.020	0.074	0.276 2.200	application of the atmeans option.	procedure volume 50-99 # 2009 0.078	0.000	0.058 - 0.098					
15	procedure volume 50-99 # 2009	0.929	0.874	0.376 - 2.298		procedure volume 50-99 # 2010 0.070	0.000	0.059 - 0.082					
16	procedure volume 50-99 # 2010	0.909	0.828	0.384 - 2.151	\rightarrow	procedure volume 50-99 # 2011 0.069	0.000	0.057 - 0.082					
10	procedure volume 50-99 # 2011	1.105	0.822	0.404 - 2.031		procedure volume 50-99 # 2012 0.062	0.000	0.049 - 0.076					
17	procedure volume 50-99 # 2012	1.200	0.337	0.512 - 5.202		procedure volume 50-99 # 2013 0.030	0.000	0.038 - 0.001					
18	procedure volume 50-99 # 2013	0.908	0.845	0 346 - 2 385		procedure volume $\geq 100 \ \# \ 2014 \ 0.055$	0.000	0.020 - 0.052	Foundh store Assessed				
10	procedure volume $\geq 100 \# 2009$	1.007	0.981	0.583 - 1.740		procedure volume >= $100 \# 2009 = 0.058$	0.000	0.034 - 0.083	Fourth step: A second				
19	procedure volume >=100 # 2010	1.120	0.598	0.735 - 1.705		procedure volume >=100 # 2010 0.059	0.000	0.044 - 0.074	random effects meta				
20	procedure volume >=100 # 2011	1.260	0.223	0.869 - 1.827		procedure volume >=100 # 2011 0.054	0.000	0.047 - 0.061	regression model was applied				
20	procedure volume >=100 # 2012	1.399	0.164	0.872 - 2.244		procedure volume >=100 # 2012 0.047	0.000	0.039 - 0.054	including also an interaction	Z	 Coeff 	p-value 9	5% CI
21	procedure volume >=100 # 2013	1.606	0.046	1.009 - 2.558		procedure volume >=100 # 2013 0.047	0.000	0.040 - 0.055	term.	Volume effect	-4.536	0.026 -8.47	30.600
วว	procedure volume >=100 # 2014	1.100	0.687	0.692 - 1.749		procedure volume >=100 # 2014 0.032	0.000	0.028 - 0.036	<u> </u>	Annual change	-0.011	0.000 -0.016	50.006
~~		0.002	0.045	0.015 0.000					Annual char	nge of volume effect	0.002	0.027 0.00	0 - 0.004
23	Female	0.902	0.045	0.815 - 0.998									
24	Age in years	1.009	0.155	1.015 - 1.022									
27	Agentic value stopperio	0.636	0.000	0.504 - 0.802									
25	Combined partic valve diseases	0.050	0.000	0.447 - 0.685									
26		0.551	0.000	0.423 - 0.717									
20	NYHA III or IV	1.550	0.000	1.264 - 1.900									
27	CAD	1.034	0.517	0.934 - 1.144									
20	Hypertension	0.698	0.000	0.612 - 0.797									
20	Previous MI (within 4 months)	0.683	0.048	0.467 - 0.997									
29	Previous MI (within 1 year)	1.042	0.881	0.608 - 1.785									
20	Previous MI (after 1 year)	0.979	0.816	0.821 - 1.169									
50	Previous CABG	1.017	0.884	0.809 - 1.278									
31	Previous cardiac surgery	0.808	0.117	0.619 - 1.055									
22	Peripheral vascular disease	1.118	0.140	0.964 - 1.295									
52	Carotid disease	0.890	0.105	0.768 - 1.046									
33	COPD Bulmanany hypothesian	0.979	0.744	0.803 - 1.111									
24		1 770	0.021	1 443 - 2 170									
54	GER <30%	1.414	0.000	1.167 - 1.714									
35	Atrial fibrillation	1.211	0.000	1.115 - 1.315									
20	Diabetes	1.024	0.640	0.926 - 1.133									
30													
37													

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2 Table S3: Results of the logistic regression model, transformation into discrete event probabilities and subsequent meta regressions

3 First step: Logistic regression model on 43,996 TAVI cases with stroke as dependent variable, an interaction

term (n_ik_year_50_100#year) between categorical time (in years) and volume categories and 22 predefined

patient and procedural characteristics as potential confounder.

6 hi_k_year_50_100 0k p-value 55% Cl	
7 procedure volume 50-9 0 029 0 886 0 339 - 2 5473	
7 procedure volume >= 100 0.969 0.945 0.398 - 2.3631	A manufacture officiale
	ep: A random effects
n ik year 50 100#year Prob. p-value 95% Cl	gression (using Stata's
9 year 2008 1 procedure volume <50 # 2008 0.022 0.000 0.012 - 0.031 comman	nd metareg) with
10 2009 1.140 0.643 0.654 - 1.989 procedure volume <50 # 2009 0.025 0.000 0.017 - 0.032 time and	volume as Coeff p-value 95% Cl
2010 0.732 0.308 0.401 - 1.335	Nus covariates was Volume effect 0.001 0.196 -0.001 - 0.003
11 2011 0.678 0.211 0.369 - 1.246 Second step: Predicted probabilities are procedure volume <50 # 2011 0.015 0.000 0.009 - 0.021 applied	Annual change -0.001 0.029 -0.002 - 0.000
12 2012 0.659 0.197 0.350 - 1.241 columed to procedure volume <50 # 2012 0.014 0.000 0.008 - 0.021	
12 2013 0.574 0.114 0.289 - 1.142 calculated by setting each combinitier to procedure volume <50 # 2013 0.013 0.000 0.006 - 0.019 rates.	
13 2014 0.759 0.426 0.385 - 1.496 Its mean value (prediction at the means) procedure volume <50 # 2014 0.016 0.000 0.008 - 0.025	
using Stata's margins command with procedure volume 50-99 # 2008 0.020 0.026 0.002 - 0.038	
I 4] n_ik_year_50_100#year application of the atmeans option. procedure volume 50-99 # 2009 0.025 0.000 0.014 - 0.035	
procedure volume 50-99 # 2009 1.079 0.896 0.344 -3.384 ////////////////////////////////////	
procedure volume 50-99 # 2010 1.310 0.637 0.428 - 4.009 procedure volume 50-99 # 2011 0.017 0.000 0.012 - 0.022	
16 procedure volume 50-99 # 2011 1.233 0.115 0.400 - 3.796 procedure volume 50-99 # 2012 0.017 0.000 0.011 - 0.022	
17 procedure volume 50-99 # 2012 1.247 0.706 0.396 - 3.921	
Procedure Volume 50-99 # 2013 1.332 0.631 0.414 - 4.288 Procedure Volume 50-99 # 2014 0.013 0.000 0.009 - 0.021 0.000 - 0.000 - 0.000 - 0.021 0.000 - 0.0000 - 0.000 - 0.000 - 0.000 - 0.000 - 0.000 -	
18 procedure volume >-100 # 2014 0.557 0.342 0.296 - 3.102	tep: A second
procedure volume >-100 # 2009 0.173 0.049 0.205 - 0.207 random	effects meta
procedure volume >=100 # 2010 1.134 0.310 0.66 - 4.440	on model was applied
20 procedure volume >100 # 2011 1.209 0.712 0.441 - 3.312	g also an interaction
procedure volume >100 # 2013 1.769 0.712 0.626 - 4.995	Volume effect -1.103 0.307 -3.311 - 1.106
21 procedure volume >=100 # 2014 1.099 0.857 0.393 - 3.076 procedure volume >=100 # 2014 0.018 0.000 0.015 - 0.020	Annual change -0.002 0.086 -0.005 - 0.000
22	Annual change of volume effect 0.001 0.306 -0.001 - 0.002
Female 0.648 0.000 0.565 - 0.744	
23 _{Age in years} 0.900 0.000 0.890 - 0.910	
On Estimated logistic EuroSCORE 68461 0.000 33804 - 138650 Comparison Com	
Artic valve stenosis 1.278 0.067 0.983 - 1.663	
25 Combined aortic valve diseases 1.329 0.045 1.006 - 1.755	
NYHA II 0.949 0.675 0.744 - 1.211	
20 NYHA III or IV 1.096 0.166 0.962 - 1.249	
27[CAD 1.011 0.8/5 0.885 1.154]	
- Hypertension U.51U U.148 U.802 - 1.054	
28 Previous MI (within 4 months) 0.270 0.000 0.107 -0.404	
29 Previous MI (Mittin 1 year) 1005 0.072 1.360	
- / Previous Mil (alter 1 year) 1.005 0.375 0.742 - 1.300	
30 Provide cardia surgery 0.120 0.000 0.029 - 0.164	
Thering a service of the strength of the service of	
32 [COPD 0.355 0.000 0.295 - 0.429	
2 Deumonary hypertension 0.198 0.000 0.164 - 0.239	
5) _{GFR <15%} 0.266 0.000 0.183 - 0.387	
34 GFR <30% 0.297 0.000 0.226 - 0.391	
Atrial fibrillation 1.093 0.165 0.964 - 1.239	
35 _{Diabetes} 1.079 0.260 0.945 - 1.231	
36	

2 Table S4: Results of the logistic regression model, transformation into discrete event probabilities and subsequent meta regressions

3 First step: Logistic regression model on 43,996 TAVI cases with bleeding as dependent variable, an interaction term (n_ik_year_50_100#year) between categorical time (in years) and volume categories and 22 predefined patient and procedural characteristics as potential confounder.

6	n_ik_year_50_100	OR	p-value	95% CI								
_	procedure volume <50	1	0.200	0.506 1.006								
/	procedure volume 50-99	0.806	0.366	0.506 - 1.286								
Q	procedure volume >=100	0.485	0.006	0.291 - 0.811					Third step: A random effects			
0						n ik waan EQ 100#waan Drah	n velve	05% CI	meta regression (using Stata's			
9	year	1				n_ik_year_50_100#year Prob.	p-value	95% CI	command metareg) with			
10	2008	0 0 1 2	0.677	0 711 1 249		procedure volume <50 # 2008 0.134	0.000	0.108 - 0.181	time and volume as	600	ff n-value	05% CI
10	2003	0.342	0.077	0.579 - 1.037		procedure volume <50 # 2009 0.128	0.000	0.109 - 0.140		Volume effect -0.0	11 p-value	-0.0160.00/9
11	2010	0.574	0.000	0.072 - 0.781	Constant and Development of the left his second	procedure volume <50 # 2010 0.107	0.000	0.050 - 0.125	continuous covariates was	Appual change -0.0	11 0.001	-0.0100.0043
	2011	0.574	0.000	0.363 - 0.696	Second step: Predicted probabilities are	procedure volume <50 # 2011 0.002	0.000	0.057 - 0.088	applied to the estimated		.1 0.000	-0.0130.0003
12	2012	0.559	0.000	0 399 - 0 785	calculated by setting each confounder to	procedure volume <50 # 2012 0.072	0.000	0.062 - 0.098	rates.			
13	2014	0.340	0.000	0.226 - 0.511	its mean value (prediction at the means)	procedure volume <50 # 2014 0.050	0.000	0.034 - 0.066				
15					using Stata's margins command with	procedure volume 50-99 # 2008 0.111	0.000	0.071 - 0.151				
14	n ik vear 50 100#vear				application of the atmosphere antion	procedure volume 50-99 # 2009 0.105	0.000	0.082 - 0.128				
1 -	procedure volume 50-99 # 2009	0.992	0.978	0.571 - 1.724	application of the atmeans option.	procedure volume 50-99 # 2010 0.102	0.000	0.089 - 0.116				
15	procedure volume 50-99 # 2010	1.176	0.541	0.699 - 1.980		procedure volume 50-99 # 2011 0.081	0.000	0.069 - 0.093				
16	procedure volume 50-99 # 2011	1.224	0.458	0.718 - 2.087	1	procedure volume 50-99 # 2012 0.077	0.000	0.064 - 0.090				
10	procedure volume 50-99 # 2012	1.321	0.321	0.762 - 2.293		procedure volume 50-99 # 2013 0.059	0.000	0.049 - 0.069				
17	procedure volume 50-99 # 2013	0.894	0.693	0.511 - 1.563		procedure volume 50-99 # 2014 0.051	0.000	0.039 - 0.063				
10	procedure volume 50-99 # 2014	1.265	0.463	0.675 - 2.374		procedure volume >=100 # 2008 0.070	0.000	0.040 - 0.100	Fourth step: A second			
10	procedure volume >=100 # 2009	1.070	0.828	0.581 - 1.970		procedure volume >=100 # 2009 0.071	0.000	0.052 - 0.090	random offects meta			
19	procedure volume >=100 # 2010	1.078	0.799	0.605 - 1.920		procedure volume >=100 # 2010 0.059	0.000	0.048 - 0.070				
20	procedure volume >=100 # 2011	2.198	0.006	1.249 - 3.866		procedure volume >=100 # 2011 0.087	0.000	0.078 - 0.096	regression model was applied			
20	procedure volume >=100 # 2012	1.669	0.080	0.941 - 2.960		procedure volume >=100 # 2012 0.059	0.000	0.053 - 0.066	including also an interaction	Coe	ff p-value	95% CI
21	procedure volume >=100 # 2013	1.371	0.286	0.768 - 2.447		procedure volume >=100 # 2013 0.055	0.000	0.049 - 0.060	term.	Volume effect -4.84	352 0.169	-11.97 - 2.27482
21	procedure volume >=100 # 2014	1.540	0.174	0.827 - 2.868		procedure volume >=100 # 2014 0.038	0.000	0.034 - 0.042		Annual change -0.01	0.001 89	-0.0240.0076
22									Annual chang	nge of volume effect 0.00	24 0.170	-0.001 - 0.00595
22	Female	1.096	0.032	1.008 - 1.193								
25	Age in years	0.982	0.000	0.974 - 0.990								
24	Estimated logistic EuroSCORE	5.813	0.000	3.386 - 9.979								
~ -	Aortic valve stenosis	0.738	0.000	0.639 - 0.852								
25	Combined aortic valve diseases	0.677	0.000	0.580 - 0.790								
26	NYHA II	0.665	0.000	0.562 - 0.786								
20	NYHA III or IV	1.313	0.000	1.216 - 1.418								
27	CAD	1.062	0.137	0.981 - 1.149								
20	Hypertension	0.798	0.000	0.741 - 0.861								
28	Previous IVII (Within 4 months)	1.071	0.524	0.030 - 1.133								
29	Previous IVII (Within 1 year)	0.000	0.742	0.711 - 1.014								
27	Previous IVII (atter 1 year)	0.609	0.157	0.721 - 1.040								
30	Previous CABG	1 275	0.000	1 077 - 1 509								
21	Poriphoral vascular disease	1 255	0.000	1 118 - 1 409								
21	Carotid disease	1 182	0.000	1 024 - 1 364								
32		0.998	0.969	0.896 - 1.111								
22	Pulmonary hypertension	0.833	0.002	0.741 - 0.935								
33	GER <15%	2.045	0.000	1.725 - 2.423								
34	GFR <30%	1.446	0.000	1.240 - 1.685								
54	Atrial fibrillation	1.418	0.000	1.316 - 1.528								
35	Diabetes	0.968	0.418	0.894 - 1.048								
26												
20												
37												

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2 Table S5: Results of the logistic regression model, transformation into discrete event probabilities and subsequent meta regressions

3 First step: Linear regression model on 43,996 TAVI cases with Length of hospital stay as dependent variable,

an interaction term (n_ik_year_50_100#year) between categorical time (in years) and volume categories and

22 predefined patient and procedural characteristics as potential confounder.

<u> </u>	1 50 400	- <i>(</i> (050/ 01	l l								
6	n_ik_year_50_100	Coeff	p-value	95% CI									
7	procedure volume <50	2 9 5 9	0.001	1 1 2 2 1 7 9 6									
/	procedure volume >=100	2.959 A 1A9	0.001	1.155 - 4.760 5.577 - 2.721									
8	procedure volume >=100	-4.140	0.000	-3.3742.721						Third step: A random effects			
	Noar					n ik voar 50 100#voar	Cooff	n-valuo	05% CI	meta regression (using Stata's			
9	2008	0				procedure volume <50 # 200	19 19 18/	0.000	18 2/1 - 20 13	command metareg) with			
10	2008	2 179	0.001	0 950 - 3 409		procedure volume <50 # 200	19 21 364	0.000	20 577 - 22 15	time and volume as	Coeff	n-value	95% (1
10	2003	1 472	0.001	0 247 - 2 697		procedure volume <50 # 200	10 20 656	0.000	19 874 - 21 44		Volume effect -1.488	0.000	-2 0210 9
11	2010	0.507	0.013	-0 731 - 1 745	Consulation: Manainal manage	procedure volume <50 # 201	11 19 691	0.000	18 890 - 20 49	continuous covariates was	Annual change -0.269	0.000	-0.5070.0
	2011	-1 002	0.100	-2 197 - 0 193	Second step: Warginal means are	procedure volume <50 # 201	12 18 182	0.000	17 448 - 18 92	applied to the estimated		0.025	0.507 0.0
12	2013	0.382	0.580	-0.970 - 1.734	calculated by setting each confounder to	procedure volume <50 # 201	13 19.566	0.000	18.599 - 20.53	means.			
13	2014	-0.060	0.931	-1.433 - 1.312	its mean value (prediction at the means)	procedure volume <50 # 201	14 19.124	0.000	18.128 - 20.12				
1.7					using Stata's margins command with	procedure volume 50-99 # 200	08 22.144	0.000	20.579 - 23.71				
14	n ik vear 50 100#vear				application of the atmosps option	procedure volume 50-99 # 200	09 18.578	0.000	17.650 - 19.51	-			
10	procedure volume 50-99 # 2009	-5.745	0.000	-7.9423.547	application of the atmeans option.	procedure volume 50-99 # 201	10 18.743	0.000	18.221 - 19.27				
IЭ	procedure volume 50-99 # 2010	-4.872	0.000	-6.9262.819		procedure volume 50-99 # 201	11 19.095	0.000	18.554 - 19.64				
16	procedure volume 50-99 # 2011	-3.555	0.001	-5.6221.488		procedure volume 50-99 # 201	12 18.967	0.000	18.413 - 19.52				
	procedure volume 50-99 # 2012	-2.174	0.037	-4.2190.130		procedure volume 50-99 # 201	13 18.074	0.000	17.576 - 18.57				
17	procedure volume 50-99 # 2013	-4.452	0.000	-6.5762.327		procedure volume 50-99 # 201	14 18.137	0.000	17.545 - 18.73				
10	procedure volume 50-99 # 2014	-3.947	0.000	-6.1101.783		procedure volume >=100 # 200	08 15.036	0.000	13.964 - 16.11	Fourth step: A second			
10	procedure volume >=100 # 2009	1.066	0.242	-0.721 - 2.853		procedure volume >=100 # 200	09 18.281	0.000	17.543 - 19.02	random effects meta			
19	procedure volume >=100 # 2010	0.788	0.365	-0.915 - 2.490		procedure volume >=100 # 201	10 17.296	0.000	16.791 - 17.8	remeasion model was applied			
20	procedure volume >=100 # 2011	1.972	0.021	0.292 - 3.652		procedure volume >=100 # 201	11 17.515	0.000	17.137 - 17.89	regression model was applied			
20	procedure volume >=100 # 2012	2.929	0.000	1.302 - 4.557		procedure volume >=100 # 201	12 16.964	0.000	16.696 - 17.23	including also an interaction	Coeff	p-value	95% CI
21	procedure volume >=100 # 2013	0.970	0.275	-0.773 - 2.713		procedure volume >=100 # 201	13 16.389	0.000	16.136 - 16.64	term.	Volume effect 22.5075	0.935 د	-554.1 - 599.
~ '	procedure volume >=100 # 2014	0.390	0.662	-1.358 - 2.139		procedure volume >=100 # 201	14 15.366	0.000	15.179 - 15.55		Annual change -0.2399	1 0.452	-0.898 - 0.41
22		0.400		0.705 0.044						Annual cha	ange of volume effect -0.0119	3 0.931	-0.299 - 0.27
22	Female	-0.483	0.000	-0.7250.241									
25	Age in years	-0.247	0.000	-0.2760.218									
24	Estimated logistic EuroSCORE	25.503	0.000	23.343 - 27.001									
25	AORTIC VAIVE STENOSIS	-0.200	0.000	-0.9125.598									
22	NVLA II	0.15/	0.000	-0.179 - 0.497									
26		2 597	0.000	2 37/ - 2 821									
2		-0.037	0.000	-0 259 - 0 184									
2/	Hypertension	-0.888	0.000	-1.1110.666									
20	Previous MI (within 4 months)	-3.355	0.000	-4.1752.534									
20	Previous MI (within 1 year)	0.015	0.980	-1.172 - 1.203									
29	Previous MI (after 1 year)	-0.303	0.250	-0.819 - 0.213									
20	Previous CABG	-2.938	0.000	-3.5962.280									
30	Previous cardiac surgery	-1.710	0.000	-2.4051.015									
31	Peripheral vascular disease	-0.917	0.000	-1.3450.489									
	Carotid disease	-1.110	0.000	-1.6140.606									
32	COPD	-0.618	0.001	-0.9730.263									
22	Pulmonary hypertension	-2.226	0.000	-2.6241.827									
ادد	GFR <15%	1.941	0.000	0.958 - 2.923									
34	GFR <30%	0.725	0.034	0.054 - 1.396									
2	Atrial fibrillation	2.575	0.000	2.365 - 2.785									
35	Diabetes	0.932	0.000	0.702 - 1.161									
36													
27													
37													

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² Table S6: Results of the logistic regression model, transformation into discrete event probabilities and subsequent meta regressions

3 First step: Linear regression model on 43,996 TAVI cases with reimbursement as dependent variable, an

interaction term (n_ik_year_50_100#year) between categorical time (in years) and volume categories and 22

predefined patient and procedural characteristics as potential confounder.

-	n_ik_year_50_100	Coeff	p-value	95% CI		
6	procedure volume <50	0				
-	procedure volume 50-99	-905.1	0.024	-1689.5120.7		
/	procedure volume >=100	-1792.9	0.000	-2614.4971.4	Third stop: A random offertr	
0	P				Third step. A failed in checks	
ð	vear				In ik vear 50 100#vear Coeff p-value 95% Cl meta regression (using	
0	2010	0			procedure volume <50 # 2010_36999 8 0.000_36302 5 - 37697 1 Stata's command metareg)	
9	2011	-1104 3	0.026	-2078 5130 1	procedure volume <50, # 2011, 35895.5, 0,000, 35214.3, - 36576.7, with time and volume as	
10	2012	-1872 9	0.000	-2810 5935 4	procedure volume <50 # 2012 35126 9 0.000 34499 5 - 35754 2 Volume effect - 503 8 0.005 - 876 4 - 18	(1.2
	2013	-1339.7	0.007	-2316 5362 9	procedure volume <50 # 2013 35560 1 0 000 34974 4 3640 7	19
11	2013	-12/0 5	0.007	-2235 4245 5	Second step: Marginal means are	.5
	2014	12-0.5	0.015	2233.4 243.3	calculated by setting each confounder procedure volume 50.9 # 2010 3609.7 0.000 35738 1 - 36051 3 means.	
12	n ik vear 50 100#vear				to its mean value (prediction at the procedure volume 50.99 ± 2011 35339 ± 0.0000 3482 3 ± 357975	
12	procedure volume 50-99 # 2011	349 5	0 545	-783 6 - 1482 5	means) using Stata's margins $\frac{1}{2}$ procedure volume 50-99 # 2012 34820 7 0 0000 34420 7 - 35170 6	
15	procedure volume 50-99 # 2012	598.9	0.269	-464 0 - 1661 8	meanly damp study in all real in a study of the study of	
14	procedure volume 50-99 # 2012	-162.6	0.775	-1276 2 - 950 9	command with application of the	
1-1	procedure volume 50-99 # 2013	-51 3	0.978	-1159 3 - 1056 7	atmeans option.	
15	procedure volume >=100 # 2011	001 1	0.020	127.9 2116.7	procedure volume >=100 # 2011 250071 0 000 247742 25440.9	
	procedure volume $>=100 \# 2011$	001 2	0.082	-127.8 - 2110.7	procedure volume >-100 # 2013 302/31 0.000 - 24/14.3 - 33442.6	
16	procedure volume $> 100 \# 2012$	554.5 614 E	0.003	471.2 1700.4	procedure volume >=100 # 2012 34326.3 0.000 34126.7 34227.5	
17	procedure volume >=100 # 2013	014.5	0.207	200.2 1005.4	procedure volume >=100 # 2014 34461.7 0.000 34253.1 34076.4	
17	procedure volume >=100 # 2014	805.0	0.150	-269.5 - 1695.4	procedure volume >=100 # 2014 34789.5 0.000 34623.4 - 34915.0 Fourth step: A second	
18	Famala	-816 /	0.000	-1022 5610 4	random effects meta	
10	Ago in yoars	-134.0	0.000	-159 5108 6	regression model was	
19	Age III years	9498.4	0.000	7514 7 - 11482 1	applied including also an Coeff p-value 95% CL	
	Agric valva stanasis	-1/180 8	0.000	-2007 4864 3		1221 /
20	Autic valve stellosis	1671 1	0.000	2007.4004.5	interaction term. Volume check 2494273 0.202 7020700 221	.221.4
21	Complined aortic valve diseases	10/1.1	0.000	-2290.01043.0	Annual charge of volume official 121 7 0 262 1052 202	o 7
21		-420.2 coc o	0.001	-003.2 -173.3 E01.2 972.2		5.7
22	NYHA III OF IV	122.0	0.000	JUI.3 - 872.2		
22	CAD	133.0	0.153	-49.7 - 310.8		
23	Hypertension	-427.8	0.000	-614.4241.3		
25	Previous MI (within 4 months)	-16//.0	0.000	-2134.61219.4		
24	Previous MI (within 1 year)	295.6	0.574	-/33.9 - 1325.2		
	Previous MI (after 1 year)	-483.1	0.009	-843.2123.0		
25	Previous CABG	-1118.8	0.000	-1687.9549.8		
~	Previous cardiac surgery	-574.4	0.061	-1174.8 - 25.9		
26	Peripheral vascular disease	86.9	0.649	-287.8 - 461.7		
27	Carotid disease	-365.0	0.106	-807.3 - 77.3		
27	COPD	-0.6	0.997	-318.6 - 317.4		
20	Pulmonary hypertension	-951.6	0.000	-1302.7600.4		
20	GFR <15%	1849.2	0.000	921.0 - 2777.4		
29	GFR <30%	322.0	0.258	-235.7 - 879.6		
2)	Atrial fibrillation	913.0	0.000	741.8 - 1084.1		
30	Diabetes	223.8	0.020	34.7 - 412.9		
21						
51						

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2 Table S7: Results of the logistic regression model, transformation into discrete event probabilities and subsequent meta regressions

3 First step: Logistic regression model on 43,996 TAVI cases with ventilation as dependent variable, an

interaction term (n_ik_year_50_100#year) between categorical time (in years) and volume categories and 22

4 predefined patient and procedural characteristics as potential confounder.

5				
5	n ik year 50 100	OR	p-value	95% CI
6	procedure volume <50	1	-	

6	procedure volume <50	1												
7	procedure volume 50-99	0.716	0.262	0.400 - 1.283										
1	procedure volume >=100	0.492	0.026	0.263 - 0.918						Third step: A random effects				
8	1007					n ik voor EO 100#voor	Droh	n value	05% 01	meta regression (using				
	2008	1				$n_k_year_{50}_{100\#year}$	0.086	p-value	0.065 - 0.107	Stata's command metareg)				
9	2008	0 946	0 745	0 677 - 1 322		procedure volume <50 # 2009	0.000	0.000	0.067 - 0.096	with time and volume as	Г	Coeff	n-value	95% CI
10	2010	0.853	0.362	0.605 - 1.201		procedure volume <50 # 2010	0.074	0.000	0.060 - 0.089	continuous covariates was	Volume effect	-0.010	0.004	-0.0160.004
10	2011	0.765	0.135	0.539 - 1.086	Second step: Predicted probabilities are	procedure volume <50 # 2011	0.067	0.000	0.053 - 0.081	applied to the estimated	Annual change	-0.004	0.002	-0.0070.002
11	2012	0.664	0.029	0.459 - 0.959	calculated by catting each confounder to	procedure volume <50 # 2012	0.059	0.000	0.045 - 0.073	applied to the estimated	\rightarrow			<u> </u>
	2013	0.623	0.018	0.420 - 0.923	calculated by setting each comounder to	procedure volume <50 # 2013	0.055	0.000	0.040 - 0.070	rates.				
12	2014	0.532	0.004	0.345 - 0.819	its mean value (prediction at the means)	procedure volume <50 # 2014	0.048	0.000	0.032 - 0.063					
13					using Stata's margins command with	procedure volume 50-99 # 2008	0.063	0.000	0.033 - 0.094					
יי	n_ik_year_50_100#year				application of the atmeans option.	procedure volume 50-99 # 2009	0.064	0.000	0.046 - 0.083	\leq				
14	procedure volume 50-99 # 2009	1.079	0.827	0.544 - 2.141		procedure volume 50-99 # 2010	0.074	0.000	0.062 - 0.085					
10	procedure volume 50-99 # 2010	1.382	0.322	0.729 - 2.622	\rightarrow	procedure volume 50-99 # 2011	0.069	0.000	0.058 - 0.079					
15	procedure volume 50-99 # 2011	1.45	0.277	0.751 - 2.725		procedure volume 50-99 # 2012	0.047	0.000	0.037 - 0.037					
16	procedure volume 50-99 # 2012	0.929	0.785	0.301 - 2.142		procedure volume 50-99 # 2013	0.035	0.000	0.025 - 0.045					
10	procedure volume 50-99 # 2014	1 016	0.967	0 489 - 2 111		procedure volume $\geq 100 \# 2008$	0.033	0.000	0.020 - 0.068	Fourth story A cocond				
17	procedure volume >=100 # 2009	1.732	0.131	0.848 - 3.537		procedure volume >=100 # 2009	0.070	0.000	0.052 0.089	Fourth step: A second				
10	procedure volume >=100 # 2010	1.232	0.555	0.616 - 2.462		procedure volume >=100 # 2010	0.046	0.000	0.037 0.056	random effects meta				
18	procedure volume >=100 # 2011	1.914	0.059	0.975 - 3.758		procedure volume >=100 # 2011	0.063	0.000	0.056 0.071	regression model was applied				
19	procedure volume >=100 # 2012	1.624	0.163	0.822 - 3.210		procedure volume >=100 # 2012	0.047	0.000	0.042 0.053	including also an interaction	7	Coeff	p-value	95% CI
	procedure volume >=100 # 2013	1.636	0.165	0.817 - 3.277		procedure volume >=100 # 2013	0.045	0.000	0.040 0.050	term.	Volume effect	-6.084	0.040	-11.8700.299
20	procedure volume >=100 # 2014	1.358	0.402	0.664 - 2.776		procedure volume >=100 # 2014	0.032	0.000	0.029 0.036		Annual change	-0.011	0.004	-0.0180.004
21		0 74 0	0.000	0.054 0.704						Annual ch	ange of volume effect	0.003	0.041	0.000 - 0.006
21	emale	0.713	0.000	0.651 - 0.781										
22	Age in years	13 81	0.000	7 797 - 24 464										
22	Antio volvo stonosio	0 722	0.000	0.618 - 0.843										
23	Combined portic valve diseases	0.663	0.000	0.561 - 0.783										
24	NYHA II	0.498	0.000	0.404 - 0.614										
27	NYHA III or IV	1.485	0.000	1.364 - 1.617										
25	CAD	1.094	0.044	1.002 - 1.193										
26	Hypertension	0.697	0.000	0.642 - 0.757										
20	Previous MI (within 4 months)	0.804	0.163	0.591 - 1.093										
27	Previous MI (within 1 year)	0.796	0.358	0.490 - 1.294										
	Previous IVII (after 1 year)	0.89/	0.208	0.740 - 1.087										
28	revious CABG	0.075	0.000	0.337 - 0.816										
20	Perinheral vascular disease	1.198	0.004	1.060 - 1.353										
29	Carotid disease	0.855	0.061	0.725 - 1.007										
30	COPD	1.211	0.001	1.085 - 1.351										
21	Pulmonary hypertension	0.758	0.000	0.669 - 0.858										
51	GFR <15%	1.364	0.001	1.129 - 1.647										
32	GFR <30%	1.252	0.008	1.059 - 1.479										
52	Atrial fibrillation	1.553	0.000	1.430 - 1.687										
33	Diabetes	1.138	0.003	1.045 - 1.239	l									
34														
35														
36														
37														

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	Item No.	STROBE items	Location in manuscript where items are reported	RECORD items	Location in manuscript where items are reported
Title and abstra	ict				
	1	(a) Indicate the study's design with a commonly used term in the title or the abstract (b) Provide in the abstract an informative and balanced summary of what was done and what was found	p1-2	RECORD 1.1: The type of data used should be specified in the title or abstract. When possible, the name of the databases used should be included. RECORD 1.2: If applicable, the geographic region and timeframe within which the study took place should be reported in the title or abstract. RECORD 1.3: If linkage between databases was conducted for the study, this should be clearly stated in the title or abstract.	R(ecord)1.1: p1 R1.2: p1-2 R1.3: n/a
Introduction				·	
Background rationale	2	Explain the scientific background and rationale for the investigation being reported	p5	00	
Objectives	3	State specific objectives, including any prespecified hypotheses	p5	1	
Methods					
Study Design	4	Present key elements of study design early in the paper	p6-9		
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	рб		
Participants	6	(a) Cohort study - Give the eligibility criteria, and the	р6	RECORD 6.1: The methods of study population selection (such as codes or	R6.1: p6 R6.2, 6.3: n/a

The RECORD statement – checklist of items, extended from the STROBE statement, that should be reported in observational studies using routinely collected health data.

		 sources and methods of selection of participants. Describe methods of follow-up <i>Case-control study</i> - Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls <i>Cross-sectional study</i> - Give the eligibility criteria, and the sources and methods of selection of participants (b) Cohort study - For matched studies, give matching criteria and number of exposed and unexposed <i>Case-control study</i> - For matched studies, give matching criteria and the number of controls per case 	er tevio	algorithms used to identify subjects) should be listed in detail. If this is not possible, an explanation should be provided. RECORD 6.2: Any validation studies of the codes or algorithms used to select the population should be referenced. If validation was conducted for this study and not published elsewhere, detailed methods and results should be provided. RECORD 6.3: If the study involved linkage of databases, consider use of a flow diagram or other graphical display to demonstrate the data linkage process, including the number of individuals with linked data at each stage.	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable.	р6-7	RECORD 7.1: A complete list of codes and algorithms used to classify exposures, outcomes, confounders, and effect modifiers should be provided. If these cannot be reported, an explanation should be provided.	p6-7
Data sources/ measurement	8	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	p6-7, Supplementary tables		
Bias	9	Describe any efforts to address potential sources of bias	p6-7, 9		
Study size	10	Explain how the study size was	n/a (national cohort)		

		arrived at	(p6-7)		
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen, and why	p7-10		
Statistical methods	12	 (a) Describe all statistical methods, including those used to control for confounding (b) Describe any methods used to examine subgroups and interactions (c) Explain how missing data were addressed (d) Cohort study - If applicable, explain how loss to follow-up was addressed <i>Case-control study</i> - If applicable, explain how matching of cases and controls was addressed <i>Cross-sectional study</i> - If applicable, describe analytical methods taking account of sampling strategy (e) Describe any sensitivity analyses 	p7-10		
Data access and cleaning methods				RECORD 12.1: Authors should describe the extent to which the investigators had access to the database population used to create the study population. RECORD 12.2: Authors should provide information on the data cleaning methods used in the study	рб
Linkage				RECORD 12.3: State whether the study included person-level, institutional-	n/a

				level, or other data linkage across two or more databases. The methods of linkage and methods of linkage quality evaluation should be provided.	
Results	1.2				
Participants	13	 (a) Report the numbers of individuals at each stage of the study (<i>e.g.</i>, numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed) (b) Give reasons for non- participation at each stage. (c) Consider use of a flow diagram 	n/a (national cohort, administrative data, no follow-up)	RECORD 13.1: Describe in detail the selection of the persons included in the study (<i>i.e.</i> , study population selection) including filtering based on data quality, data availability and linkage. The selection of included persons can be described in the text and/or by means of the study flow diagram.	n/a (national cohort, administrative data, no follow- up)
Descriptive data	14	 (a) Give characteristics of study participants (<i>e.g.</i>, demographic, clinical, social) and information on exposures and potential confounders (b) Indicate the number of participants with missing data for each variable of interest (c) <i>Cohort study</i> - summarise follow-up time (<i>e.g.</i>, average and total amount) 	p8	2071	
Outcome data	15	Cohort study - Report numbers of outcome events or summary measures over time Case-control study - Report numbers in each exposure category, or summary measures of exposure Cross-sectional study - Report numbers of outcome events or summary measures	p13		
Main results	16	(a) Give unadjusted estimates	p10-14		

		and, if applicable, confounder- adjusted estimates and their precision (e.g., 95% confidence interval). Make clear which confounders were adjusted for and why they were included (b) Report category boundaries when continuous variables were categorized (c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period			
Other analyses	17	Report other analyses done—e.g., analyses of subgroups and interactions, and sensitivity analyses	n/a		
Discussion					
Key results	18	Summarise key results with reference to study objectives	p14-15		
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	p3, 9-10	RECORD 19.1: Discuss the implications of using data that were not created or collected to answer the specific research question(s). Include discussion of misclassification bias, unmeasured confounding, missing data, and changing eligibility over time, as they pertain to the study being reported.	p3, 9-10
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	p 14-17		
Generalisability	21	Discuss the generalisability (external validity) of the study results	p3, 14-17		

1	Other Information	n				
ו כ	Funding	22	Give the source of funding and	p4		
2 2	-		the role of the funders for the	-		
4			present study and, if applicable,			
5			for the original study on which			
6			the present article is based			
7	Accessibility of				RECORD 22.1: Authors should provide	Access to public
3	protocol, raw				information on how to access any	dataset: p6
9 10	data, and				supplemental information such as the	Further data:
11	programming		\wedge		study protocol, raw data, or	Supplemental
12	code				programming code.	tables
13		•		•		

*Reference: Benchimol EI, Smeeth L, Guttmann A, Harron K, Moher D, Petersen I, Sørensen HT, von Elm E, Langan SM, the RECORD Working Committee. The REporting of studies Conducted using Observational Routinely-collected health Data (RECORD) Statement. PLoS Medicine 2015; in press.

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