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RESEARCH ARTICLE

Centre procedural volume and adverse in-hospital outcomes in patients undergoing percutaneous transvenous edge-to-edge mitral valve repair using MitraClip® in Germany

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Aims The number of transcatheter mitral valve repair (TMVr) procedures has increased substantially during the last years. A better understanding of the relationship between hospital volume of transcatheter transvenous mitral valve repairs using MitraClip® and patient outcomes may provide information for future policy decisions to improve patient management.

Methods and results We analysed patient characteristics and in-hospital outcomes for all TMVr procedures using MitraClip® performed in Germany from 2011 to 2017. Hospitals were stratified according to centre volumes and patients were compared for baseline characteristics and adverse in-hospital events. Overall, 24 709 inpatients were treated during the observational period. Patients treated in centres with a volume of ≤10 procedures annually developed more often pulmonary embolism (odds ratio 2.22, 95% confidence interval 1.19–4.13; $P = 0.012$) compared to those treated in centres with a volume of >10 procedures annually, whereas no association of centre volume (≤10 or >10) was found with in-hospital mortality ($P = 0.728$). Although patients treated in centres with an annual volume >25 TMVr procedures had higher numbers of comorbidities compared to those treated in centres with an annual volume of ≤25 TMVr procedures, in-hospital mortality did not differ (3.6% vs. 3.5%, $P = 0.485$). Similarly, when centre volumes were stratified for ≤50 vs. >50 procedural volumes, no association with in-hospital mortality was recorded ($P = 0.792$). A lower rate of mitral valve surgery after MitraClip® was observed over time, particularly in high-volume centres.

Conclusion Annual numbers of MitraClip® implantations increased from 2011 to 2017 in Germany, whereas in-hospital mortality remained stable. Although patients treated in high-volume centres had a more unfavourable risk profile, in-hospital mortality was comparable to that of low-volume centres.

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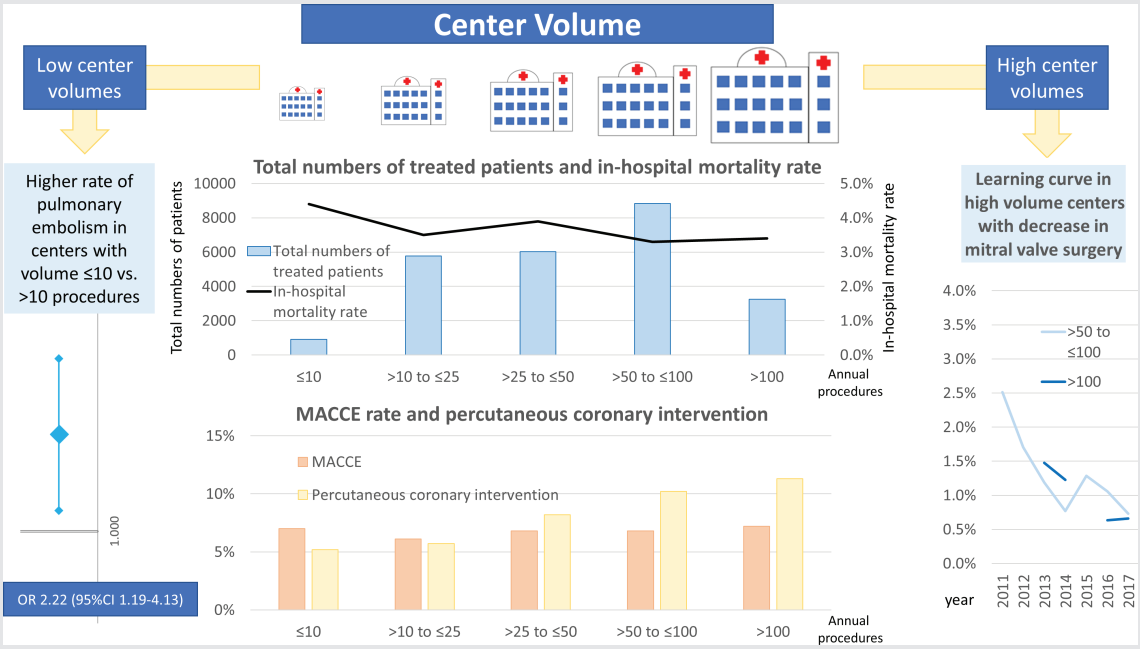
Graphical Abstract



Centre volumes, absolute numbers of treated patients, in-hospital mortality, major adverse cardiac and cerebrovascular event (MACCE) rate and percutaneous coronary intervention. Learning curve showing a lower number of mitral valve surgeries in high-volume centres over the observational period and higher risk of pulmonary embolism in low-volume centres. CI, confidence interval; OR, odds ratio.

Keywords Centre expertise • Procedural volume • Mitral regurgitation • Mitral valve repair • Death

Introduction

Mitral valve regurgitation (MR) is the most common heart valve disease in Europe as well as the United States (US)[1–3] and is accompanied by substantial morbidity and mortality.[3–7] Transcatheter mitral valve repair (TMVr) using the MitraClip® system is an established treatment for patients suffering from MR of both primary and secondary aetiology who are at high or prohibitive surgical risk following existing guidelines.[4,8–10] TMVr using MitraClip® diminishes clinical symptoms and results in improved survival among selected patients.[9] Interventional procedures are increasingly performed in Germany and worldwide.[11] Acute procedural success of TMVr with MitraClip® implantation was reported to be >90% with favourable safety profile.[9,11–15] Nevertheless, complications and adverse outcomes including death are not uncommon.[9,11,15] TMVr using MitraClip® is a complex procedure, therefore it is mandatory to establish a strong cooperation of a multidisciplinary team of specialists for appropriate patient selection as well as for technical performance.[9] Given that TMVr centres have to address multidisciplinary objectives by a heart team approach of interventionalists, surgeons, imaging and heart failure specialists, the centre procedural volumes and acquired experience seem to be of outstanding importance.[9,16,17] While an inverse volume–mortality association was observed for transcatheter aortic valve replacement,[18] data of the Transcatheter Valve Registry regarding TMVr from the Society of Thoracic Surgeons/American College of Cardiology of the US revealed no significant impact of centre volume on in-hospital mortality and other important outcomes. Given that these published data are from the US[9] and similar data for European centres are missing,[9,11] we aimed to fill this gap of knowledge and provide reliable data about the impact of centre volumes in Germany. Nevertheless, as a result of these considerations, the German Cardiac Society already requests from hospitals a minimum number of at least 25[19] or even 30 interventions per year to achieve an accreditation as a TMVr centre.[20] However, as mentioned above, data regarding the impact of institutional experience with TMVr using MitraClip® on patient outcomes are sparse and the burden of evidence for such recommendations is unsatisfactory.[9]

Thus, we aimed to investigate the impact of institutional TMVr numbers using the MitraClip® system on patient in-hospital outcomes in a large German implant cohort with complete in-hospital follow-up.

Methods

Study design

This is an observational retrospective study analysing data of the German nationwide in-patient sample including all treatment data (diagnoses, surgeries, diagnostic and interventional procedures) from hospitalized patients in Germany with 100% in-hospital mortality data.

For this analysis, we selected all hospitalized patients who were coded with a TMVr using the MitraClip® procedure between 2011 and 2017 in Germany.

Diagnoses are coded according to the International Classification of Diseases and Related Health Problems, 10th Revision with German Modification (ICD-10-GM) and surgical or interventional procedures according to the German Procedure Classification [surgery and procedure codes (Operationen-und Prozedurenschlüssel, OPS)].[11] We identified all hospitalized patients who underwent TMVr using MitraClip® by the OPS code 5-35a.41.

Since this study did not involve direct access to data of individual patients by the investigators, approval by an ethics committee and informed consent were not required, in accordance with the German law.

Population

Patients undergoing TMVr using MitraClip® during the observational period between 2011 and 2017 were stratified for centre volumes. Patients were divided based on the number of procedures performed in the centre where they were treated using different cut-off values: equal to/lower than or higher than an average of 10, 25, or 50 procedures per year.

Additionally, we included an analysis comparing the patient groups treated in centres with ≤10 procedures on average per year (corresponding to ≤70 procedures in 7 years), >10 and ≤25 procedures on average per year (between >70 and ≤175 procedures in 7 years), >25 and ≤50 procedures on average per year (between >175 and ≤350 procedures in 7 years), >50 and ≤100 procedures on average per year (between >350 and ≤700 procedures in 7 years), and >100 procedures on average per year (>700 procedures in 7 years).

Furthermore, we included an analysis comparing the highest and lowest 10% of the centres with each other in order to analyse differences between the highest-volume centres of the top 10% (absolute treatment number >450 procedures in 7 years) and the ultra-low-volume centres of the lowest 10% (absolute treatment numbers <16 procedures in 7 years).

Study safety outcomes

Safety outcomes of this study include death from any cause during the hospital stay (in-hospital death), major adverse cardiac and cerebrovascular events (MACCE, including in-hospital death, myocardial infarction and/or ischaemic stroke), pulmonary embolism (PE), deep venous thrombosis and/or thrombophlebitis of the leg veins, acute kidney injury, endocarditis, cardiopulmonary resuscitation, shock, myocardial infarction, stroke (ischaemic or haemorrhagic), pericardial effusion, mitral valve surgery and clinically relevant bleeding events such as haemopericardium, intracerebral bleeding and the need for transfusion of erythrocyte concentrates.[11] Outcome codes are reported in online supplementary *Table S1*.

Statistical methods

Descriptive statistics for relevant baseline comparisons are provided as median and interquartile range (IQR), or as absolute numbers and corresponding percentages. Continuous variables were tested using the Mann–Whitney U test and categorical variables with Fisher's exact or chi-square test, as appropriate.

We calculated the Charlson index score[21] and the revised cardiac risk index for preoperative risk[22] to compare the patient groups in terms of comorbidity risk and perioperative risk of in-hospital mortality.

Univariate and multivariate logistic regression models were performed to investigate the impact of centre volumes on safety outcomes/in-hospital events including in-hospital mortality. In addition, we calculated the prognostic impact of the Charlson index and the revised cardiac risk index for preoperative risk on in-hospital mortality and other outcomes. The results were presented as odds ratios (OR) and corresponding 95% confidence intervals (Cis). The multivariate logistic regression model, testing the independence of predictors for in-hospital mortality, was adjusted for age, sex, cancer, coronary artery disease, heart failure, chronic obstructive pulmonary disease, renal insufficiency (including diagnosis of chronic renal insufficiency stages 3 to 5 with glomerular filtration rate <60 mL/min/1.73 m^2), essential arterial hypertension and diabetes mellitus.

For analyses of the annual trends from 2011 to 2017, the absolute numbers of all TMVr using MitraClip® and the relative mortality rate were calculated annually. Linear regressions were used to test any increase/decrease in these parameters. The results were presented as β-coefficient and corresponding 95% CIs. The β-coefficient is the degree of change in the outcome variable for every one-unit change in the predictor variable.

The software SPSS® (version 20.0; SPSS Inc., Chicago, IL, USA) was used for computerized analysis. *P*-values of <0.05 (two-sided) were considered to be statistically significant.

Statistical analyses were performed on our behalf by the Research Data Center (RDC) of the Federal Statistical Office and the Statistical Offices of the federal states in Wiesbaden, Germany (source: RDC of the Federal Statistical Office and the Statistical Offices of the federal states, DRG Statistics 2005–2017, own calculations). The RDC provides the aggregated statistical results based on SPSS codes (SPSS® software, version 20.0, SPSS Inc.), which we sent to the RDC.

Results

Baseline characteristics

The nationwide sample included 24 709 inpatients undergoing TMVr using MitraClip® system in Germany between 2011 and 2017. The calculated annual prevalence for the performance of MitraClip® implantations was 4.33 per 100 000 citizens per year in the overall cohort (over this 7-year timeframe) increasing from 1.67 annually in the years 2011/2012 to 6.75 per 100 000 citizens annually in 2016/2017. The majority of patients were male (59.0%) and mean age was 78 years.

The total numbers of MitraClip® implantations increased significantly from 2011 to 2017 (β = 845, 95% CI 772–919, $P < 0.001$), whereas the in-hospital mortality rate remained constant over time from 3.1% in 2011 to 3.5% in 2017 (β = 0.08, 95% CI −0.05 to 0.21), $P = 0.180$) (*Figure 1*).

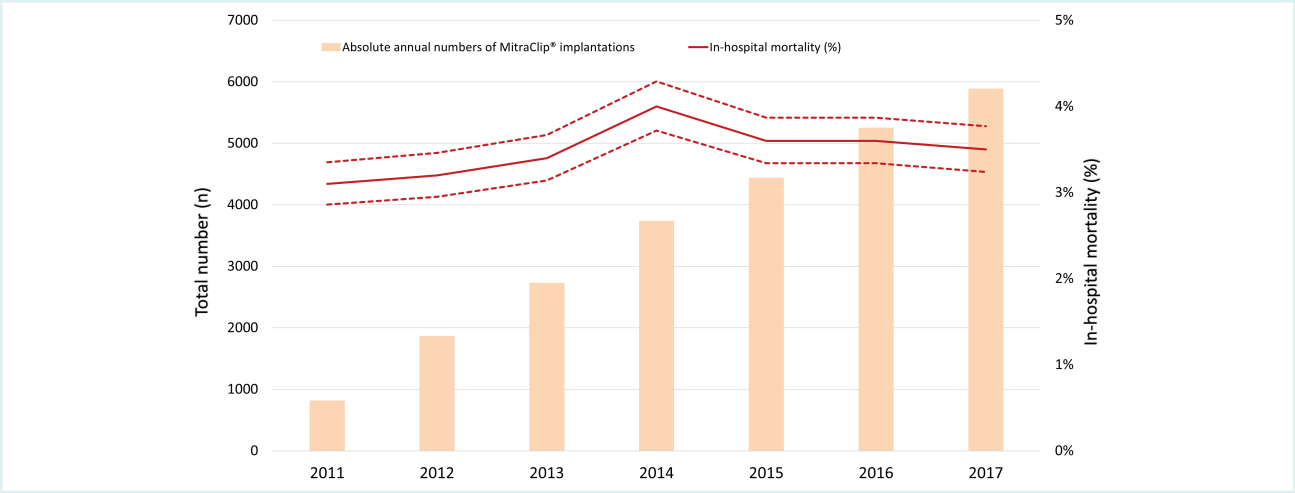


Figure 1 Absolute annual numbers of transcatheter mitral valve repair (TMVr) using MitraClip® and in-hospital mortality (with 95% confidence intervals as dashed red lines) from 2011–2017.

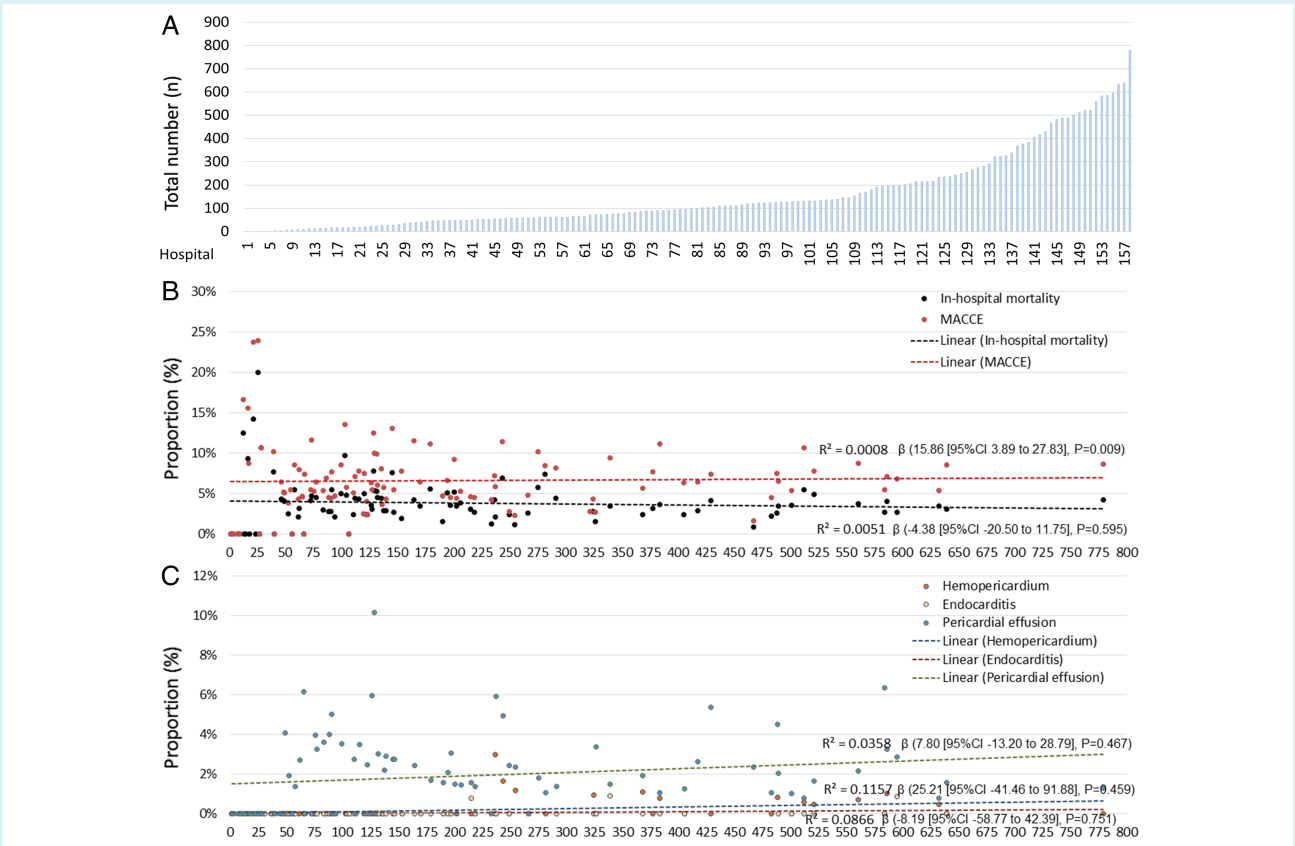


Figure 2 (*A*) Absolute numbers of patients undergoing transcatheter mitral valve repair using MitraClip® in the 158 German hospitals from 2011–2017, (*B*) trends of in-hospital mortality and major adverse cardiac and cerebrovascular events (MACCE), (*C*) haemopericardium, endocarditis and pericardial effusion according to increasing volume of TMVr procedures using MitraClip® in the German hospitals. Linear regression results for the increase of centre volume numbers regarding the increase of one case of each outcome. CI, confidence interval.

Procedural volume and patient characteristics

Patients who have undergone with MitraClip® implantations were treated in 158 different hospital sites between 2011 and 2017 in Germany. The numbers of treated patients vary strongly from only one implantation during the 7-year timeframe to 779 procedures in the largest centre (*Figure 2A*). Most of the patients were treated in centres with centre volumes between 25 and 100 MitraClip® procedures on average per year (online supplementary *Figure S1*).

Overall, 2132 patients (8.6%) were treated in hospitals with a volume of ≤10 procedures on average annually (≤70 procedures in 7 years), while 22 577 patients (91.2%) were treated in centres with a volume of >10 procedures on average per year. If stratified for 25 implantations annually on average, 17 042 patients (69.0%) were treated in centres with >25 procedures and 7667 (31.0%) in those with ≤25 procedures annually on average. Consecutively, while when stratifying for 50 implantations on average [>50 procedures annually on average 10 736 (43.4%) vs. ≤50 procedures per year 13 973 (56.6%)], the distribution was widely balanced, only 779 patients (3.2%) were treated in the largest centre with a volume of >100 procedures on average per year during the observational period, while 23 930 (96.8%) were treated in centres with a volume of ≤100 procedures annually on average.

Patients in the different centre volume groups were of similar age at the time of the procedure (online supplementary *Table S2*). While patients treated in high and low-volume centres did not differ in most comorbidities, coronary artery disease was more common in patients treated in high-volume centres (online supplementary *Figures S2–S4*). Consecutively, patients in high-volume centres were treated more often with percutaneous coronary intervention (online supplementary *Figure S5*). An increase of the total procedure number of five was independently associated with a higher number of percutaneous coronary interventions (univariate: OR 1.060, 95% CI 1.033–1.088, $P < 0.001$; multivariate: OR 1.057, 95% CI 1.030–1.085, $P < 0.001$). These findings were also observed when comparing patients treated in centres with a volume of ≤25 or >25 procedures (*Table 1*).

Although the Charlson index as well as the revised cardiac risk index for preoperative risk were comparable between centres with a TVMr volume of ≤25 or >25 procedures annually on average (*Table 1*), centres with a TVMr volume of ≤100 procedures had treated a higher number of patients with Charlson index >6 points (43.8% vs. 41.5%, $P < 0.001$) as well as patients with a revised cardiac risk index for preoperative risk score of ≥1 (90.9% vs. 90.8%, $P < 0.001$). An increase in the Charlson index (univariate: OR 1.47, 95% CI 1.44–1.51, $P < 0.001$) and the revised cardiac risk index for preoperative risk (OR 1.80, 95% CI 1.70–1.90, $P < 0.001$) score of one point was associated with a higher MACCE rate. In addition, a one point higher score of the Charlson index (univariate: OR 1.43, 95% CI 1.38–1.47, $P < 0.001$) and the revised cardiac risk index for preoperative risk (OR 1.82, 95% CI 1.68–1.96, $P < 0.001$) was associated with increased in-hospital mortality. The prognostic impact of the Charlson index and the revised cardiac risk index for preoperative risk on MACCE rate and in-hospital mortality increased with centre volume (online supplementary *Figure S6*). Nevertheless, similar mean values of the Charlson index and the revised cardiac risk index for preoperative risk were recorded in the different groups (online supplementary *Table S2*). A significant rise in the Charlson index was observed in the different centre volume groups (online supplementary *Table S3*). In contrast, the revised cardiac risk index for preoperative risk increased especially in centres with a volume of ≤50 procedures in average per year (online supplementary *Table S3*).

Female patients and patients aged ≥70 years were treated in high-volume centres nearly on the same level during the observational period, whereas low-volume centres treated less often female patients and older patients especially in the years 2011–2013 (online supplementary *Figure S2*).

Procedural volume and in-hospital events, mortality and complications

In-hospital mortality showed a slight downward trend with increasing volume of TMVr using MitraClip® in German hospitals (increasing volume number by five implantations overall: univariate: OR 0.98, 95% CI 0.95–1.01, $P = 0.114$; multivariate: OR 0.98, 95% CI 0.95–1.01, $P = 0.111$) (*Figure 2B* and online supplementary *Figure S9A*), whereas the MACCE rate was not influenced by centre volumes of TMVr (increasing volume number by five implantations overall: univariate: OR 0.99, 95% CI 0.97–1.01, $P = 0.434$; multivariate: OR 0.99, 95% CI 0.97–1.01, $P = 0.293$) (*Figure 2B*). However, in centres that performed <300 TMVr procedures using MitraClip® during the 7-year observational period (≤42 procedures per year on average), in-hospital mortality ranged between 0–20%. In contrast, high-volume centres with >300 TMVr (>42 procedures per year on average) had only a maximum in-hospital mortality variability of 0.9–5.5% (*Figure 2B*). In-hospital mortality and MACCE rate remained stable in all investigated centre volume study groups over the observational period 2011–2017 (online supplementary *Figure S9A* and *Table S4*).

Haemopericardium showed a slight uptrend with increasing centre volumes (*Figure 2C*).

The impact of procedural volume on the length of in-hospital stay was small. Patients treated in centres with ≤10 vs. >10, ≤25 vs. >25 and ≤50 vs. >50 procedures on average annually had a median hospital stay of 10 days (mean 14–15 days) (online supplementary *Table S2*). While in-hospital length of stay increased in low-volume centres with ≤10 procedures in average per year from 2011–2017, in-hospital length of stay decreased significantly in centres with >10 up to ≤100 procedures (online supplementary *Table S3*).

Comparison of centres with a volume of ≤10 vs. >10 procedures on average per year

Patients treated in centres with a volume of ≤10 vs. >10 procedures annually on average had comparable in-hospital mortality (3.7% vs. 3.5%, $P = 0.710$; multivariate regression: OR 0.96, 95% CI 0.76–1.22, $P = 0.728$), MACCE (6.1% vs. 6.7%, $P = 0.362$; OR 1.07, 95% CI 0.89–1.29, $P = 0.487$) and most other adverse

Table 1 Characteristics, medical history, presentation, treatments and outcomes of the 24 709 patients undergoing transcatheter mitral valve repair using MitraClip® stratified for centre volume of 25 procedures per year on average during the observational period 2011–2017

Parameters	Patients treated in hospitals with ≤25 procedures on average per year (*n* = 7667; 31.0%)	Patients treated in hospitals with >25 procedures on average per year (*n* = 17 042; 69.0%)	*P*-value
Age (years)	76.43 ± 8.63	76.21 ± 8.79	**0.047**
Age ≥70 years	6160 (80.3%)	13 607 (79.8%)	0.363
Female sex	3133 (40.9%)	7010 (41.1%)	0.690
In-hospital stay (days)	10 (7–18)	10 (7–17)	0.727
Obesity	553 (7.2%)	1372 (8.1%)	0.126
Risk scores			
Charlson index	6.0 (5.0–8.0)	6.0 (5.0–8.0)	0.588
Revised cardiac risk index for preoperative risk	2.0 (1.0–2.0)	2.0 (1.0–2.0)	0.435
Comorbidities			
Cancer	179 (2.3%)	352 (2.1%)	0.177
Coronary artery disease	5120 (66.8%)	11 674 (68.5%)	**0.007**
Heart failure	6110 (79.7%)	14 010 (82.2%)	**<0.001**
Atrial fibrillation/flutter	4977 (64.9%)	11 423 (67.0%)	**0.001**
Chronic obstructive pulmonary disease	1165 (15.2%)	2543 (14.9%)	0.578
Essential arterial hypertension	4343 (56.6%)	9991 (58.6%)	**0.004**
Hyperlipidaemia	2825 (36.8%)	7500 (44.0%)	**<0.001**
Renal insufficiency (stages III–V with GFR <60 mL/min/1.73 m^2)	3527 (46.0%)	7796 (45.7%)	0.708
Diabetes mellitus	2458 (32.1%)	5008 (29.4%)	**<0.001**
Peripheral arterial disease	585 (7.6%)	1259 (7.4%)	0.502
Treatment			
Coronary angiography	2070 (27.0%)	5505 (32.3%)	**<0.001**
Percutaneous coronary intervention	424 (5.5%)	1688 (9.9%)	**<0.001**
Bleeding complications			
Intracerebral bleeding	14 (0.2%)	31 (0.2%)	0.991
Gastro-intestinal bleeding	112 (1.5%)	217 (1.3%)	0.234
Haemopericardium	21 (0.3%)	65 (0.4%)	0.184
Transfusion of erythrocyte concentrates	1182 (15.4%)	2867 (16.8%)	**0.006**
Safety outcomes			
All-cause death	279 (3.6%)	590 (3.5%)	0.485
Mitral valve surgery	42 (0.5%)	195 (1.1%)	**<0.001**
Cardiopulmonary resuscitation	171 (2.2%)	436 (2.6%)	0.123
Shock	380 (5.0%)	764 (4.5%)	0.101
MACCE	489 (6.4%)	1145 (6.7%)	0.319
Myocardial infarction	196 (2.6%)	504 (3.0%)	0.079
Stroke	70 (0.9%)	187 (1.1%)	0.187
Acute kidney injury	722 (10.8%)	1922 (10.6%)	0.673
Endocarditis	12 (0.2%)	37 (0.2%)	0.322
Pulmonary embolism	25 (0.3%)	49 (0.3%)	0.608
Deep vein thrombosis and/or thrombophlebitis	65 (0.8%)	154 (0.9%)	0.665
Pericardial effusion	166 (2.2%)	344 (2.0%)	0.453

GFR, glomerular filtration rate; MACCE, major adverse cardiac and cerebrovascular event.

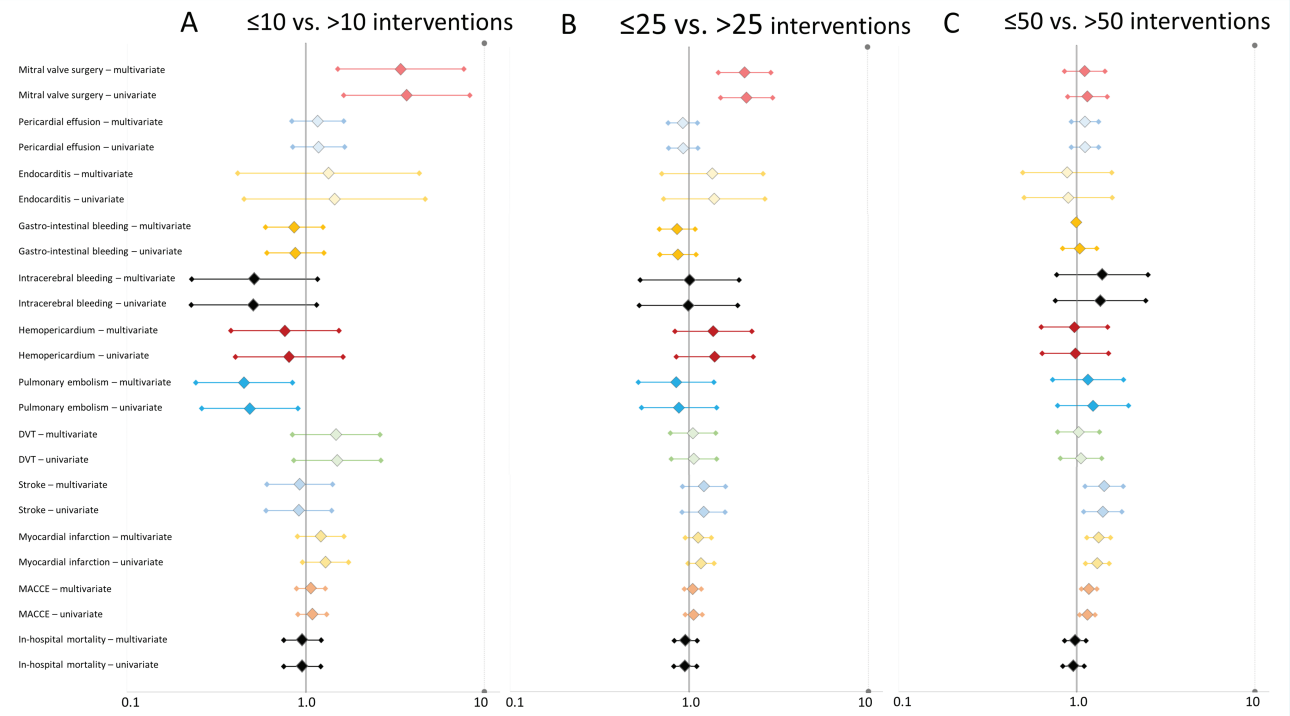


Figure 3 Forest plot for different outcomes, complications and in-hospital adverse events stratified for centre volumes of transcatheter mitral valve repair (TMVr) procedures using MitraClip® (*A*: ≤10 vs. >10 procedures; *B*: ≤25 vs. >25 procedures; *C*: ≤50 vs. >50 procedures). MACCE, major adverse cardiac and cerebrovascular event; DVT, deep vein thrombosis.

in-hospital events, but patients treated in centres with a volume of ≤10 procedures developed more often PE [12 (0.6%) vs. 62 (0.3%), $P = 0.020$] confirmed in the multivariate regression model (OR 2.22, 95% CI 1.19–4.13, $P = 0.012$). Mitral valve surgeries after TMVr using MitraClip® were more often performed in centres with a volume of >10 procedures per year (OR 3.39, 95% CI 1.51–7.65, $P = 0.003$), independently of age, sex and comorbidities (*Figure 3A*), likely because of higher availability of in-hospital cardiac surgery departments.

Comparison of centres with a volume of ≤25 vs. >25 procedures on average per year

Patients treated in centres with a volume of ≤25 procedures annually on average did not differ from patients treated in high-volume centres with >25 procedures in terms of in-hospital mortality (3.6% vs. 3.5%, $P = 0.485$), MACCE, and most adverse in-hospital outcomes (*Table 1*). In contrast, patients treated in high-volume centres with >25 procedures per year on average had a 1.4% higher transfusion rate of erythrocyte concentrates and were 0.6% more likely operated for mitral valve surgery (*Table 1*). Centre volume, stratified for ≤25 vs. >25 procedures on average per year, was not associated with PE (OR 0.85, 95% CI 0.53–1.38, $P = 0.515$), MACCE (OR 1.04, 95% CI 0.94–1.17, $P = 0.429$) and in-hospital mortality (OR 0.95, 95% CI 0.83–1.10, $P = 0.526$). Again, mitral valve surgery after TMVr was performed more commonly in high-volume centres with >25 procedures (OR 2.05, 95% CI 1.47–2.87, $P < 0.001$) (*Figure 3B*).

Comparison of centres with a volume of ≤50 vs. >50 procedures on average per year

In line with the aforementioned findings, most main outcomes, complications and in-hospital adverse events, including in-hospital mortality (3.6% vs. 3.4%, $P = 0.550$), did not differ when comparing centre volumes of ≤50 vs. >50 procedures on average per year (online supplementary *Figure S7*). A centre volume of >50 procedures on average per year was independently associated with higher MACCE rate (OR 1.17, 95% CI 1.06–1.30, $P = 0.003$), stroke (OR 1.43, 95% CI 1.11–1.83, $P = 0.005$) and myocardial infarction (OR 1.33, 95% CI 1.14–1.55, $P = 0.001$), but not with in-hospital mortality (OR 0.98, 95% CI 0.86–1.13, $P = 0.792$), mitral valve surgery (OR 1.11, 95% CI 0.86–1.44, $P = 0.430$) and PE (OR 1.16, 95% CI 0.73–1.83, $P = 0.537$) (*Figure 3C*).

Comparison of centres with a volume of ≤25 vs. >50 procedures on average per year

Additionally, when analysing in-hospital mortality of centres with a volume of ≤25 vs. >50 procedures annually on average, no

substantial differences were observed (3.6% vs. 3.4%, $P = 0.464$); this was also seen in the multivariate regression model (OR 0.96, 95% CI 0.82–1.13, $P = 0.626$).

Learning curve in low and high-volume centres

The number of mitral valve surgeries during in-hospital stay in patients who underwent MitraClip® implantation decreased in high-volume centres with >50 procedures on average per year as well as in centres with a volume of ≤10 implantations annually, demonstrating a learning curve of this important complication after MitraClip® implantation (online supplementary *Figure S9B* and *Table S4*).

In addition, also the number of transfusions of erythrocyte concentrates decreased, particularly in larger implant valve centres (online supplementary *Figure S9C* and *Table S4*), supporting a learning curve on complications.

Comparison of the upper and lower 10% of the centres

A comparison of the highest and lowest 10% of the centres was also performed to analyse differences between high-volume centres of the top 10% (absolute treatment number >450 procedures over the 7-year timeframe) and low-volume centres of the lowest 10% (absolute treatment numbers <16 procedures over the 7-year timeframe).

Although patients treated in ultra-low-volume centres were in median 2 years older, the revised cardiac risk index for preoperative risk was higher in patients treated in the highest national volume centres [2.0 (1.0–2.0) vs. 1.0 (0.0–2.0), $P = 0.002$). In-hospital mortality was similar between groups, but 1.4% lower in high-volume centres ($P = 0.477$) (online supplementary *Table S5*). High-volume centres of the highest 10% were not independently associated with lower in-hospital death rate (OR 0.62, 95% CI 0.20–2.00, $P = 0.420$), MACCE (OR 0.65, 95% CI 0.28–1.53, $P = 0.326$) and mitral valve surgery (OR 0.50, 95% CI 0.07–3.68, $P = 0.496$).

Temporal trends in outcomes

The number of patients aged ≥70 years treated with MitraClip® increased in all centre volume groups (online supplementary *Figure S2B*), as confirmed by a significantly increasing age at procedure in each centre volume study group from 2011 to 2017 (online supplementary *Table S3*). The Charlson index score ($\beta = 0.07$, 95% CI 0.06–0.08, $P < 0.001$) as well as that of the revised cardiac risk index for preoperative risk ($\beta = 0.07$, 95% CI 0.05–0.09, $P < 0.001$) increased over the timeframe 2011–2017.

There were only marginally trends over the observational period (online supplementary *Figures S8* and *S9*). Temporal trends of total numbers of patients treated in the centres with a volume of ≤10 vs. >10, ≤25 vs. >25 and ≤50 vs. >50 procedures (annually on average) in terms of in-hospital mortality, MACCE, haemopericardium and mitral valve surgery revealed no substantial changes during the observational period from 2011–2017 in Germany (online supplementary *Figure S9*).

Discussion

The analysis of this large German nationwide inpatient sample of more than 24 700 TMVr using MitraClip® during the 7-year observational period provides several important information.

While the annual total numbers of TMVr procedures using MitraClip® increased substantially from 2011 to 2017 in Germany, in-hospital mortality remained stable over time. Patients treated in high-volume centres were sicker, suffering more often from cardiovascular diseases such as coronary artery disease, heart failure, atrial fibrillation/flutter, as well as arterial hypertension and correspondingly, pre-procedural revascularization was significantly higher. Despite these differences regarding more unfavourable patient characteristics, higher annualized hospital procedural volumes were not associated with poor outcomes. Beyond that, small TMVr centre volumes of ≤10 procedures on average per year are associated with an increased risk of PE during in-hospital stay. We detected a learning curve particularly in high-volume centres regarding decreasing numbers of mitral valve surgeries in patients treated with MitraClip®. In particular, the comparison of highest vs. ultra-low valve centres showed a comparable outcome of MitraClip® procedures despite higher pre-interventional risk score (*Graphical Abstract*).

Mitral regurgitation is the most prevalent form of valve disease in developed countries[1–3,23] increasing significantly with age.[7,11,15] MR is a frequent valve disorder referred for surgical or interventional correction,[2,6,8,11] since significant MR is accompanied by substantial morbidity and mortality.[3–7,11] Surgical mitral valve repair still is the gold-standard approach recommended by the guidelines in patients with severe chronic primary MR, who are at low surgical risk and younger age. Percutaneous mitral valve repair has become the therapy of choice in high-risk patients with primary MR and in COAPT-like patients with secondary MR, as defined in the latest 2020 valvular heart disease guidelines of the American College of Cardiology/American Heart Association (ACC/AHA).[4,8,10,11,23,24] Thus, approximately half of the patients with severe MR are not referred for surgery.[25] The management of MR is dependent on the cause, pathophysiology, natural history, and expected efficacy of treatment.[23,26]

In line with these recommendations, our results from current practice in Germany show the increasing usage of TMVr with MitraClip® as an important treatment option for MR. The total numbers of TMVr with MitraClip® implantation in Germany increased substantially (7.2-fold) from 815 in 2011 to 5885 in 2017.[11] Despite the increasing number of treated patients with an unfavourable comorbid profile, in-hospital mortality did not change over time.

Germany is one of the leading countries in TMVr implantations worldwide.[11] Over the last years, experience with TMVr increased markedly in both younger and more critically ill patients with severe MR, resulting in increased implantation numbers.[11]

Recent literature demonstrated an impact of procedural experience and centre volume on the outcomes after transcatheter aortic valve replacement,[18] therefore it was suggested that, in addition to the experience with TMVr using MitraClip® in the country (testified by the increasing overall number of TMVr

procedures in Germany), the centre volume of TMVr procedures with MitraClip® might have a critical impact on the outcomes after TMVr.[9] However, data regarding the impact of institutional experience on patient outcomes are sparse and available evidence for such recommendations is unsatisfactory.[9]

Our study revealed that patients undergoing TMVr with MitraClip® in larger volume centres had more unfavourable comorbidity profiles likely due to a referral selection bias. They had an almost twofold higher need for revascularization before the valve procedure than patients in low-volume centres. As expected, these patients with an unfavourable cardiovascular profile showed more often atherosclerotic events such as myocardial infarction and stroke during in-hospital stay. Since these atherosclerotic events are not common complications of TMVr procedures,[13–15] the higher rate of MACCE, and in particular of myocardial infarction and stroke, are likely due to differences in patient characteristics.

Despite the unfavourable clinical profile of these patients treated in higher volume centres (>25 procedures annually on average), in-hospital mortality and most of the other investigated adverse events were comparable between higher (>25 procedures) and lower (≤25 procedures) volume centres. Remarkably, in-hospital mortality was not affected by centre volumes of TMVr using MitraClip®. In addition, no substantial trend regarding outcomes and in-hospital adverse events in low and high-volume centres could be detected in Germany from 2011 to 2017. However, the comparison of the highest vs. ultra-low volume centres showed a comparable outcome of MitraClip® procedures despite higher pre-interventional risk score.

Low-volume centres performing ≤10 procedures per year on average reported more often potentially life-threatening complications of PE (0.6% vs. 0.3%). In one previous study, PE was identified as a strong predictor of in-hospital death.[11] Periprocedural PE occurs as an interventional complication[27] or as a consequence of physical inactivity after MitraClip® implantation.[28,29] In addition, particularly in high-volume centres, a learning curve describing a decrease in the need for mitral valve surgery in patients treated with MitraClip® could be observed.

Therefore, it seems important that the volume of the centre performing TMVr using MitraClip® exceeds a critical number of annual implantations. In accordance with previous reports, our results emphasize that acquired experience, which finds expression in centre volume numbers of TMVr procedures, is of outstanding importance for patient outcome.[9] Our study supports the recommendation and regulation of the German Cardiac Society, which requires hospitals to perform a minimum of at least 30 interventions per year to get accredited as a TMVr centre.[20]

The results obtained in Germany are consistent with the recent data from the Society of Thoracic Surgeons (STS)/ACC TVT (Transcatheter Valve Therapy) MitraClip® registry on 12 334 patients in the US, demonstrating that increasing institutional TMVr procedure experience was associated with improvements in procedural success, procedural time, and procedural complications, but had no impact on mortality, myocardial infarction and stroke rate.[9]

Limitations

There are several limitations of our study that require consideration. The analysis is based on ICD discharge codes, which might lead to incomplete data due to underreporting/undercoding. Therefore, the focus of our study was on clear endpoints such as in-hospital death and complications (among others MACCE), which are very unlikely to be miscoded or not coded. In addition, we could not distinguish between functional MR and chronic primary MR aetiology. Due to coding reasons, we used the calculable Charlson index and revised cardiac risk index for preoperative risk instead of the EuroSCORE and STS score. Detailed information about left ventricular systolic ejection fraction, pulmonary hypertension and periprocedural medication were not accessible in this high-volume federal national data set. The same applies to MR reduction, benefits of heart failure symptoms, hospitalizations or improvements in quality of life nor later follow-up after hospitalization due to German legal restrictions for data privacy rules. Thus, data regarding procedural results with MR reduction/improvement and post-discharge hospitalizations are not available in the German nationwide inpatient sample, which has to be mentioned as a major limitation of the present study.

The nature of the data provides complete in-hospital follow-up but misses data on the quality of valve repair that has an impact on long-term mortality of the patients treated. Due to data collection and cleaning of the data set by the RDC of the Federal Statistical Office and the Statistical Offices of the federal states in Wiesbaden, the data are only available with about 2-year delay.

Conclusion

In a large German nationwide population with mitral regurgitation undergoing TMVr with MitraClip® implantation, the number of procedures increased 7.2-fold from 815 in 2011 to 5885 in 2017, whereas in-hospital mortality remained stable. Although patients treated in high-volume centres had a higher comorbidity burden compared to those treated in low-volume centres, they had a similar in-hospital mortality and complication rate.

Centre volume of the hospital sites performing TMVr with MitraClip® should exceed a critical number of implantations to guarantee procedural safety and low rates of adverse in-hospital outcomes.

Supplementary Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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from Abbott Cardiovascular and Edwards Lifesciences R.S.v.B. reports having received advisory board and speakers honoraria from Abbott Cardiovascular and Edwards Lifesciences. All other authors have nothing to disclose.

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