Impact of the learning curve on outcomes after percutaneous mitral valve repair with MitraClip® and lessons learned after the first 75 consecutive patients

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Aims
Mitral valve regurgitation plays a significant role in the aetiology and course of heart failure. We investigated the impact of the learning curve on outcomes after percutaneous mitral valve repair with MitraClip.

Methods and results
Outcomes of the first 75 consecutive patients treated with MitraClip at our centre were stratified by subsequent treatment periods (25 patients each). Median total procedure time and device time decreased from 180 and 105 min in period 1 to 95 and 55 min in period 3 ($P < 0.005$ each). There was an excess of total safety events in period 1 ($n = 16$) that decreased in periods 2 and 3 ($n = 6$ and 3, $P = 0.0003$). Acute procedural success [APS; clip successfully placed and mitral regurgitation (MR) grade $\leq 2+$ at discharge] was 80% in periods 1 and 2, but 92% in period 3 ($P = 0.46$). At 6 months, improvement in durability and completeness of mitral valve repair was evident: 89.4% of patients in period 3 and 65.0% in period 1 had MR $\leq 2+$ at 6 months ($P = 0.03$). Within 30 days, no patient sustained myocardial infarction or stroke, and mortality was 2.7% for all patients without significant differences regarding periods. Furthermore, while treatment period did not affect mid-term survival and hospitalization for heart failure, failure of APS, STS (Society of Thoracic Surgeons) score $\geq 15%$, and overt right heart failure at baseline predicted increased mortality.

Conclusion
MitraClip showed a learning curve regarding mid-term durability and completeness of mitral valve repair, and APS predicted mortality. Recently published studies should be interpreted in consideration of these findings.

Keywords
MitraClip • Percutaneous mitral valve repair • Mitral valve regurgitation • Heart failure • Learning curve

Introduction
Recent publications have reported on the MitraClip technology (Abbott Vascular, Structural Heart, Menlo Park, CA, USA), a novel percutaneous method for mitral valve (MV) repair in severe mitral regurgitation (MR)7–8 that is modelled on the surgical Alfieri technique.9 MitraClip is effective in both organic and functional MR.7–9 It has proven safety in patients with moderate6 to high surgical risk.2–5,7,8 The presence of MR in heart failure is associated with a particularly adverse outcome.10–12 Recently, a beneficial role for MitraClip has also been shown in patients with severely depressed left ventricular (LV) function9 and in non-responders to cardiac resynchronization therapy.8 However, the procedure is technically complex and all currently published studies are likely to contain part of the learning curve. Several authors reported on a decrease in procedural times as a function
of the learning curve. However, no data dealing with the impact of the learning curve on efficacy and safety are currently available. Accordingly, we have analysed outcomes at 30 days and at 6 months of the first 75 patients at our centre stratified by treatment period. In addition, survival and medium-term outcomes as well as durability of MV repair at 12 months were analysed.

**Methods**

**Study design and patients**

The trial was a prospective observational study of the first 75 patients with severe MR treated with MitraClip at the University Medical Centre of Göttingen. Sixty-six patients (88%) showed severe heart failure symptoms according to New York Heart Association (NYHA) functional classes III and IV (Table 1). Patients were assigned to MitraClip therapy following the decision of the Heart Team consisting of an experienced interventional cardiologist, a heart failure physician, and a cardiac surgeon in consideration of current guidelines, surgical risk, anatomical aspects, and eligibility for percutaneous treatment. Enrolment and treatments were performed from April 2009 until January 2011. The learning curve was analysed after creating three subgroups of 25 patients each according to treatment time (period 1, patients 1–25; period 2, patients 26–50; period 3, patients 51–75). The study was reviewed and approved by the ethics committee of the University Medical Centre of Göttingen, and each participant gave written informed consent.

**Procedure**

MitraClip and the procedure have been described in detail previously. All procedures were performed by the same interventional cardiologist (W.S.) and a team of two experienced echocardiographers (T.A. and R.W.).

| Table 1 Baseline characteristics for the total cohort and stratified by treatment period |
|---------------------------------|----------------|----------------|----------------|----------------|----------------|----------------|
|                                | Total cohort | Period 1 | Period 2 | Period 3 | P-value |
| Mean ± 95% CI                  |               |          |          |          |         |
| Age, years                     | 73 ± 2        | 74 ± 4   | 69 ± 4   | 77 ± 3*  | 0.004   |
| Calculated surgical risk       |               |          |          |          |         |
| Logistic EuroScore, %          | 29 ± 4        | 32 ± 6   | 24 ± 8   | 30 ± 7   | 0.27    |
| STS score, %                   | 11 ± 2        | 13 ± 5   | 8 ± 4    | 12 ± 4   | 0.15    |
| LVF, %                         | 37 ± 4        | 39 ± 6   | 30 ± 6   | 43 ± 7*  | 0.02    |
| 6 min walk distance, m         | 239 ± 38      | 205 ± 70 | 271 ± 65 | 227 ± 66 | 0.37    |
| *n (%)                         |               |          |          |          |         |
| Female sex                     | 23 (31)       | 7 (28)   | 8 (32)   | 8 (32)   | 1.00    |
| NYHA functional class III/IV   | 66 (88)       | 24 (96)  | 21 (84)  | 21 (84)  | 0.37    |
| Severity of MR                 |               |          |          |          |         |
| Grade 2 +                       | 1 (1)         | 0 (0)    | 1 (4)    | 0 (0)    | 1.00    |
| Grade 3 +                       | 25 (33)       | 9 (36)   | 7 (28)   | 9 (36)   | 0.38    |
| Grade 4 +                       | 49 (65)       | 16 (64)  | 17 (68)  | 16 (64)  | 0.58    |
| Aetiology of MR                |               |          |          |          |         |
| Organic                         | 26 (35)       | 9 (36)   | 7 (28)   | 10 (40)  | 0.75    |
| Functional                      | 49 (65)       | 16 (64)  | 18 (72)  | 15 (60)  | 0.75    |
| LVF ≤ 30%                       | 36 (48)       | 10 (40)  | 17 (68)  | 9 (36)   | 0.68    |
| Coronary artery disease         | 44 (59)       | 13 (52)  | 12 (48)  | 19 (76)  | 0.11    |
| Previous cardiac surgery        | 28 (37)       | 12 (48)  | 5 (20)   | 11 (44)  | 0.11    |
| Pulmonary hypertension          | 49 (65)       | 16 (64)  | 18 (72)  | 15 (60)  | 0.32    |
| Atrial fibrillation             | 51 (68)       | 13 (52)  | 19 (76)  | 19 (76)  | 0.15    |
| Peripheral artery disease       | 17 (23)       | 7 (28)   | 4 (16)   | 4 (16)   | 0.62    |
| Cerebrovascular disease         | 3 (4)         | 0 (0)    | 0 (0)    | 3 (12)   | 0.10    |
| Previous stroke                 | 4 (5)         | 1 (4)    | 0 (0)    | 3 (12)   | 0.32    |
| Chronic renal failure           |               |          |          |          |         |
| GFR < 30 mL/min/1.73 m²         | 13 (17)       | 9 (36)*  | 1 (4)    | 3 (12)   | 0.015   |
| GFR 30–59 mL/min/1.73 m²        | 37 (49)       | 12 (48)  | 14 (56)  | 11 (44)  | 0.77    |
| COPD                            | 16 (21)       | 6 (24)   | 6 (24)   | 4 (16)   | 0.83    |
| Diabetes mellitus               | 22 (29)       | 6 (24)   | 10 (40)  | 6 (24)   | 0.39    |
| Inotropic support               | 11 (15)       | 1 (4)    | 5 (20)   | 5 (20)   | 0.21    |
| Eligibility for EVEREST II      | 20 (27)       | 4 (16)   | 8 (32)   | 8 (32)   | 0.37    |

COPD, chronic obstructive pulmonary disease; GFR, glomerular filtration rate; LVF, left ventricular ejection fraction; MR, mitral regurgitation; NYHA, New York Heart Association; STS, Society of Thoracic Surgeons.

*Significant differences vs. period 2.
Follow-up
Thorough clinical and echocardiographic examinations were performed at baseline, at discharge, and after 6 and 12 months, including a 6 min walk test and Minnesota Living With Heart Failure (MLWHF) quality of life (QoL) score. The following major adverse events were documented: death, hospitalization due to congestive heart failure, severe bleeding according to GUSTO (intracranial bleeding or bleeding that causes substantial haemodynamic compromise requiring treatment), myocardial infarction, cerebral ischaemia, cardiovascular surgery, mechanical support, prolonged ventilation (>24 h), thrombosis, acute renal failure, and partial or complete clip detachment. Qualitative and quantitative echocardiography was performed according to current recommendations. In addition, before the manuscript was submitted, each patient (or representative) was questioned about mortality and previous hospitalization by telephone call. Median follow-up duration was 11 [interquartile range (IQR) 7–17] months.

Statistical analyses
Statistical analyses were performed with the statistics software R V2.13.0 or with Statistics V9.1. Data are expressed as medians ± IQR or means ± 95% confidence intervals (CIs) as indicated. Differences in repeated measures were tested by one-way repeated measures analysis of variance (ANOVA) followed by paired t-test with Bonferroni adjustment. Differences in treatment periods were tested by one-way ANOVA followed by unpaired t-test with Bonferroni adjustment or by Kruskall–Wallis ANOVA followed by Dunn’s test. Differences in the percentage or frequency of events, classes, or grades were tested by Fisher’s exact test or χ² test where appropriate. A P-value <0.05 was accepted as statistically significant.

Results
Baseline characteristics
Total cohort
Baseline characteristics are given in Table 1. All patients suffered from significant MR (median grade 4, IQR 2–4). The aetiology was functional in 65% and organic in 35% of patients. Mean age was 73 ± 2 years. Most patients presented with relevant co-morbidities, which is reflected by a high mean logistic Euro-Score of 29 ± 4% and a high mean Society of Thoracic Surgeons (STS) score of 11 ± 2%. Only 27% of patients would have met the eligibility criteria for enrolment in the randomized controlled trial EVEREST II comparing MitraClip with conventional surgery.

Patients stratified by treatment period
No significant differences existed between period 1 and 3. Patients of period 2 were slightly younger as compared with patients of periods 1 and 3 and showed a significantly lower LVEF (LVEF). The number of patients presenting with severe chronic renal failure was higher in period 1. No other significant differences existed between periods (Table 1).

Procedural data
Total cohort
Median total procedure time (complete time from puncture to closure of the femoral vein) was 125 (IQR 96–173) min. Median device time (complete time from insertion of the steerable MitraClip-guiding catheter until removal of the clip delivery system) was 75 (IQR 57–112) min. Both times are gross times. The time needed for transseptal puncture is included in the total procedure time, but not in the device time.

Patients stratified by treatment period
There was a significant influence of learning curve on procedural times. Median total procedure time and device time decreased continuously from 180 and 105 min in period 1 to 123 and 78 min in period 2 and to 95 and 55 min in period 3 (P = 0.0001 and P = 0.002, respectively). In period 1, 4 patients (16%) had a device time ≤60 min; in periods 2 and 3 this applied to 3 (12%) and 14 patients (56%, P < 0.0001 vs. periods 1 and 2). Also, in period 3, maximum total procedure time as well as maximum device time could be reduced to half of those in period 1. The mean numbers of implanted clips in periods 1, 2, and 3 were 1.24 ± 0.25, 1.84 ± 0.2, and 1.36 ± 0.24, respectively, with no significant differences between periods 1 and 3. Thus, the decrease in procedural times can be ascribed to the learning curve and is not a result of differences in the number of implanted clips.

Acute efficacy outcomes
Total cohort
Successful clip placement with the creation of a double orifice was achieved in 74 patients (99%). In one patient with MR grade 4, clip placement failed because of excessive dilation of the MV annulus. This patient was treated in period 1. In subsequent periods, clip placement was achieved in 100% of patients. Successful clip placement was associated with a median reduction of MR severity by two grades as compared with baseline. This corresponded to a reduction in MR severity by four, three, two, one, and zero grades in 1 (1.4%), 24 (32.4%), 29 (39.2%), 19 (25.7%), and 1 (1.4%) patient. The latter patient had a MR grade 4 because of myxoid disease of both leaflets. In this patient, a reduction to grade 3 was achieved with one clip. However, during attempts to place a second clip, the initial result deteriorated. Therefore, the procedure was aborted and the patient was sent to surgery a few weeks later. This patient was treated in period 3. The acute procedural success (APS), which was defined as successful clip placement and MR grade ≤2+ at discharge, was achieved in 63 patients (84%, Table 2).

Patients stratified by treatment period
APS was 80% in periods 1 and 2, but 92% in periods 3. However, this trend was not statistically significant (P = 0.46).

Acute safety outcomes at 30 days
Total cohort
Two patients (2.7%) died from refractory sepsis because of pneumonia (Table 2). No patient sustained myocardial infarction, cerebral ischaemia, or pericardial tamponade. There was no need for mechanical assistance or immediate surgery. One patient sustained a thrombosis of the femoral vein at the access site. Three patients (4%) sustained severe bleeding, but no patient sustained intracranial bleeding. Four patients (5.3%) had a partial clip detachment from one leaflet. In two patients with partial clip detachment during the initial procedure, MR could be successfully treated with two additional clips during the same procedure. One further
patient was sent for surgical valve repair. One patient was scheduled for surgery but sustained a severe pneumonia and died from sepsis. No complete clip detachment with embolization occurred. Eight patients (10.7%) were hospitalized within 30 days because of congestive heart failure. Seven of these patients had reduced ejection fraction (LVEF ≤ 30%) at baseline. Only one patient with early hospitalization had an insufficient result of MV repair with a residual MR grade 3+. Patients stratified by treatment period

When adding all pre-specified safety events, there was a statistically significant decrease of events from period 1 to period 3 (16 vs. 6 and 3 events, \(P = 0.0003\), Table 2). These events occurred in eight, five, and three patients, respectively (non-significant). No statistically significant association of treatment period with mortality or hospitalization for congestive heart failure was found.

Patients stratified by treatment period

When adding all pre-specified safety events, there was a statistically significant decrease of events from period 1 to period 3 (16 vs. 6 and 3 events, \(P = 0.0003\), Table 2). These events occurred in eight, five, and three patients, respectively (non-significant). No statistically significant association of treatment period with mortality or hospitalization for congestive heart failure was found.

Six months outcomes (matched data)

Total cohort

Seventy-five patients could be accounted for 6 months follow-up. Fifty-nine patients were available for follow-up, five patients withdrew, and 11 patients had died (four from cardiac, six from non-cardiac, and one from unknown causes; see Supplementary material online). At 6 months, 75.9% of patients had an MR grade ≤2 and 71.2% pertained to NYHA functional classes I/II. There was a substantial improvement in heart failure symptoms, with a median decrease by one NYHA functional class. The 6 min walk distance increased by 54 m (\(P = 0.002\)) and MLWHF QoL score improved by eight points (Table 3).

Patients stratified by treatment period

There was a statistically significant influence of the learning curve on residual MR grade ≤2+. At 6 months, 65.0% of patients in period 1, but 89.4% of patients in period 3 had MR grade ≤2+ (Figure 1, \(P = 0.03\)). Improvements in 6 min walk distance and MLWHF QoL score were regularly found in all treatment periods, without any differences between periods that could be ascribed to the learning curve (Table 3).

Twelve months outcomes of total cohort (matched data)

Fifty-four patients could be accounted for 12 months follow-up. Thirty-seven patients were available for follow-up, four patients withdrew, and 13 patients had died (six from cardiac, six from non-cardiac, and one from unknown causes; see Supplementary material online). At 12 months, 78.4% had MR grade ≤2+ and 73.0% pertained to NYHA functional classes I/II. As compared with baseline, there was a median decrease by two MR grades and one NYHA functional class. This was accompanied by a decrease in LV end-diastolic diameter (LVEDD) (61 ± 4 mm vs. 58 ± 4 mm, \(P = 0.0001\)) and an increase in LVEF (37 ± 6% vs. 41 ± 6%, \(P = 0.04\)). In addition, there was a significant increase in 6 min walk distance (306 ± 54 m vs. 387 ± 50 m, \(P = 0.003\)) and a significant improvement in MLWHF QoL score (42 ± 8 vs. 24 ± 7, \(P = 0.0001\)).

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**Table 2 Acute procedural success and 30 days safety outcome data for all patients and stratified by treatment period**

|                     | Total cohort | Period 1 | Period 2 | Period 3 | \(P\)-value |
|---------------------|--------------|----------|----------|----------|-------------|
| **Efficacy**        |              |          |          |          |             |
| Acute procedural success | 63 (84)      | 20 (80)  | 20 (80)  | 23 (92)  | 0.46        |
| **Safety**          |              |          |          |          |             |
| Death               | 2 (2.7)      | 2 (8)    | 0 (0)    | 0 (0)    | 0.32        |
| Hospitalization due to heart failure | 8 (10.7)   | 3 (12)   | 4 (16)   | 1 (4)    | 0.51        |
| Severe bleeding     | 3 (4)        | 3 (12)   | 0 (0)    | 0 (0)    | 0.10        |
| Myocardial infarction | 0 (0)       | 0 (0)    | 0 (0)    | 0 (0)    | NT          |
| Stroke              | 0 (0)        | 0 (0)    | 0 (0)    | 0 (0)    | NT          |
| Cardiac surgery     | 0 (0)        | 0 (0)    | 0 (0)    | 0 (0)    | NT          |
| Mechanical support  | 0 (0)        | 0 (0)    | 0 (0)    | 0 (0)    | NT          |
| Pericardial tamponade | 0 (0)      | 0 (0)    | 0 (0)    | 0 (0)    | NT          |
| Ventilation >24 h   | 5 (6.7)      | 4 (16)   | 1 (4)    | 0 (0)    | 0.12        |
| Phlebothrombosis     | 1 (1.3)      | 0 (0)    | 0 (0)    | 1 (4)    | 1.00        |
| Acute renal failure  | 2 (2.7)      | 2 (8)    | 0 (0)    | 0 (0)    | 0.32        |
| **Clip detachment** |              |          |          |          |             |
| Partial             | 4 (5.3)      | 2 (8)    | 1 (4)    | 1 (4)    | 1.00        |
| Complete            | 0 (0)        | 0 (0)    | 0 (0)    | 0 (0)    | NT          |
| **All events**      | 25 (NA)      | 16 (NA)  | 6 (NA)*  | 3 (NA)*  | 0.0003      |
| Patients with event | 16 (21.3)    | 8 (32)   | 5 (20)   | 3 (12)   | 0.26        |

\(NA,\) not applicable; NT, not tested.

*Significant differences as compared with period 1.
Corrective mitral valve procedures after MitraClip

Six patients (8.0%) had to undergo corrective MV procedures 45–301 days after MitraClip (two second clip procedures, four MV replacements). Two patients did not meet APS. Four patients had a recurrent MR despite APS after the initial procedure. These four patients had severe functional MR (LVEF ≤30%), and MR recurred within 6 months. Two patients with corrective procedures were initially treated in period 1, three patients in period 2, and one patient in period 3 (non-significant).

Kaplan–Meier analyses of survival, hospitalization because of heart failure, and the primary efficacy endpoint from EVEREST II

Total cohort

Survival was 97.3% at 30 days, and 85.2% and 76.8% at 6 and 12 months (Figure 2A). No death related to the clip was observed. Freedom from hospitalization because of congestive heart failure was 89.2% at 30 days, and 76.8% and 63.6% at 6 and 12 months (Figure 2B). In 84.6% of patients who were hospitalized because of heart failure this was necessary within 6 months. In addition, freedom from death, from MV surgery, and from MR grade 3+ or 4+ that was defined as the primary efficacy endpoint in EVEREST II was 84.0, 74.5, and 72.7% at 30 days, 6 and 12 months, respectively (Figure 2C).

Patients stratified by treatment period

There was no statistically significant influence of treatment period on survival, freedom from hospitalization because of heart failure, and the primary efficacy endpoint from EVEREST II. At 6 months, survival was 84.0, 86.0, and 87.5% (P [logrank] 0.35), freedom from hospitalization because of heart failure was 73.0, 57.0, and 73.8% (P [logrank] 0.70), and the primary efficacy endpoint from EVEREST II was met by 72.0, 68.0, and 83.6% of patients (P [logrank] 0.35) in periods 1–3, respectively.

Patients stratified by baseline characteristics and acute procedural success

In order to identify risk factors predicting adverse outcomes, patients were stratified by baseline characteristics and APS (Table 4). Failure of APS, STS score ≥15%, and overt right heart failure at baseline predicted increased mortality. Trends for increased mortality were also found with chronic obstructive pulmonary disease (COPD), previous cardiac surgery, and logistic EuroScore ≥30%. LVEF ≤30% and dyspnoea at rest (NYHA IV) before MitraClip significantly impaired freedom from hospitalization. No other additional risk factors predicting adverse outcomes were found. In particular, the underlying valvular disease (organic or functional) and the underlying myocardial disease (ischaemic or dilated) did not affect mortality and hospitalization.

Discussion

The present study investigated learning curves of percutaneous MV repair with MitraClip in a single centre. The main findings are that (i) procedural times steadily decreased; (ii) there was an excess of total safety events in the first procedures; (iii) durability and completeness of MV repair increased as a function of the learning curve which became evident at 6 months; (iv) failure of APS, STS score ≥15%, and overt right heart failure at baseline predicted increased mortality, whereas LVEF ≤30% and dyspnoea at rest (NYHA IV) before MitraClip significantly impaired freedom from hospitalization; (v) mortality and hospitalization up to 6 months were not significantly influenced by the learning curve; (vi) patients in the present study who represent a surgical high risk cohort with increased co-morbidities and mainly functional MR showed similar good functional and clinical outcomes to patients from the randomized controlled EVEREST II trial⁶ that had enrolled mainly patients with moderate surgical risk and predominantly degenerative MR.

The learning process in percutaneous MV procedures is dependent on a complex team approach. This includes patient selection

Table 3 Six months efficacy data (matched data)

|                      | Total cohort | Period 1 | Period 2 | Period 3 |
|----------------------|-------------|----------|----------|----------|
|                      | Baseline    | 6 Months | Baseline | 6 Months |
| Clinical outcomes    |             |          |          |          |                |
| 6 min walk distance, m | 257 ± 45    | 311 ± 45* | 227 ± 89 | 305 ± 99* | 304 ± 70 |
| MLWHF QoL score*     | 43 ± 6      | 35 ± 6*  | 43 ± 11  | 29 ± 9*   | 41 ± 12  |
| LVEF, %              | 39 ± 5      | 39 ± 5   | 42 ± 7   | 42 ± 7    | 31 ± 8   |
| LVEDD, mm            | 59 ± 3      | 59 ± 5   | 59 ± 4   | 63 ± 6    | 60 ± 6   |
| NT-proBNP, ng/L      | 5022 ± 1843 | 4519 ± 2081 | 4859 ± 4723 | 4987 ± 5868 | 6290 ± 3478 |

LVEF: left ventricular ejection fraction; MLWHF QoL: Minnesota Living With Heart Failure quality of life; NT-proBNP: N-terminal pro brain natriuretic peptide.

*A higher score indicates a worse quality of life.

*P < 0.05 vs. baseline; see also Figure 1.
by an interdisciplinary team discussing the risk of surgery and the chance of having a successful MitraClip procedure, interaction with the echocardiographer during the procedure, and the strategy of the interventional team choosing one or more clips. Data on the impact of the learning curve with MitraClip are sparse. Several studies have analysed procedural times during MitraClip implantation as a function of the learning curve. Feldman and co-workers reported on data from the initial EVEREST cohort with 107 patients at 31 different North-American sites.\textsuperscript{1} 70% of procedures of which represented the first, second, or third procedure at a site. For all patients, the overall device time was 175 min. The investigators found a steep procedural learning curve with rapid reduction in the procedure and device times throughout the study. Franzen and co-workers reported on the learning curve in their first 52 procedures which reflected the learning curve of the first European centre performing MitraClip procedures. They found a trend towards shorter median device times in the second 26 procedures (66 min) as compared with the first 26 procedures (118 min). This was particularly relevant because multiple clips were implanted in only 12% of patients from the first period, but in 50% of patients from the second period.\textsuperscript{2} In accordance with the initial EVEREST experience and with the experience of

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure1.png}
\caption{Six month efficacy outcomes stratified by treatment periods (matched cases). Mitral regurgitation (MR) grades (A) and New York Heart Association functional classes (B) in periods 1–3. See also Table 3.}
\end{figure}
Figure 2. Kaplan–Meier analyses of freedom from death (A), freedom from hospitalization because of heart failure (B), and the combined primary efficacy endpoint from EVEREST II (C) in the total cohort. The proportion at 6 and 12 months is indicated.
Franzen, we found a significant reduction of procedural times in our initial single centre cohort of 75 patients. In the present study, median device times decreased from 105 min in the first 25 patients to 78 min in the second 25 patients and to 55 in the third 25 patients, which was not related to the number of clips implanted in different periods. Notably, this does not only reflect the individual learning curves of persons involved in the procedure. Targeted measures were taken to reduce procedural times systematically: for example, during the first procedures, the guiding catheter and clip delivery system were not prepared until having performed successful transseptal puncture. After having gained confidence in the safety and efficacy of this transoesophageal echocardiography (TOE)-guided technique, all material was prepared before the procedure started.

In addition to the analyses of procedural times, the present study is the first one to analyse the impact of the learning curve on patients’ outcomes. The procedure proved to be safe. For all 75 patients, 30-day mortality was 2.7% and no death related to the procedure or the device occurred. In the initial EVEREST cohort, 30-day mortality was 0.9%,1 and in EVEREST II it was 1%.6 However, in the present study, more patients were in NYHA functional classes III/IV (88% vs. 46% and 52%), mean LVEF was considerably lower (37% vs. 62% and 60%), and patients were older (73 vs. 71 and 67 years). Three patients (4%) sustained severe bleeding. No patient sustained myocardial infarction, clip embolization, or stroke, or needed acute cardiac surgery. When adding all pre-specified safety events within 30 days, there was a significant excess of events in the first procedures that decreased over time. In particular, severe bleeding occurred only in the first 25 patients. One bleeding occurred at the left femoral artery. As a consequence, in subsequent procedures, puncture of the femoral artery was only performed in select cases and invasive blood pressure monitoring was routinely performed at the radial artery. There was no statistically significant association of mortality with treatment period.

The percentage of patients with APS was 84% in the present cohort, which was somewhat higher than in the initial EVEREST cohort (74%)1 and in EVEREST II (77%).6 APS was already high in our patients from period 1 (80%). The high APS in the first patients of the present cohort and of other series is probably related to the fact that the whole procedure is performed under TOE guidance on the beating heart and that virtually infinite corrective steps with repositioning of the clip are possible until an optimum result is achieved. Thus, MitraClip could be performed with high efficacy in the very first procedures at the expense of longer procedural times. In patients from period 3, APS tended to be higher (92%). After 6 months, the durability and completeness of MV repair in patients from period 3 proved to be superior. A total of 89% of patients from period 3 showed MR ≤2+ as compared with 65% of patients from period 1. Apart from the learning process of the MV intervention team, incremental improvement in the equipment is likely to affect outcomes. Recent publications have shown that routine use of 3D-TOE is likely to increase the percentage of patients having optimum results as a consequence of an optimized guidance of clip placement.17,18 In the present study, 3D-TOE was used starting with patient no. 46, and was routinely used in all patients from period 3. We found a decrease in procedural times with 3D-TOE (not shown). However, the pure effect of 3D-TOE was difficult to distinguish from other factors and has therefore not been analysed in detail.

Cumulative evidence from trials determines a global learning curve. Patient-related factors predicting outcomes after using a clip are still under investigation. The first studies investigated patients with predominantly organic MV disease.1,6 More recent studies have shown favourable results in patient cohorts with predominantly functional MR7 as well as in patients with severely depressed LV function8 and in heart failure patients not responding to cardiac resynchronization therapy.8 We have analysed baseline data and APS to identify risk factors for mortality and hospitalization. Failure of APS, STS score ≥15%, and overt right heart failure at baseline were found to predict increased mortality, whereas LVEF ≤30% and dyspnoea at rest (NYHA IV) before MitraClip significantly impaired freedom from hospitalization. Notably, in 84.6% of patients

| Risk factor present | Freedom from death | | Freedom from hospitalization because of heart failure | |
|---------------------|-------------------|-------------------|-------------------|
|                      | Proportion (%)    | No (%)            | Proportion (%)    | No (%)            |
|                      | Yes               | No                | Yes               | No                |
| Failure of APS       | 50.0              | 92.0              | <0.0001           | 66.1              | 81.5              | NS               |
| Overt right heart failure | 75.3            | 92.9              | 0.02              | 70.8              | 65.1              | NS               |
| COPD                | 68.7              | 89.7              | 0.05              | 56.3              | 69.7              | NS               |
| Previous cardiac surgery | 78.3             | 89.4              | 0.09              | 66.7              | 68.7              | NS               |
| Logistic EuroScore ≥30% | 79.9            | 88.9              | 0.07              | 65.5              | 69.7              | NS               |
| STS score ≥15%, n (%) | 72.7             | 88.3              | 0.03              | 73.1              | 66.6              | NS               |
| NYHA IV             | 77.8              | 87.5              | NS                | 45.5              | 74.0              | 0.02             |
| LVEF ≤30%           | 85.9              | 84.5              | NS                | 53.6              | 80.2              | 0.03             |

APS, acute procedural success; COPD, chronic obstructive pulmonary disease; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; STS, Society of Thoracic Surgeons.
who were hospitalized after the clip procedure, this was necessary within 6 months. Patients with advanced heart failure and functional MR might therefore be good candidates for MitraClip therapy, but due care has to be exercised in the post-procedural management of these patients over several months.

To date, we do not have appropriate tools to predict long-term outcomes after MitraClip accurately. EVEREST II has shown that MitraClip was very effective at reducing MR, but was less effective than surgery. After 12 months, the primary composite endpoint of freedom from death, from MV surgery, and from grade 3- or 4+ MR was reached in 55% of patients in the percutaneous group and in 73% of patients in the surgical group. Yet, the benefit of surgery over the clip was entirely driven by patients in the clip group who needed subsequent surgery because of clip failure. One out of five patients had clip failure, and the majority of these patients had surgery within 6 months. Beyond that, the results after the clip procedure were stable for up to 24 months. In view of the present study, it is tempting to speculate that at least the low contributing centres of EVEREST II might have been in the ascending part of the learning curve which might have impaired MitraClip performance in comparison with MV surgery.

In conclusion, we could demonstrate that MitraClip could be effectively used in a surgical high risk cohort of patients with predominantly functional MR right from the first procedures. There was an institutional learning curve that became evident in decreasing procedural times and safety events over time. In addition, the durability and completeness of MV repair increased over time. The University Medical Centre of Göttingen was among the first European centres performing percutaneous MV repair with MitraClip and therefore also experienced the initial part of the global learning curve. Centres that have recently initiated percutaneous MV repair programmes probably benefit from first-generation centres and start at a higher level.

**Supplementary material**

Supplementary material is available at European Journal of Heart Failure online.

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