

Use of the MitraClip Device in Practice

An update on the European registry experience.

BY RALPH STEPHAN VON BARDELEBEN, MD, AND WOLFGANG SCHILLINGER, MD

Interventional therapy for symptomatic severe mitral valve regurgitation serves an increasing need due to the prevalence of the disease in a growing number of patients who are considered to be high risk for conventional surgery. There are more octogenarians in the Western world, including patients with elevated risks due to previous open-heart surgeries, pulmonary hypertension, renal insufficiency, or other relevant comorbidities. Multiple transcatheter techniques have been developed, and a majority has remained in the experimental animal model phase or just began small first-in-man studies or CE Mark populations. These techniques address either the mitral valve annulus via the coronary sinus, interventional band implantations near the annulus, or focus on the mitral valve leaflets themselves.

One of these techniques, an “edge-to-edge” approach via the MitraClip system (Abbott Vascular, Santa Clara, CA), which is similar but not identical to the surgical Alfieri procedure, has reached a mature level of patient experience. As of August 2013, a total population of more than 10,000 patients has been treated just 10 years after the first-in-man procedure in Caracas, Venezuela in 2003. The device has been tested in the EVEREST II randomized controlled trial (RCT) in a 2:1 randomization against surgery in patients with predominantly primary or degenerative mitral valve regurgitation disease.¹ This study demonstrated an inferior efficacy in patients without elevated risks for surgery but demonstrated a very good peri-interventional safety profile.

The European experience began with CE Mark approval of the MitraClip device in 2008, focusing on a significantly older patient population than in the United States RCT who were high risk for surgery and the secondary or functional/ischemic nature of the mitral valve regurgitation. The German experience (in

approximately 80 interventional centers) accounts for more than half of the worldwide implantation rate. European and German guidelines have been cautious due to the limited data from RCTs but acknowledge that there is a large number of patients in registries such as the United States high-risk cohort in EVEREST II and REALISM, plus the upcoming European Eurobservational Research Programme Registry on Transcatheter Valve Treatment, ACCESS-EU,² the smaller MitraSwiss registry (with 100 patients),³ and the larger German TRAMI (Transcatheter Mitral Valve Interventions) registry (with 1,400 patients).^{4,5} The aim of the TRAMI registry is to document real-world implantation and to analyze both the safety and efficacy of the transcatheter approach to mitral valve regurgitation treatment. More than 99% of all mitral valve interventions in the German registry were performed using the MitraClip device, as of August 2013. Additional data resources include the onsite registration of patient characteristics, device use, and periprocedural success in Abbott Vascular’s implantation database (APOLLO).

TRAMI METHODS AND STUDY DESIGN

The TRAMI registry involves 21 large implanting centers, including 12 university hospitals and nine large, specialized interventional hospitals in private or community ownership. The database is based at the Institute of Myocardial Infarction Research (IHF Institute) of the University of Heidelberg in Ludwigshafen, Germany.⁴⁻⁶ It records basic demographic factors and comorbidities of the patients treated and the technical procedural data, including outcome parameters of consecutive implantation procedures in the participating centers. The registry was started with a retrospective patient cohort of 504 patients and a prospective patient cohort of 560 patients who were

TABLE 1. PATIENT DEMOGRAPHICS IN TRAMI COMPARED TO EVEREST II⁵

	EVEREST II (N = 184)	German TRAMI Registry (N = 1,064)
Age, y	67.3 ± 12.8 ^a	75 (70–81) ^b
Female sex, n (%)	69 (38)	406 (38.2)
NYHA functional class III/IV, n (%)	94/184 (51.1)	881/1015 (86.8)
LVEF		
LVEF, %	60 ± 10.1 ^a	NA
LVEF < 30%, n (%)	NA	294/893 (32.9)
LVEF 30%–50%, n (%)	NA	325/893 (36.4)
LVEF > 50%, n (%)	NA	274/893 (30.7)
Etiology of mitral regurgitation, n (%)		
Functional	49 (27)	590/836 (70.6) ^c
Degenerative	135 (73)	246/836 (29.4) ^c
Severity of mitral regurgitation, n (%)		
3+/4+ (grading: 1+, 2+, 3+, 4+)	176 (95.7)	NA
Severe (grading: mild, moderate, severe)	NA	827/872 (94.8)
Comorbidities, n (%)		
Coronary artery disease	86/183 (47)	610/1,013 (60.3)
Previous myocardial infarction	40/183 (22)	283/1,014 (27.9)
Atrial fibrillation	59/175 (34)	418/1,016 (41.1)
Diabetes mellitus	14/184 (8)	307/1,008 (30.5)
COPD	27/183 (15)	204/1,010 (20.2)
Renal failure, moderate to severe	6 (3)	527/998 (52.8)
Previous CABG	38/184 (21)	284/1,015 (2)
Previous AVR or TAVR	NA	87/1,015 (8.6)
Previous mitral valve surgery or intervention	0	22/1,020 (2.2)
^a Mean ± standard deviation. ^b Median, interquartile range. ^c Sum not 100% because of mixed etiology. Abbreviations: AVR, aortic valve replacement; CABG, coronary artery bypass grafting; COPD, chronic obstructive pulmonary disease; LVEF, left ventricular ejection fraction; NA, not available; TAVR, transcatheter aortic valve replacement.		

enrolled until March 4, 2013, which has been increased to nearly 900 patients as of August 2013.

At an interim analysis of patients included until March, 1,064 patient datasets had been analyzed (Table 1). The participating centers included a median of 36 patients, with a range from four to 271 patients. Patients are followed at 30 days and at 1, 3, and 5 years after the procedure. The follow-up is performed at the implanting center in the retrospective subgroup and centrally through telephone interviews by the IHF Institute for all patients in the prospective patient subgroup. The initial financial background for the programming and maintenance of the central database was provided independent of the industry by the IHF Institute itself. In 2012, additional funding was provided by Abbott Vascular to enable additional biometric analyses. Database ownership, server access, and data mining remain industry independent within the IHF Institute.⁶

PRELIMINARY EUROPEAN REGISTRY RESULTS

Preliminary results of the European and the German experiences in the TRAMI registry have been published in two articles, as well as presented at congresses, including EuroPCR,⁷ the European Society of Cardiology annual meeting,⁸ PCR London Valves, TCT, and the ACC and AHA annual meetings.⁹

Based on an analysis of the first 486 patients, Baldus et al published the demographics and the acute outcome, which at that time was the largest patient cohort followed in a European registry.⁴ In contrast to the EVEREST patients, the mean age in TRAMI was 75 years, and there was a very high number of comorbidities.

More than 70% of all patients demonstrated a reduced ejection fraction of < 50% in severe mitral regurgitation, and the nature of the disease was functional or secondary in 67% of all implanted patients. Ninety-three percent of patients were New York Heart Association (NYHA) class III or IV. The median logistic EuroSCORE was 23% (range, 12%–38%), and the median Society of Thoracic Surgeons (STS) score was 12% (range, 4%–19%). Approximately 17% of all patients were on implantable cardioverter-defibrillator or cardiac resynchronization therapy. Ischemic heart disease as an underlying etiology accounted for approximately 80% of patients and dilative cardiomyopathy, for approximately 11%. Thirty-six percent of all patients had renal insufficiency with a creatinine level above 1.5 mg/L.

The importance of an interdisciplinary heart team in the decision process of directing the patient treatment pathways according to standard risk scores (STS, log

More than 70% of all patients demonstrated a reduced ejection fraction of < 50% in severe mitral regurgitation, and the nature of the disease was functional or secondary in 67% of all implanted patients.

EuroScore, EuroScore II) and individual factors (previous thoracic surgery, therapeutic radiation exposure in cancer therapy, and frailty) toward conservative treatment versus surgical or interventional procedures was observed in more than 30% of all cases in the TRAMI registry, even 2 years ahead of official guideline recommendations for a heart team.⁴

Despite the elevated risk scores documented with logistic EuroSCORE and STS scores plus additional comorbidities, which were not adequately focused on in these mortality estimations (ie, therapeutic radiation exposure, neoplasm, age older than 90 years, and frailty), the in-hospital mortality rate was demonstrated to be very low at 2.5%. The stroke rate, even with a left heart intervention, was an extremely low < 0.5%. Major bleeding was encountered in approximately 3.9% and vascular complications, in 2.8%.

A second publication in 2013 on a further interim subgroup analysis of 1,064 patients in the TRAMI registry by Schillinger et al focused on age as a predictor of procedural success or outcome.⁵ This comparison was important following an analysis by Chikwe et al, which showed that in both surgical mitral valve repair and replacement with and without coronary artery bypass grafting, 50% of patients 80 years of age or older had elevated 30- and 90-day mortality rates compared to national society reports in the US STS registry and the UK and the German registries for surgical valve interventions in the total cohort.¹⁰

The group in Göttingen compared an age group older than 76 years with those 76 years or younger. Due to a selection bias for high-risk patients, the younger patients had a lower percentage of preserved left ventricular function in 21.8% versus 40.1%, and the prevalence of primary mitral regurgitation (PMR) was greater in the older group (35.3% vs 25.6%), indicating that younger patients with PMR, as according to guidelines, were predominantly sent to surgery. Age and frailty were the most important criteria for transcatheter over surgical treatment, whereas comorbidities

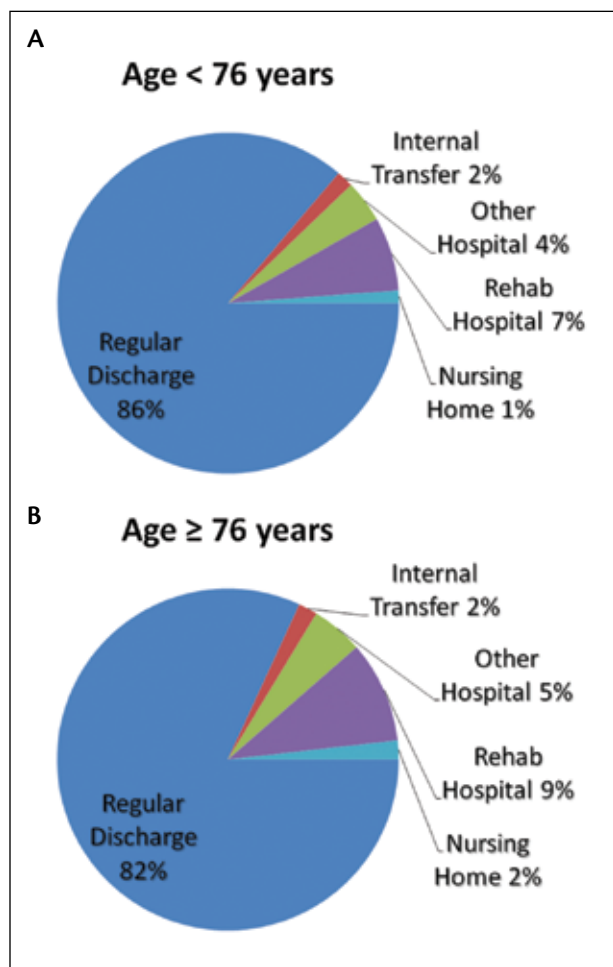


Figure 1. Discharge destination of MitraClip patients after the procedure in patients both younger than 76 years (A) and 76 years and older (B).

ties and preference of the patient in informed consent played a larger role in the younger population.

The heart valve team was involved in 50% of the decisions about whether to operate surgically, initiate conservative treatment, or perform interventional MitraClip therapy—this approach was later considered standard of care in the April 2013 German Guidelines.^{4-6,12} This shows a clear trend for discussions among specialized valve teams in the implanting centers, which is also emphasized by the European guidelines on valve therapy in 2012 and the German guidelines in 2013.^{11-13,16}

Even though the estimated risk for patients based on surgical interventional scores was higher in the older patient group (25% vs 18%), the combined major adverse cardiovascular and cerebral event (MACCE) rate of mortality, myocardial infarction, and stroke was not significantly different between both groups and

was relatively low (3.5% vs 3.4%). More than 80% of all patients could be directly discharged home to their referring setting (Figure 1).⁵

In addition to the German TRAMI registry, there is a smaller national Swiss multicenter registry (MitraSwiss) that recently reported results for the first 100 consecutive patients treated between 2009 and 2011.³ Patient demographics showed a similar distribution as reported by the vendor implantation database, ACCESS-EU, and TRAMI. Mean age was 77 years versus 75 years in TRAMI, with a two-thirds male cohort that predominantly had a functional type of secondary mitral valve regurgitation (SMR) of 62% compared to 67% in the vendor database or ACCESS-EU and 70.6% in the latest TRAMI analysis (Table 1).^{2,3,5,7}

The prevalence of coronary artery disease was lower in the MitraSwiss group and EVEREST II compared to TRAMI (45%, 47%, and 60.3%, respectively). Patients in NYHA class III or IV accounted for 82% in MitraSwiss, 51.1% in EVEREST II, and 86.8% in TRAMI, correlating with the difference in prevalence of SMR in these registries and the RCT with operable patients. The registry emphasizes the importance of the acute procedural success rate and residual discharge mitral valve regurgitation as prognostic parameters of patient outcome.

Smaller subanalyses were presented at congress presentations focusing on severe left ventricular function depression by Bekerredjian et al in 2012. In 256 patients, an ejection fraction < 30% was more predominant in an older subgroup (4 years) with a high prevalence of functional or secondary mitral regurgitation (87% vs 65%), with a higher rate of both comorbidities and elevated mortality scores.¹⁴ Patient sex differences were studied by Zahn et al, involving 971 patients in the TRAMI registry, and findings were presented in 2013 at the annual meeting of the German Society of Cardiology. They showed that the female subpopulation was older (4 years), received fewer MitraClip systems during the intervention due to differences in size (1.3 vs 1.5 devices), and had slightly more elevated logistic EuroSCOREs of 23% versus 21%. These differences did not result in any changes in safety or efficacy in those who received the device.¹⁵

However, outcome is influenced by renal function, as reported by Hammerstingl et al at the AHA meeting in 2011, showing that a glomerular filtration rate of ≤ 30 is associated with higher MACCE rates, more blood transfusions, and longer length of hospital admission before discharge in these patients.⁹ Further analyses on the value of a logistic EuroSCORE > 20% showed a higher prevalence of low ejection fraction below 30% (41% vs 28%) and slightly less efficacy in procedural

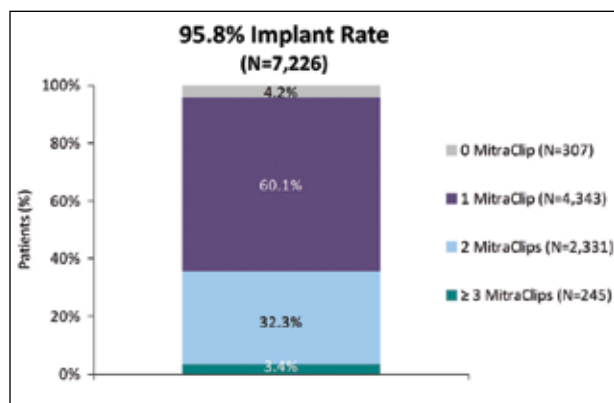


Figure 2. Number of MitraClip devices used in first interventions (N = 7,226). Reprinted from *EuroIntervention*, von Bardeleben RS, Butter C, Schillinger W, et al, in press, Copyright (2013), with permission from Europa Digital & Publishing.⁷

success. The procedural and hospital complication rates were not significantly affected, as reported by Franke et al.⁸

In an epidemiologic analysis (outside TRAMI in the vendors' implantation database) on the overall European MitraClip experience in 7,457 MitraClip interventions until May 17, 2013, von Bardeleben and coauthors from Germany, Italy, the Netherlands, and Switzerland showed a high first implantation rate of 7,226 interventions with "redo procedures" in only 231 cases.⁷ The mean patient age in these onsite recorded cases was 76 years, with good correlation to the TRAMI patient characteristics. The percentage of SMR was equal to what was reported in the German registry (67%); only 23% were PMR, and 10% showed a combination of both degenerative and functional disease. The implant success rate in the 7,226 first intervention procedures was 95.8%.

The procedure was performed using one MitraClip device in 60.1% of all cases, two devices were used in 32.3%, and three or more devices were used in only 3.4% (Figure 2). Using a paired per-patient procedure analysis, 94% achieved a periprocedural reduction from grade III or IV severity to grade 0, I, or II in the cath lab. The mean device time of the 7,226 procedures from crossing of the steerable sheath over the septum to the retraction of the MitraClip delivery catheter into the sheath over the septum was 91 minutes, with a standard deviation of 61 minutes. This result is concordant with the report of 100 patients in the MitraSwiss registry, with a mean device time of 90 minutes, and a learning curve reduction of the device time from the first 10 to the last 10 implants per center of 51 minutes in the MitraSwiss registry and 41 minutes in the total commercial European implant database report.^{3,7}

DISCUSSION

Data from the first and to date only RCT, EVEREST II, have shown an excellent safety profile, as acknowledged in an 8-0 vote at the US Food and Drug Administration expert panel hearing in March 2013 in Washington, DC. However, efficacy was lower compared to a standard surgical approach. One-fifth of the patients in an operable patient population with a large percentage of degenerative disease (73%), including mitral valve prolapse, had an early or late crossover to surgical therapy. Even 5 years after the commercial introduction of the MitraClip therapy in Europe, data on the long-term success of the therapy are limited to some reports from monocentric and a few multicentric registries.

The REALISM US and ACCESS EU registries and the Abbott implantation database are vendor-initiated data sources with significant patient numbers, but they lack inherent control arms. The TRAMI registry is an industry-independent German mitral valve interventional registry with a total of 1,400 patients in August 2013. It contains a small number of coronary sinus interventions and a majority of > 99% MitraClip interventions as the therapeutic procedural device. Due to its start after CE Mark approval, 506 patients are retrospective, whereas approximately 900 patients have central core facility follow-up.

With more than 1,060 patients in data analysis and 21 implanting centers in the TRAMI registry, it is the world's largest industry-independent source of information on procedural performance, safety, and efficacy until we have further data from the randomized European RESHAPE-HF trial (target patient number, 800) and the US COAPT trial (target, 400 patients), with both focusing on SMR in heart failure only. Thus, the only future information on elderly patients with high comorbidities and PMR will be from registries in the next 5 years. Approximately 25% of all German implantation procedures and approximately 13% of all worldwide commercial procedures are included in this registry.

The main conclusions based on this registry are as follows. First, there is a shift in patient population from the younger patient with degenerative (PMR) disease to an older patient population at high risk for surgery and predominantly, but not exclusively, functional or secondary (SMR) disease. This shift can be explained by data from a subgroup analysis in EVEREST II, showing that the lack of efficacy may not be predominant in this selected patient group.^{1,2,5,7,12,16}

Second, patients 80 years or older have a higher mortality rate, even in subgroups with preserved ejection fraction in both mitral valve repair and replace-

Although registries typically provide less robust data compared to RCTs, they offer important data for hypotheses and treatment until RCT data become available.

ment. This effect has not been shown in an even larger patient group (> 1,000 patients) in the TRAMI registry.⁵

Finally, the benefit of mitral valve surgery in functional and especially ischemic forms of SMR are less well defined than in PMR. This high-risk group might benefit from the reduced peri-interventional and hospital mortality in a beating-heart procedure without major blood loss like the percutaneous mitral valve repair using the MitraClip.

Although registries typically provide less robust data compared to RCTs, they offer important data for hypotheses and treatment until RCT data become available. The limitations of the registry data presented are the open-label design and the observational nature, including the absence of a control group. These data, however, especially in large patient numbers, show valuable information concerning patient distribution and procedural use of the number of MitraClip systems per procedure and identify possible benefits in groups like those with impaired ejection fractions and comorbidities/scores, the elderly, and those based on sex, which were not associated with significant increases in MACCE or mortality. Renal function may also influence MitraClip therapy, especially in cases of end-stage renal disease and renal replacement therapy.^{9,10}

A heart valve team should be used for an interdisciplinary expert panel on mitral valve therapy, directing the individual patient to surgical or interventional procedures based on their individual risk/benefit ratio and profile. The importance of a heart valve team was emphasized in a recently published consensus article from the German Society of Thoracic and Heart Surgery and the German Society of Cardiology, and was defined as a requirement for the selection of interventional patient treatment options in the 2012 European Heart Valve Guidelines and discussed during the US Food and Drug Administration expert panel hearing on the MitraClip treatment in March 2013.^{11-13,16} The TRAMI registry documents this development; the number of heart valve team decisions has increased from 30% of all

MitraClip procedures in patients treated in years before the guideline statements to 50% (including previous data) just before the German consensus. The TRAMI registry will continue to be a relevant source of information before and after publication of RESHAPE-HF and COAPT. ■

Ralph Stephan von Bardeleben, MD, is Head of CV Imaging and GUCH, and Vice Head of Interventional Structural Heart, Department of Cardiology, Angiology and Intensive Care Medicine, Universitätsmedizin in Mainz, Germany. He has disclosed that he is a speaker and consultant for Abbott Vascular. Dr. von Bardeleben may be reached at +49-6131-17-2385; stephan.von_bardeleben@unimedizin-mainz.de.

Wolfgang Schillinger, MD, is Vice Director of the Department of Cardiology, Heart Center, Universitätsmedizin in Göttingen, Germany, and is Principal Investigator of the TRAMI registry, located in cooperation with the IHF Foundation in Ludwigshafen, Germany. He has disclosed that he is a speaker and consultant for Abbott Vascular.

1. Feldman T, Foster E, Glower DG, et al. Percutaneous repair or surgery for mitral regurgitation. *N Engl J Med*. 2011;364:1395-1406.
2. Maisano F, Franzen O, Baldus S, et al. Percutaneous mitral valve interventions in the real world: early and one year results from the ACCESS-EU, a prospective, multicenter, non-randomized post-approval study of the MitraClip therapy in Europe. *J Am Coll Cardiol*. 2013;62:1052-1061.
3. Sünder D, Pedrazzi G, Gaemperli O, et al. Predictors for efficacy of percutaneous mitral valve repair using the MitraClip system: the results of the MitraSwiss registry. *Heart*. 2013;99:1034-1040.
4. Baldus S, Schillinger W, Franzen O, et al. MitraClip therapy in daily in daily clinical practice; initial results from the German transcatheter mitral valve interventions (TRAMI) registry. *Eur J Heart Fail*. 2012;14:1050-1055.
5. Schillinger W, Hünlich M, Baldus S, et al. Acute outcomes after MitraClip therapy in highly aged patients: results from the German Transcatheter Mitral Valve Interventions (TRAMI) registry. *EuroIntervention*. 2013;9:84-90.
6. Schillinger W, Senges J. TRAMI (Transcatheter Mitral Valve Interventions)-Register: Das deutsche Mitralklappenregister. *Herz*. 2013;38:453-459.
7. von Bardeleben RS, Butter C, Schillinger W, et al. Real-world European experience with percutaneous treatment of significant mitral regurgitation: demographics and procedural outcomes [abstract 394]. *EuroIntervention*. In press.
8. Franke J, Baldus S, Wachter R, et al. Percutaneous mitral valve repair with the MitraClip system according to predict risk by logistic EuroSCORE: first results from the German mitral valve registry. *Eur Heart J*. 2011;32(abstract suppl):1081.
9. Hammerstingl C, Sinning JM, Meinertz T, et al. Impact of renal insufficiency on outcome after MitraClip-procedure: results from the German TRAMI registry. *Circulation*. 2011;124:A11644.
10. Chikwe J, Goldstone AB, Passage J, et al. A propensity score-adjusted retrospective comparison of early and mid-term results of mitral valve repair versus replacement in octogenarians. *Eur Heart J*. 2011;32:618-626.
11. Nickenig G, Mohr FW, Kelm M, et al. Konsensus der Deutschen Gesellschaft für Kardiologie—Herz- und Kreislaufforschung und der Deutschen Gesellschaft für Thorax-, Herz- und Gefäßchirurgie zur Behandlung der Mitralklappeninsuffizienz. *Kardiologie*. 2013;7:76-90.
12. Boeckstegers P, Hausleiter J, Baldus S, et al. Interventionelle Behandlung der Mitralklappeninsuffizienz mit dem MitraClip-Verfahren. *Kardiologie*. 2013;7:91-104.
13. Vahanian A, Alfieri O, Andreotti F, et al. Guidelines on the management of valvular heart disease (version 2012): the joint task force on the management of valvular heart disease of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS). *Eur J Cardiothorac Surg*. 2012;42:S1-44.
14. Bekeredjian R, Baldus S, Ouarrak T, et al. Clinical efficacy and safety of MitraClip implantation in patients with low ejection fraction: data from the German mitral valve registry. *Clin Res Cardiol*. 2012;101(suppl 1):abstr V1569.
15. Zahn R, Bauer T, Schillinger W, et al. Welche Rolle spielt das Geschlecht bei der kathetertechnischen Behandlung der Mitralklappeninsuffizienz mit dem MitraClip? *Clin Res Cardiol*. 2013;102(suppl 1):abstr P468.
16. Boeckstegers P, Hausleiter J, Baldus S, et al. Percutaneous interventional mitral regurgitation treatment using the MitraClip system. *Clin Res Cardiol*. 2013. doi:10.1007/s00392-013-0614-x.