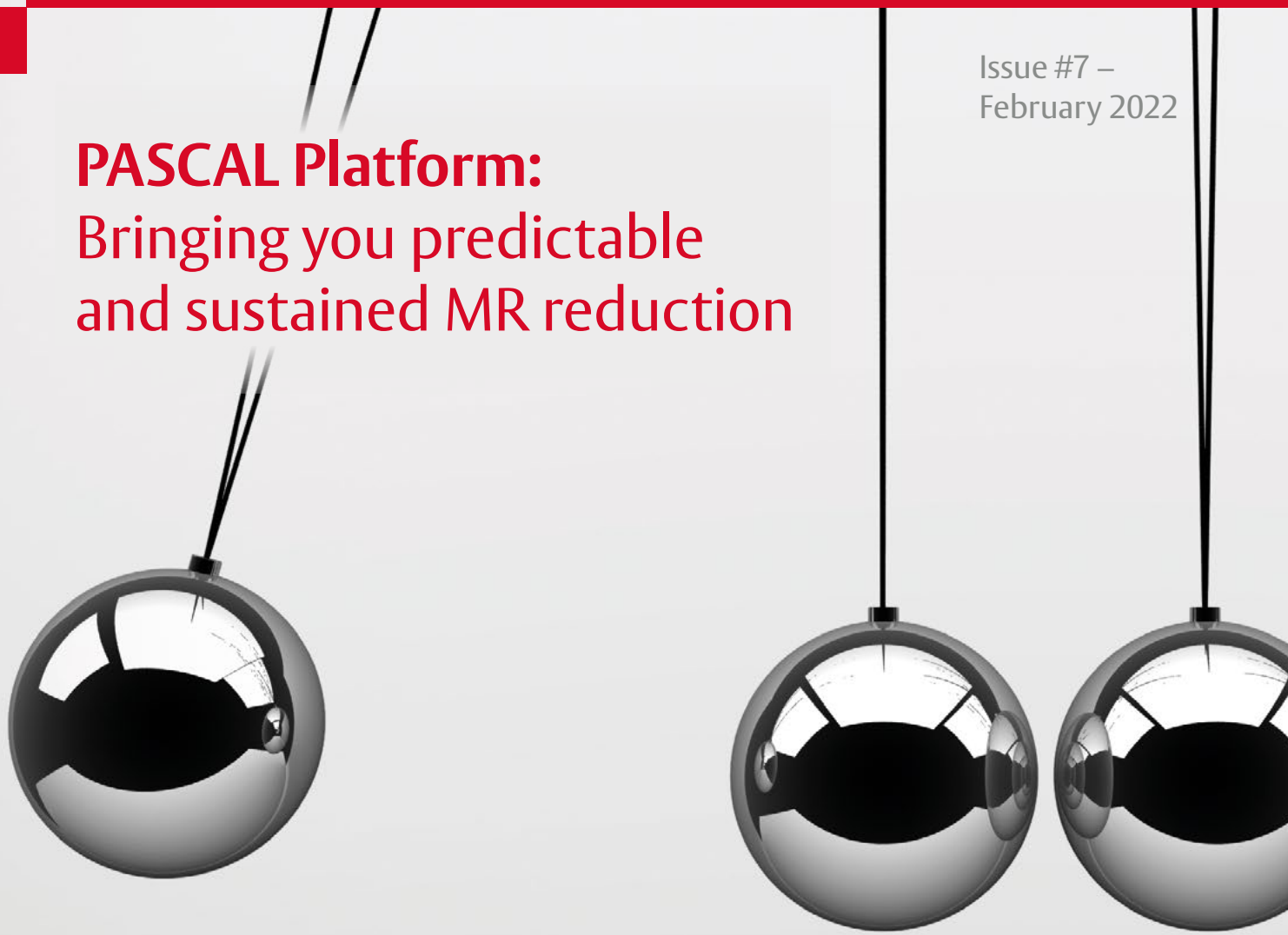
TMTT Today

Your source for innovations in Edwards' transcatheter mitral and tricuspid therapies

Issue #7 – February 2022

PASCAL Platform: Bringing you predictable and sustained MR reduction



95% achieved predictable* residual MR on implant deployment**

*Stable or improved residual MR between leaflet capture and implant delivery
Using PASCAL repair system; Lüdike P *et al. JACC Cardiovasc Interv* 2021; **14: 2638–40. (retrospective, single-centre analysis, 2017–2020)

Read more about the consistent benefits of the PASCAL platform in MR:

- MiCLASP study post-market and real-world outcomes
- CLASP study 2-year outcomes: Durable MR reduction

Look inside for updated treatment guidelines

Expert's View: Transcatheter treatment of TR in 2026? (see inside)

Edwards

Dear Reader,

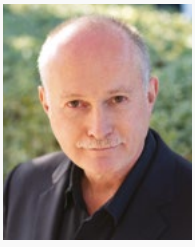
At Edwards Lifesciences, we are committed to developing and facilitating the use of cutting-edge technologies that can help you improve outcomes for your patients with mitral regurgitation (MR) and tricuspid regurgitation (TR). In that endeavour, we have developed the PASCAL platform, comprising the PASCAL and PASCAL Ace implants, for the transcatheter repair of mitral and tricuspid valvular pathologies.

In previous editions of Transcatheter Mitral and Tricuspid Therapies (TMTT) Today, we have explored with you how the PASCAL Stabilizer Rail System assists in steering the PASCAL and PASCAL Ace implants, giving you fine movement control to obtain predictable capture, positioning and release of implants. In this edition, we show the predictability of the PASCAL repair system in minimising residual MR (rMR) at the final stage of implant deployment. We hope that these data provide you with the confidence to release the PASCAL implant knowing that rMR achieved during leaflet capture is maintained in the majority of cases, and in some cases is improved.

We also bring you the latest data from clinical and real-world studies highlighting the efficacy and safety of the PASCAL platform across selected and unselected patients with severe symptomatic MR. These include early data from the MiCLASP registry, mid-term outcomes from a single-centre real-world study and 2-year outcomes from the CLASP study. The growing confidence in the safety and efficacy of transcatheter mitral valve repair (TMVr) is now reflected in recent updates to the ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure (ESC-HF) and ESC/EACTS Guidelines on the management of valvular heart disease (ESC/EACTS-VHD), discussed in detail in the following pages.

Finally, Dr Ralph Stephan von Bardeleben provides his perspectives on the potential role of transcatheter valve repair and annuloplasty technologies in the future treatment of TR.

Rodolfo Estay, MSc, MBA
Vice President, Europe
Edwards Lifesciences

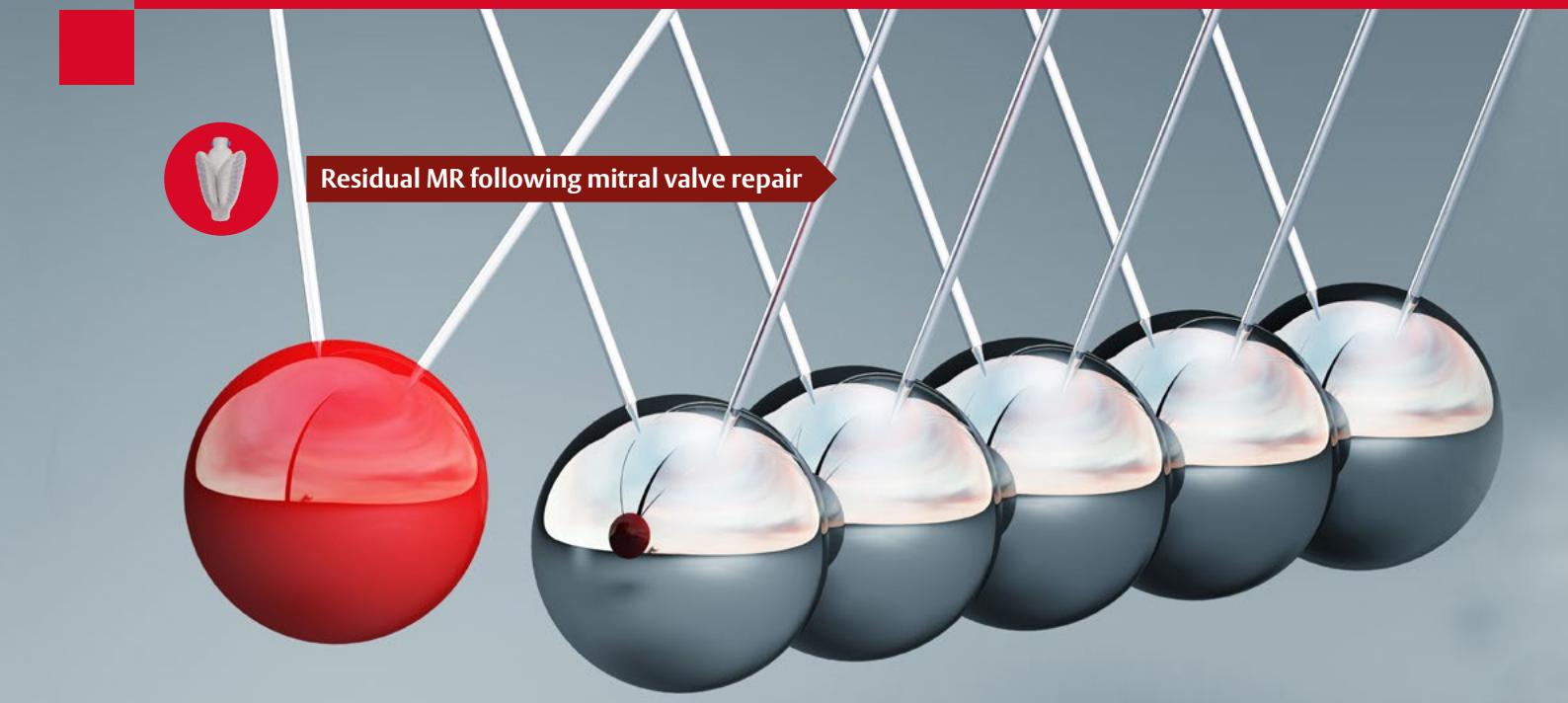


Dr Ted Feldman, MD MSCAI FACC FESC
Vice President of Global Medical Affairs
Edwards Lifesciences

Enjoy reading!

FRONT COVER IMAGE: SHUTTERSTOCK.COM/LP STUDIO

Contents



Residual MR following mitral valve repair

Predictability

of post-delivery rMR following treatment with the MitraClip and PASCAL Repair System

ISTOCK.COM/TIERO

Professor Dr med. Peter Lüdike

Westdeutsches Herz- und Gefäßzentrum, Klinik für Kardiologie und Angiologie, Essen, Germany

Professor Lüdike is Senior Physician of the Heart Failure and Intensive Care section in the Department of Cardiology and Vascular Medicine at the West German Heart and Vascular Center, University Hospital Essen. He achieved venia legendi for internal medicine in 2018 and was appointed as full Professor for heart failure in 2020. His research interests include intensive care medicine, emergency medicine, heart failure, mitral valve disease and the role of macrophage migration inhibitory factor in the development of ischaemic heart disease.

Evidence from observational studies suggests that post-delivery rMR may be an important prognostic factor for patients with MR receiving TMVr.[1–4] However, the predictability of post-delivery rMR with different mitral valve repair technologies requires further research. Here, Professor Peter Lüdike presents data from a retrospective single-centre study assessing the predictability of post-delivery rMR after treatment of patients with either the MitraClip or PASCAL repair system.[5]

Post-delivery rMR is typically used as a measure of procedural success following mitral valve repair and appears to be a prognostic factor for patient outcomes.[1–4] Data from a single-centre, retrospective, observational study in 458 patients with functional MR (FMR) suggest that achieving rMR ≤1+ at discharge and 12 months after mitral valve repair leads to improved long-term outcomes.[4] Similarly, rMR ≥2+ has been shown to correlate with poor outcomes, including recurrence of higher-grade MR and the requirement for redo mitral valve surgery.[1–3]

To help the interventional cardiologist judge when to deploy the implant during TMVr, intraprocedural rMR is routinely measured after leaflet capture but before implant deployment. However, intraprocedural rMR may not necessarily predict post-delivery rMR, as rMR can change when the implant is released. The predictability of post-delivery rMR is therefore an important consideration when performing mitral valve repair, especially when treating patients with a small mitral valve opening for whom a second mitral valve repair device may not be an option.

> It is very important to be able to predict rMR when treating MR using transcatheter edge-to-edge repair because many patients have a small mitral valve opening area and would only be able to receive one device.
>
> **Professor Peter Lüdike**

A retrospective single-centre study in Essen looked at the predictability of post-delivery rMR in 100 patients treated with the MitraClip (91% treated between 2017 and 2018) and 100 patients treated with the PASCAL repair system (all treated between 2019 and 2020). The mean age of patients was 77 years. Baseline characteristics were similar between the two groups, except for higher numbers of patients with atrial

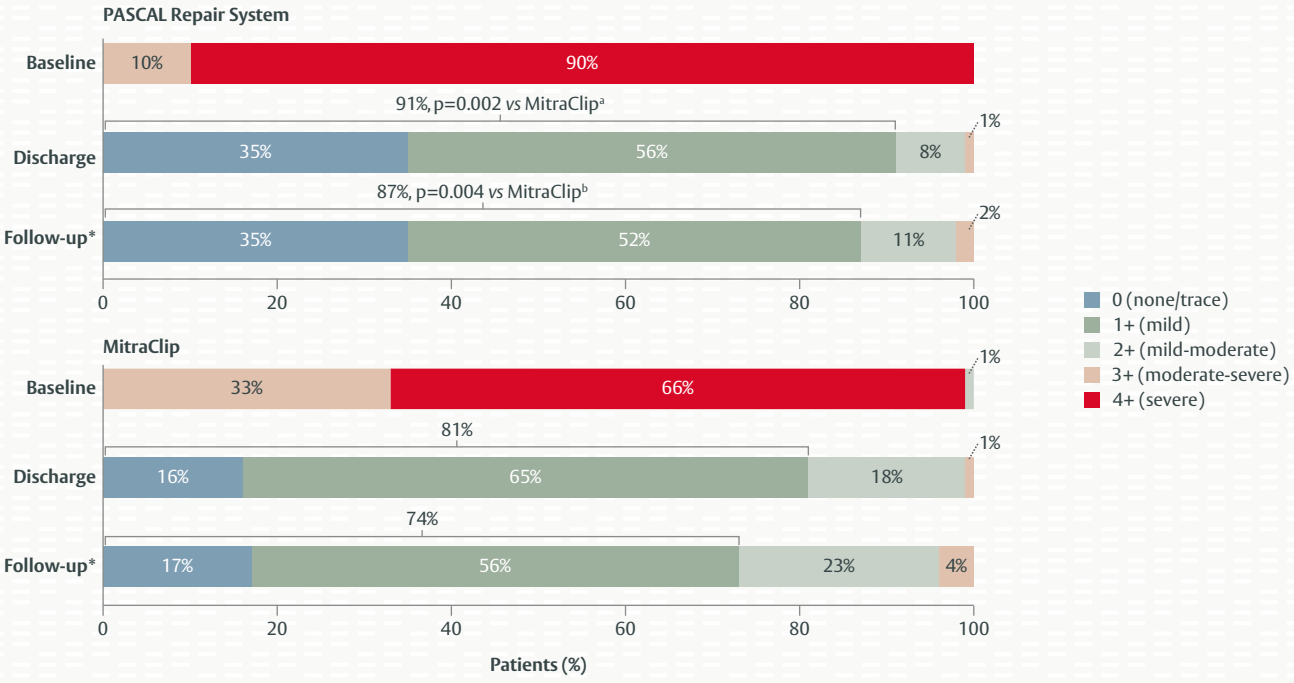


Figure 1. Post-procedural rMR following treatment with the MitraClip or PASCAL repair system in patients with MR ≥3+ at baseline.[5]

*PASCAL repair system : 113 days (n=63); MitraClip: 164 days (n=71). MR ≤1+ with the PASCAL repair system *versus* MitraClip at [a]discharge (91% *vs* 81%) and [b]follow up (87% *vs* 74%).

MR, mitral regurgitation; rMR, residual mitral regurgitation.

Adapted from Lüdike P *et al*. 2021.

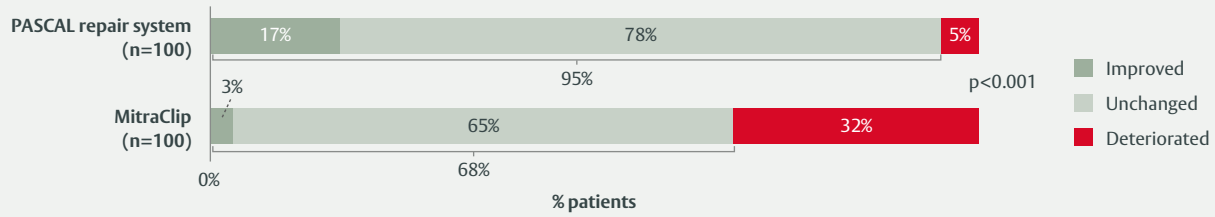


Figure 2. Predictability of post-delivery rMR after treatment with the MitraClip or PASCAL repair system.[5]

rMR, residual mitral regurgitation.

Adapted from Lüdike P *et al*. 2021.

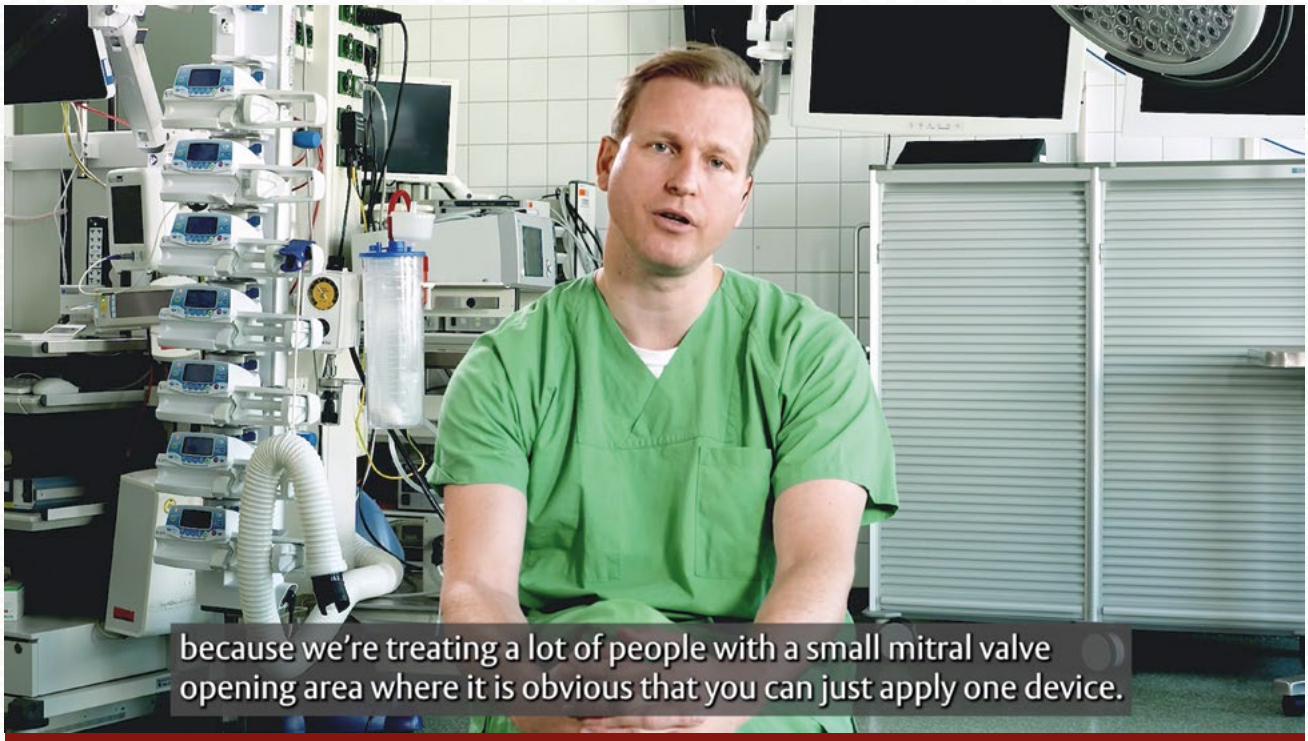
fibrillation (72% *vs* 49%; p<0.0001) and pre-interventional MR grade 3+ (33% *vs* 10%; p=0.0002) in the MitraClip *versus* PASCAL repair system group, respectively.[5] The rMR outcomes were classified into three groups depending on whether rMR deteriorated, remained stable or improved in the period from leaflet capture (pre-release) to implant deployment (post-delivery) based on the size, number, location and eccentricity of Doppler jets and analysis of quantitative echo parameters.[5]

> The ability to predict post-release rMR probably depends on a number of factors, including anatomy of the patient, technical aspects such as the release of tension before implant release, and also the individual technology itself.
>
> **Professor Peter Lüdike**

Overall, MR was effectively reduced following mitral valve repair with both the MitraClip and the PASCAL repair system (Figure 1). A significantly greater proportion of patients achieved rMR ≤1+ with the PASCAL repair system (91%) than with the MitraClip (81%; p=0.002). There was also a significantly greater improvement in rMR at discharge (p=0.002) and at follow-up (p=0.004) with the PASCAL repair system (mean follow-up 113 days) compared with the MitraClip (mean follow-up 164 days) (Figure 1).[5]

Post-delivery rMR was more likely to be maintained or improved with the PASCAL repair system compared with the MitraClip (p<0.001; Figure 2). Following implant deployment, rMR was unchanged or improved in 95% of patients treated using the PASCAL repair system and in 68% of patients treated using the MitraClip (Figure 2). Significantly more patients in the PASCAL repair system group experienced a reduction of rMR between leaflet capture and implant deployment compared with the MitraClip group (17% *vs* 3%; p=0.0015). Furthermore, almost one third of patients (32%) treated with the MitraClip experienced a deterioration in post-delivery rMR compared with only 5% of patients treated using the PASCAL repair system (p<0.0001; Figure 2).[5]

Compared with the PASCAL repair system, use of the MitraClip was associated with an almost 9-fold increased risk of acute deterioration in MR reduction following implant release



Listen to Professor Peter Lüdike's insights

(odds ratio 8.94 [95% confidence interval (CI) 3.31–24.13]; p<0.0002), which was independent of the patient's age, annular diameter, MR aetiology, leaflet lengths, tethering or the presence of calcification.[5]

One important limitation of this dataset is the lack of propensity matching or randomisation between the two cohorts. While this study suggests that implant design has the potential to contribute to the predictability of post-delivery rMR, further studies will be required to verify these conclusions.

Conclusion

This observational study suggests that intraprocedural rMR is more predictive of post-delivery rMR when patients are treated using the PASCAL repair system compared with the MitraClip.[5] While these findings may have implications for the choice of technology when conducting mitral valve repair, especially in patients with a small mitral valve opening, firm conclusions cannot yet be drawn and the data require further confirmation in prospective studies.

Post-market and real-world data with the PASCAL Platform in MR

Professor Dr med. Philipp Lurz
Herzzentrum Leipzig, Universitätsklinik für Kardiologie, Leipzig, Germany

Professor Philipp Lurz, an interventional cardiologist, is the Deputy Head of Cardiology at the Heart Center Leipzig and leads the programme for Grown-up Congenital Heart Disease and for mitral/tricuspid interventions. He is Principal Investigator of the MiCLASP registry and an investigator in the CLASP IID/IIF trial as well as in trials for multiple other therapies.

Dr med. Christian Besler
Herzzentrum Leipzig, Germany

Dr Christian Besler is an interventional cardiologist and Senior Physician at the Heart Center Leipzig. He has been actively involved in the clinical implementation and scientific advancement of tricuspid interventions, contributing as an investigator to the CLASP IID/IIF and HERACLES-HFpEF clinical studies.

The PASCAL platform has demonstrated robust and sustained clinical efficacy in highly selected patients with MR in the CLASP study.[6] Here, Professor Philipp Lurz and Dr Christian Besler highlight impressive outcomes from broader patient populations included in the MiCLASP registry and in a real-world study.[7,8]

The MiCLASP Registry

The **MiCLASP registry** is an ongoing European, prospective, multicentre, clinical follow-up study assessing the safety and effectiveness of the PASCAL platform in improving MR, functional status and quality of life in a post-market setting. Eligible patients were 18 years or older with symptomatic MR (grade ≥2+ as assessed by an Echo Core Lab), and were candidates for TMVr as determined by a Heart Team. Patients were typical of those at risk of MR, with a mean age of 77 years and poor functional status (82% had New York Heart Association [NYHA] functional class ≥III at baseline). Over half of patients (56%) had FMR at baseline, 26% had degenerative MR (DMR), 3% had MR of mixed aetiology and 16% had unknown MR aetiology.[8]

'Implant success rate was very high (97%) and most patients were discharged home without the need for rehabilitation or nursing care.'
Professor Philipp Lurz

'The PASCAL platform had a very good safety profile. Over 90% of patients had no major adverse events at all.'
Professor Philipp Lurz

Within the 262 patients enrolled so far, implant success rate was remarkable (97%), and a mean of 1.3 devices were implanted per patient, with a procedure time of 93 minutes. The overall length of hospital stay was short (4.7 days), and 90% of patients were discharged home.[8]

In the interim analysis, 204 patients had reached 30-day follow-up. The safety profile with the PASCAL platform was good, with a composite major adverse event (MAE) rate of 9.9% at 30 days according to the Clinical Events Committee. The most common MAE was severe bleeding (6.9%). Cardiovascular mortality (1.1%) and all-cause mortality (1.5%) rates were low, despite the high-risk patient population.[8]

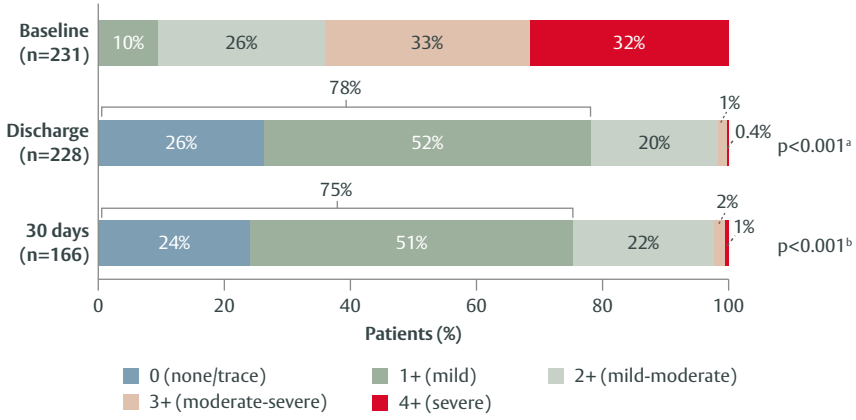


Figure 3. MR severity before and after treatment with the PASCAL platform in the MiCLASP study.[8]

Figure shows unpaired data. p-values calculated from paired analysis using Wilcoxon signed rank test for baseline *versus* [a]discharge (n=202; 77% MR ≤1+; 98% MR ≤2+) and [b]30 days (n=152; 75% MR ≤1+; 97% MR ≤2+).

MR, mitral regurgitation.

Adapted from Lurz P. 2021.

Early evidence of left ventricular reverse remodelling.[8]

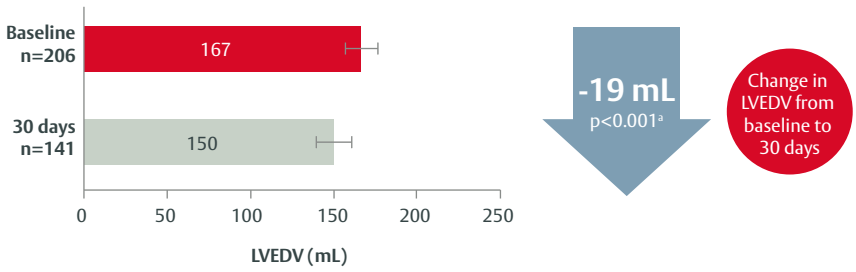


Figure 4. LVEDV before and after treatment with the PASCAL platform in the MiCLASP study.[8]

Graph shows unpaired data. Change in LVEDV and p-value presented for paired analysis; p-value calculated using Student's t-test, [a]baseline *versus* 30 days (n=119). Error bars represent 95% confidence interval.

LVEDV, left ventricular end-diastolic volume.

Adapted from Lurz P. 2021.

MR outcomes at 30 days

The MiCLASP study data demonstrated a significant MR reduction at 30 days following mitral valve repair using the PASCAL platform (p<0.001; Figure 3). Based on Core Lab assessment, 98% of patients achieved MR ≤2+ and 75% achieved MR ≤1+ at 30-day follow-up.[8]

'MR reduction with the PASCAL platform resulted in pronounced symptomatic improvement, including a vast improvement in NYHA class, a clear signal in terms of better quality of life, and a highly significant reduction in left ventricular end-diastolic volume indicating left ventricular reverse remodelling.'
Professor Philipp Lurz

There was also evidence of left ventricular (LV) reverse remodelling. Overall, LV end-diastolic volume (LVEDV) decreased by 19 mL between baseline and 30 days post-procedure (Figure 4).[8]

The reduction in MR observed at 30 days was complemented by significant improvements in functional status (p<0.001). At the 30-day follow-up, 62% of patients in the overall population achieved NYHA class ≤II (Figure 5). Significant improvements in quality-of-life measures were also

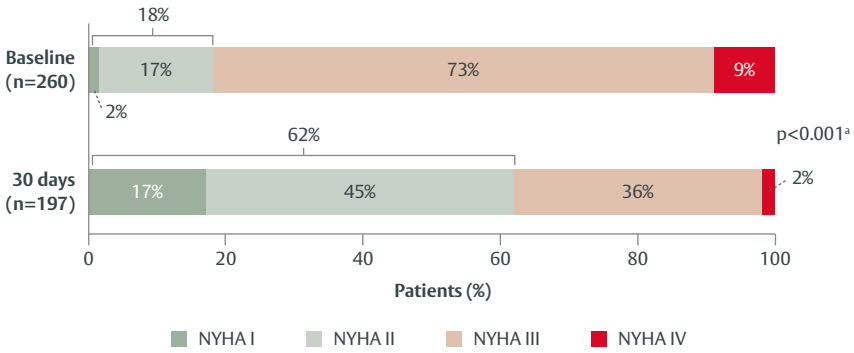


Figure 5. NYHA functional class before and after treatment with the PASCAL platform in the MiCLASP study.[8]

Figure shows unpaired data. p-value calculated from paired analysis using Wilcoxon signed rank test for [a]baseline *versus* 30 days (n=197; NYHA class I/II=62%).

NYHA, New York Heart Association.

Adapted from Lurz P. 2021.

'The real-world study from Bad Neustadt suggests that the MR reduction achieved with the PASCAL platform is durable at mid-term follow-up.'
Dr Christian Besler

observed at 30 days. In the overall population, the mean Kansas City Cardiomyopathy Questionnaire (KCCQ) score improved by 12 points (p<0.001) and the mean EuroQol 5 Dimensions Health Questionnaire (EQ5D) score improved by 6 points (p<0.001) between baseline and 30 days post-procedure.[8]

Outcomes from the MiCLASP study at 30 days post-implantation are similar to those observed in the CLASP study.[6,8] However, patient populations were slightly different in the two studies: the CLASP study included a more selected population consistent with the clinical trial design, whereas the MiCLASP study was a post-market study in a broader, real-world population more reflective of the daily clinical setting. Notably, the MiCLASP study also included a large number of centres, many of which had limited experience of the PASCAL platform, so outcomes from these centres are likely to improve even further as they progress along the learning curve for this technology.

ISTOCK.COM/CECILIE_ARCURS

'The MiCLASP study data show similar outcomes to the CLASP study but in a more real-world setting.'
Professor Philipp Lurz

Real-world mid-term outcomes from Bad Neustadt with the PASCAL Platform

A single-centre study conducted in 92 consecutive patients with symptomatic MR 3+/4+ between July 2019 and May 2021 at the Cardiovascular Center, Bad Neustadt adds further weight

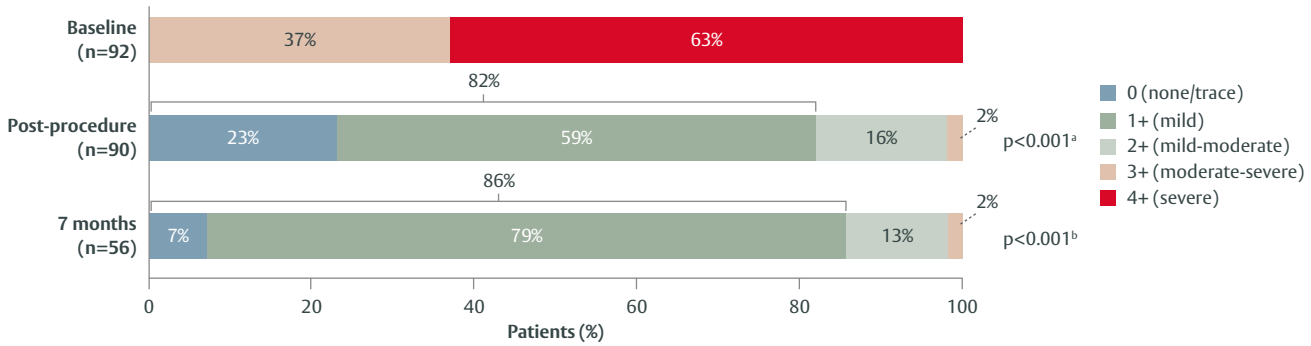


Figure 6. MR severity before and after treatment with the PASCAL platform in a real-world study.[7]

p-values calculated from paired analysis using Wilcoxon signed rank test; [a]baseline *versus* post-procedure and [b]baseline *versus* 7 months.

MR, mitral regurgitation.

Adapted from Barth S *et al.* 2021.

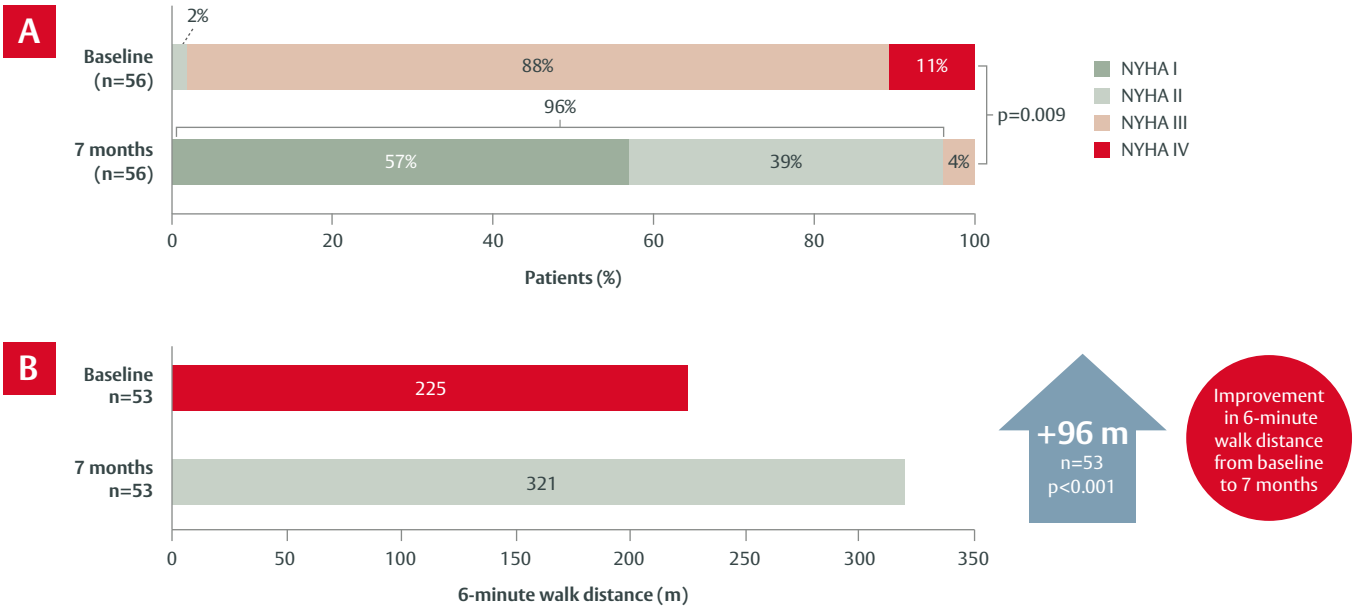


Figure 7. NYHA functional class (A) and 6-minute walk distance (B) at baseline and at 7 months after treatment with the PASCAL platform in a real-world study.[7]

p-values calculated using the Wilcoxon signed rank test for paired patients.

NYHA, New York Heart Association.

Adapted from Barth *et al.* 2021.

of evidence supporting the efficacy and safety of the PASCAL platform in a real-world setting.[7] Patients with symptomatic severe MR showed significant improvements in MR grade ($p<0.001$) and functional status ($p=0.009$) between baseline and 7 months after deployment of the PASCAL implant. While all patients had MR ≥3+ at baseline, 82% of patients had MR ≤1+ post-procedure and 86% had MR ≤1+ at 7 months (Figure 6). Nearly all patients (96%) achieved NYHA class ≤II at 7 months,

'The overall picture that appears from all of the available data is that MR can be very safely and effectively treated using the PASCAL platform.'
Dr Christian Besler

ISTOCK.COM/HALFPOINT

'With the positive results observed for MR reduction, LV reverse remodelling, improvements in functional capacity and quality of life across studies, this provides a robust basis for the application of the PASCAL platform to treat patients with MR.'
Dr Christian Besler

and 6-minute walking distance improved by 96 m compared with baseline (p<0.001; Figure 7).[7]

These positive outcomes were matched by quality-of-life benefits, including a 19-point improvement in KCCQ score (p<0.001) and an 18-point improvement in EQ5D score (p<0.001). Together, these data add to the growing body of evidence supporting the efficacy and safety of the PASCAL platform for the treatment of severe symptomatic MR in real-world patient populations.[7,8]

Conclusion

The 30-day data from the ongoing MiCLASP registry reinforce outcomes from the CLASP study but in a post-market setting, including a broad patient population and centres with varied experience of the technology.[6,8] These data confirm significant reductions in MR grade, improvements in symptoms and quality of life, and evidence of LV remodelling following mitral valve repair with the PASCAL platform.[6,8] Complementing these data, real-world outcomes from a single-centre study further emphasise the impressive results observed with the PASCAL platform in unselected patients with MR.[7] The PASCAL platform is now considered an important transcatheter technique for mitral valve repair. Understanding which patients would benefit most from specific transcatheter edge-to-edge repair (TEER) devices will be addressed over the next few years in the CLASP IID/IIF study (NCT03706833).

PASCAL Repair System

In your hands we can navigate amazing.

Your tricuspid regurgitation patients can benefit from the unique PASCAL implant elongation, minimising chordal entanglement, promoting safe subvalvular manœuvring.

Navigate even complex anatomies during transcatheter tricuspid valve repair procedures.

Learn more at Edwards.com/PASCAL-TR

Edwards

PASCAL Platform in MR

Latest data on the PASCAL Platform for TMVr: 2-year outcomes from the CLASP Study

Professor Dr med. Ulrich Schäfer

Bundeswehrzentral-krankenhaus Koblenz, Germany | Global Principal Investigator of the CLASP Study

Professor Ulrich Schäfer is Director of the Medizinische Klinik at Bundeswehrzentralkrankenhaus Koblenz and is Global Principal Investigator of the CLASP study. With a special focus in the therapy of structural heart diseases within the framework of catheter-interventional valve therapy and other structural heart defects, Professor Schäfer has been instrumental in the development of therapy programmes for the treatment of structural heart diseases.

'The CLASP study now shows very promising 2-year outcomes, with huge reductions in symptoms in patients treated for MR.'
Professor Ulrich Schäfer

A growing body of evidence supports the safety and performance of TMVr for the treatment of patients with MR.[6,9] One-year data from the CLASP study, highlighted in *Issue 3*, showed sustained MR reduction and significant improvement in functional status and quality of life in patients with severe MR following implantation of the PASCAL repair system.[9] Now, Professor Ulrich Schäfer presents outcomes from patients who have reached 2-year follow-up in the CLASP study.[6]

The CLASP Study

The **CLASP study,** an ongoing single-arm, multicentre, prospective study, is assessing the safety and performance of the PASCAL platform as an intervention for patients with severe MR. Eligible patients have MR ≥3+ at baseline despite medical therapy according to echocardiography conducted by an independent Echo Core Lab. Of 124 patients enrolled in the study, 69% had FMR, 31% had DMR and 60% had NYHA functional class III–IVa at baseline.[6] Implant success rate* in the CLASP study was high, standing at 96% in the overall patient population, 96% in patients with FMR and 95% in patients with DMR.[6]

Adverse events, survival and hospitalisation rates

As at the 1-year follow-up, a favourable safety profile was observed with the PASCAL platform at 2 years.[6,9] The site-reported composite MAE rate in patients treated with the PASCAL platform was 16.9%, and rates of all-cause mortality and heart failure (HF) rehospitalisation were 15.3% and 13.7%, respectively (Table 1).[6]

Table 1. Major adverse event rates in the CLASP study.[6]

Major adverse events (n=124)	CEC-adjudicated		Site-reported
	30 days n (%)	1 year n (%)	2 years n (%)
Cardiovascular mortality	1 (0.8)	7 (5.6)	11 (8.9)
Stroke	1 (0.8)	2 (1.6)	4 (3.2)
Myocardial infarction	0	2 (1.6)	3 (2.4)
New need for renal replacement therapy	1 (0.8)	1 (0.8)	1 (0.8)
Severe bleeding[a]	9 (7.3)	14 (11.3)	9 (7.3)
Reintervention for study device-related complications	1 (0.8)	2 (1.6)	3 (2.4)
Composite MAE rate	10 (8.1)	23 (18.5)	21 (16.9)
Other events			
All-cause mortality	1 (0.8)	10 (8.1)	19 (15.3)
Heart failure rehospitalisation	3 (2.4)	15 (12.1)	17 (13.7)

* Device deployed as intended and delivery system successfully retrieved as intended at time of patient's exit from cardiac catheterisation laboratory.

[a] Major, extensive, life-threatening or fatal bleeding defined by the Mitral Valve Academic Research Consortium.

CEC, Clinical Events Committee; MAE, major adverse event.

Table adapted from Szerlip M *et al.* 2021.

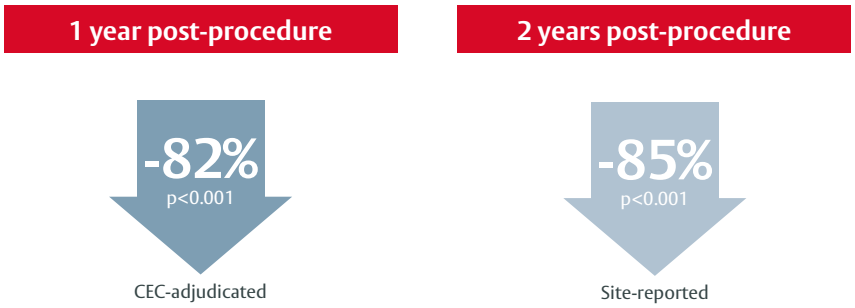


Figure 8. Annualised HF hospitalisation rates in the CLASP study *versus* 1 year pre-procedure.[6]

CEC, Clinical Events Committee; HF, heart failure.

Adapted from Szerlip M *et al.* 2021.

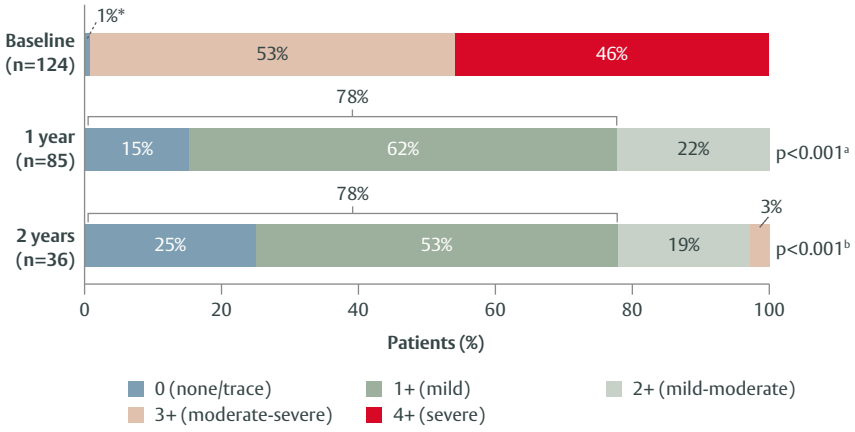


Figure 9. MR severity before and after treatment with the PASCAL platform in the CLASP study.[6]

Figure shows unpaired data. p-values calculated from paired analysis using Wilcoxon signed rank test; [a]baseline *versus* 1 year (n=85) and [b]baseline *versus* 2 years (n=36); *One patient had MR 1+ by TTE although 3+ by TEE.

MR, mitral regurgitation; TEE, transoesophageal echocardiography; TTE, transthoracic echocardiography.

Adapted from Szerlip M *et al.* 2021.

The 2-year follow-up data demonstrate a high rate of survival and freedom from HF rehospitalisation and a significant reduction in annualised HF hospitalisation rate following implantation of the PASCAL repair system. Two-year survival rates were 80.3 ± 4.2% (mean ± standard error) in the overall population and were higher in patients with DMR (94.3 ± 3.9%) than in patients with FMR (72.3 ± 6.0%). A similar pattern was seen for 2-year freedom from HF rehospitalisation rates (84.3 ± 3.6% overall), with a higher rate in patients with DMR (97.3 ± 2.7%) than in patients with FMR (77.5 ± 5.1%). Overall, the site-reported annualised HF hospitalisation rate at 2 years was significantly reduced compared with 1-year pre-procedure (reduction rate 85.0% [95% CI 78.1–89.7]; p<0.001), mirroring the Clinical Events Committee-adjudicated benefit observed at 1-year post-procedure (Figure 8).[6]

'Nearly all patients (97%) achieved mild-to-moderate MR and 78% achieved mild or trace MR at the 2-year follow-up.'
Professor Ulrich Schäfer

MR outcomes at 2 years

The 2-year CLASP study data confirm the significant and durable MR reduction previously observed at 1 year following treatment with the PASCAL platform.[6] Based on Core Lab assessment, nearly all patients (97%) achieved mild–moderate MR or less (grade ≤2+) and 78% achieved mild or no MR (grade ≤1+) at 2-year follow-up (Figure 9).[6] The significant reductions in MR were achieved irrespective of MR aetiology; MR grades ≤2+ and ≤1+, respectively, were achieved in 100% and 71% of the DMR subset and in 95% and 84% of the FMR subset.[6]

There was also evidence of LV reverse remodelling following treatment with the PASCAL platform, with a 33 mL reduction in LVEDV between baseline and 2 years (Figure 10).[6]

These impressive clinical outcomes were matched by significant and sustained functional improvements in patients treated with the PASCAL platform.

'As we see a very promising reduction in MR with the PASCAL repair system, it is not surprising that this translates into LV reverse remodelling.'
Professor Ulrich Schäfer

At the 2-year follow-up, a significantly higher proportion of patients in the overall patient population (93%) were NYHA class ≤II compared with baseline (40%; Figure 11).

'Functional class (NYHA class ≤II) remained stable in over 90% of patients at 2 years, which is remarkable.'
Professor Ulrich Schäfer

Conclusion

The 2-year follow-up data from the CLASP study confirm significant and durable reductions in MR grade in patients treated with the PASCAL platform, irrespective of their MR aetiology.[6] These findings complement the 30-day and 1-year CLASP study data, confirming impressive long-term efficacy of the PASCAL platform in patients with severe MR.[6,9,10] Alongside improvements in MR grade and a favourable safety profile, there were significant and sustained improvements in functional class, as well as evidence of LV remodelling. These data provide strong support for the use of the PASCAL platform in patients with moderate-to-severe MR.

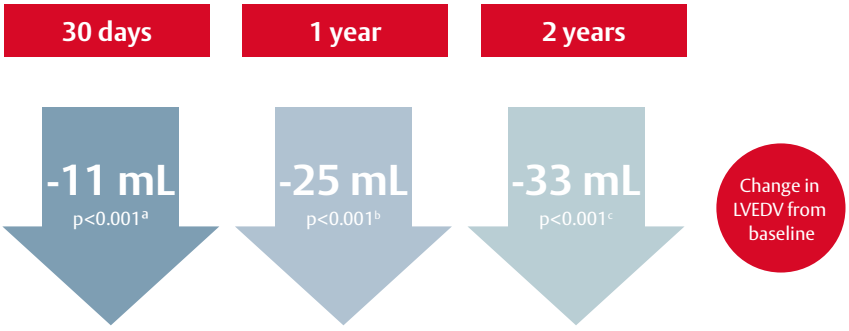


Figure 10. Mean LVEDV before and after treatment with the PASCAL platform in the CLASP study.[6]

Change in LVEDV and p-values presented for paired analysis; p-value calculated using Student's T-test, baseline *versus* [a]30 days (n=91), [b]1 year (n=67) and [c]2 years (n=30).

LVEDV, left ventricular end-diastolic volume.

Adapted from Szerlip M *et al.* 2021.

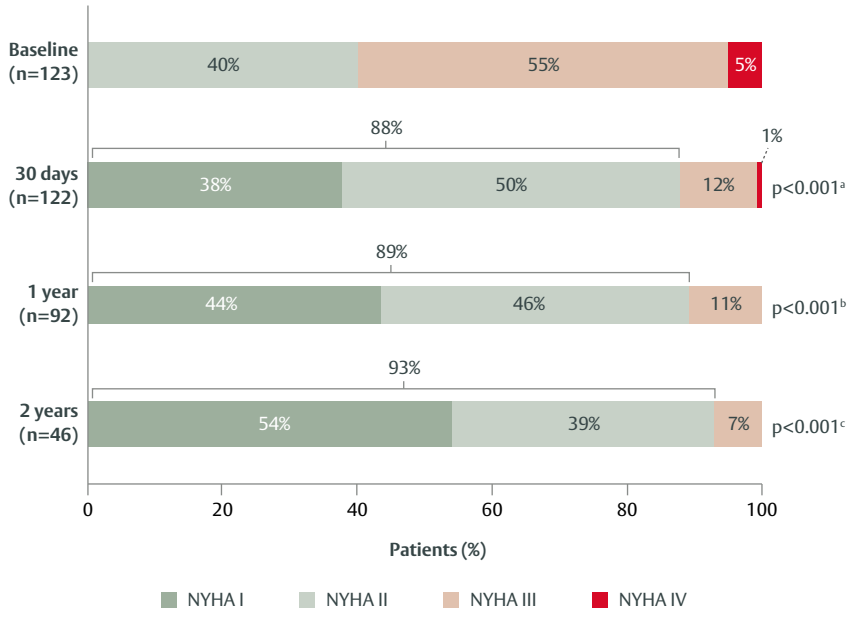


Figure 11. NYHA functional class before and after treatment with the PASCAL platform in the CLASP study.[6]

p-values calculated from paired analysis using Wilcoxon signed rank test, baseline *versus* [a]30 days (n=121), [b]1 year (n=91) and [c]2 years (n=46).

NYHA, New York Heart Association.

Adapted from Szerlip M *et al.* 2021.

New ESC-HF and ESC/EACTS-VHD Guidelines: Implications for the treatment of MR and TR

The treatment of patients with MR and TR continues to evolve with the emergence of new devices and an expanding dataset from clinical trials and real-world studies. Two recently published treatment guidelines, the 2021 ESC/EACTS Guidelines on the management of valvular heart disease (ESC/EACTS-VHD Guidelines) and the 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic HF (ESC-HF Guidelines), now provide updated recommendations for MR and TR based on the latest available evidence.[11,12] Here, Professor Ulrich Schäfer, Dr Marianna Adamo and Professor Marco Metra give their perspectives on these updates and how they impact the treatment algorithms for MR and TR.

Professor Dr med. Ulrich Schäfer
Bundeswehrzentral-krankenhaus Koblenz, Germany | Global Principal Investigator of the CLASP Study

Dr Marianna Adamo
University and ASST Spedali Civili of Brescia, Brescia, Italy

Dr Marianna Adamo is an interventional cardiologist at ASST Spedali Civili in Brescia and Senior Researcher at the University of Brescia. She obtained the Certificate of Advanced Studies in Mitral and Tricuspid Valve Structural Interventions at Zurich University in April 2020. Her main topic of research is managing valvular heart disease in heart failure. She is a member of the ESC, Heart Failure Association (HFA), European Association of Percutaneous Cardiovascular Interventions (EAPCI) and Italian Society of Interventional Cardiology (GISE).

Professor Marco Metra
University and ASST Spedali Civili of Brescia, Brescia, Italy

Marco Metra is Professor of Cardiology and Director of the Institute of Cardiology ASST Spedali Civili di Brescia. He co-chaired the committee for the 2021 ESC Guidelines on Heart Failure and is Editor-in-Chief of *European Journal of Heart Failure*. Professor Metra has been Principal Investigator for many clinical trials.

Role of the Heart Team

A cornerstone of the new treatment guidelines is the recommendation for a multidisciplinary Heart Team to decide on the eligibility of patients for specific interventions (**Class I** recommendation).[11,12]

The Heart Team is responsible for managing and integrating clinical evaluations, imaging assessments, individual anatomical and procedural aspects, and patients' perspectives and expectations when deciding on a particular intervention. As such, the Heart Team should include experts from a range of disciplines, including cardiac surgeons, interventional cardiologists, clinical cardiologists, imaging specialists, cardiovascular anaesthesiologists and other disciplines who need to collaborate to reach a patient-centred decision (Figure 12).

'The updated guidelines now provide a common pathway for patients with MR and TR and acknowledge that there are catheter-based treatments that are really helping these patients.'
Professor Ulrich Schäfer

Treatment of patients with severe MR

A key driver for amending MR treatment guidelines was the data from the COAPT trial, which demonstrated a prognostic benefit of TEER of the mitral valve in selected patients with at least moderate-to-severe secondary MR and symptomatic HF despite optimal medical therapy.[13] Importantly, the benefit of TEER appears specific for patients meeting the COAPT inclusion criteria (i.e. LV ejection fraction 20–50%, left ventricular end-systolic diameter ≤70 mm, systolic pulmonary pressure <70 mmHg, absence of moderate or severe right ventricular dysfunction), as a

'An important driver for the guideline updates was the availability of new devices for both MR and TR, which show promising results.'
Dr Marianna Adamo

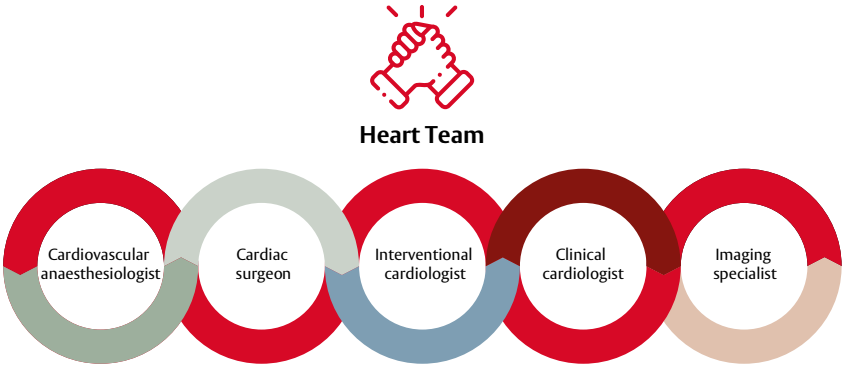


Figure 12. Multidisciplinary Heart Team at the centre of treatment decision-making.[12]

similar benefit was not observed in the MITRA-FR trial, which enrolled patients with less severe secondary MR.[12–14]

In chronic, severe, secondary MR, the new ESC/EACTS-VHD Guidelines and ESC-HF Guidelines now provide a clearer route for selecting patients for TEER, based on the COAPT trial data.[11–13] For patients who are not eligible for surgery or do not require coronary revascularisation, have persistence of symptoms and significant MR despite optimal medical therapy, and who fulfil COAPT inclusion criteria, TEER of the mitral valve is upgraded to a **Class IIa** recommendation with level B evidence (Table 2). For patients who do not fulfil COAPT inclusion criteria, TEER remains a **Class IIb** recommendation and may be considered for improving symptoms or as a bridge to transplantation or an LV assist device (Table 2).[11,12]

'The revised guidelines now recognise two distinct groups of patients who can receive TEER for secondary MR, but with different indications and different expectations of clinical benefit.'
Dr Marianna Adamo

'TEER is now reinforced from a Class IIb to a Class IIa indication for COAPT-like patients with secondary MR, providing stronger support for this therapy.'
Professor Ulrich Schäfer

Treatment of patients with severe TR

Tricuspid valve interventions are underused in clinical practice and often initiated too late, even though appropriate timing of interventions is considered a crucial factor in avoiding irreversible right ventricular damage and organ failure.[12] Guidelines emphasise the need for more comprehensive evaluation and earlier surgery for **primary TR**, including a **Class IIa** recommendation for consideration of surgery in asymptomatic or mildly symptomatic patients with isolated severe primary TR and right ventricular dilatation who are appropriate for surgery.[11,12]

Table 2. Key updates to the ESC/EACTS-VHD Guidelines and ESC-HF Guidelines related to the percutaneous treatment of MR and TR.[11,12]

Key updates	2021 ESC/ EACTS-VHD Guidelines	2021 ESC-HF Guidelines
Eligibility for intervention decided by a Heart Team	I	I
Secondary MR and meets COAPT-like criteria*	IIa for TEER	IIa for TEER
Secondary MR but does not meet COAPT-like criteria • No change in guidance for TEER	IIb for TEER or other transcatheter therapy	IIb for TEER only
Secondary TR • TTVr only in symptomatic inoperable patients at a Heart Valve Centre with TV expertise	TTVr IIb (C)	No specific guidance

*LVEF 20–50%, LVESD ≤70 mm, systolic pulmonary pressure <70 mmHg, absence of moderate or severe right ventricular dysfunction or severe TR, absence of haemodynamic instability.[13]

EACTS, European Association for Cardio-Thoracic Surgery; ESC, European Society of Cardiology; HF, heart failure; LVEF, left ventricular ejection fraction; LVESD, left ventricular end-systolic diameter; TEER, transcatheter edge-to-edge repair; TR, tricuspid regurgitation; TTVr, transcatheter tricuspid valve repair; TV, tricuspid valve; VHD, valvular heart disease.

For patients with **secondary TR**, the new ESC/EACTS-VHD Guidelines recognise the feasibility of transcatheter therapies. The guidelines include a new **Class IIb** recommendation for transcatheter intervention for symptomatic, severe, secondary TR in inoperable patients, provided this is performed at a Heart Valve Centre with expertise in the treatment of tricuspid valve disease (Table 2).[12] Percutaneous management of TR is also referred to in the ESC-HF Guidelines as a potential treatment option, although not as a specific recommendation.[11]

'With a new Class IIb indication for edge-to-edge repair in inoperable patients with symptomatic, severe, secondary TR, the tricuspid valve is no longer forgotten in the guidelines.'
Professor Ulrich Schäfer

Conclusion

Guidelines for the treatment of MR and TR continue to evolve as they incorporate the latest clinical evidence for mitral and tricuspid valve repair. In the latest guidelines, early intervention is considered beneficial in the treatment of both primary MR and primary TR.[11,12] The guidelines also now recognise two distinct groups of patients who can receive TEER for secondary MR, but with different indications and different expectations of clinical benefit, and transcatheter therapies are also considered feasible in patients with secondary TR.[11,12] Additional data from clinical studies, observational studies and patient registries may lead to further expansion of the indications for the transcatheter treatment of valvular heart disease.

'The treatment guidelines should continue to evolve, especially to address the treatment of asymptomatic patients and patients with combined disease.'
Professor Ulrich Schäfer

Treatment options for patients with TR: Looking to the future

Dr med. Ralph Stephan von Bardeleben
Heart Valve Center,
Universitätsmedizin
Mainz, Germany

Dr Ralph Stephan von Bardeleben is an interventional cardiologist and Head of the Center of Structural Heart Disease Interventions and the Heart Valve Center in Mainz. He is a Principal Investigator for the CLASP IID/IIF study and a Steering Committee member for the TRISCEND II study. Dr von Bardeleben specialises in percutaneous valve therapy and has been involved in many other clinical trials, including REPAIR, TRI-REPAIR and MiCLASP.

A range of transcatheter approaches are becoming available or are in development for the treatment of patients with TR, including transcatheter tricuspid valve repair, annuloplasty and tricuspid valve replacement. Understanding how these different treatment approaches should be applied to specific patient populations will be key to optimising clinical outcomes. Here, Dr Ralph Stephan von Bardeleben provides his perspectives on how tricuspid valve repair and annuloplasty fit into the treatment landscape and how this may evolve over time. The future outlook for tricuspid valve replacement will be discussed in a later edition of *TMTT Today*.

> A significant challenge for successful treatment of patients with TR is to catch them early in the disease process, before ventricular and atrial remodelling has become too extensive.
>
> **Dr Ralph Stephan von Bardeleben**

Q: What are the current treatment options for patients with TR?

'Currently, most patients with TR are treated using guideline-directed medical therapy, predominantly based on diuretic therapy, and these patients are followed conservatively. A minority of patients, less than 1%, are treated surgically, and even fewer currently receive transcatheter interventions.'

Q: What are the challenges in treating patients with TR?

'Patients with TR typically exhibit non-specific symptoms, such as fatigue, leg oedema, renal impairment, effusions of the pleural space, ascites, congestion of the liver or gastric perfusion. While patients may feel unwell, they may not be overly burdened by their disease and are often overlooked for treatment. A significant challenge for successful treatment of these patients is to catch them early in the disease process, before ventricular and atrial remodelling has become too extensive. If this can be achieved, we have a growing toolbox of approaches we can use to treat these patients, including annuloplasty, leaflet repair and combination therapy.'

Q: What will be the key developments in the treatment of TR over the next few years?

'Improving the benefit–risk ratio for patients will be a key development for the treatment of patients with TR. Historically, patients with isolated TR have not been treated owing to high 30-day mortality. However, this burden may potentially be reduced by transcatheter approaches, including leaflet repair, annuloplasty and tricuspid valve replacement, which take advantage of minimally invasive access to the right atrium and tricuspid valve via blood vessels.'

Q: What will a typical procedure in a cathlab look like in 2026?

'I believe we will move away from general anaesthesia at intubation to procedures in which the patient is conscious. Ideally, procedures will be faster, around 0.5–1 hour in duration, will involve transcatheter approaches, such as leaflet repair, annuloplasty or valve replacement, and will not require contrast agents. I expect that minimally invasive procedures will reduce interventional, intraprocedural and in-hospital risks to patients, which will be reflected in low mortality rates.'

Q: How will leaflet repair fit into the treatment landscape in 2026?

'I believe leaflet repair will become the treatment of choice for most patients with severe TR owing to its favourable benefit-to-risk profile. One-year data from a compassionate-use study of 30 patients with severe TR treated with the PASCAL platform showed 93% survival, alongside significant TR reduction (86% of patients had moderate TR or less) and improvements in clinical symptoms.'[15]

Q: What are the key benefits and limitations of tricuspid valve repair over other treatment modalities, such as annuloplasty?

'With tricuspid valve repair, there is no impairment of the heart's electrical conduction system. Also, extremely tethered leaflets, especially the septal leaflets, can be brought together using leaflet repair devices. Modern nitinol systems with independent clasp actuation, such as the PASCAL platform, can be used to treat coaptation gaps of approximately 8–10 mm, whereas larger coaptation gaps may require leaflet repair in combination with annuloplasty.'

Q: How will percutaneous annuloplasty fit into the treatment landscape in 2026?

'Percutaneous annuloplasty may play an important role alongside leaflet repair for selected patients who are limited in their potential to undergo oral anticoagulation. I also see a role for percutaneous annuloplasty that is adapted to more severe disease processes, with a varied length of annuloplasty band.'

Q: How will a TR portfolio offering repair, replacement and annuloplasty be used in 2026?

'The answer to this question will rely heavily on the information we gain from clinical trials, such as CLASP TR,[16] CLASP II TR,[17] TriBAND,[18] TRISCEND[19] and TRISCEND II.[20] I expect we will see not only the importance of the benefit–risk ratio but also that of the benefit–time ratio, as shorter procedures will likely benefit patient outcomes in addition to maximising cathlab resources. Devices that offer a contrast-dye-free procedure may benefit patients with renal impairment. Percutaneous annuloplasty offers the potential to keep further therapy options open and may be preferred as a first step in the treatment procedure. However, I expect most procedures will be leaflet repairs.'

Q: Which patients are likely to benefit most from this comprehensive TR portfolio approach?

'A toolbox approach to the treatment of TR is important because we will face many different aetiologies. Although secondary TR accounts for approximately 90% of cases, we must also consider other situations, such as TR caused by pacemaker and implantable cardioverter defibrillator leads, severe tethering, and atrial dilatation due to atrial fibrillation. Different diagnostic approaches may highlight patients requiring different therapeutic approaches.'

> 'I believe leaflet repair will become the treatment of choice for most patients with severe TR owing to its favourable benefit-to-risk profile'
>
> **Dr Ralph Stephan von Bardeleben**

Conclusion

For patients with MR, the PASCAL platform provides a highly predictable and stable reduction in MR and excellent mid-to-long-term improvements in functional class, exercise capacity and quality of life (Table 3).[5–8] With these benefits, the PASCAL platform is an important transcatheter technique for mitral valve repair that more and more European hospitals are adopting. Treatment of chronic, severe, secondary MR using TEER has now been upgraded to a Class IIa recommendation in newly updated clinical guidelines, reflecting the growing body of evidence supporting its efficacy and safety in this setting.[11,12] Studies are currently underway to assess the relative benefits of MR treatment approaches within specific patient populations to provide a clearer picture of how these exciting new technologies will best be deployed within the MR treatment landscape. For inoperable patients with symptomatic severe secondary TR, new ESC/EACTS-VHD Guidelines recognise the feasibility of transcatheter therapies,[12] and a toolbox approach to treatment is likely to include leaflet repair, annuloplasty and valve replacement in the future.

Table 3. Summary of latest studies on the treatment of MR using the PASCAL platform.[5–8]

Study	Design	No. of patients	% patients with MR ≤1+ post-repair	Other key results
CLASP study[6]	Multicentre, prospective	124 (PASCAL platform)	PASCAL: 78% at 2 years	Significant improvements in LVEDV and NYHA class, 80% survival, 84% freedom from HF rehospitalisation
MiCLASP study[8]	Multicentre, prospective, post-market	262 (PASCAL platform)	PASCAL: 75% at 30 days	Significant improvements in LVEDV, NYHA class, and KCCQ and EQ5D scores
Essen[5]	Single-centre, retrospective, real-world	100 (PASCAL repair system) 100 (MitraClip)	PASCAL: 87% at 113 days MitraClip: 74% at 164 days	No deterioration in post-delivery rMR: 95% of PASCAL patients *vs* 68% of MitraClip patients
Bad Neustadt[7]	Single-centre, retrospective, real-world	92 (PASCAL platform)	PASCAL: 86% at 7 months	Significant improvements in NYHA class, 6-minute walk distance, and KCCQ and EQ5D scores

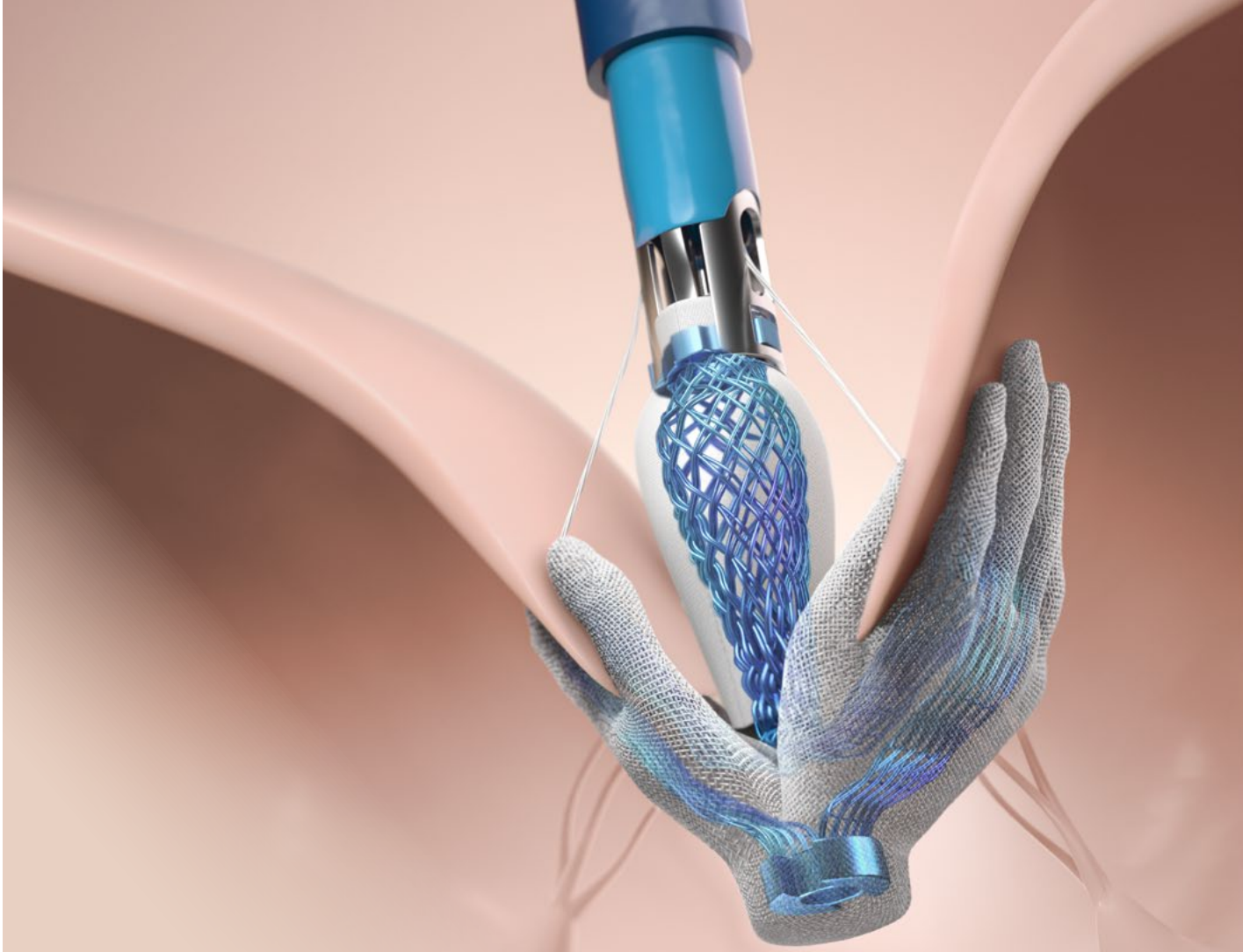
Ask your questions...

We can be reached at TMTT-Today@edwards.com to answer your questions about this issue of TMTT Today.

EQ5D, EuroQol 5 Dimensions Health Questionnaire; HF, heart failure; KCCQ, Kansas City Cardiomyopathy Questionnaire; LVEDV, left ventricular end-diastolic volume; NYHA, New York Heart Association; rMR, residual mitral regurgitation.

References

1. De Bonis M, Lapenna E, Lorusso R *et al.* Very long-term results (up to 17 years) with the double-orifice mitral valve repair combined with ring annuloplasty for degenerative mitral regurgitation. *J Thorac Cardiovasc Surg.* 2012; **144:** 1019–26.
2. Heikkinen J, Biancari F, Uusimaa P *et al.* Long-term outcome after mitral valve repair. *Scand Cardiovasc J.* 2005; **39:** 229–36.
3. Meyer MA, von Segesser LK, Hurni M *et al.* Long-term outcome after mitral valve repair: a risk factor analysis. *Eur J Cardiothorac Surg.* 2007; **32:** 301–7.
4. Reichart D, Kalbacher D, Rubsamen N *et al.* The impact of residual mitral regurgitation after MitraClip therapy in functional mitral regurgitation. *Eur J Heart Fail.* 2020; **22:** 1840–8.
5. Lüdike P, Riebisch M, Schindhelm F *et al.* Impact of mitral valve repair technologies on predictability of post-delivery residual mitral regurgitation. *JACC Cardiovasc Interv.* 2021; **14**: 2638–40 (retrospective, single-centre analysis, 2017–2020).
6. Szerlip M, Spargias KS, Makkar R *et al.* 2-year outcomes for transcatheter repair in patients with mitral regurgitation from the CLASP study. *JACC Cardiovasc Interv.* 2021; **14:** 1538–48.
7. Barth S, Shalla A, Kikec J *et al.* Functional and hemodynamic results after transcatheter mitral valve leaflet repair with the PASCAL device depending on etiology in a real-world cohort. *J Cardiol.* 2021; **78:** 577–85.
8. Lurz P. 30-day outcomes for mitral repair with the PASCAL Transcatheter Valve Repair System from the MiCLASP post-market clinical follow-up study. Oral presentation Lond21A-OP009 at PCR London Valves, 2021.
9. Webb JG, Hensey M, Szerlip M *et al.* 1-year outcomes for transcatheter repair in patients with mitral regurgitation from the CLASP study. *JACC Cardiovasc Interv.* 2020; **13:** 2344–57.
10. Lim DS, Kar S, Spargias K *et al.* Transcatheter valve repair for patients with mitral regurgitation: 30-day results of the CLASP study. *JACC Cardiovasc Interv.* 2019; **12:** 1369–78.
11. McDonagh TA, Metra M, Adamo M *et al.* 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. *Eur Heart J.* 2021; **42:** 3599–726.
12. Vahanian A, Beyersdorf F, Praz F *et al.* 2021 ESC/EACTS Guidelines for the management of valvular heart disease. *Eur Heart J.* 2021: doi:10.1093/eurheartj/ehab395.
13. Asch FM, Grayburn PA, Siegel RJ *et al.* Echocardiographic outcomes after transcatheter leaflet approximation in patients with secondary mitral regurgitation: The COAPT trial. *J Am Coll Cardiol.* 2019; **74:** 2969–79.
14. Iung B, Armoiry X, Vahanian A *et al.* Percutaneous repair or medical treatment for secondary mitral regurgitation: Outcomes at 2 years. *Eur J Heart Fail.* 2019; **21:** 1619–27.
15. Kitamura M, Fam NP, Braun D *et al.* 12-month outcomes of transcatheter tricuspid valve repair with the PASCAL system for severe tricuspid regurgitation. *Catheter Cardiovasc Interv.* 2021; **97:** 1281–9.
16. ClinicalTrials.gov. Edwards CLASP TR EFS (CLASP TR EFS). Available at: https://clinicaltrials.gov/ct2/show/NCT03745313 [Accessed 9 December 2021].
17. ClinicalTrials.gov. Edwards PASCAL Transcatheter Valve Repair System Pivotal Clinical Trial (CLASP II TR). Available at: https://clinicaltrials.gov/ct2/show/NCT04097145 [Accessed 9 December 2021].
18. ClinicalTrials.gov. Transcatheter Repair of Tricuspid Regurgitation With Edwards Cardioband TR System Post Market Study (TriBAND). Available at: https://clinicaltrials.gov/ct2/show/NCT03779490 [Accessed 9 December 2021].
19. ClinicalTrials.gov. 2019-06 TRISCEND Study. Available at: https://clinicaltrials.gov/ct2/show/NCT04221490 [Accessed 9 December 2021].
20. ClinicalTrials.gov. TRISCEND II Pivotal Trial. Available at: https://clinicaltrials.gov/ct2/show/NCT04482062 [Accessed 9 December 2021].



PASCAL Repair System

In your hands we can flex amazing.

For your mitral regurgitation patients, our spring based passive-closing system respects native anatomy. Nitinol design – PASCAL Repair System.

Innovation in leaflet repair. Learn more about the PASCAL Platform at Edwards.com/PASCAL

For professional use. For a listing of indications, contraindications, precautions, warnings, and potential adverse events, please refer to the Instructions for Use (consult eifu.edwards.com where applicable).

Edwards devices placed on the European market meeting the essential requirements referred to in Article 3 of the Medical Device Directive 93/42/EEC bear the CE marking of conformity.

Edwards Lifesciences • Route de l'Etraz 70, 1260 Nyon, Switzerland • edwards.com

Edwards