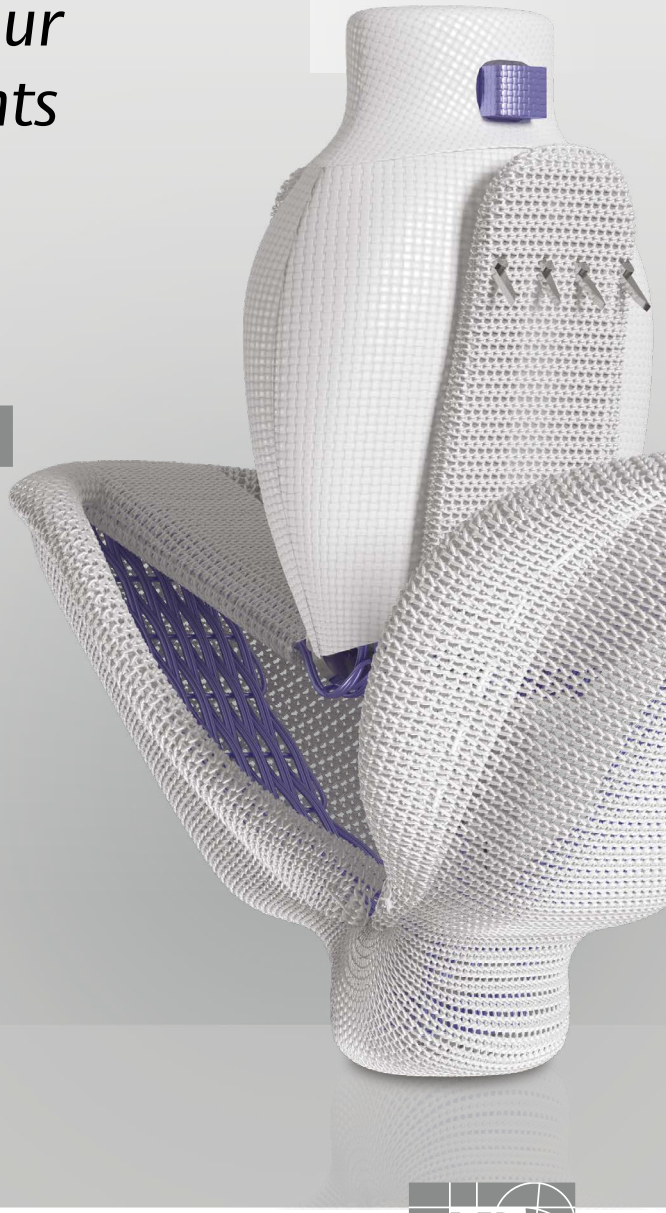
TMTT Today

Your update on Edwards' Mitral & Tricuspid innovations

Explore the Edwards PASCAL Transcatheter Valve Repair System

An important option for your mitral regurgitation patients



Do you need the PASCAL Repair System?

New report from 1000+ real-world, consecutive, all-comer cases says YES

Starting a PASCAL Repair System programme

Real-world data highlights swift learning curve

CLASP Study Core Lab Adjudicated Data

Discover why some consider it a breakthrough

Accelerate your learning

Review practical advice from experienced PASCAL Repair System users

Issue #1 – July 2020

Edwards

Dear Reader,

It is our pleasure to share with you the latest advances from our Transcatheter Mitral and Tricuspid Therapies (TMTT) through the *TMTT Today* series.

Across the three issues of *TMTT Today* that will be published this year, you will be updated on the latest news regarding Edwards' Mitral and Tricuspid Therapies currently in use across Europe. The goals are threefold: (1) share insights into key data sets generated by the community of interventional cardiologists, (2) share updates on clinical trials through articles and interviews, and (3) provide practical tools from experienced PASCAL repair system implanters to help you accelerate your learning curve with this device.

In this first issue, you will read about the PASCAL repair system "1200 patients" Real World Experience. In looking at Edwards Lifesciences internal data, we felt it was useful to share the learnings and insights gained on the value of the PASCAL repair system after a significant number of procedures. We invite you, the reader, to engage with us to learn more.

The articles are complemented by direct quotes from our main contributors, Professors Hausleiter, Lurz, Pfister and Schäfer alongside additional quotes from Professors Scott Lim, Medical Director of the University of Virginia's Advanced Cardiac Valve Center and John Webb, McLeod Professor of Heart Valve Intervention at the University of British Columbia.

It is our hope that through a strong commitment to good-practice sharing and evidence generation, we can, together, make a meaningful mark on the lives of patients with mitral and tricuspid regurgitation.

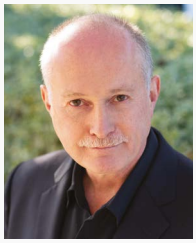
Enjoy reading!

Sincerely,

Rodolfo Estay, MSc, MBA

Vice President, Europe

Transcatheter Mitral and Tricuspid Therapies (TMTT)



Ted Feldman, MD, MSCAI, FACC, FESC

Vice President of Global Medical Affairs

Transcatheter Mitral & Tricuspid Therapies (TMTT)

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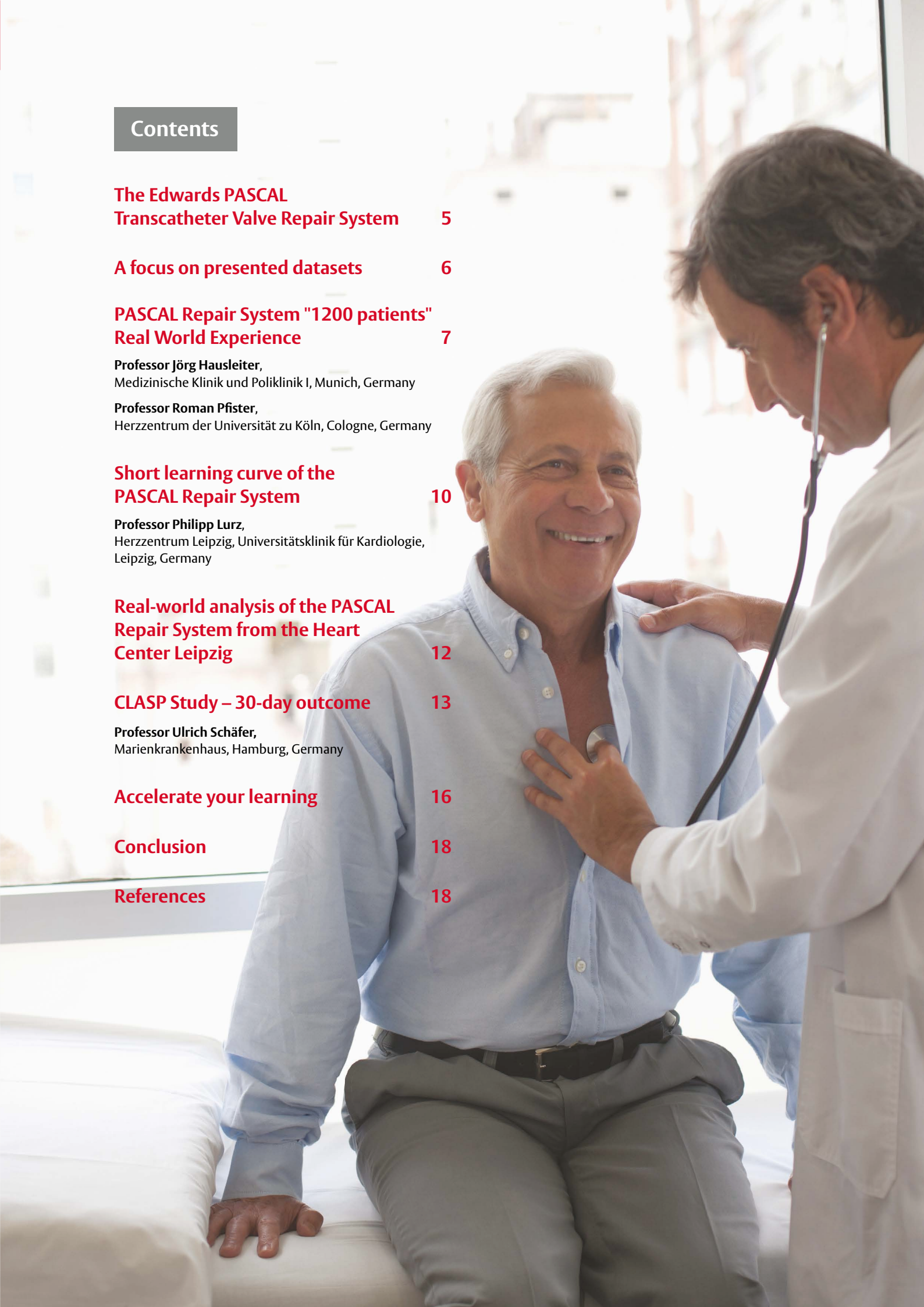


Personalised Solutions

by Edwards Lifesciences

Providing the broadest portfolio of therapies

Personalised Touch

by You

Delivering optimal care to the most patients

Together, we are making a meaningful mark on the lives of patients with mitral and tricuspid regurgitation.

Visit MakeAMark.com to learn more about the Edwards TMTT Portfolio.

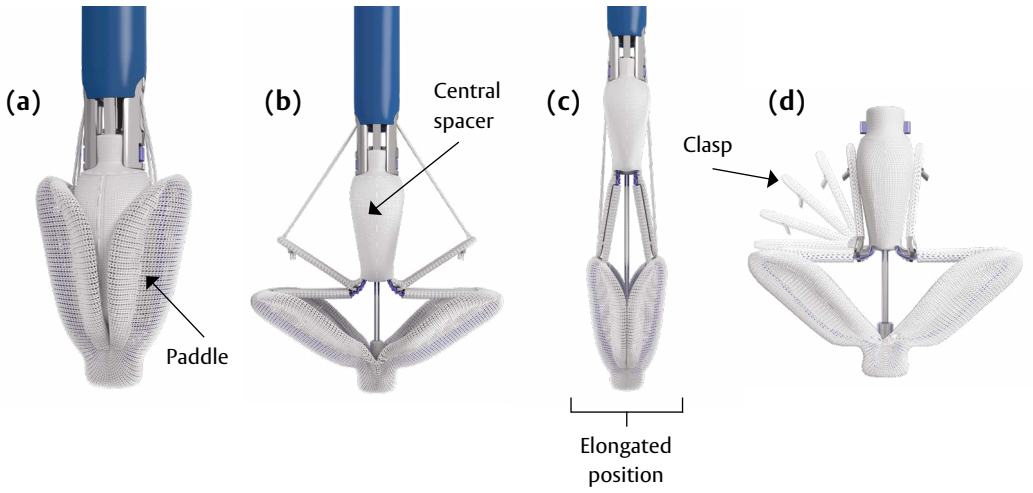
Edwards

The Edwards PASCAL Transcatheter Valve Repair System

Moderate-to-severe mitral regurgitation (MR) – a common valvular heart disease affecting around 10% of the general population aged ≥75 years – is associated with significant overall morbidity and mortality if left untreated, including left ventricular volume overload, decreased quality of life, increased heart failure hospitalisation rates and shortened survival.[1-5]

The PASCAL repair system is a new therapeutic option for MR that might expand the population of patients who can be treated successfully with leaflet repair.[6] The design features of the PASCAL repair system facilitate an effective and safe reduction in MR while respecting the native valve anatomy through a variety of key elements (Figure 1).[6]

Figure 1. Key features of the PASCAL repair system; (a) broad contoured paddles with a wide capture area maximise leaflet coaptation; (b) a central spacer fills the regurgitant orifice area and blocks more of the MR jet; (c) elongation ability makes subvalvular navigation safe; (d) independent clasp actuation allows precise leaflet capture optimisation



'The high rate of MR reduction to grade 1+ achieved by the PASCAL repair system is due to the device's unique features: the independent grasping, the mechanism of grasping itself to reduce stress on leaflets and the composition of the device which includes the central spacer to fill the coaptation gap.' Professor Lurz

A focus on presented datasets

In this first issue of *TMTT Today*, we review evidence coming from three datasets, including clinical study data and real-world evidence from both endorsed evaluations and independent studies (Table 1).

PASCAL Repair System "1200 patients" Real World Evidence

The PASCAL repair system has demonstrated safety and effectiveness in the real-world setting. On page 7, we unveil a retrospective analysis of the first 1200 PASCAL repair system procedures in MR patients.[7] Our most experienced implanters, Professors Jörg Hausleiter and Roman Pfister comment on this analysis and of their early experiences with the PASCAL repair system, which demonstrates excellent safety and acute efficacy, with high rates of MR 0–1+ outcomes achieved after a short learning curve.[7]

Real-world analysis of the PASCAL Repair System from the Heart Center Leipzig

We review the first single-centre independent study describing a cohort of 50 patients treated with the PASCAL repair system and published very recently by the Heart Center Leipzig.

On page 12, Professor Philipp Lurz, Principal Investigator and corresponding author of this publication, shares his experience with the PASCAL repair system and describes his data, highlighting effective MR reduction and functional improvement for patients after a short-term follow-up.

The CLASP Study 30-day outcome

Finally, the safety, performance and clinical outcomes of the PASCAL repair system are being evaluated in the CLASP Study – a 5-year, single arm, multicentre, prospective study in patients with clinically significant MR.[8,9] Early 30-day data from 62 patients published in *JACC: Cardiovascular Interventions* showed the PASCAL repair system to be safe and performing as intended for patients with clinically significant MR.[8] On page 13, we review this body of evidence with the perspective of Professor Ulrich Schäfer, one of the study's Principal Investigators.

Table 1. Datasets involving the PASCAL repair system presented in this issue

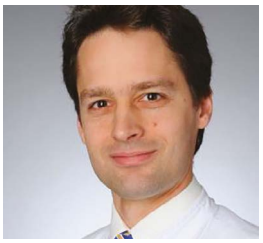
	Experience from Heart Center Leipzig	PASCAL repair system "1200 patients" Real World Evidence	CLASP Study 30-day outcome
Study type	Real-world evidence	Real-world evidence	Clinical trial
Study sponsor	Independent – Heart Center Leipzig	Edwards Lifesciences	Edwards Lifesciences
Number of centres	1	84	14
Number of patients	50	1200	62
Follow-up	30 days	Acute procedural efficacy	30 days

PASCAL Repair System "1200 patients" Real World Experience

Early experience confirms excellent safety & efficacy profile

Professor Dr med. Jörg Hausleiter,
Medizinische Klinik und Poliklinik I, Munich, Germany

As an interventional cardiologist expert in the field of valvular and coronary heart diseases, Professor Dr Jörg Hausleiter has board certification in internal medicine and cardiology. Currently, Professor Hausleiter is Professor of Medicine and the Deputy Clinic Director at the Ludwig-Maximilians-Universität in Munich, Germany, and is invested in finding new percutaneous treatments for coronary and valvular diseases.



Professor Dr med. Roman Pfister,
Herzzentrum der Universität zu Köln, Cologne, Germany

Board certified in internal medicine, cardiology and pneumology, Professor Dr Roman Pfister received his medical degrees from the University of Cologne, Germany. He was a research fellow at the MRC Epidemiology Unit, the Institute of Metabolic Science in Cambridge for two years before returning to the University of Cologne. He has led the Heart Failure and Transplantation Programme since 2014, and the Interventional AV-Valve Treatment Programme since 2018, when he also became Deputy Head of the Department of Internal Medicine III.

Real-world experience provides information on the use of devices in routine clinical practice outside the rigor of trial conditions and protocols. This article provides a retrospective analysis of the first 1200 PASCAL repair system procedures in MR patients performed after CE mark[10] in more than 80 centres. Analyses were performed by Edwards Lifesciences, and do not include Echo Core Lab analysis or Clinical Events Committee assessment.

In this dataset of 1200 patients, 56% had FMR, 18% had DMR and 26% had mixed aetiologies. A sub-analysis of data on procedural times and outcomes for the last 200 patients treated was included to highlight the impact of clinicians' experience with this new device. Safety was assessed through intraprocedural death, a shift to surgery and intraprocedural complications,* while efficacy† was measured in terms of acute efficacy, procedural time and devices per case.[7]

The PASCAL repair system showed a remarkable safety profile in a real-world setting, with 99.8% of patients free from intraprocedural death or shift to surgery and 98.3% of patients free from intraprocedural complications.[7]

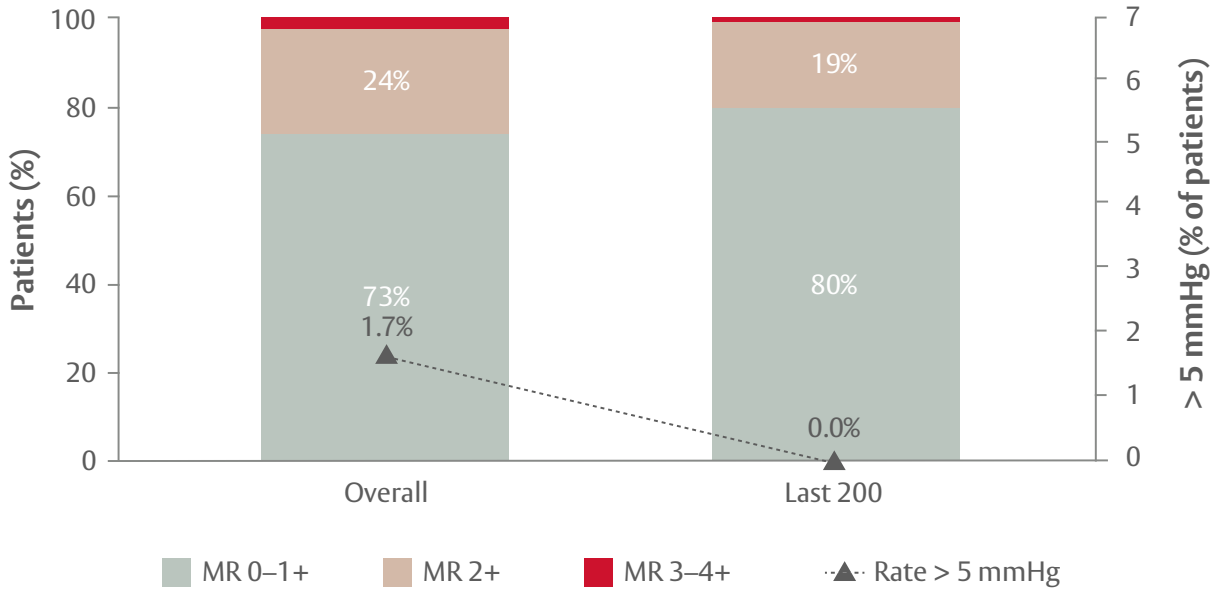
'The PASCAL repair system is very efficacious, very safe and leads to good MR reduction in a vast majority of patients'
Professor Hausleiter

The rate of single leaflet device attachment (SLDA) was only 1.1%, and further decreased to 0.5% in the last 200 patients.[7]

* Intraprocedural complications as per implanter/echo physician feedback to the onsite Edwards' Clinical Specialist who supported the case. 100% of cases reported were supported.

† Residual regurgitation grade as per implanter/echo physician acute assessment and reported by the onsite Edwards' Clinical Specialist, in non-aborted procedures.

Figure 2. Post procedural MR and gradient



'The results are impressive. Usually during leaflet repair procedures, we see a deterioration of MR results after device deployment ... we did not experience that with the PASCAL repair system and, surprisingly, results improved after deployment of the implant in observed cases' Professor Pfister

Acute efficacy was excellent: 73% of the 1200 patients had MR 0–1+ after the procedure, and 97% of patients had MR 2+ or less. Outcomes in the last 200 patients were even more striking: 80% of patients had MR 0–1+ and 99% of patients had MR 2+ or less (Figure 2). This performance did not come at the cost of high gradients, as demonstrated in Figure 2 by the low occurrence of gradients above 5 mmHg.[7]

'What was particularly striking was the learning curve ... essentially half the time of the early clinical trials' Professor Lim

The median procedure time was less than 70 minutes and the mean number of devices used per procedure was 1.3 (Table 2), which lies in the lower range of published mean device use for mitral leaflet repair therapies.[11] Moreover, early users highlighted key features of the PASCAL repair system that contribute to a more efficient procedure, such as the high predictability of results pre- versus post-implant release and the additional safety provided by the device's nitinol frame.

'The nitinol-based structure introduces significant flexibility in the device that helps to better translate the tension on the leaflets to the annulus, so tension is not focused on one location' Professor Hausleiter

Table 2. Procedural outcomes[7]

	Overall (N=1200)	Last 200 patients
Median procedural time, min	67	67
Mean number of devices per patient, n	1.30	1.28

Key achievements

PASCAL repair system received its

CE mark in

February 2019

used in **1200+** patients with MR

across more than

80 centres

In the **last 200** patients:

99.5%
of patients

are free from intraprocedural death/shift to surgery

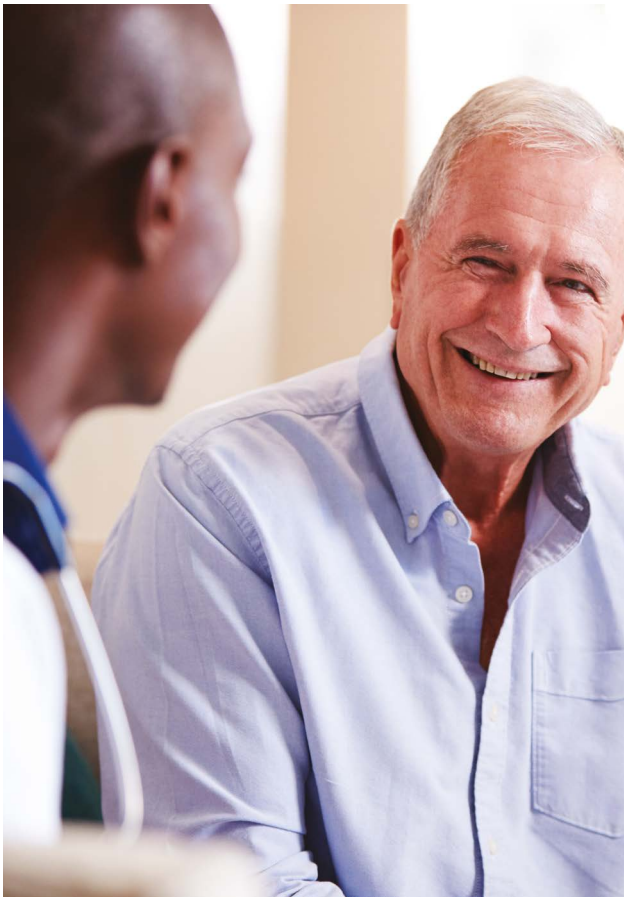
0.5% SLDA

80%
of patients

achieve MR 0–1+
at no cost of high transmitral gradient

Overall, in a real-world cohort, the PASCAL repair system is safe and effective in both patients with functional MR (FMR) and degenerative MR (DMR) and shows great promise in complex procedures involving mixed aetiologies. The therapy provides an excellent safety profile, with very low intraprocedural complications and SLDA rates. After a short learning curve, up to 80% of patients achieve MR 0–1+ with acceptable gradients and with low need for multiple devices.[7]

'An excellent system improving and extending the target population we want to treat'
Professor Pfister



Short learning curve of the PASCAL Repair system

Optimal outcomes possible

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

An interventional cardiologist, Professor Lurz is a Principal Investigator of the MiCLASP Registry and an investigator in trials for multiple therapies including MitraClip, HighLife, Tendyne, Symplicity Spyral and Paradise RDS systems, and more. A board-certified specialist in adult congenital heart disease, interventional cardiology and magnetic resonance imaging (SCMR competence level III), his major area of research is related to structural heart disease and heart failure.

A short learning curve: Evidence from the first 1200 procedures

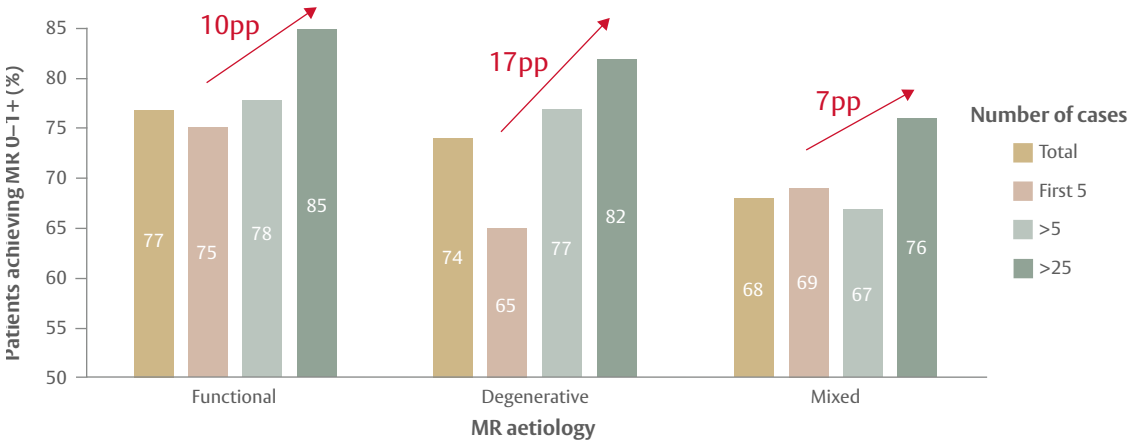
With any new device or procedure there is a learning curve for clinicians; their procedure times and outcomes improve along with familiarity and increasing experience. In the case of valve repair devices, the learning curve also differs for the different aetiologies – degenerative, functional and mixed.

Evidence from the first 1200 procedures with the PASCAL repair system[7] shows that MR 0–1+ rates above 80% can be achieved in both FMR and DMR after a short learning curve of 25 procedures. Indeed, clinicians tend to improve the proportion of patients achieving MR 0–1+ by 10% in FMR and 17% in DMR aetiologies between the first five cases and after more than 25 procedures, reaching MR 0–1+ rates of 85% in FMR and 82% in DMR (Figure 3).[7] Interestingly, when treating FMR or DMR, impressive outcomes close to 80% MR 0–1+ can be achieved after only five cases.

'I very quickly became comfortable and confident with PASCAL due to intuitive steering and manoeuvring, instructive and clear training, excellent safety, good control … after 10 procedures I, as the user, felt confident to approach more challenging cases' Professor Lurz

The learning curve for patients with a mixed aetiology follows a relatively similar profile, with 76% MR 0–1+ rates achieved after 25 cases, which illustrates the higher complexity of these procedures.[7]

Figure 3. Proportion of patients achieving MR 0–1+ by number of cases and aetiology: functional (n=565), degenerative (n=257) and mixed (n=185),[7] increase shown as percentage points (pp)

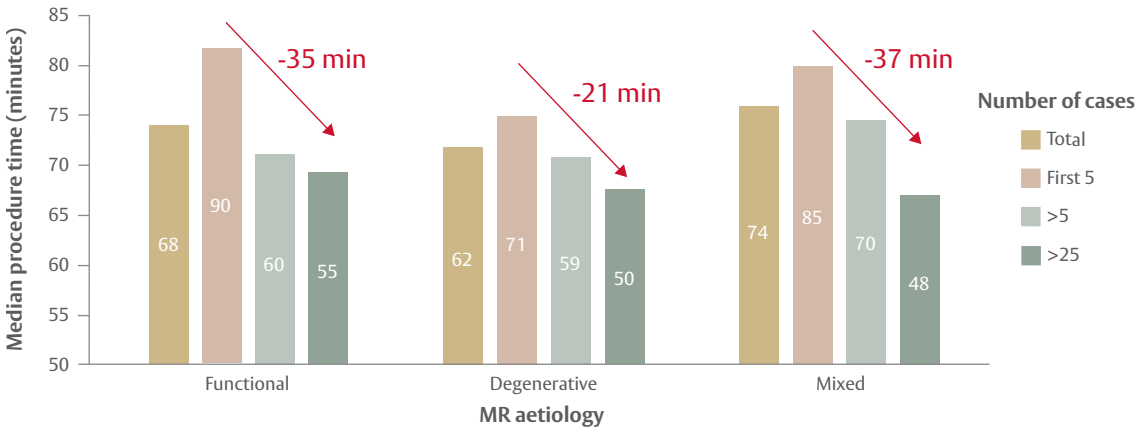


'Improved MR outcomes are achieved by independent grasping with leaflet optimisation. The ability to grasp multiple times without evident damage to leaflets provides efficacy and safety' Professor Lurz

This short learning curve is also illustrated by a rapid reduction in procedural time as operators gain experience with the device. When comparing procedural times for the first five cases with those after 25 cases, procedural time was reduced by 35 minutes in FMR patients, 21 minutes in DMR patients, and 37 minutes in patients with mixed aetiologies (Figure 4).[7] It is again worth mentioning that procedure-time reductions can already be observed after five cases. These data highlight how quickly clinicians gain familiarity with the PASCAL repair system while improving the MR reduction outcomes, with median procedural times around 60 minutes or less after a short learning curve of a maximum of 25 cases.[7]

Based on evidence from the first 1200 procedures, the PASCAL repair system has a very short learning curve to reach optimal outcomes, with MR 0–1+ achieved in 80% of patients by the time clinicians have performed 25 procedures, and with procedure time dropping rapidly to less than 60 minutes without any compromise on safety.[7]

Figure 4. Procedural time for placement of the PASCAL implant by number of cases and aetiology: functional (n=565), degenerative (n=257) and mixed (n=185)[7]



Real-world analysis of the PASCAL Repair system from the Heart Center Leipzig

While others were the first to publish a multicentre study on PASCAL repair system real-world practice with 18 patients being analysed,[6] the group at Leipzig has recently published an independent single-centre real-world analysis of transcatheter mitral valve repair using the PASCAL repair system. Based on a prospective analysis of 50 consecutive patients with moderate-to-severe or severe MR (MR 3+ and MR 4+), the authors evaluated the ability of the PASCAL repair system to effectively reduce MR, and its impact on patients' functional status over a 1-month follow-up.[12]

Patients included in the analysis had primary (24%), secondary (68%) or mixed (8%) aetiology MR. Approximately half of patients underwent implantation of a single PASCAL device, 46% received two devices, and 2% received three devices. The authors observed a device-specific learning curve, with a reduction in average procedure times from 77.8 minutes to 57.5 minutes after the first 15 cases.[12,13]

'You can achieve excellent results with the PASCAL repair system after a short learning curve of 10–15 patients. In a significant proportion of patients, we were able to implant two devices in the same time period we were initially using to implant just one device' Professor Lurz

Overall, the technical success rate in this patient cohort was 100% and the procedural success rate was 98%. At discharge, 78% of patients had MR grade ≤1, and this proportion was maintained at 1-month follow-up (Figure 5). Notably, the authors did not observe any cases of transvalvular mean gradients >5 mmHg, even after implantation of more than one PASCAL device.

After one month, 73% of patients reported an improvement in New York Heart Association (NYHA) class (Figure 6) and 6-minute-walk-test (6MWT) distance significantly increased by 73 ± 12 m in patients without relevant tricuspid regurgitation.[12]

Overall, this independent single-centre analysis confirms the PASCAL repair system's performance in the real-world setting, showing that it effectively reduces MR and positively impacts patients' functional status.

'PASCAL is very good in terms of patient functional improvement and something we don't always see when we treat MR' Professor Lurz

Figure 5. MR grade distribution at baseline, at discharge, and at one month after implantation of the PASCAL repair system[12]

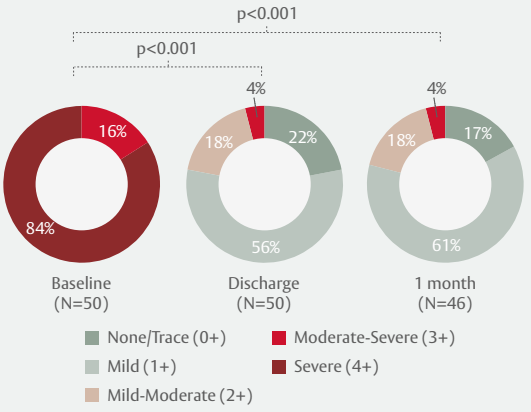
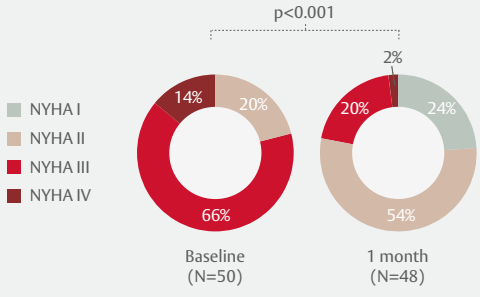


Figure 6. NYHA class at baseline and at one month after implantation of the PASCAL repair system[12]



CLASP Study 30-day outcome

Optimal outcomes with PASCAL Repair System

Professor Dr med. Ulrich Schäfer, Marienkrankenhaus, Hamburg, Germany | Global PI of the CLASP Study

Chief Physician in the Department of Cardiology, Angiology and Intensive Care Medicine, Professor Ulrich Schäfer is a Global PI of the CLASP Study and was instrumental in the development of therapy programmes for the treatment of structural heart diseases. Professor Schäfer's special focuses include the therapy of structural heart diseases within the framework of catheter-interventional valve therapy and other structural heart defects.

The safety, performance and clinical outcomes of the PASCAL repair system are being evaluated in a single-arm, multicentre, prospective study – the CLASP Study – in adult patients with NYHA functional class ≥II and clinically significant MR ≥3+ despite optimal therapy.

The primary endpoints of the CLASP Study are a composite of MAEs† at 30 days and efficacy – measured as device, procedural and clinical success. Secondary endpoints at 30 days, 6 months and 12 months include all-cause mortality, composite of MAEs, reduction in MR, functional capacity and quality of life. So far, data for up to 30 days in 62 patients with diverse aetiologies have been published. The main baseline characteristics of the CLASP Study patients are summarised in Table 3.[8]

Table 3. Preoperative patient characteristics[8]

Number of patients	62
Male gender, n (%)	39 (62.9)
Mean age (years)	76.5
NYHA Class III–IV, n (%)	32 (51.6)
MR aetiology	
Functional, n (%)	34 (55.7)
Degenerative, n (%)	22 (36.1)
Mixed, n (%)	5 (8.2)
MR severity ≥3+*, n (%)	62 (100)

*Assessed by Echo Core lab

The PASCAL repair system showed a high successful implantation rate of 95%, with an average procedural time of 127 minutes and a mean number of 1.5 devices implanted.[8] The PASCAL repair system had a favourable safety profile at 30 days, with a composite MAE rate of 6.5%; this comprised six events in four patients – all four had procedure-related (although not device-related) severe bleeding, which led to cardiovascular mortality in one patient. Another patient had bleeding during the reintervention for study device-related complications.[8]

Of the 62 patients, 60 were included in the reported 30-day efficacy analysis. The PASCAL repair system resulted in a highly significant reduction in MR at 30 days, with 86% of patients having mild (1+) or no/trace (0+) MR and 98% achieving mild–moderate MR (2+) or less (n=57) (Figure 7).[8]

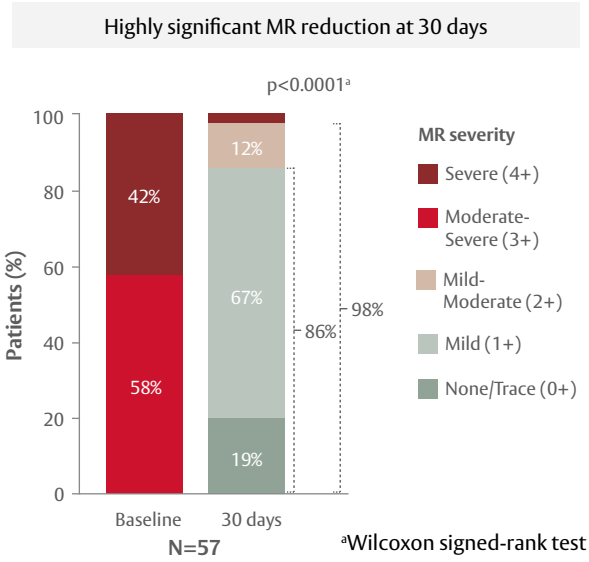
'For a first in-human study with limited implanter experience, this device is superb'
Professor Schäfer

Mean transmitral valve gradient is an important consideration, with an accepted maximum gradient of 5.0 mmHg.[14] The mean transmitral valve gradient with the PASCAL repair system was consistently below this level: 4.1 mmHg at discharge and 4.0 mmHg at 30 days.[8]

When investigating the secondary endpoints of the CLASP Study, clinically significant improvements

†Cardiovascular mortality, stroke, myocardial infarction, new need for renal replacement therapy, severe bleeding, and re-intervention for study device-related complications.[14]

Figure 7. Severity of MR at baseline and 30 days[8]



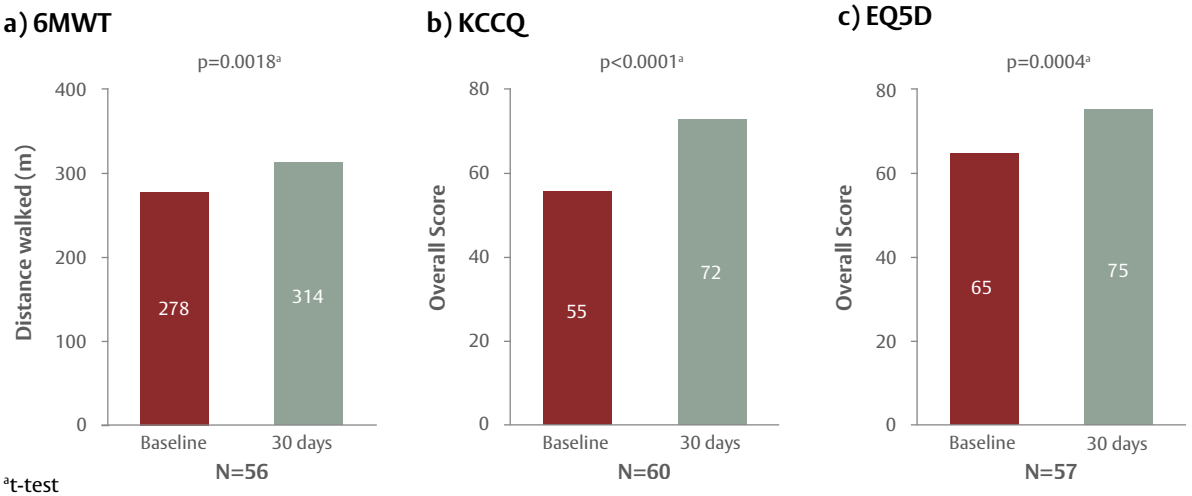
in functional status, exercise capacity and quality of life were observed at 30 days. Whereas 51.6% of patients at baseline were in NYHA class III or IV, importantly, 37% of patients were in class I and 85% in class I or II by day 30. Furthermore, at day 30, exercise capacity measured with the 6WMT had significantly increased by 36 m (Figure 8a) and scores on the Kansas City Cardiomyopathy Questionnaire (KCCQ) and EuroQol (EQ5D) had significantly increased by 17 and 10 points, respectively (Figure 8b, c).[8]

Data from the CLASP Study confirm that the PASCAL repair system is safe and can be implanted as intended. Clinically, the PASCAL repair system delivers statistically significant improvements in functional status, exercise capacity and quality of life for patients with clinically significant reductions in MR.[8] Several features of the device were highlighted in the literature as potential reasons for these good results:[15] the PASCAL repair system overcomes some of the difficulties of other mitral valve repair technologies with a delivery system that enables manoeuvring in three planes, thereby offering simplified navigation in the left atrium. The large size of the implant, wide paddles and optional independent leaflet grasping may also contribute to the reduction of MR in challenging anatomies, with no negative impact on post-procedural mitral valve gradient.[15]

'The independent grasping options with PASCAL mean that you can independently optimise one leaflet if it is not perfectly grasped, which is clearly a plus'
Professor Schäfer

New data from the CLASP Study show that favourable outcomes with the PASCAL repair system observed at 30 days are sustained at 6 months and 1 year. These include high survival and low complication rates, low rates of heart failure hospitalisation, robust and sustained MR reduction at one year (82% MR ≤1+ and 100% MR ≤2+), and improvements in functional status, exercise capacity, and quality of life. The 6-month and 1-year data have recently been presented at EuroPCR in June 2020.[9]

Figure 8. Outcomes reported at baseline and Day 30[8]



at-test
6MWT: 6-minute walk test; KCCQ: Kansas City Cardiomyopathy Questionnaire; EQ5D: EuroQol

Take a look at the slides and the CLASP Study's 1-year follow-up results presented at the PCR eCourse in June 2020

Scan QR code to access slides

CLASP Study Investigator, Professor Scott Lim, UVA Advanced Cardiac Valve Center, Virginia, US

> Patients had significantly improved functional class that sustained up to a year

CLASP Study Investigator, Professor John Webb, University of British Columbia, Vancouver, Canada

> At 1 year 82% of patients had MR reduced to ≤1+ and 100% had MR ≤2+

Don't miss the next edition of ***TMTT Today*** for further insights and expert analysis of the CLASP Study 1-year results.

Accelerate your learning

Practical advice offered by the most experienced implanters

We asked our contributors for their top advice on using the PASCAL repair system based on their experience.

Professor Hausleiter

It is helpful if you already have experience with MR repair. The PASCAL repair system is nice and flexible, with a learning curve comparable to other devices. The procedure feels safe after 10–20 cases, ***and the more you do, the better you feel about the device!***

Simultaneous use of fluoroscopy is a major help for the PASCAL procedure, in addition to the use of echocardiography

Check you are perpendicular to the mitral valve plane and line of coaptation before you get started, as this makes it easier to capture the leaflets

Professor Pfister

Patient selection is important to achieve high MR reduction, including the extent of pre-existing MR compared with the overall opening area; whether two devices can be implanted, if needed; the leaflet structure and more challenging anatomies – for example those with mixed aetiology

Double-check orientation during the clasping process and have a good imager at hand to help visualise

Do not hesitate to attempt re-clasping – ***the PASCAL repair system allows independent clasping****, which puts less stress on the leaflets, avoids leaflet damage, and improves results*

Professor Lurz

If you want to run a high-level TMVR programme treating a variety of different and challenging anatomies, ***the PASCAL repair system is a 'must have' on the shelf*** *… do 10 cases before you make a judgment on the system, as it requires a bit of adjustment of your technique and procedure, but it is totally worth the investment*

Do not be misled by the size of the device; the flexibility of the device with some degree of opening of the paddles during diastole seems to restrict leaflet mobility less and results in low/acceptable gradients

Leaflet optimisation, particularly positioning of the paddle on the posterior mitral leaflet after the initial grasp, given the safety and controllability of independent grasping, is a huge step forward and worth the effort, always aiming for an optimal outcome (MR grade 0–1+)

Professor Schäfer

While ***the PASCAL repair system works well in patients across the spectrum****, it is especially interesting:*

- *if you have the impression that leaflet morphology is fragile, given the gentle profile of the system*
- *if the patient has a more commissural disease, as opposed to A2-P2 disease, as subvalvular chordae entanglement is less likely with PASCAL*
- *for patients with a small anatomy, as it is less likely to create significant gradients*

Conclusion

Early clinical study experience with the PASCAL repair system shows that it is safe and performed as intended for patients with clinically significant MR, with low intraprocedural complications, low/acceptable mean mitral valve gradient and substantial reductions in MR in the vast majority of patients.[8] Importantly, the impressive outcomes from the CLASP Study have been confirmed by the first 1200 patients treated in real-life settings, where the PASCAL repair system was both safe and effective, with operators achieving increasingly higher rates of MR reduction and shorter procedure times with experience. These outcomes are further supported in a recent paper by Besler et al., which presents single-centre real-world results demonstrating that the PASCAL repair system effectively reduces MR, leading to functional improvements on short-term follow up.[12] In real-world practice, our data on file suggest that a short learning curve of 25 cases leads to optimal outcomes (MR 0–1+) in >80% of patients in less than one hour with the PASCAL repair system.[7]

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