TMTT Today

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

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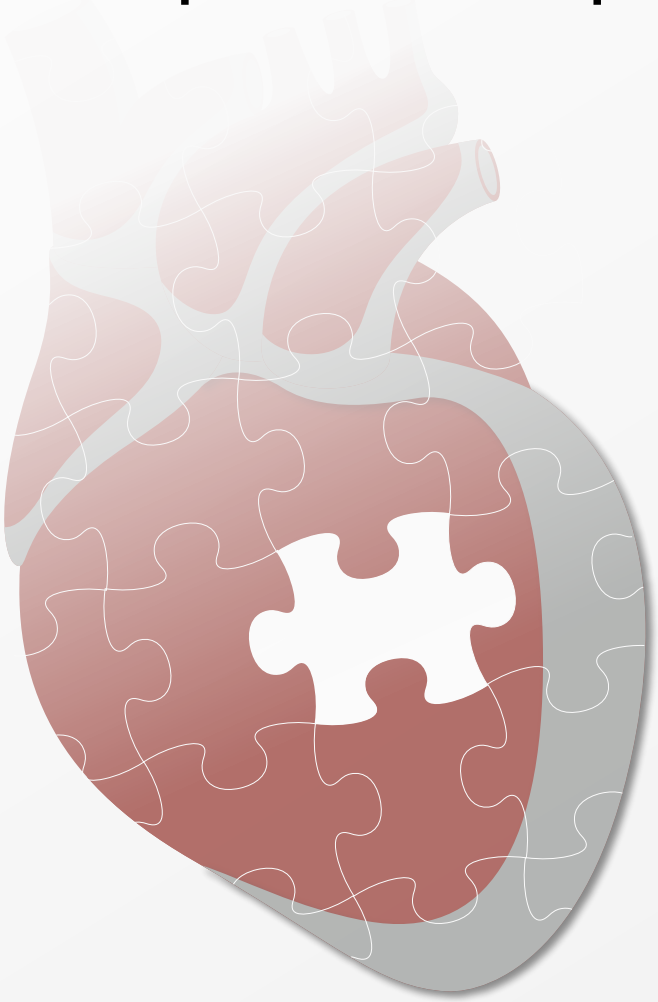
Evidence from post-market and real-world studies:

Another piece of the TEER puzzle



Significant, sustained MR and TR reduction with the PASCAL repair system

At 1 year:

83% MR ≤1+
in the MiCLASP study[1]

81% TR ≤2+
in the PASTE registry[2]

In this issue:

Edwards

Dear Reader,

Recently, data from several important randomised controlled trials (RCTs) on mitral and tricuspid regurgitation (MR and TR) were released, reinforcing the safety and efficacy of transcatheter edge to-edge repair (TEER).[6–8] However, strict inclusion criteria can mean that the populations included in RCTs may not reflect the patients you treat in your daily practice.

In this issue of *TMTT Today*, we share real-world and post-market studies and the valuable evidence they can contribute to decision-making. On the mitral side, investigators examine 1-year outcomes from the MiCLASP post-market study,[1] alongside results from two real-world, comparative studies of mitral TEER with the PASCAL repair system and the MitraClip system.[3,4] On the tricuspid side, leading interventional cardiologists reflect upon 1-year results from the TRILUMINATE RCT[6] and discuss the 1-year data from the PASTE registry, which is examining tricuspid TEER in a real-world population.[2,5] Lastly, experts share their tips and tricks via four diverse anatomy case studies highlighting how the PASCAL Precision system can be used to treat MR and/or TR. If you have an interesting case to share, please do get in touch at TMTT-Today@edwards.com.

Here at Edwards Lifesciences, we are invested in building a robust body of clinical evidence for the PASCAL platform, and, as Dr Mirjam Wild states on page 13, data from real-world studies form 'another important piece of the puzzle' when deciding what is best for patients.

Enjoy reading!

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Three-year data from the CLASP study demonstrate that mitral valve repair with the PASCAL repair system led to sustained reduction in MR and a significant improvement in functional status in highly selected patients with severe MR.[9] Here, Professor Philipp Lurz gives an update from the MiCLASP post-market study.[1] In addition, Dr Victor Mauri, Dr Mirjam Keßler and Dr Leonhard-Moritz Schneider present encouraging outcomes from two real-world, comparative studies of the PASCAL repair system and the MitraClip system.[3,4]

Professor Dr med. Philipp Lurz
University Clinic for Cardiology, Leipzig Heart Center, Germany

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

One-year outcomes from the MiCLASP study

The MiCLASP study is an ongoing European, prospective, multicentre, single-arm, post-market clinical follow-up study assessing the safety and effectiveness of the PASCAL repair system in improving MR, functional status and quality of life. Participants must have symptomatic MR ≥2+ (as assessed by an Echo Core Lab) and be candidates for transcatheter mitral valve repair as determined by a Heart Team.[1,10] Post-market studies like this are important, explains Professor Lurz: 'Patients in RCTs are highly selected. Our community needs to understand how devices will perform in larger, less selected cohorts.'

For the 450 patients included in this analysis, mean age was 77 years old, and 77% of patients were in New York Heart Association (NYHA) class III or IV at baseline. The range of anatomies was more diverse than seen in RCTs: the majority of patients (64%) had functional MR (FMR), while 32% had degenerative MR (DMR), 4% had MR of mixed aetiology and 1% had MR of unknown or other aetiology.[1]

Implant success rate was 97%; a mean of 1.4 devices were implanted per patient. After a mean stay of 4.2 days in hospital, 92% of patients were discharged home.[1]

Safety outcomes

'The PASCAL repair system has a very good safety profile, with almost no acute procedural complications and encouraging 1-year survival,' Professor Lurz reports. Indeed, all-cause mortality was 10.7% and cardiovascular mortality was 7.8% at 1 year. The overall Kaplan–Meier estimate for survival was 87% at 1 year, with little difference between patients with FMR and DMR (86% *vs* 89%). Similarly, the overall Kaplan–Meier estimate for freedom from heart failure hospitalisation (HFH) was 86% (FMR 85% *vs* DMR 90%). The 1-year composite major adverse event rate was 16.2% (as adjudicated by a clinical events committee), and the rate of single leaflet device attachment (SLDA) was low at 1.8%.[1]

According to Professor Lurz, the flexible, nitinol-based design of the PASCAL repair system contributes to this positive safety profile. 'It respects the anatomy and is gentle to the leaflets,' he says. 'Also, the ability to elongate the implant is handy if the PASCAL repair system gets stuck in the subvalvular apparatus: you can get out of trouble safely without causing any leaflet injury.'

MR outcomes

Mitral valve repair with the PASCAL repair system led to a significant and sustained MR reduction (Figure 1). Almost all (99%) evaluated patients achieved MR ≤2+ and 83% achieved MR ≤1+ at 1 year, and results were positive for both FMR and DMR (MR ≤1+: FMR 81% *vs* DMR 86%). 'There was a small increase in mean gradient across the mitral valve acutely from baseline, as expected,' Professor Lurz explains, 'But, encouragingly, there was no further increase over time.' (Figure 2[1])

Functional and quality-of-life improvements

Professor Lurz describes how the MiCLASP study included several measures of symptomatic implications: 'We saw a robust signal of improvement in NYHA functional class: at 1 year, 70% of patients were in NYHA class I or II (p<0.001 *vs* baseline). We also saw a strong improvement in quality of life: a 15-point increase in mean Kansas City Cardiomyopathy Questionnaire score (p<0.001) and an 8-point increase in mean EQ-5D-5L score (p<0.001).' Again, results were positive for both FMR and DMR.[1]

These results build on the 30-day results reported in *TMTT Today* issue 7,[11] confirming significant and sustained improvements in MR grade, functional class and quality of life after mitral valve repair with the PASCAL repair system at 1 year.[1] 'These 1-year data add clinical relevance to the 30-day

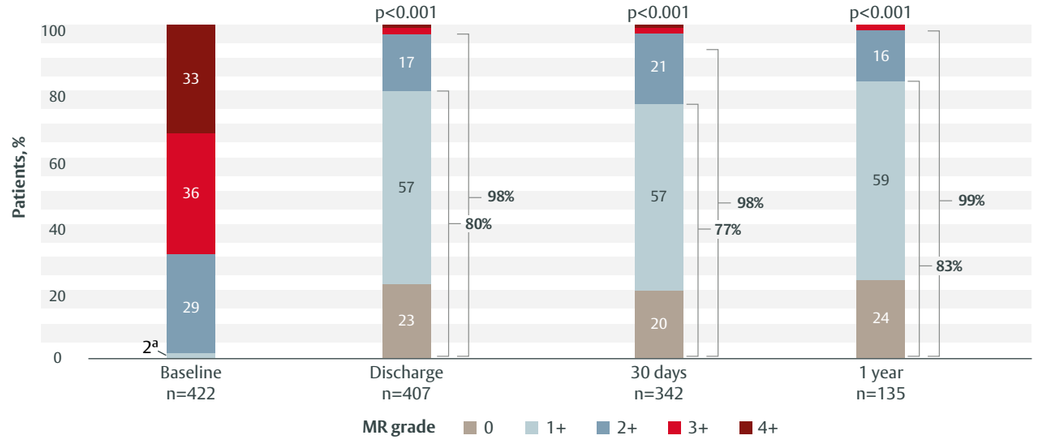


Figure 1. MR severity before and after treatment with the PASCAL repair system in the MiCLASP study.[1]

Chart shows unpaired analysis. p values calculated from paired analysis using Wilcoxon signed-rank test for baseline *versus* discharge (n=385; MR ≤1+ = 80%; MR ≤2+ = 98%), 30 days (n=323; MR ≤1+ = 77%; MR ≤2+ = 98%), and 1 year (n=128; MR ≤1+ = 83%; MR ≤2+ = 98%). [a]Some patients had MR <2+ at baseline prior to introduction of core lab-adjudicated echocardiographic exclusion criteria in protocol. MR, mitral regurgitation.

data and inform us about what to expect from the PASCAL repair system in these patients,' explains Professor Lurz. 'This supports the transcatheter approach for MR treatment and helps when obtaining patient consent.' Professor Lurz is confident that even better outcomes are possible since the introduction of the PASCAL Precision system. 'The PASCAL Precision system has improved steering and stability, so I would expect results to improve further, especially in less experienced centres which will benefit from a shorter learning curve.'

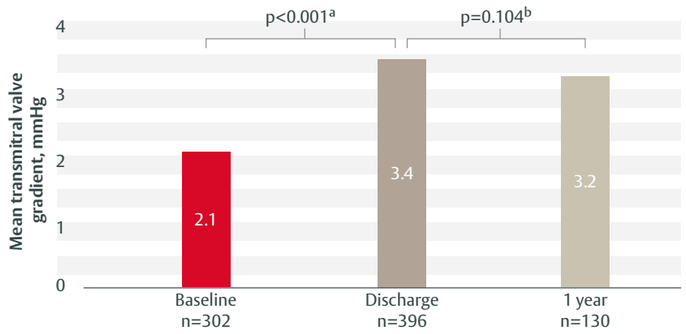


Figure 2. Core lab-determined mean transmitral valve gradient before and after treatment with the PASCAL repair system in the MiCLASP study.

Transmitral valve gradient determined by the Cardiovascular Core Lab at Morristown Medical Center, NJ, USA. Chart shows unpaired analysis. p value presented for paired analysis using Student's t-test. [a]Baseline *versus* discharge (n=269); [b]discharge *versus* 1 year (n=119).

Adapted from Lurz P. 2022.[1]

Dr med. Victor Mauri

Department of Cardiology, Heart Center, Faculty of Medicine, University of Cologne, Germany

Dr Victor Mauri is an interventional cardiologist and Senior Physician at the Heart Centre of the University of Cologne. His clinical and research focus is catheter-based strategies for the treatment of valvular heart disease.

Comparative real-world multicentre studies

Mauri *et al*.: Early outcomes of two mitral valve transcatheter leaflet approximation devices[3]

Landmark studies in the field of mitral valve repair are well designed, according to Dr Victor Mauri, but only include a fraction of the patients he sees in his day-to-day practice. With a pressing need for real-world evidence, he set out with his colleagues to find out how the PASCAL repair system (generation 1, PASCAL implant only) and the MitraClip system (96% generation 1 or 2) compared in clinical practice. 'We included the first consecutive 309 patients with moderate-to-severe to severe MR seen at 10 sites in Germany between February and December 2019, including those who would never meet the inclusion criteria of a RCT,' he explains. 'We propensity score-matched them with patients treated with the MitraClip system included in the Heart Failure Network Rhineland Registry.'

As expected, the propensity score-matched cohort (n=307 in each group) was elderly (mean age 77 years) with a large burden of comorbidities, resulting in a relatively high mean EuroSCORE II (PASCAL repair system 5.8% *vs* MitraClip system 6.9%; p=0.002). All patients had MR ≥3+ at baseline.[3]

Technical success was high and comparable in both groups (PASCAL repair system 96.7% *vs* MitraClip system 98.0%; p=0.624), as was the median procedural time (PASCAL repair system 91 min *vs* MitraClip system 90 min; p=0.865). However, the number of implanted devices differed significantly between the two groups (one/two/three device[s]: PASCAL repair system 73.6%/23.8%/0.3% *vs* MitraClip system 59.0%/35.5%/3.9%; p<0.001).[3]

Outcomes at discharge

Acknowledging the limitations of a non-randomised, retrospective design, MR reduction to grade ≤2+ was comparable in both groups at discharge; however, more patients achieved MR ≤1+ in the PASCAL repair system group (Figure 3). The post-procedural mean transmitral gradient increased for both treatment cohorts. More specifically, this study reported that the post-procedural transmitral gradient, the increase in transmitral pressure, and the proportion of patients with a mean gradient 5 mmHg or higher were significantly greater in the MitraClip group than in the PASCAL repair system group (Figure 4); this difference remained after adjusting for baseline gradient (p<0.05).[3]

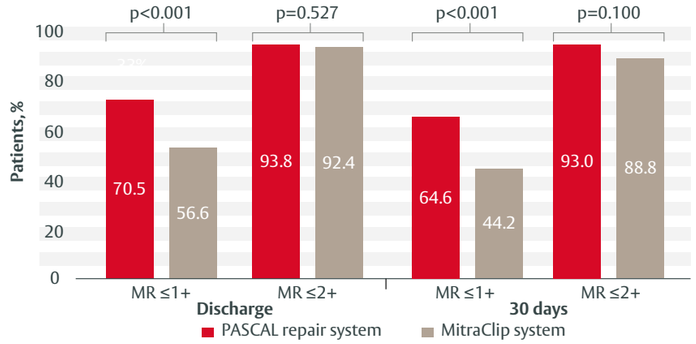


Figure 3. Proportion of patients with MR ≤1+ and ≤2+ at discharge and 30 days after mitral valve repair with the PASCAL repair system or the MitraClip system.

MR, mitral regurgitation.

Adapted from Mauri V *et al*. 2022.[3]

30-day outcomes

At 30 days, the rates of all-cause mortality, major adverse events and SLDA were low and comparable between the two groups, reports Dr Mauri (Figure 5).

Patients showed a significant improvement in NYHA class over baseline, regardless of treatment device: 72.6% of the PASCAL repair system group and 65.4% of the MitraClip group achieved NYHA class ≤II at 30 days (p=0.089). Similarly, both groups saw a significant improvement in MR over baseline, Dr Mauri notes (Figure 3), adding: 'The difference in the proportion of patients who achieved MR ≤1+ at baseline persisted to 30 days and was statistically significant'.[3]

Overall, the results from this large, multicentre study demonstrate that the PASCAL repair system is at least as safe and effective as the MitraClip system for treating real-world patients with moderate-to-severe to severe symptomatic MR. Patients in the PASCAL repair system group had significantly lower post-procedural transmitral gradients, and significantly more of them achieved MR ≤1+ at 30 days. Dr Mauri points out that most of the operators in this study were highly experienced with the MitraClip system but new to using the PASCAL repair system. The lack of difference in procedure duration and adverse event rates between the two groups suggests that the PASCAL repair system is easy to use for teams experienced in transcatheter mitral valve repair.[3]

Figure 4. Comparison of post-procedural mean transmitral gradients in patients who underwent mitral valve repair with the PASCAL repair system or the MitraClip system.

Adapted from Mauri V *et al*. 2022.[3]

'In this study we used the PASCAL implant. These days we mostly use the PASCAL Ace implant, which is a great addition to our armamentarium for treating MR,' Dr Mauri remarks. 'We now successfully treat more complex patients than we did 5 years ago, thanks to greater operator experience and the PASCAL platform, which has recently undergone improvements in

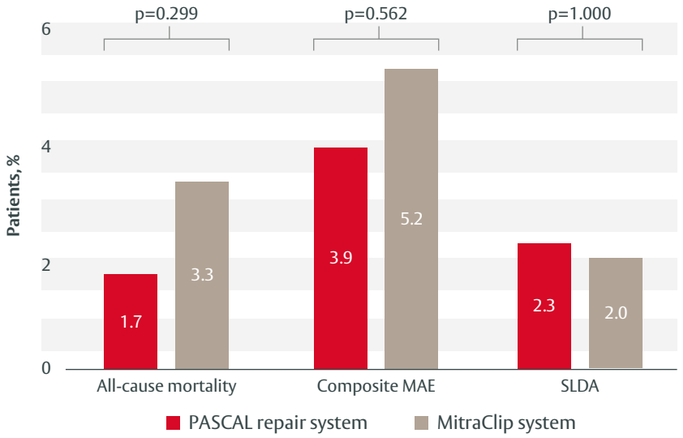


Figure 5. Outcomes 30 days after mitral valve repair with the PASCAL repair system or the MitraClip system.

MAE, major adverse events; SLDA, single leaflet device attachment.
Adapted from Mauri V *et al.* 2022.[3]

Dr med. Leonhard-Moritz Schneider

Department of Cardiology, Ulm University Heart Center, Germany

Dr Leonhard-Moritz Schneider is a specialist physician at Ulm University Heart Center with a focus on echocardiography and interventional valve repair. He has participated in over 500 mitral or tricuspid valve procedures.

Professor Dr med. Mirjam Keßler

Department of Cardiology, Ulm University Heart Center, Germany

Professor Mirjam Keßler is an interventional cardiologist and Senior Physician at Ulm University Heart Center. She has 5 years' experience in edge-to-edge repair and has been using the PASCAL repair system since 2019.

Schneider *et al.*: Mitral valve transcatheter edge-to-edge repair using MitraClip or PASCAL repair system[4]

Another team interested in evaluating the MitraClip and PASCAL repair systems in a real-world setting included Professor Mirjam Keßler and Dr Leonhard-Moritz Schneider from Ulm. 'When the PASCAL repair system came on the market, we, as interventional cardiologists, did not know which device to choose,' explains Professor Keßler. 'We were experienced with the MitraClip system, but the PASCAL repair system had technical features that we thought might be beneficial.'

They performed a retrospective study at three German high-volume sites, where 412 patients with symptomatic MR ≥3 underwent mitral TEER with the MitraClip system (n=216) or the PASCAL repair system (n=196) between 2018 and 2020. After propensity score matching, 92 patients were included in each treatment group in the final analysis. 'Importantly, our study included the most recent, contemporary TEER devices on the market at the time: the third and fourth generations of the MitraClip system, and the PASCAL repair system with both the PASCAL and PASCAL Ace implants,' says Professor Keßler.[4]

'The patients were typical of those requiring mitral TEER: they were sick with high surgical risk,' notes Dr Schneider. 'We included patients with FMR and DMR, as well as some with mixed aetiology.' Mean age in the matched cohort was 76 years, and 88% were in NYHA class III or IV.[4]

Study limitations[3]

- Non-randomised, retrospective study
- Incomplete clinical and instrumental characteristics for some patients
- Lack of core laboratory assessment but data quality assessed by an expert panel
- Use of older generation devices (i.e. does not represent current clinical practice)
- Limited contribution to the MitraClip group (3/10 centres)
- Different recruitment time periods for the two cohorts

Outcomes at discharge

The primary endpoint was residual MR at discharge, says Professor Keßler, and it was comparable between devices (Figure 6). 'At discharge, trace MR was achieved in nearly 10% of the propensity score-matched cohort, with a trend towards a higher proportion (14.1% *vs* 3.3%) in the PASCAL repair system group,' she adds. The majority of patients achieved an MR reduction of at least two grades (PASCAL repair system 92.4% *vs* MitraClip system 83.7%; p=0.13).[4]

Technical success – a secondary endpoint – was particularly notable for the PASCAL repair system given the relative lack of operator experience, explains Dr Schneider. 'We had a lot of experience with the MitraClip, but much less with the PASCAL repair system. Nevertheless, we had comparable technical success of over 97%.' The median number of implanted devices was comparable between groups (PASCAL repair system 1 *vs* MitraClip system 2; p=0.70).[4]

30-day outcomes

All-cause mortality was 1.1% in the matched cohort, with no difference between groups (p=0.98). SLDA occurred in 3.3% of patients in the PASCAL repair system group and 1.1% of patients in the MitraClip group (p=0.53). Device success rate was high and comparable in both groups (PASCAL repair system 94.6% *vs* MitraClip system 95.5%; p=0.78).[4]

1-year follow-up

The lack of long-term outcomes in some of the comparative studies published previously has been an issue, says Professor Keßler. 'Our results are encouraging,' she comments. 'We demonstrated stable results, with 82% of the PASCAL repair system group and 78% of the MitraClip group having optimal MR ≤1 at a median follow-up of 363 days.' (Figure 6) In addition, survival was comparable between the two groups (PASCAL repair system 93.5% *vs* MitraClip system 85.9%; p=0.14).[4]

'Our study is the only one so far that had enough patients with DMR and FMR to look at the outcomes separately after propensity score-matching,' says Dr Schneider. The aetiology subanalysis revealed no significant differences in residual MR between the MitraClip and PASCAL repair system groups (Figure 7). Overall, in the propensity score-matched cohort, 73.1% of patients with DMR/mixed MR and 85.5% of patients with FMR achieved MR ≤1 at 1 year.[4]

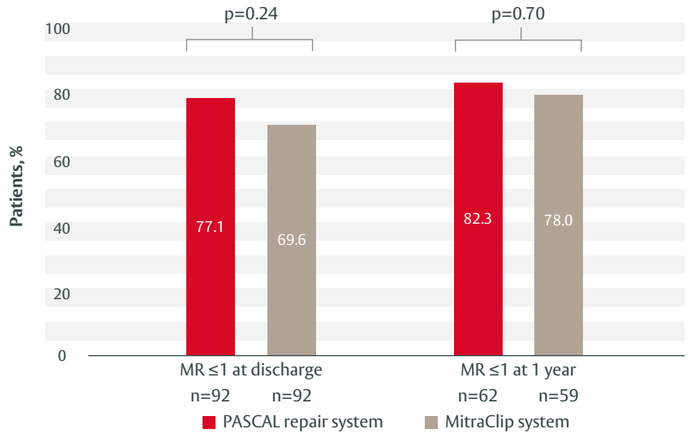


Figure 6. Proportion of patients with MR ≤1 at discharge and 1 year after mitral valve repair with the PASCAL repair system or the MitraClip system.

Chart shows data for the propensity score-matched cohort.
MR, mitral regurgitation.
Adapted from Schneider L *et al.* 2022.[4]

In summary, these data show that mitral valve repair with the PASCAL repair system achieves comparable results to the MitraClip system, with a tendency towards more optimal MR results for the PASCAL repair system and fewer SLDAs with the MitraClip system.[4] 'If we had more experience with the PASCAL repair system at the time we collected these data, I'm sure outcomes would have been even better. What we are now capable of with the PASCAL repair system is extraordinary,' enthuses Dr Schneider.

Study limitations[4]

- Non-randomised, retrospective study
- Differences in baseline characteristics of the two propensity score-matched cohorts

- Limited 12-month survival status data (79% total cohort, 75% propensity score-matched cohort)
- Greater operator experience with the MitraClip system than with the PASCAL repair system

Conclusion

Together, these results present a compelling case for the use of the PASCAL repair system for mitral valve repair in a broad patient population, regardless of MR aetiology (Table 1). The strong safety profile and high device success rate combined with a significant, sustained reduction in MR severity and improvements in functional class and quality of life demonstrate that the PASCAL repair system is at least comparable with the MitraClip system for treating patients with symptomatic MR ≥2+.[1,3,4]

A recent meta-analysis compared the clinical outcomes of the PASCAL repair system and the MitraClip system in patients with severe MR.[12] It included one RCT,[7] one prospective single-centre study,[13] and four retrospective studies, including the two discussed in this article.[3,4,14,15] The meta-analysis supports the findings discussed in this article by showing a risk ratio favouring the PASCAL repair system in terms of residual MR ≤1+ (p=0.03) and comparable safety to the MitraClip system.[12]

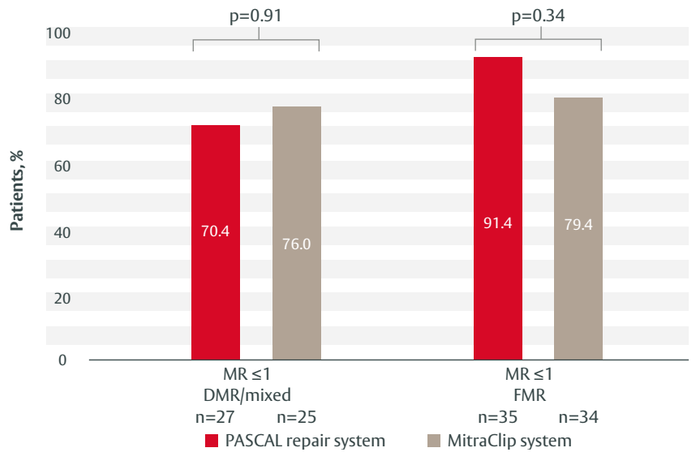


Figure 7. Proportion of patients with MR ≤1 at 1 year after mitral valve repair with the PASCAL repair system or the MitraClip system, by MR aetiology.

Chart shows data for the propensity score-matched cohort.

DMR, degenerative mitral regurgitation; FMR, functional mitral regurgitation; MR, mitral regurgitation.

Adapted from Schneider L *et al*. 2022.[4]

Table 1. Summary of the latest studies using the PASCAL repair system to treat MR.

	MiCLASP Study[1]	Mauri *et al*.[3]	Schneider *et al*.[4]
Study timing	Ongoing	PASCAL repair system: 2019 MitraClip system; 2010–2018	PASCAL repair system and MitraClip system: 2018–2020
Study type	Multicentre, prospective, single-arm, post-market	Multicentre, retrospective, comparative	Multicentre, retrospective, comparative
Time points reported	1 year	Discharge, 30 days	Discharge, 30 days, 1 year
TEER system	PASCAL repair system	PASCAL repair system with the PASCAL implant MitraClip system 96% generations 1–2	PASCAL repair system with the PASCAL and PASCAL Ace implants MitraClip system generations 3 and 4
Propensity score-matched patients	-	n=307 in each group	n=92 in each group
Patients achieving MR≤1+	1 year: 83%	Discharge: PASCAL repair system 70.5% *vs* MitraClip system 56.6% (p<0.001) 30 days: PASCAL repair system 64.6% *vs* MitraClip system 44.2% (p<0.001)	Discharge: PASCAL repair system 77.1% *vs* MitraClip system 69.6% (p=0.24) 1 year: PASCAL repair system 82.3% *vs* MitraClip system 78.0% (p=0.70)

MR, mitral regurgitation; TEER, transcatheter edge-to-edge repair.

Sustained TR reduction after TEER: Evidence from the real-world PASTE registry

Dr med. Marianna Adamo

University and ASST Civil Hospitals of Brescia, Italy

Dr Marianna Adamo is an interventional cardiologist and heart failure (HF) specialist at ASST Civil Hospitals and University of Brescia. Her main area of expertise is managing valvular heart disease in HF. She was Task Force Coordinator of the 2021 European Society of Cardiology (ESC) guidelines on HF. She is a board member of the Heart Failure Association and member of the PCR Tricuspid Focus Group.

"In 2021, for the first time, transcatheter treatment of inoperable patients with symptomatic secondary severe TR was included in the ESC/European Association for Cardio-Thoracic Surgery guidelines, with a class IIb, level of evidence C recommendation.[16] At the time, evidence from RCTs to support this new therapy was lacking.

For this reason, the first data report from the TRILUMINATE pivotal RCT sponsored by Abbott Medical Devices (NCT03904147) was highly anticipated. It is the first study to compare optimal medical therapy (OMT) with tricuspid TEER plus OMT in patients with symptomatic severe TR who were considered intermediate or greater risk for tricuspid valve surgery. It demonstrated the good safety profile of TEER and an impressive improvement in quality of life in the device arm compared with the control arm.[6]

TRILUMINATE patients were different to those treated in everyday practice, as patients with severe TR come to our attention too late. TRILUMINATE patients were enrolled earlier, but they were still sick with a poor quality of life. In fact, TRILUMINATE-like patients are probably the ones we should be treating. They had mild or moderate right ventricular dysfunction, most had a normal left ventricular ejection fraction and were rarely hospitalised for HF in the previous year. Probably, these patients are not evaluated by cardiologists or surgeons in daily practice. That's why increasing TR awareness among GPs and internal medicine specialists is so important. They need to recognise the early signs and symptoms to give patients the best chance.

HFH and mortality were similar between the two arms in the TRILUMINATE RCT.[6] To see difference in these endpoints, larger studies and longer follow-up, and, therefore, more events, are needed."

Professor Dr med. Jörg Hausleiter

Medical Clinic and Polyclinic I, Ludwig-Maximilians University (LMU), Munich, Germany

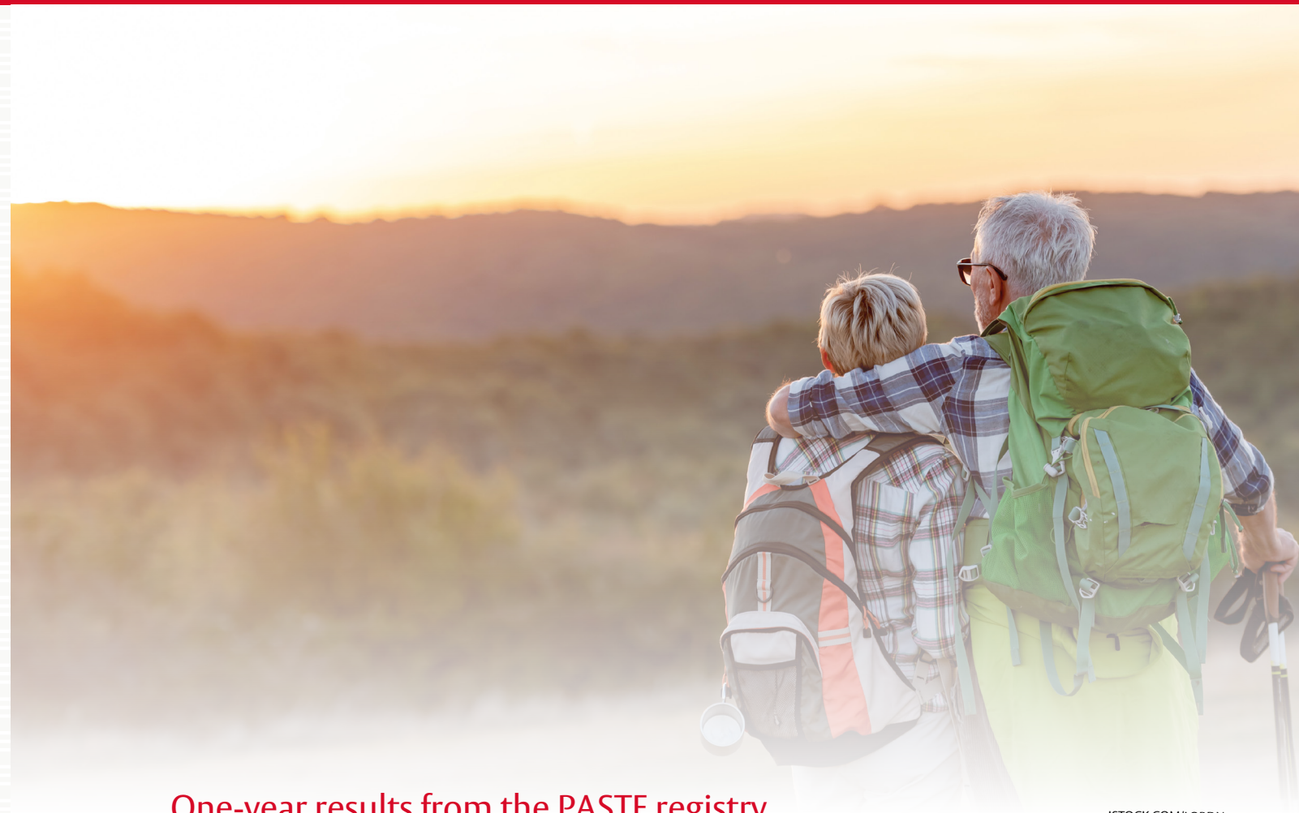
Professor Jörg Hausleiter is Professor of Medicine and the Deputy Clinic Director at LMU in Munich. He focuses on bringing new percutaneous treatments to patients with coronary and valvular diseases and is Principal Investigator in many clinical trials and registries, including TRICI-HF, MiCLASP, TRILUMINATE, CLASP IID/IIF, EuroSMR, EuroTR and PASTE.

"Encouragingly, the TRILUMINATE trial confirmed that tricuspid TEER had a strong safety profile, reduced the severity of TR, and was associated with an improvement in quality of life over OMT alone. However, it did not demonstrate differences in mortality or HFH.[6]

In my view, the main reason for this is that the patients included in the trial were less sick compared with the patients I treat in my daily practice. Typically, our patients have a preintervention HFH rate of around 1.2 HFH/patient-year.[17] In addition, almost 80% of them have kidney disease[17] and 45% have liver disease.[18] In the TRILUMINATE trial, only 25% of patients had been hospitalised for HF in the preceding year, 35% had kidney disease, and less than 10% had liver disease.[6] If the HFH rate had been higher before intervention, the trial may well have demonstrated differences in HFH.

I am hopeful that other RCTs, such as TRI-FR[19] and TRICI-HF,[20] will, in time, be able to show that tricuspid TEER does improve mortality and HFH. Certainly for TRICI-HF, for which I am Principal Investigator, patients enrolled so far have a higher risk spectrum than those in the TRILUMINATE trial, so we expect to see more events.

In the meantime, real-world studies continue to show that in the hands of experienced operators, TEER results in good TR reduction with a low rate of complications, and, as Dr Wild describes next, the results are durable. These data support tricuspid TEER as a therapy for a broad patient population."



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One-year results from the PASTE registry

PASTE (NCT05328284) is an ongoing, retrospective, observational, multicentre registry, investigating the safety and efficacy of the PASCAL repair system for the treatment of TR in a real-world patient population.[21] We reported early results up to 6 months in *TMTT Today* issue 8.[22,23] Here, Dr Mirjam Wild gives a 1-year update from the registry.

Dr med. Mirjam Wild

University Heart Center Freiburg Bad Krozingen, Germany

Dr Mirjam Wild is an interventional cardiologist at Universitäts-Herzzentrum Freiburg Bad Krozingen. Her research interests include new devices and treatment strategies for percutaneous mitral and tricuspid valve interventions, and cardiovascular imaging. Dr Wild has been involved in several registry-based clinical trials, including CHOICE-MI, TENDER and PASTE.

"No two patients with TR are alike. Over the years, we have improved our understanding of this patient population, but many uncertainties remain: who should we treat, when and using which approach? In addition, we still do not know how to best measure success in the patients we treat.

The TRILUMINATE trial results were eagerly awaited by our community. Expectations were high but were not fully met since we did not see an impact on hard clinical endpoints. Nonetheless, the results were encouraging, demonstrating the safety and efficacy of the procedure, as well as significant improvements in symptoms, functional status and quality of life for the patients treated.[6]

Data from real-world studies, including the PASTE registry, form another important piece of the puzzle. While the evidence from a registry will never translate into a class IA guideline recommendation, we can learn a lot from the experienced centres involved and the non-preselected patient population.

We previously reported our early clinical experience with the PASCAL repair system in the PASTE registry, showing high technical and procedural success rates, efficient TR reduction and significant clinical and echocardiographic improvement at a median 6-month follow-up.[23]

More recently, we reported an interim analysis of this registry at EuroPCR 2023, including up to 603 high-risk patients (mean STS-PROM score 8.4%), almost all of whom had TR ≥3+ (Figure 8).[2] One major point of difference compared with other studies, such as the TRILUMINATE pivotal trial, is the very high symptomatic burden (89% were in NYHA class III or IV) and high prevalence of comorbidities (70% had glomerular filtration rate <60 mL/min and 83% had elevated bilirubin or gamma-glutamyl transferase indicating kidney dysfunction). Moreover, 28% of the patients had a cardiac implantable electronic device with a transvalvular lead, and 28% had a coaptation gap of at least 8 mm,[2] both of which can make the procedure more challenging. Despite that, technical success was high at 99%, with 68% of the implants released in antero-septal position. Procedural success was higher for coaptation gaps less than 8 mm, with residual TR ≤2+ achieved in 87% of patients compared with 70% of patients with a coaptation gap of 8 mm or greater.[2] This result highlights the importance of considering other transcatheter options, such as annuloplasty, when treating patients with large coaptation gaps, as previously proposed by Praz *et al*.[24]

The safety profile was good, with SLDA occurring in only 3% of patients.[2] This compares favourably with the TRILUMINATE SLDA rate (7%).[6]

In around 90% of cases, TR is functional,[25] so there is the concern that underlying disease progression could cause TR to recur over time, despite intervention. Due to the nitinol device design, the PASCAL and PASCAL Ace implants allow more valve movement during the cardiac cycle, and some operators may be concerned that this could lead to recurrent TR in the course of disease progression. Therefore, for me, the key finding from recent PASTE registry results is that the technical result is durable at the 1-year follow-up. Patients demonstrated a significant and sustained TR reduction, with 81% achieving TR ≤2+ at discharge and maintaining it at 1-year follow-up (Figure 8).[2]

The sustained improvement in TR severity was accompanied by sustained functional improvements. At 1 year, 64% of patients were in NYHA class I or II, an improvement of over 50 percentage points from baseline (Figure 9).[2,5] In a previous interim analysis, presented at PCR London Valves 2022, we showed how the 6-minute walk distance (+43 m) and patients' quality of life (−12 points in Minnesota Living with Heart Failure Questionnaire [MLHFQ]) also improved significantly from baseline (p<0.001; Figure 10).[5]

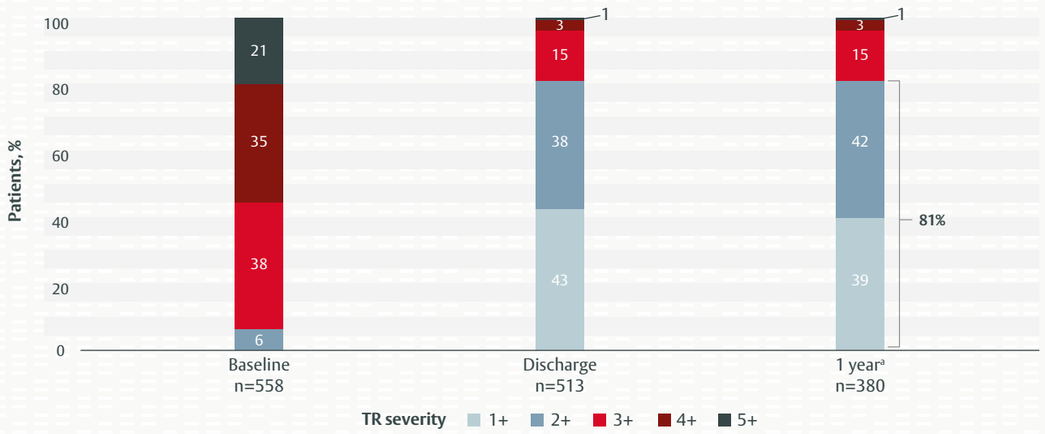

Figure 8. TR severity before and after treatment with the PASCAL repair system in the PASTE registry.[2]

Number of patients: 603. [a]Median follow-up: 352 days.
TR, tricuspid regurgitation.
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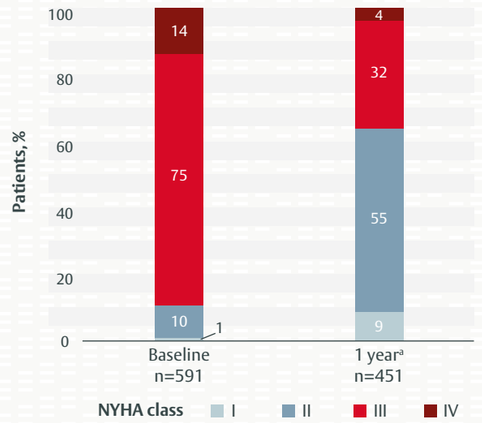


Figure 9. NYHA functional class before and after treatment with the PASCAL repair system in the PASTE registry.[2]

Number of patients: 603. [a]Median follow-up: 352 days.
NYHA, New York Heart Association.
Reproduced with permission from Hausleiter J. 2023.

At 1 year, freedom from death was 82.2%, while freedom from death or HFH was 76.5%.[5] These are not as high as in some other studies, for example the bRIGHT registry;[27] however, compared with the natural course of the disease, we think these outcomes are acceptable in this high-risk population. We believe that other patient factors are influencing the clinical course independently of the characteristics that we know of, independently of TR reduction, which is very good in our cohort.

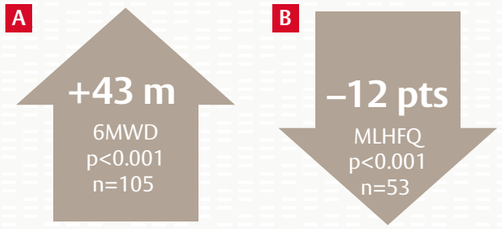
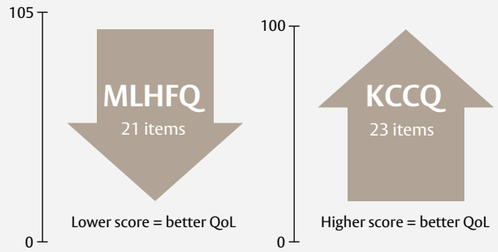


Figure 10. Change in 6-minute walk distance (A) and Minnesota Living with Heart Failure Questionnaire score (B) from baseline to 1 year after treatment with the PASCAL repair system in the PASTE registry.[5]

Number of patients: 302. Median follow-up: 1 year.
6MWD, 6-minute walk distance; MLHFQ, Minnesota Living with Heart Failure Questionnaire.

Remember, when interpreting quality-of-life questionnaire scores:[25]



The MLHFQ is a 21-item questionnaire, with a total score ranging from 0 to 105; *lower* scores are indicative of better quality of life. The KCCQ is a 23-item questionnaire, with an overall summary score ranging from 0 to 100; *higher* scores are indicative of better quality of life.

KCCQ, Kansas City Cardiomyopathy Questionnaire; MLHFQ, Minnesota Living with Heart Failure Questionnaire; QoL, quality of life.

Conclusion

These data from the PASTE registry support the safety and efficacy of the PASCAL repair system for treating TR in a real-world setting. Improvements in TR severity and functional status were sustained to 1 year,[2] with satisfactory rates of mortality and HFH in this elderly and high-risk patient population.[5] Several other studies continue to evaluate the safety and effectiveness of the PASCAL repair system, including the CLASP TR early feasibility study, for which 1-year data were recently published,[28] and the CLASP II TR RCT, which will compare tricuspid TEER and OMT with OMT alone in patients with symptomatic, severe TR.[29]

> One feature of the PASCAL repair system that facilitates TR reduction is the ability to reposition the implant without damaging the leaflets. If the initial result is not satisfactory, we can either completely reposition the implant or optimise its position by independently regrasping the leaflets, which was done in 81% of the procedures in the PASTE registry.[2] Also, the small spacer and narrow design of the PASCAL Ace implant are particularly useful for the complex tricuspid anatomy. Inexperienced operators sometimes find the large freedom of movement with the PASCAL repair system challenging; however, I believe they will find the PASCAL Precision system easier to navigate, which should lead to broader application in the future.
>
> **Dr Mirjam Wild**

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Tips and tricks with the PASCAL Precision System

Every patient is different and presents a unique case for the Heart Team. Here, six experts share case studies illustrating how they use the PASCAL Precision system to achieve optimal results for their patients and how they decide which implant to use.

Treating degenerative mitral regurgitation with the PASCAL Precision System and the PASCAL Ace Implant

Case study 1

Dr Rodrigo Estévez-Loureiro is a consultant in interventional cardiology at Álvaro Cunqueiro Hospital in Vigo, Spain.

The patient

An 86-year-old male with hypertension, mild renal disease and permanent atrial fibrillation. The echocardiogram showed that he had **a large, central P2 prolapse resulting in severe MR** (Figures 11A and 12A). He also had mild left ventricular dysfunction. While he was not overly symptomatic, left ventricular function declined over time, so we felt that treatment was necessary.

The strategy

The patient's EuroSCORE II was approximately 2.5%, which represents quite a low surgical risk; however, due to his age and frailty, we decided to take the transcatheter route, as older patients tend to have more complications and poorer outcomes after surgery than younger and fitter patients. Our team is experienced in transcatheter approaches and achieves good results in octogenarians – and the surgeons agreed with this approach too.

We decided to treat the patient with the PASCAL Precision system because it offers several advantages in cases with large prolapses. Firstly, multiple leaflet captures can be performed without damaging the valve. The clasps on the PASCAL Ace implant are long, so you can capture as much tissue as possible – up to 10 mm – which is important in DMR cases. Also, we anticipated that we would need to use at least two implants, but we did not expect any post-procedural gradient issues because the PASCAL Ace implant is nitinol-based and allows for some leaflet movement.

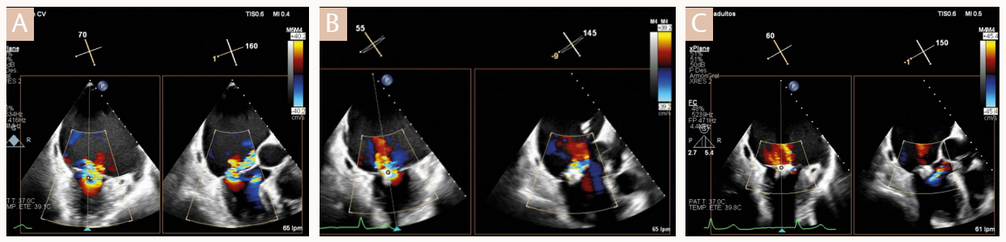

Figure 11. Transoesophageal echocardiography of the mitral valve pre procedure (A) and after one (B) and two (C) PASCAL Ace implants (bicommissural and X-plane views).

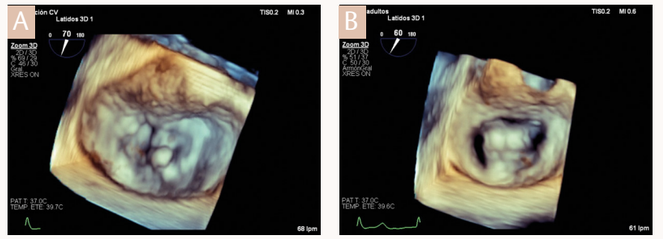

Figure 12. 3D echocardiography of the mitral valve before (A) and after (B) implantation of two PASCAL Ace implants.

> 'You can optimise and reposition multiple times because the PASCAL and PASCAL Ace implants are gentle on the leaflets.'
>
> **Dr Rodrigo Estévez-Loureiro**

Our usual strategy is to aim for the centre of the prolapse first as this is normally the largest part and the most difficult to capture. If the result is good, we use only that one device. However, when treating large prolapses, such as the one I describe here, we often see residual tissue on both sides of the implant. Hence, for this specific patient, we decided to capture the medial edge of the prolapse with the first implant, then capture the lateral edge with the second implant.

The challenge

The patient had a very large left atrium, so we had to be very careful to ensure the transseptal puncture was in the correct position and not too high, to limit the need for extra manoeuvres to reach the valve. Positioning the first device perfectly was challenging, largely because of the movement of the posterior leaflet. We performed multiple leaflet capture optimisations to ensure we were in the right place and were grasping the right amount of tissue. I was comfortable doing this, because the PASCAL Ace implant interacts gently with the leaflets, with low probability of damage.

The procedure

As discussed above, first, we implanted a PASCAL Ace implant on the medial edge of the prolapse. After several captures and optimisations, we were happy with the result (Figure 11B). After that, implanting the second PASCAL Ace implant, on the lateral side, was straightforward (Figure 11C).

At baseline, the MR grade was 4+. Post procedure, it was 0–1+, and remained stable in the following days. The result was amazing (Figure 12B), and the patient is doing very well.

Key tips

In DMR cases like this one, redundant tissue is an issue, so I recommend the PASCAL Ace implant, because you can grasp more tissue than with the PASCAL implant. Also, the narrow design of the PASCAL Ace implant makes navigating chordae easier, reducing the risk of entanglement.

Another reason why I favour the PASCAL Precision system in complex anatomies is the ability to elongate the implant. If you are concerned that the implant might be entangled in chordae, release the leaflets and elongate the implant. Once you feel that the implant is free in the valve, redo the clasping. Always aim for the best result: you can optimise and reposition multiple times because the PASCAL and PASCAL Ace implants are gentle on the leaflets.

Treating functional mitral regurgitation with the PASCAL Precision System and the PASCAL Implant

Case study 2

Professor Jan-Malte Sinning is a Chief Doctor in the Department of Cardiology, St. Vincent Hospital in Cologne. As an interventional cardiologist, his research interests include transcatheter interventions of the aortic valve and, in particular, the mitral and tricuspid valves. Professor Sinning has been using the PASCAL repair system since 2018.

Dr Bao Du-Quoc is an interventional cardiologist and senior physician at St. Vincent Hospital in Cologne with a special focus in evaluation, therapy and treatment of structural heart diseases. He is an expert in cardiovascular imaging and has 5 years' experience with percutaneous mitral and tricuspid valve interventions.

The patient

A 77-year-old female with two-vessel coronary artery disease, for which she underwent percutaneous coronary intervention in 2022. She also had severe post-capillary pulmonary hypertension, arterial hypertension and obesity. Echocardiography (Figures 13A and 14B) showed severe atrial FMR (MR grade 3; effective regurgitant orifice area 0.3 cm^2, vena contracta area 1.1 cm^2), with an indentation between the P2 and P3 segments in the posterior mitral leaflet. The Heart Team agreed that she was inoperable, so we decided on an interventional approach.

The strategy

We prefer to use the PASCAL implant in patients with FMR because it has a broader profile than the PASCAL Ace implant. If we had used the PASCAL Ace implant in this patient, we predict that we would have needed more than one, because the vena contracta area was so large. The strategy was to use one PASCAL implant and hopefully achieve an optimal result.

The challenge

We had to be careful regarding the indentation between P2 and P3. We had previously experienced leaflet tearing in two patients with similar indentations. Therefore, for this case, we chose the PASCAL implant, because we thought it would distribute the tension more evenly across the leaflet.

The procedure

We did not deviate from our initial strategy. We performed a transseptal puncture as usual and then inserted the PASCAL implant, navigating in a 3D view. The imaging quality in this patient was high, enabling us to achieve an **optimal result with the first clasping attempt** (Figure 14C).

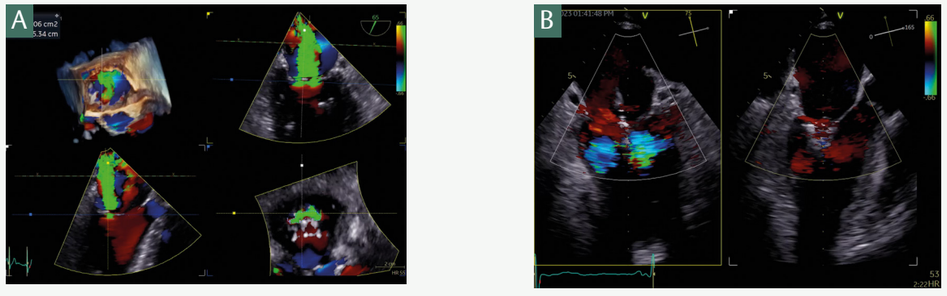

Figure 13. Transoesophageal echocardiography of the mitral valve pre procedure (A) and at final assessment before PASCAL implant release (B).

There was a small residual jet, less than mild, due to the indentation between P2 and P3, but tissue bridge was satisfactory, as confirmed by echocardiography at the end of the procedure (Figures 13B and 14D). We were both happy with the result.

Key tips

As mentioned earlier, we recommend using the PASCAL implant for most FMR cases. It simplifies the procedure – one implant is usually enough – and its spacer and broad clasping area reduce tension on the leaflets, preventing tearing, and, in our experience, often result in a relatively low gradient. In this specific situation, the PASCAL implant seems especially beneficial for addressing the indentation between the P2 and P3 segment of the posterior mitral leaflet.

If you have never used the PASCAL Precision system before, just go for it. The system is an evolution of everything we have learned about TEER so far. If you are already using the PASCAL Precision system for tricuspid TEER, try it in the mitral position too. With its stabiliser, precise control, sliders and independent clasping, it is intuitive and easy to use. You will find the PASCAL Precision system straightforward.

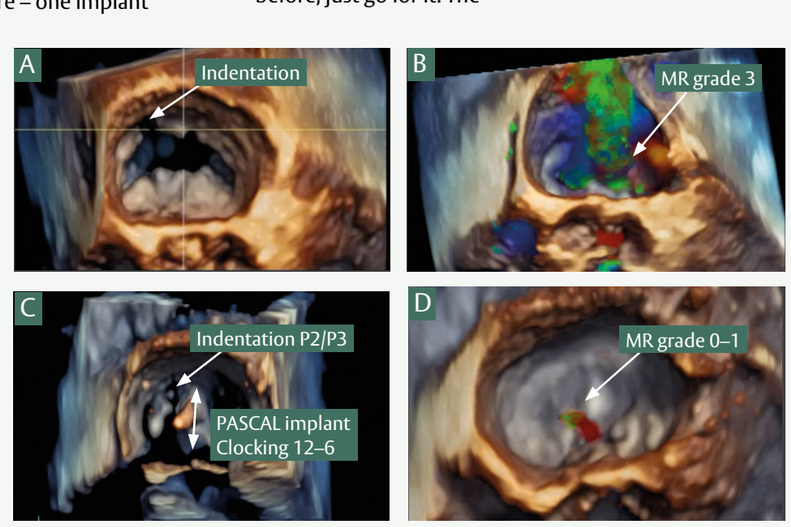

Figure 14. 3D echocardiography of the mitral valve showing the indentation between the P2 and P3 segments (A), the MR jet pre procedure (B), the PASCAL implant in position (C) and the MR jet post implantation of the PASCAL implant (D).

MR, mitral regurgitation.

> Last summer, we switched to using the PASCAL Precision system. Now, we use it for around 95% of our TEER cases.
>
> **Professor Jan-Malte Sinning**

Treating severe tricuspid regurgitation with the PASCAL Precision System

Case study 3

Dr Mehdi Eskandari is a consultant cardiologist at King's College Hospital in London. After training in cardiology and echocardiology in Australia, he moved to King's College Hospital in 2015 to complete an advanced fellowship with a focus on structural heart imaging. His research interests are applying advanced imaging, 3D printing and computer-assisted modelling in structural heart interventions.

Dr Jonathan Byrne is an interventional cardiologist and Clinical Director of Cardiovascular Services at King's College Hospital. Since 2008, Dr Byrne has been involved in developing the structural heart programme at the hospital, with the use of novel percutaneous techniques to treat aortic and mitral valve disease.

The patient

A 76-year-old woman with exertional breathlessness was referred with a 12-month history of progressive symptomatic HF. She had NYHA class II–III symptoms dominated by right-sided heart disease, although she had HF with preserved ejection fraction as well. Her initial echocardiogram demonstrated preserved biventricular function, enlarged atria, mild to moderate MR and severe TR; TR was believed to be the main contributor to her symptoms. She had been resistant to aggressive treatment with oral diuretics and had been hospitalised twice within a short period.

Her medical history included type II diabetes, diabetic nephropathy and moderate left anterior descending artery disease.

Right heart catheterisation demonstrated a left ventricular end diastolic pressure of 17 mmHg, a pulmonary wedge pressure of 16 mmHg, pulmonary vascular resistance of 3 mmHg·min/L and right atrial pressure of 13 mmHg.

The approach

The case was presented and thoroughly discussed in a multidisciplinary team meeting. The regurgitation jet was central, resulting from a coaptation defect not exceeding 8 mm. The general consensus was to offer tricuspid TEER, because we felt that a PASCAL Ace implant between the anterior and septal leaflets in a near central position would significantly reduce the regurgitation jet.

In general, we use the PASCAL Ace implant in the tricuspid position. The longer clasps and narrower spacer enable us to grasp a larger amount of tissue than we can with the PASCAL implant. This is important during tricuspid TEER, where leaflet grasping is often harder, and the septal leaflet is often short or retracted.

The challenge

The tricuspid valve appeared to have four scallops, with a notable indentation in the anterior leaflet (Figure 15). Despite this, we felt that both the anterior and septal leaflets were long enough and of sufficient quality for effective TEER.

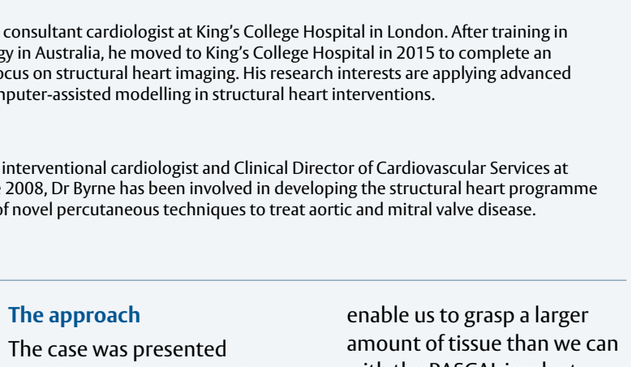

Figure 15. Multiplanar reconstruction of the 3D dataset for the tricuspid valve, with leaflets labelled.

The result

After our initial grasping attempt, we repositioned the implant to ensure optimal grasping. Such optimisation is common in TEER because deploying the implant in the correct anatomical position is crucial to avoid distorting the valve geometry. Additionally, capturing an adequate length of the leaflet is essential to prevent SLDA.

The procedure was successful and carried out according to the pre-procedural plan, which highlights the importance of thorough pre-procedural imaging and careful evaluation of the patient's anatomy. The patient had only mild residual TR post procedure (Figure 16), and she has been followed up in a structural valve clinic. She has experienced strong symptomatic improvement and regained her independence.

Key tips

We recommend multiplanar reconstruction (MPR) of the 3D dataset obtained through transoesophageal echocardiography, because it allows one to generate 2D views of the tricuspid valve at any angle. This means you can meticulously analyse the valve, avoiding the inherent limitation of 2D imaging. In this case, we used it to delineate the four-scallop morphology of the tricuspid valve (Figure 15).

Additionally, intraprocedural MPR can be employed to facilitate tricuspid TEER.

One particularly useful view, known as the PASCAL implant home view, provides a standardised layout encompassing the required TEER views (Figure 17). It can help to maintain an optimal position while attempting to grasp the leaflets.

> **The PASCAL Precision system enabled us to position the implant accurately, thanks to its flexibility, stability and one-to-one torque transfer.**
> **Dr Jonathan Byrne**

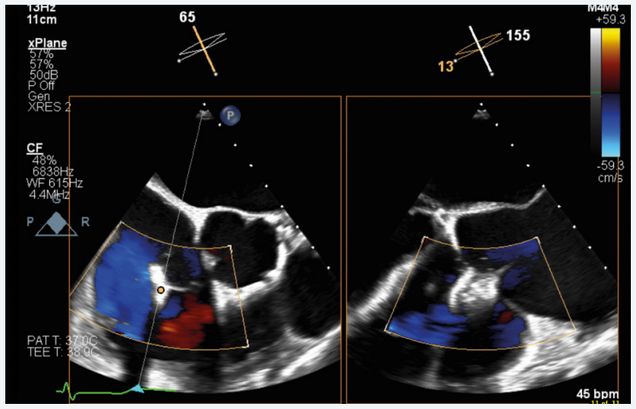

Figure 16. Transoesophageal echocardiography showing PASCAL Ace implant positioned between the anterior and septal leaflets, with only mild residual tricuspid regurgitation.

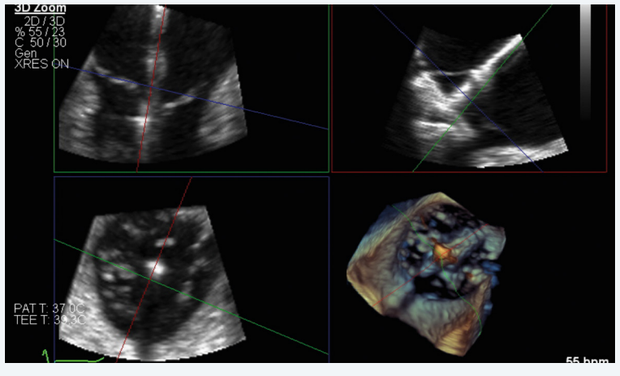

Figure 17. Intraprocedural multiplanar reconstruction of the tricuspid valve, PASCAL implant home view layout. Right ventricular inflow/outflow (top left), reversed four-chamber view (top right), trans-gastric short axis view (bottom left) and the 3D view of the tricuspid valve (bottom right).

Combined TEER of the mitral and tricuspid valves with the PASCAL Precision System

Dr Federico De Marco is an interventional cardiologist and Director of the Structural Heart programme at Monzino Heart Centre in Milan, Italy.

The patient

A 70-year-old man with multiple comorbidities. His cardiac history dates back 15 years, when he had a heart attack and coronary artery bypass grafting. He also had myelodysplastic syndrome and diffuse vascular disease, with an aneurysm in his carotid artery and a large abdominal aortic aneurysm.

The patient had shortness of breath and a moderately reduced left ventricular ejection fraction, with significant MR of mixed aetiology (Figure 18A). The MR jet was mainly caused by restricted motion of the posterior mitral leaflet due to post-ischaemic cardiomyopathy. The anterior mitral leaflet had degenerative abnormalities, making its distal portion quite thick, and it was sliding above the posterior leaflet.

The patient also had severe TR, again of mixed aetiology (Figure 19A). He had a mildly reduced right ventricular ejection fraction due to right ventricular dilatation and failure, but also significant dilatation of his right atrium.

The strategy

My usual strategy for MR with secondary TR that is ventricular in origin is to treat the MR only, then wait. However, since this patient had a dilated right atrium, I did not think that isolated MR treatment would reduce the TR over time. Therefore, I decided to concomitantly treat the mitral and tricuspid valves.

For patients with secondary post-ischaemic MR, I would usually select a PASCAL Ace implant. However, as this patient had degenerative disease of the anterior leaflet and a wide jet, I instead opted for a PASCAL implant, which is larger, to attempt to treat the MR with a single device.

Here, the strategy was to place a PASCAL implant at the centre of the mitral valve and then to treat the tricuspid valve with a PASCAL Ace implant.

The challenge

The combination of multiple diseases, previous surgery and vascular disease made imaging really challenging during both the mitral and tricuspid repairs. This was exacerbated by mild shadowing in the tricuspid valve due to the mitral implant, which is rare. In addition, treating a patient with mixed aetiology is always more challenging than treating patients with FMR or DMR only. As a result, I had multiple attempts at grasping before achieving a satisfactory result.

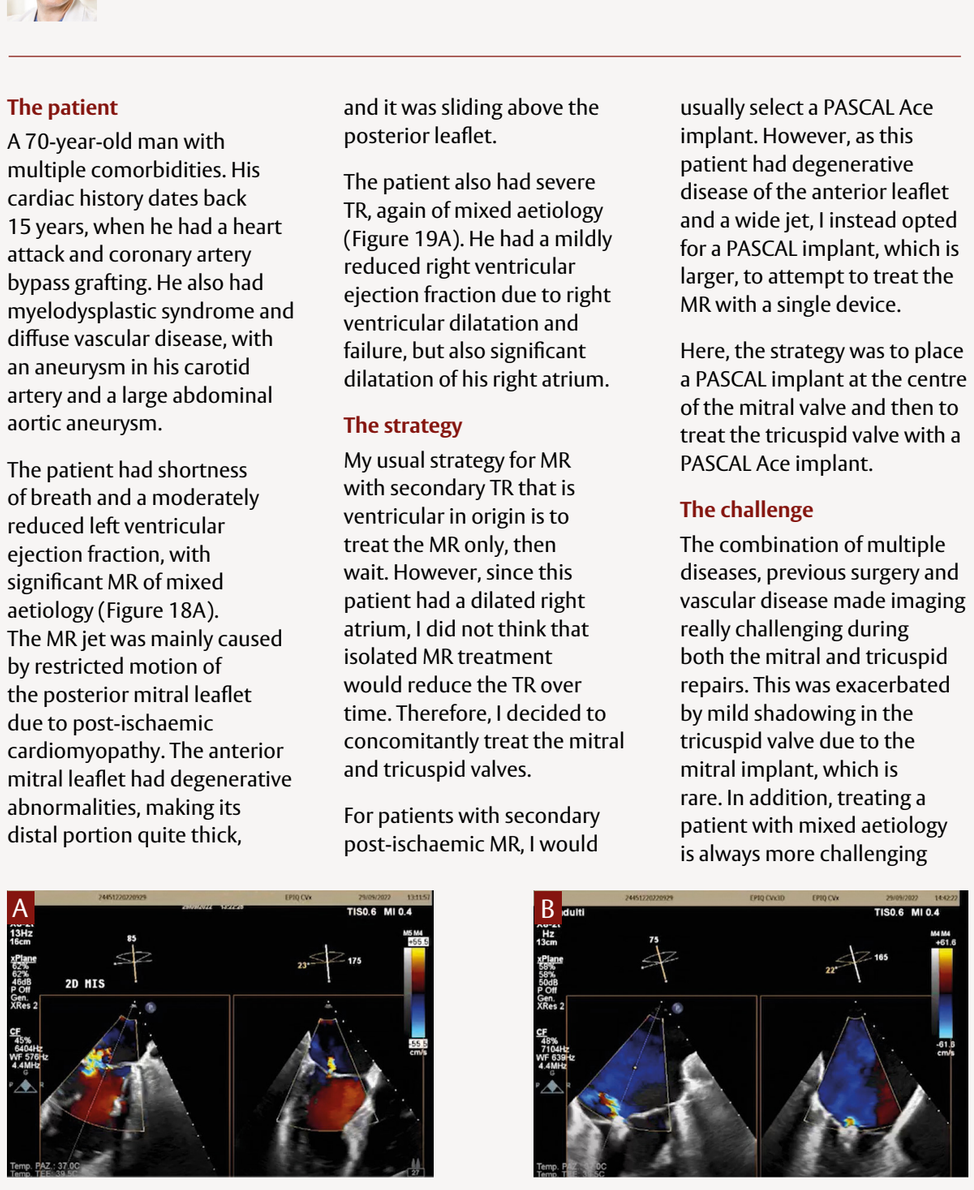

Figure 18. Pre- (A) and post-procedural (B) transoesophageal echocardiography of the mitral valve.

The procedure

The patient received three PASCAL implants: a PASCAL implant in the mitral valve and two PASCAL Ace implants between the septal and anterior leaflets of the tricuspid valve. I was pleased with the result: the case was challenging but we achieved a good outcome (Figures 18B, 19B and 20). The patient ended up with mild MR and moderate TR. He has benefited considerably from the procedure.

Key tips

Challenging cases like this one require a lot of patience. The PASCAL Precision system is stable and responsive, enabling you to make delicate adjustments to the implant's position. Take your time evaluating different positions to achieve the best result. In retrospect, a case like this one with very poor imaging may have benefited from intracardiac echo imaging – I would try that in future.

Treatment of concomitant TR at the same procedure as MR remains controversial. Many patients have improvement of TR after mitral TEER, and the timing of these procedures requires further prospective study. For now, the timing is a matter of judgment.

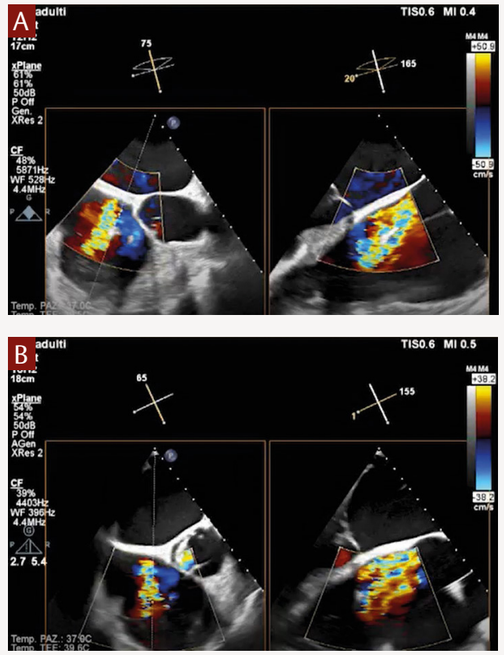

Figure 19. Pre- (A) and post-procedural (B) transoesophageal echocardiography of the tricuspid valve.

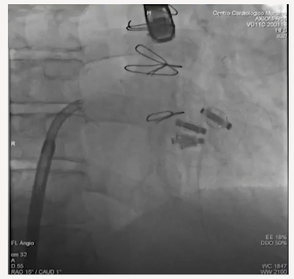

Figure 20. Fluoroscopic angiography showing the PASCAL and PASCAL Ace implants in the mitral and tricuspid valves.

> The PASCAL Precision system is stable and responsive. Take your time evaluating different implant positions to achieve the best result.
> **Dr Federico De Marco**

All figures in these cases were reproduced with permission from the authors.

Conclusion

The PASCAL Precision system and the earlier generation PASCAL repair system are effective at treating both MR and TR in the real world. Significant, sustained reductions in MR and TR are combined with improvements in functional status and quality of life in broad patient populations.[1–5,12] In addition, as we have learnt from our experts' tips and tricks, the choice of two implants enables cardiologists to tailor procedures to an individual's anatomy and disease aetiology, while the improved stability and responsiveness of the PASCAL Precision system gives them confidence to tackle challenging TEER cases.

Ask your questions...

We can be reached at TMTT-Today@edwards.com to answer your questions about the portfolio of therapies for transcatheter mitral and tricuspid valve therapies.

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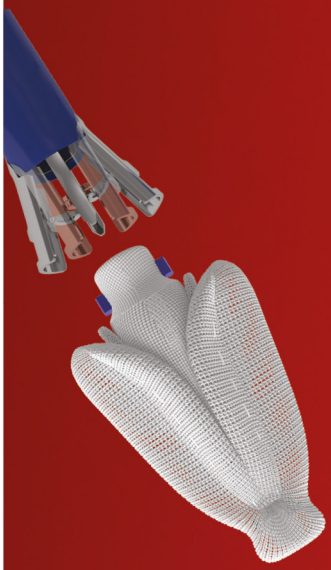

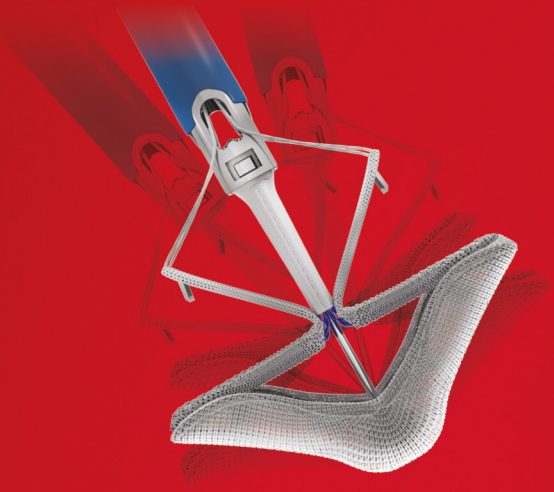

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