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REVIEW

MitraClip in Asia
— Current Adoption and Regional Data —

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In the United States and Europe, percutaneous edge-to-edge repair of the mitral valve with the MitraClip device for patients with severe degenerative mitral regurgitation who are at prohibitive surgical risk has been well-established. Recent randomized controlled trials have also demonstrated significant clinical benefits with the use of the device in selected patients with functional mitral regurgitation. Thus far, >80,000 patients in more than 50 countries have undergone the MitraClip procedure. Despite the exponential growth worldwide, the rate of MitraClip adoption in Asia has been more gradual. In addition, very few publications describe the use of MitraClip in Asian populations. This review aims to describe the Asian experience with the MitraClip device and the challenges faced.

Key Words: Asia; MitraClip; Mitral regurgitation

In the early 1990s, Ottavio Alfieri developed a surgical technique ("edge-to-edge" technique or Alfieri's stich) for the treatment of mitral valve prolapse by suturing the free edge of the prolapsing leaflet with the free edge of the opposing leaflet to create a double-orifice mitral valve.[1–3] This paved the way for the development of the MitraClip system (Abbott Vascular, Abbott Park, IL, USA), a percutaneous edge-to-edge repair technique of the mitral valve to address mitral regurgitation (MR).[4–7] Since the seminal Endovascular Valve Edge-to-Edge Repair Study (EVEREST II), MitraClip has become an established treatment option for patients with severe degenerative MR (DMR) who are at prohibitive surgical risk.[8–10] After obtaining the Conformité Européenne (CE) mark in Europe in 2008 and United States (US) Food and Drug Administration (FDA) approval for its use in DMR in 2013, more than 80,000 patients in more than 50 countries have undergone the MitraClip procedure. Multiple large US and European registries have subsequently validated its efficacy and safety in real-world settings.[11–15] The recent COAPT and MITRA-FR trials provided clinical insights on how to best select patients with functional MR (FMR) who will reap the maximum benefits from the MitraClip.[16–18] Thereafter, the FDA approved its use for FMR in March 2019.

Asia Experience

Asia is the largest continent in the world and has a population of >4 billion people with richly diverse cultures. Compared to the US and Europe, however, the use of the MitraClip has been slow to start. The initial adoption has largely been hampered by several factors. First, the MitraClip is costly, at USD$20,000–$30,000 (estimated cost due to commercial sensitivity), this is considered prohibitively expensive to some. The lack of national reimbursement in almost all Asian countries (except Japan) affects the rate of uptake. Second, regulatory approvals take time and effort to obtain. Furthermore, some countries such as Japan and China require local trials before approval for use. Third, the conservative nature of Asian societies, both patients and physicians, may make adoption of relatively newer technologies a slower process. The first MitraClip procedure in the Asia-Pacific was performed at Sir Charles Gairdner Hospital, Australia, on 23 March 2011, while the first in Asia was performed soon after at the National Heart Centre Singapore on 14 April 2011 (**Table 1**).[19] This paved the way for other Asian countries to open their MitraClip programs. The most recent country to start the MitraClip program is Japan, which received regulatory approval for the MitraClip in 2017 and subsequently national reimbursement in 2018. This was only after completion of the Japanese AVJ-514 trial, which provided the regulatory authorities with the requisite data for approval of the use of the device.[20] Once the MitraClip was approved in Japan, the accompanying reimbursement allowed for rapid adoption of the therapy. **Figure** shows the gradual increase in MitraClip cases over the years for each region, with an exponential jump last year with the introduction of Japan.

MitraClip Data in Asia

Limited data on MitraClip therapy have been published in Asia (**Table 2**),[20–23] as compared with the extensive global experience and literature. The MitraClip Asia-Pacific Registry (MARS) is a multi-national, multi-center registry started in February 2011 in an effort to describe the MitraClip experience in the Asia-Pacific region. Thus far, 17 centers from 10 countries (Australia, Singapore, Taiwan, Hong Kong, New Zealand, Indonesia, Vietnam, Thailand, China and Malaysia) are included. In 2014, the 30-day outcomes

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Table 1. MitraClip Milestones in the Asia-Pacific Region

Country	Date of first implant	Site of first implant	Type of MR indicated	Reimbursement
Australia	2011, 23 March	Sir Charles Gairdner Hospital	FMR, DMR	No
Singapore	2011, 14 April	National Heart Centre Singapore	FMR, DMR	No
Malaysia	2011, 14 December	Institut Jantung Negara	FMR, DMR	No
Hong Kong	2012, 18 July	Hong Kong Adventist Hospital	FMR, DMR	No
Indonesia	2013, 23 February	Medistra Hospital	FMR, DMR	No
Brunei	2014, 25 February	Gleneagles Jerudong Park Medical Centre	FMR, DMR	No
New Zealand	2014, 22 March	Braemar Hospital: Midland Cardio-Vascular Services	FMR, DMR	No
Philippines	2014, 23 May	St Luke's Medical Center	FMR, DMR	No
Vietnam	2014, 21 September	Bach Mai Hospital	FMR, DMR	No
Thailand	2015, 12 October	Central Chest Institute of Thailand	FMR, DMR	No
Taiwan	2016, 1 May	Taipei Veterans General Hospital	FMR, DMR	No
Pakistan†	2017, 17 September	Rawalpindi Institute of Cardiology	FMR, DMR	No
Japan	2018, 2 April	Sendai Kousei Hospital	FMR, DMR	Yes
India†	2018, 26 November	Fortis Escorts Heart Institute	FMR, DMR	No

†Special access. Information courtesy of Abbott. DMR, degenerative mitral regurgitation; FMR, functional mitral regurgitation; MR, mitral regurgitation.

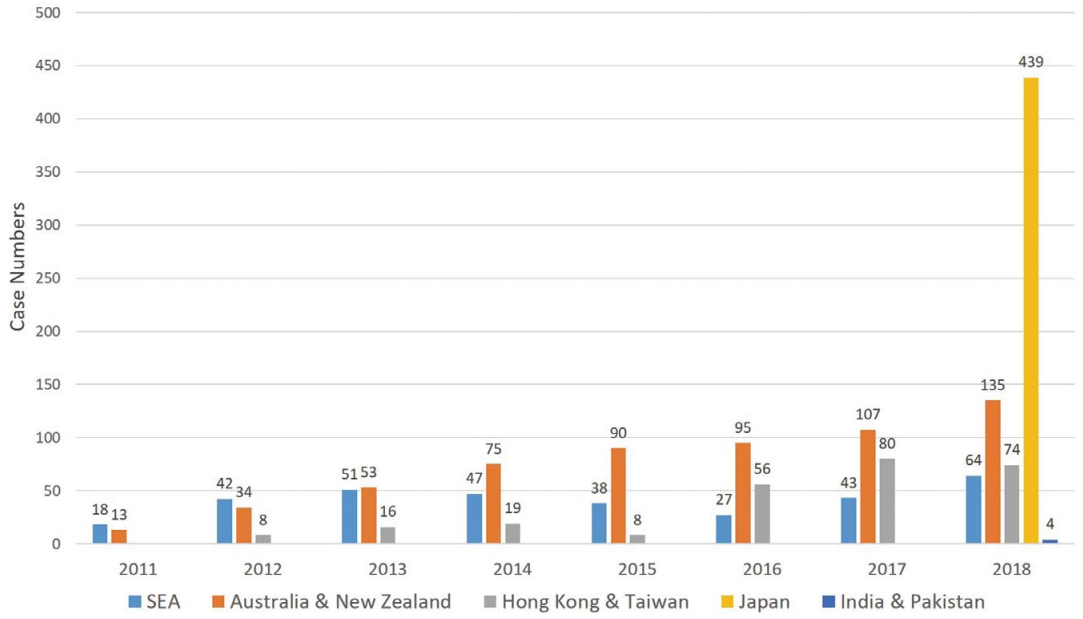

Figure. Asia-Pacific MitraClip Cases. SEA (Southeast Asia), Singapore, Malaysia, Indonesia, Brunei, Philippines, Vietnam, Thailand. Information courtesy of Abbott.

of 145 patients from 5 countries (Australia, China, Indonesia, Malaysia and Singapore) treated between February 2011 and October 2013 were studied.[22] Mean age was 71.4±11.9 years and the logistic European System for Cardiac Operative Risk Evaluation (EuroSCORE) and Society of Thoracic Surgeons (STS) risk score were 16.8±14.6% and 7.4±8.1%, respectively. This puts the risk profile of patients in the MARS registry numerically higher than that of those in EVEREST II (STS score, 5.0±4.0%), similar to the US Society of Thoracic Surgery/American College of Cardiology Transcatheter Valve Therapy Registry (STS/ACC TVT) (median STS score, 6.1%; IQR: 3.7–9.9%) and slightly lower than those in the European registries [Logistic EuroSCORE: ACCESS-Europe A Two-Phase Observational Study of the MitraClip System in Europe (ACCESS-EU), 23.0±18.3%; Transcatheter Valve Treatment Sentinel Pilot Registry (TCVT), 20.4±16.7%; Transcatheter mitral valve interventions (TRAMI), median, 20.0%; IQR: 12.0–31.0%)]. This could partly be explained by the higher proportion of patients with DMR in the MARS and the STS/ACC TVT registry as compared with the European registries (45.8% in MARS, 73.4% in EVEREST II, 85.9% in STS/ACC TVT vs. 22.9% in ACCESS-EU, 28.0% in TCVT and 27.8% in TRAMI). Not unexpectedly, patients

Table 2. MitraClip Publications in the Asia-Pacific Region

Publication	Location	n	DMR/FMR/Mixed	Baseline characteristics†	Outcomes
Percutaneous mitral valve repair in a high-risk Australian series [Edelman et al.[21]]	Australia	25	DMR 16.0% FMR 84.0%	Age 74.1±9.1 years STS score 4.7% (0.6–22.72%) EuroSCORE 13.25% (3.7–55.40%)	Mortality at 30 days, 0%; 6 months, 8% MR ≤2+ at 30 days, 88%; 6 months, 88% NYHA I–II at 30 days, 64%; 6 months, 76%
Percutaneous mitral valve repair with the MitraClip: Early results from the MitraClip Asia-Pacific Registry [Yeo et al.[22]]	Australia, China, Indonesia, Malaysia and Singapore	142	DMR 45.8% FMR 53.5% Mixed 0.7%	Age 71.4±11.9 years STS score 7.4±8.1% Logistic EuroSCORE 16.8±14.6%	Acute procedural success, 93.7% Mortality at 30 days, 5.6% MR ≤2+ at 30 days, 76.8% NYHA I–II at 30 days, 82.1%
AVJ-514 Trial: Baseline characteristics and 30-day outcomes following MitraClip® treatment in a Japanese cohort [Hayashida et al.[20]]	Japan	30	DMR 53.3% FMR 46.7%	Age 80.4±7.0 years STS score 10.3±6.59% EuroSCORE II 5.6±3.70%	Acute procedural success, 86.7% Mortality at 30 days, 0% MR ≤2+ at 30 days, 86.7% NYHA I–II at 30 days, 96.7%
Initial experience with percutaneous edge-to-edge transcatheter mitral valve repair in a tertiary medical center in Taiwan. [Lee et al.[23]]	Taiwan	20	DMR 55.0% FMR 40.0% Mixed 5.0%	Age 73.4±11.1 years STS score 8.7±9.0% EuroSCORE II 13.2±17.7%	Acute procedural success, 95.0% Mortality at 30 days, 5.0% MR ≤2+ at 30 days, 90.0% NYHA I–II at 30 days, 95.0%

†Data given as mean±SD or median (IQR). DMR, degenerative mitral regurgitation; FMR, functional mitral regurgitation; MR, mitral regurgitation; NYHA, New York Heart Association.

with FMR would be at higher risk, with most having depressed left ventricular ejection fraction and prior revascularization. Patients included in the EVEREST II trial were suitable for both surgery or MitraClip, and this explains the lower risk profile as compared with those in the registries. Acute procedural success (MARS, 93.7%) was higher than in EVEREST II (77.0%) and similar to that of the other registries (91% in ACCESS-EU, 95.4% in TCVT, 97% in TRAMI and 92% in STS/ACC TVT). Thirty-day mortality in MARS (5.6%) was similar with ACCESS-EU (3.4%), TRAMI (4.5%) and STS/ACC TVT (5.2%) but higher than EVEREST II (1.0%), reflecting the differences in risk profiles. There was significant improvement in New York Heart Association (NYHA) functional class (82.1% in class I or II at 30 days compared with 31.7% at baseline, P<0.001) as well as MR reduction to ≤2+ (76.8% at 30 days compared to 0% at baseline, P<0.01). The degree of MR reduction was lower compared with the ACCESS-EU registry (91.2% with MR ≤2+ at 30 days), likely reflecting the early experience in the region.

Another publication on the MARS registry in 2015 compared the use of MitraClip therapy between patients with DMR and FMR in the Asia-Pacific population.[24] A total of 163 patients were evaluated: 88 (54%) with FMR and 75 (46%) with DMR. Similar outcomes were demonstrated: acute procedural success (FMR 95.5% vs. DMR 92.0%, P=0.515), 30-day mortality rate (FMR 4.5% vs. DMR 6.7%, P=0.555) and 30-day major adverse events (MAE) rate (FMR 9.2% vs. DMR 14.7%, P=0.281). Although there was a trend towards greater 30-day reduction in MR grade to ≤2+ in patients with FMR (FMR 82.5% vs. DMR 70.6%), this was not statistically significant (P=0.062). Both groups had similar improvements in NYHA functional class to I or II at 30 days (FMR 78.2% vs. DMR 83.0%, P=0.525). Results from the European registries with a higher proportion of FMR patients as well as the recent COAPT trial validated the present findings, and also validated the efficacy of MitraClip in the FMR population.

In 2014, Sir Charles Gairdner Hospital in Australia published their initial MitraClip experience of 25 patients.[21] The majority had FMR (84%) and the mean age was 74.1±9.1 years with a median STS score of 4.7% (IQR, 0.6–22.72%) and median EuroSCORE of 13.25% (IQR, 3.7–55.40%). There was only 1 mortality at 6 months (8%). MR reduction to ≤2+ at 30 days was 88% and this was sustained at 6 months. There was also significant clinical improvement: 64% in NYHA functional class I or II at 30 days, which improved to 76% at 6 months.

In Japan, the AVJ-514 trial was a prospective multicenter study to demonstrate the use of MitraClip technology in their population.[20] A total of 30 patients underwent the MitraClip procedure with a mean age of 80.4±7.0 years, STS score was 10.3±6.59%; EuroSCORE II, 5.6±3.70% and 53.3% with DMR while the rest were functional. Acute procedural success was achieved in 86.7% and there was no occurrence of MAE. There was also remarkable clinical improvement at 30 days with no mortality, 86.7% with MR ≤2+ and 96.7% with NYHA functional class I or II. This study demonstrated the feasibility, safety and clinical efficacy of the MitraClip in a Japanese population and was the basis for the device regulatory approval in Japan in 2017.

Lee et al reported their early experience of MitraClip in Taiwan in 20 patients and demonstrated excellent acute procedural success (95%), safety (no periprocedural MAE) and 30-day mortality (5%) in a high-risk group of patients (EuroSCORE II, 13.2±17.7%; STS score, 8.7±9.0%).[23] There was also significant improvement in MR as well as NYHA functional class at 1 month compared with baseline.

These studies, although small in numbers and with relatively short-term follow-up, are reassuring with regard to the early experience of the MitraClip device in Asia.

Challenges and Questions in Asia

Asian people have smaller left atria compared with their Western counterparts.[25,26] The smaller space makes maneu-

vering more challenging with the same device specifications. With the recent introduction of the XTR system, its longer clip arms are designed for greater reach and improved grasp to achieve better technical success in more complex anatomies.[27] Its applicability and challenges in a smaller Asian heart size, however, are yet to be determined.

Thus far, MitraClip therapy has been reserved for patients who are at high or prohibitive surgical risk. With the Asian aversion to open-heart surgery, however, there are certain patients who are at intermediate or even low surgical risk who adamantly refuse surgery.[28] Indeed, there are those who would rather settle for a suboptimal quality of life than go under the knife. Although surgical mitral valve repair or replacement is still the gold standard for DMR, there may be a role for transcatheter therapy in this subset of patients.

Conclusions

MitraClip therapy has been available in Asia for 8 years. With the recent introduction of the therapy in Japan and India, and perhaps Korea in the near future, MitraClip therapy is ready to address the unmet clinical need in an Asian population averse to open heart surgery. In time to come, larger and more robust studies on MitraClip in Asia will allow for comparison with the extensive experience in the USA and Europe.

Disclosures

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References

1. Maisano F, Torracca L, Oppizzi M, Stefano PL, D'Addario G, La Canna G, et al. The edge-to edge technique: A simplified method to correct mitral insufficiency. *Eur J Cardiothorac Surg* 1998; **13:** 240–246.
2. Maisano F, Schreuder JJ, Oppizzi M, Fiorani B, Fino C, Alfieri O. The double-orifice technique as a standardized approach to treat mitral regurgitation due to severe myxomatous disease: Surgical technique. *Eur J Cardiothorac Surg* 2000; **17:** 201–205.
3. Alfieri O, Maisano F, De Bonis M, Stefano PL, Torracca L, Oppizzi M, et al. The double-orifice technique in mitral valve repair: A simple solution for complex problems. *J Thorac Cardiovasc Surg* 2001; **122:** 674–681.
4. Maisano F, La Canna G, Colombo A, Alfieri O. The evolution from surgery to percutaneous mitral valve interventions: The role of the edge-to-edge technique. *J Am Coll Cardiol* 2011; **58:** 2174–2182.
5. Maisano F, Viganò G, Blasio A, Colombo A, Calabrese C, Alfieri O. Surgical isolated edge-to-edge mitral valve repair without annuloplasty: Clinical proof of the principle for an endovascular approach. *EuroIntervention* 2006; **2:** 181–186.
6. Fann JI, St Goar FG, Komtebedde J, Oz MC, Block PC, Foster E, et al. Beating heart catheter-based edge-to-edge mitral valve procedure in a porcine model: Efficacy and healing response. *Circulation* 2004; **110:** 988–993.
7. St Goar FG, Fann JI, Komtebedde J, Foster E, Oz MC, Fogarty TJ, et al. Endovascular edge-to-edge mitral valve repair: Short-term results in a porcine model. *Circulation* 2003; **108:** 1990–1993.
8. Feldman T, Foster E, Glower DD, Kar S, Rinaldi MJ, Fail PS, et al; EVEREST II Investigators. Percutaneous repair or surgery for mitral regurgitation. *N Engl J Med* 2011; **364:** 1395–1406.
9. Mauri L, Foster E, Glower DD, Apruzzese P, Massaro JM, Herrmann HC, et al; EVEREST II Investigators. 4-year results of a randomized controlled trial of percutaneous repair versus surgery for mitral regurgitation. *J Am Coll Cardiol* 2013; **62:** 317–328.
10. Feldman T, Kar S, Elmariah S, Smart SC, Trento A, Siegel RJ, et al; EVEREST II Investigators. Randomized comparison of percutaneous repair and surgery for mitral regurgitation: 5-year results of EVEREST II. *J Am Coll Cardiol* 2015; **66:** 2844–2854.
11. Maisano F, Franzen O, Baldus S, Schäfer U, Hausleiter J, Butter C, et al. Percutaneous mitral valve interventions in the real world: Early and 1-year results from the ACCESS-EU, a prospective, multicenter, nonrandomized post-approval study of the MitraClip therapy in Europe. *J Am Coll Cardiol* 2013; **62:** 1052–1061.
12. Sürder D, Pedrazzini G, Gaemperli O, Biaggi P, Felix C, Rufibach K, et al. Predictors for efficacy of percutaneous mitral valve repair using the MitraClip system: The results of the MitraSwiss registry. *Heart* 2013; **99:** 1034–1040.
13. Nickenig G, Estevez-Loureiro R, Franzen O, Tamburino C, Vanderheyden M, Lüscher TF, et al; Transcatheter Valve Treatment Sentinel Registry Investigators of the EURObservational Research Programme of the European Society of Cardiology. Percutaneous mitral valve edge-to-edge repair: In-hospital results and 1-year follow-up of 628 patients of the 2011–2012 Pilot European Sentinel Registry. *J Am Coll Cardiol* 2014; **64:** 875–884.
14. Puls M, Lubos E, Boekstegers P, von Bardeleben RS, Ouarrak T, Butter C, et al. One-year outcomes and predictors of mortality after MitraClip therapy in contemporary clinical practice: Results from the German transcatheter mitral valve interventions registry. *Eur Heart J* 2016; **37:** 703–712.
15. Sorajja P, Vemulapalli S, Feldman T, Mack M, Holmes DR Jr, Stebbins A. Outcomes with transcatheter mitral valve repair in the United States: An STS/ACC TVT Registry report. *J Am Coll Cardiol* 2017; **70:** 2315–2327.
16. Stone GW, Lindenfeld J, Abraham WT, Kar S, Lim DS, Mishell JM, et al; COAPT Investigators. Transcatheter mitral-valve repair in patients with heart failure. *N Engl J Med* 2018; **379:** 2307–2318.
17. Obadia JF, Messika-Zeitoun D, Leurent G, Iung B, Bonnet G, Piriou N, et al; MITRA-FR Investigators. Percutaneous repair or medical treatment for secondary mitral regurgitation. *N Engl J Med* 2018; **379:** 2297–2306.
18. Grayburn PA, Sannino A, Packer M. Proportionate and disproportionate functional mitral regurgitation: A new conceptual framework that reconciles the results of the MITRA-FR and COAPT Trials. *JACC Cardiovasc Imaging* 2019; **12:** 353–362.
19. Yeo KK, Ding ZP, Chua YL, Lim ST, Sin KY, Tan JW, et al. Percutaneous mitral valve repair with MitraClip for severe functional mitral regurgitation. *Singapore Med J* 2013; **54:** e9–e12.
20. Hayashida K, Yasuda S, Matsumoto T, Amaki M, Mizuno S, Tobaru T, et al. AVJ-514 Trial: Baseline characteristics and 30-day outcomes following MitraClip® treatment in a Japanese cohort. *Circ J* 2017; **81:** 1116–1122.
21. Edelman JJ, Dias P, Passage J, Yamen E. Percutaneous mitral valve repair in a high-risk Australian series. *Heart Lung Circ* 2014; **23:** 520–526.
22. Yeo KK, Yap J, Yamen E, Muda N, Tay E, Walters DL, et al. Percutaneous mitral valve repair with the MitraClip: Early results from the MitraClip Asia-Pacific Registry (MARS). *EuroIntervention* 2014; **10:** 620–625.
23. Lee CW, Sung SH, Tsai YL, Chang TY, Hsu CP, Lu CC, et al. Initial experience with percutaneous edge-to-edge transcatheter mitral valve repair in a tertiary medical center in Taiwan. *J Chin Med Assoc* 2018; **81:** 305–310.
24. Tay E, Muda N, Yap J, Muller DW, Santoso T, Walters DL, et al. The MitraClip Asia-Pacific registry: Differences in outcomes between functional and degenerative mitral regurgitation. *Catheter Cardiovasc Interv* 2016; **87:** E275–E281.
25. O'Neill J, Swoboda PP, Plein S, Tayebjee MH. Left atrial size and function in a South Asian population and their potential influence on the risk of atrial fibrillation. *Clin Cardiol* 2018; **41:** 1379–1385.
26. Zemrak F, Ambale-Venkatesh B, Captur G, Chrispin J, Chamera E, Habibi M, et al. Left atrial structure in relationship to age, sex, ethnicity, and cardiovascular risk factors: MESA (Multi-Ethnic Study of Atherosclerosis). *Circ Cardiovasc Imaging* 2017; **10:** e005379.
27. Praz F, Braun D, Unterhuber M, Spirito A, Orban M, Brugger N, et al. Edge-to-edge mitral valve repair with extended clip arms: Early experience from a multicenter observational study. *JACC Cardiovasc Interv* 2019; **12:** 1356–1365.
28. Tay EL, Lew PS, Poh KK, Saclolo R, Chia BL, Yeo TC, et al. Demographics of severe valvular aortic stenosis in Singapore. *Singapore Med J* 2013; **54:** 36–39.