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Australia and New Zealand Horizon Scanning Network

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Horizon Scanning Technology Prioritising Summaries

Percutaneous mitral valve repair utilising MitraClip®

June 2006
(Updated August 2007)



ASERNIPs

**Australian
Safety
and Efficacy
Register
of New
Interventional
Procedures -
Surgical**



**Royal Australasian
College of Surgeons**



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Enquiries about the content of the report should be directed to:

HealthPACT Secretariat
Department of Health and Ageing
MDP 106
GPO Box 9848
Canberra ACT 2606
AUSTRALIA

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The production of this Horizon scanning prioritising summary was overseen by the Health Policy Advisory Committee on Technology (HealthPACT), a sub-committee of the Medical Services Advisory Committee (MSAC). HealthPACT comprises representatives from health departments in all states and territories, the Australia and New Zealand governments; MSAC and ASERNIP-S. The Australian Health Ministers' Advisory Council (AHMAC) supports HealthPACT through funding.

This Horizon scanning prioritising summary was prepared by Mr. Irving Lee from the Australian Safety and Efficacy Register of New Interventional Procedures – Surgical (ASERNIP-S).

**Name of Technology:**

Percutaneous mitral valve repair utilising MitraClip® (Evalve Inc., California).

Purpose and Target Group:

Patients suffering from severe mitral regurgitation.

Stage of Development (in Australia):

- Experimental
- Investigational
- Nearly established
- Established
- Established but changed indication or modification of technique
- Should be taken out of use
- Not yet emerged

The MitraClip is currently not available in Australia. Hence it is not listed or registered in the Australian Register of Therapeutic Goods database.

International Utilisation:

COUNTRY	LEVEL OF USE		
	Trials underway	Limited use	Widely diffused
Unites States	✓		
Venezuela	✓		

Impact Summary:***Background***

Mitral regurgitation is a condition characterised by an abnormal reversal of blood flow from the left ventricle to the left atrium. It is a result of abnormalities within the mitral or bicuspid atrioventricular valve, a fibrous structure lined with endocardium, which is located between the left atrium and left ventricle of the heart. Abnormalities of the mitral valve can be caused by disease (e.g. rheumatic fever, ruptured chordae tendinaea, leaflet perforation) or a functional lesion (Jha 2006). Congenital mitral regurgitation is rare but has been associated with myxomatous mitral valve disease, a hereditary connective tissue disorder that causes a jellylike deterioration of tissue, (Merck Manual 2006) and cleft of the mitral valve in individuals with Down Syndrome (Jha 2006).

Mild mitral regurgitation is often asymptomatic, whereas severe mitral regurgitation can cause palpitations. Eventually, severe mitral regurgitation will result in enlargement and thickening of the left ventricle as the heart attempts to compensate for the leakage of blood back into the left atrium by pumping out more blood. Similarly, the left atrium will enlarge as



well due to the increased blood volume caused by backflow of blood. Continual enlargement of the atrium can lead to atrial fibrillation, a condition whereby the atrium beats rapidly in an irregular fashion, which can lead to thromboembolism and stroke (Merck Manual 2006).

Mild mitral regurgitation is usually managed by medical therapy using after-loading agents such as nitrates and antihypertensive drugs which can help maintain the forward-flow state. In cases where atrial fibrillation has developed, digitalis may be utilised. However, if mitral regurgitation is severe, surgical intervention is required. To date, mitral valve repair and mitral valve replacements are the best surgical options for the treatment of mitral regurgitation. Recently, the development of percutaneous mitral valve repair or replacement has allowed surgeons to treat this disease with minimally invasive techniques. The MitraClip (Evalve Inc., California), is a new percutaneous extension of the edge-to-edge mitral valve repair technique (a relatively simple technique of suturing the middle portion of the anterior leaflet to the opposite portion of the posterior leaflet, creating a double orifice) (Dang *et al.* 2005). The MitraClip is a 2-armed polyester-covered device with a central barbed gripping mechanism that is delivered transseptally to the left atrium and left ventricle (Beekman 2006). Utilising echocardiographic guidance, the clip is rotated so that its arms align perpendicularly to the line of mitral leaflet coaptation. Once aligned, the system is withdrawn and the clip closes, resulting in the approximation of the anterior and posterior mitral leaflets therefore creating a functional double-orifice mitral valve (Beekman 2006).

Clinical Need and Burden of Disease

In the United States, mitral regurgitation affects approximately 5 in 10,000 people. International estimates revealed that mitral valve disease is the second most common vulvular lesion, preceded by aortic stenosis (Jha 2005). Every year, approximately 50,000 mitral valve operations are performed in the United States (Dang *et al.* 2005).

An estimate of the prevalence of mitral regurgitation in Australia is not available. However, in the past financial year (June 2004 to July 2005), there has been 2539 claims to treatments related to mitral regurgitation (Table 1); this provides a conservative estimate of the prevalence of this disease within the Australian population (Medicare Australia 2006).

Estimated Speed, Geographic and Practitioner Use, Patterns of Diffusion in the Health System

At the time of writing, the MitraClip is being evaluated for safety and efficacy in the FDA approved Endovascular Valve Edge-to-Edge Repair Study (EVEREST) II Clinical Trial. Currently, investigators are recruiting patients across several centres in the United States; results for this trial is expected to be presented sometime late 2007 (Evalve Inc. 2006).



Existing Comparators

- Mitral valve replacement
- Mitral valve repair
- Other percutaneous mitral valve repair/replacement devices:
 - CoreValve (Corevalve, USA)
 - Edwards percutaneous edge-to-edge repair system (Edwards Lifesciences, USA)
 - Edwards percutaneous mitral annuloplasty system (Edwards Lifesciences, USA)
 - Viacor Mitral Annuloplasty Device (Viacor, USA)
 - Carillon mitral contour system (Cardiac Dimensions, USA)
 - QuantumCor System (QuantumCor, USA)
 - Mitralign system (Mitralign, USA)

Note: None of the devices listed above are available in Australia at the time of writing

Estimated Cost Impact

The cost of the MitraClip was unavailable at the time of writing. According to the Medicare Benefits Schedule, the reimbursement fees for procedures relating to mitral regurgitation are listed below (Table 1) (Medicare Australia 2006):

Table 1: Medical Benefits Schedule of Fees for procedures related to mitral regurgitation

Category	Item Number	Benefit (AU\$)	Number of Claims (July 2004 to June 2005)
Reconstruction of the mitral annulus after decalcification when performed in association with valve surgery	38485	707.20	144
Reconstruction and reimplantation of sub-vulvular structures associated with mitral and tricuspid valve replacement	38490	479.90	181
Valve replacement with bioprosthesis or mechanical prosthesis	38488	1652.70	1905
Valve replacement with allograft (subcoronary or cylindrical implant) or unstented xenograft	38489	1965.50	101
Valve repair, 2 or more leaflets	38481	1973.85	205



Efficacy and Safety Issues

List of Studies Found

Total number of studies	3
Case series	2
Case report	1

The studies included in this summary are highlighted in bold in the reference list.

Safety and efficacy data from 2 case series studies and one case report have been selected for inclusion in this summary.

The Endovascular Valve Edge-to-Edge Repair Study (EVEREST) is a FDA approved phase I safety and feasibility trial of the MitraClip. A total of 27 patients were enrolled to this study, with successful implantation of the clip in 24/27 (88.8%) patients. One clip was implanted in 20 patients while the remaining 4 patients received two clips. In three patients (12.2%), the MitraClip was removed after initial testing due to inadequate reduction of mitral regurgitation. In another patient, the MitraClip was placed on the leaflets but the control of mitral regurgitation was inadequate, however in this case it was not possible to re-open the clip. As a result of this, the clip was deployed and left in place while the patient later underwent an uneventful elective surgical repair of the mitral valve. Another patient experienced clip malfunction and therefore the clip was removed. Hence, 22/27 (82%) patients were discharged from the hospital with the MitraClip in place. The average procedure time was 204 ± 116 minutes, for procedures with one clip the average was 168 ± 73 minutes while deployment of two clips averaged 396 ± 145 minutes. The duration of hospitalisation after treatment averaged 2.5 days (range 0.75 to 16 days) (Feldman *et al.* 2005).

At 30 days post-treatment, the investigators of EVEREST I reported that 85% of patients were free from major adverse events. However, one patient suffered from a non-embolic stroke which was associated with post-procedure hypotension, symptoms had resolved by the 30-day follow-up examination. There were no incidences of clip failure that resulted in emergency cardiac surgery, however there were three cases (3/27, 11%) of clip detachment from one of the two mitral leaflets. The investigators reported no deaths, clip embolisation, myocardial infarction, cardiac tamponade or septicaemia in any patient. With regards to severity of mitral regurgitation 30-days post-treatment, 14/22 (63.6%) patients had mitral regurgitation $\leq 2+$, of these 13/14 (92.8%) patients maintained this level of improvement six months post-treatment. Four patients who had baseline mitral regurgitation of 4+ improved to 3+ at discharge but did not achieve ≤ 2 severity at 30-days post-treatment. A total of 6/22 (27.3%) patients who continued to experience symptomatic mitral regurgitation



after percutaneous treatment underwent surgical repair or replacement (these patients were later describe in detail by Dang *et al.* 2005). Of these, five patients had their clips removed with no complications, but in one patient, no attempt was made to remove the clip during mitral valve replacement surgery. The reason for this was not described by the investigators. Atrial septal shunting was present in 4 of the 19 (21%) patients who had 6 month transthoracic echocardiograms. In the remaining patients, atrial septal shunting was indeterminable in 8/19 (42.1%) patients and absent in 7/19 (36.8%) patients. Overall freedom from mitral valve surgery at 6 months post-treatment was 82% (18/22 patients) (Feldman *et al.* 2005).

As stated previously, six patients (27.3%) from the EVEREST I trial underwent surgical revision due to persistence of symptomatic mitral regurgitation. The lack of improvement from percutaneous treatment was due to inadvertent malpositioning of the clip in 4 patients, which resulted in clip detachment in 3 of these patients. One patient required surgical revision due to a malfunctioning delivery system prior to clip placement while the last patient did not achieve sufficient improvement despite proper clip deployment. Clip removal during open surgery was uneventful and five patients recovered from surgery with no complications. However, one patient developed a right-sided ilio-femoral deep venous thrombosis on the same site of catheter insertion 3 days after surgical intervention (4 days after percutaneous treatment). This patient also suffered from symptomatic pericardial effusion which required percutaneous pericardiocentesis (Dang *et al.* 2005). All patients experienced significant improvement of symptoms post-surgery and no reoperations were required.

Concado *et al.* (2006) published a case report on the safety and effectiveness of MitraClip implanted in one patient. The authors stated that proper placement of the clip required three attempts, however post-procedural angiography revealed mild residual mitral regurgitation. Despite this, the patient experienced complete resolution of exertional dyspnea 30 days post-procedure and she remains asymptomatic with mild mitral regurgitation 2 years after the procedure. In addition to this, echocardiography revealed substantial positive ventricular remodelling 2 years after treatment (left ventricular internal dimension diastole improved from 5.77cm to 5.16cm; left ventricular internal dimension systole improved from 4.6cm to 3.6cm).



2007 update

A search of relevant databases, online journals and the Internet was conducted in June 2007, following the recommendation in June 2006 that percutaneous mitral valve repaired using the MitraClip be monitored for 12 months. One new case series study on the safety and effectiveness of this device was identified and retrieved.

Herrmann and colleagues (2006) evaluated the effects of MitraClip implantation on mitral valve gradients (MVG) and mitral valve area (MVA) in 24 patients who were enrolled in the EVEREST I trial; all patients suffered moderate to severe or severe mitral regurgitation (four patients received two clips). In one of these patients one clip was not optimally positioned and surgery was required within 30 days. Six patients required explantation of their clip(s) by the six month time point (range: 1 to 133 days). Although the reason for MitraClip explantation was not reported, the authors reported that mitral stenosis was not involved in any patient.

Post-procedure results taken on the day of discharge (mean of 1.8 days after clip placement) demonstrated a significant increase in the mean MVG (by Doppler ultrasound) from 1.79 ± 0.89 to 3.31 ± 2.09 mm Hg ($p = 0.004$, $n = 16$), MVA (by planimetry) from 6.49 ± 1.61 to 4.46 ± 2.14 cm² ($p < 0.001$, $n = 7$) and MVA (by pressure half time) from 4.35 ± 0.98 to 3.01 ± 1.42 ($p < 0.038$, $n = 7$). However, MVA by Gorlin formula did not demonstrate a significant decrease while peak mitral valve gradient (by Doppler) did not change significantly following clip placement.

At 12 months post-implantation the results demonstrated a decrease in the mitral valve area by pressure half time from 4.60 ± 0.63 to 2.90 ± 0.91 cm² ($p = 0.02$, $n = 5$), however when the mitral valve area was calculated by planimetry the decrease was no longer statistically significant ($n = 13$). A significant increase in peak mitral valve gradient (by Doppler) from 5.92 ± 2.53 to 9.90 ± 4.28 mm Hg ($p = 0.008$, $n = 12$) was also observed. However as noted by the authors, the increase in peak gradient is no longer statistically significant if the analysis is limited to the six patients acute procedural success. Despite the post-procedure improvement in the mean mitral valve gradient, the 12 month follow-up revealed no significant improvement in this parameter in the 13 patients evaluated.

Overall, this study demonstrates that percutaneous edge-to-edge mitral valve repair for mitral regurgitation with the MitraClip results in a small decrease in MVA when measured by pressure half time (but not significant when calculated by planimetry) with no evidence of clinical mitral stenosis immediately after clip deployment or after 12 months post-implantation.



2007 HealthPACT action

The new case series study retrieved does not contribute much to the current evidence base available on MitraClip and is limited by a small patient cohort. Based on the evidence available, the efficacy and safety of MitraClip remains uncertain. Pending the release of the EVEREST II trial results, it is unlikely that research on elucidating the effectiveness of MitraClip will yield significant discoveries with regards to its long term safety and effectiveness. Based on the current lack of evidence and the uncertainty surrounding the completion date of the EVEREST II trial, it is recommended that MitraClip is archived.

Number of studies included

Total number of studies	1
Level IV intervention evidence	1

References

Herrmann HC, Rohatgi S, Wasserman HS et al. Mitral valve hemodynamic effects of percutaneous edge-to-edge repair with the MitraClip device for mitral regurgitation. *Catheterization and Cardiovascular Interventions* 2006; 68(6): 821-828.

Ethical Issues

No issues were identified from the retrieved materials.

Cultural or Religious Considerations

No issues were identified from the retrieved materials.

Other Issues

All included studies received financial support from Evalve Inc.

Recommendation

The evidence available on the safety and efficacy of the MitraClip is limited, despite the promising results larger and longer-term studies are required. The EVEREST II trial should provide valuable information upon its completion. Based on the advantages offered by this device, it is proposed that MitraClip should be monitored for 12 months.

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| <input type="checkbox"/> Horizon Scanning Report | <input type="checkbox"/> Full Health Technology Assessment |
| <input checked="" type="checkbox"/> Monitor | <input type="checkbox"/> Archive |



References:

Beekman III RH. Transcatheter cardiac valve replacement and repair. *Congenital Heart Disease* 2006;1: 2-9.

Candado JA, Acquatella H, Rodriguez L, Whitlow P, Velez-Gimo M, Goar FS.
Percutaneous edge-to-edge mitral valve repair: 2-year follow-up in the first human case. *Catheterization and Cardiovascular Interventions* 2006;67: 323-325.

Dang NC, Aboodi MS, Sakaguchi T, Wasserman HS, Argenziano M, Cosgrove DM, Rosengart TK, Feldman T, Block PC, Oz MC. Surgical revision after percutaneous mitral valve repair with a clip: Initial multicenter experience. *Annals of Thoracic Surgery* 2005;80(6): 2338-2342.

Evalve Inc. Last updated 2006. <http://www.evalveinc.com/press/8.html> [Accessed April 2006].

Feldman T, Wasserman HS, Herrmann HC, Gray W, Block PC, Whitlow P, Goar FS, Rodriguez L, Silvestry F, Schwartz A, Sanborn TA, Candado JA, Foster E.
Percutaneous mitral valve repair using the edge-to-edge technique. *Journal of the American College of Cardiology* 2005;46(11): 2134-2140.

Jha S. Mitral Regurgitation. Last updated 2006.
<http://www.emedicine.com/med/topic1485.htm> [Accessed April 2006].

Medicare Australia. Last updated 2006. <http://www9.health.gov.au/mbs/> [Accessed April 2006].

Merck Manual. Mitral Regurgitation. Last updated 2006.
<http://www.merck.com/mmhe/sec03/ch028/ch028b.html> [Accessed April 2006].



Search Criteria:

A search of MEDLINE, PubMed, *The Cochrane Library*, the Current Controlled Trials metaRegister, the UK National Research Register, the International Network of Agencies for Health Technology Assessment, relevant online journals and the Internet was conducted in April 2006.

Search terms used were: 'MitraClip', 'Percutaneous mitral repair', 'Percutaneous edge-to-edge repair', 'EVEREST trial' and 'mitral valve repair'.

This Horizon Scanning Prioritising Summary was prepared by Mr. Irving Lee from the NET-S Project, ASERNIP-S for the Health Policy Advisory Committee on Technology (Health PACT), on behalf of the Medical Services Advisory Committee (MSAC) and the Australian Health Ministers' Advisory Council (AHMAC).