HealthPACT
Health Policy Advisory Committee
on Technology
Australia and New Zealand

Technology Brief: Update

Carillon Mitral Contour System for Mitral Regurgitation

February 2012
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Register ID: WP089

**Name of Technology:** Carillon™ Mitral Contour System

**Purpose and Target Group:** Patients with Functional Mitral Regurgitation

**Stage of Development in Australia**
- ✗ Yet to emerge
- □ Experimental
- □ Investigational
- □ Nearly established
- □ Established
- □ Established but changed indication or modification of technique
- □ Should be taken out of use

**Australian Therapeutic Goods Administration Approval**
- □ Yes (ARTG number)
- ✗ No
- □ Not applicable

**International Utilisation**

<table>
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<th>Country</th>
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<th>Limited use</th>
<th>Widely diffused</th>
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<td></td>
<td></td>
</tr>
<tr>
<td>Netherlands</td>
<td>✔</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Poland</td>
<td>✔</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**2012 Safety and Effectiveness Issues**

*Study description*

A total of three studies, including one comparative study (Lipiecki et al 2010) and two case series studies (Woloszyn et al 2011 and Reuter et al 2010), were included in this update.

The aim of the study by Woloszyn et al (2011) was to perform a functional assessment of patients undergoing implantation of the Carillon system at one centre (level IV intervention evidence). A total of 14 consecutive patients (11 men and 3...
women) were enrolled in the study. The mean age of patients was 61.1 ± 1.9 years (range 45–71 years).

Patients were included in the study if they suffered from functional mitral regurgitation secondary to dilated cardiomyopathy or ischaemic heart disease and had undergone successful implantation of the Carillon™ device. Other inclusion criteria included: Carpentier type 1 mitral regurgitation, New York Heart Association (NYHA) functional classes II to IV, a walk distance in the 6-minute walk test (6MWT) from 150 m to 450 m, left ventricular ejection fraction (LVEF) < 40%, LVEDD/BSA of 3.0 cm/m², LVEDD > 55 mg and age 18 years and above. Patients were excluded from the study if they had coexistent significant tricuspid regurgitation, structural changes in the mitral valve cusps, indications for surgical revascularisation, recent (< 3 months previously) hospitalisation for myocardial infarction, unstable angina pectoris or coronary artery bypass grafting. Other exclusion criteria included coronary angioplasty in the past 30 days, thrombus in the right atrial appendage, a foreign body in the coronary sinus or the great cardiac vein, serum creatinine exceeding 2.2 mg/dL and grade 2 mitral regurgitation in a patient with NYHA functional class II heart failure.

All patients enrolled in the study received standard drug therapy for heart failure, unless any of the drugs was not tolerated. Patients underwent echocardiography before, immediately after and one month after surgery for the assessment of parameters including vena contracta and the effective regurgitant orifice area (EROA). Before and one month after the procedure, exercise tolerance was assessed by the 6MWT and the Naughton stress test, the severity of heart failure symptoms was assessed according to the NYHA functional classification, and quality of life was assessed using the Kansas City Cardiomyopathy Questionnaire (KCCQ). Additionally, one month after the procedure, patients assessed their wellbeing compared to how they had felt before the procedure. One patient did not attend the one month follow-up visit, and did not undergo the 6MWT and stress test or complete the quality of life questionnaire. However, the same patient did complete an echocardiogram one month after the procedure.

The studies by Lipiecki et al (2010) and Reuter et al (2010) were conference abstracts presented at the 22nd Annual Symposium of Transcatheter Cardiovascular Therapeutics. These studies reported preliminary results from the Tighten the annulus now (TITAN) trial, which used the second generation Carillon XE2 device. In this trial, which was conducted at seven centres located in Germany, Poland, and France, 36 patients received a permanent Carillon implant, while 17 patients had the device recaptured due to either transient coronary artery compromise or insufficient functional mitral regurgitation reduction. These non-implanted patients were
assessed and followed-up in a similar manner to implanted patients, and thus acted as a non-randomised, non-blinded control group.

The TITAN study aimed to assess the safety and efficacy of the Carillon mitral contour system at 1, 6, 12, 18 and 24 months and at 3, 4, and 5 years. Patients were included in the study if they suffered from dilated ischaemic or non-ischaemic cardiomyopathy and moderate to severe functional mitral regurgitation. Other inclusion criteria included NYHA functional class II to IV, a walk distance in the 6MWT from 150 m to 450 m, and LVEF < 40%. A peri-procedural reduction in functional mitral regurgitation and confirmation of unaltered coronary flow were prerequisites for permanent implantation of the device. The primary safety endpoint was the major adverse event (MAE) rate at 30 days follow-up. Secondary endpoints at 1, 6, and 12 months included echo core lab derived quantitative measures of functional mitral regurgitation such as regurgitant volume, as well as NYHA class, 6MWD, and quality of life assessed using the KCCQ.

The aim of the study by Lipiecki et al (2010) was to compare functional outcomes at baseline, 6 months and 12 months in implanted and non-implanted patients (level III-2 intervention evidence). Reuter et al (2010) conducted a subgroup analysis of the haemodynamic and clinical response to the device, and compared outcomes at baseline and 6 months (level IV intervention evidence).

Safety

No safety outcomes were reported in the study by Woloszyn et al (2011).

In the TITAN trial, the rate of MAEs at 30 days follow-up for all 53 attempted patients was 1.9% (1/53 patients) (Lipiecki et al 2010 and Reuter et al 2010).

Effectiveness

Woloszyn et al (2011) reported that the severity of heart failure, as indicated by the NYHA functional class, was significantly improved following percutaneous mitral valvuloplasty ($P<0.005$) (Table 1). Specifically, prior to the procedure, the majority of patients were in NYHA functional class III, while after the procedure the majority of patients were in class II (Table 2).
Table 1: Effects of valvuloplasty on NYHA functional class, 6MWT, duration of stress test and quality of life (Woloszyn et al 2011)

<table>
<thead>
<tr>
<th></th>
<th>Before procedure</th>
<th>After procedure</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>n = 14</td>
<td>n = 14</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean NYHA functional class</td>
<td>2.93 ± 0.07</td>
<td>1.93 ± 0.2</td>
<td>&lt;0.005</td>
</tr>
<tr>
<td>Mean distance in the 6MWT (m)</td>
<td>311.0 ± 15.7</td>
<td>390.0 ± 26.3*</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Mean duration of stress test (min)</td>
<td>3.49 ± 0.27</td>
<td>5.06 ± 0.47*</td>
<td>&lt;0.005</td>
</tr>
<tr>
<td>Mean quality of life score</td>
<td>67.9 ± 3.3</td>
<td>88.3 ± 4.02*</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

All figures given are mean ± standard error, *Assessed in 13 patients, 6MWT: 6-minute walk test; NYHA: New York Heart Association.

Table 2: Severity of heart failure symptoms before and one month after the valvuloplasty procedure (Woloszyn et al 2011)

<table>
<thead>
<tr>
<th>NYHA functional class</th>
<th>Before procedure</th>
<th>1 month after procedure</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n = 14</td>
<td>n = 14</td>
</tr>
<tr>
<td>I</td>
<td>0% (0/14)</td>
<td>21% (3/14)</td>
</tr>
<tr>
<td>II</td>
<td>7% (1/14)</td>
<td>71% (10/14)</td>
</tr>
<tr>
<td>III</td>
<td>93% (13/14)</td>
<td>0% (0/14)</td>
</tr>
<tr>
<td>IV</td>
<td>0% (0/14)</td>
<td>7% (1/14)</td>
</tr>
</tbody>
</table>


Similarly, a significant improvement was observed in other functional parameters one month after the procedure, including the walking distance in the 6MWT (P<0.001) and the duration of the Naughton stress test (P<0.005) (Table 1).

A significant improvement in the quality of life of patients was observed one month after the procedure (P<0.001) (Table 1), with all patients reporting that they were feeling a bit better, much better or considerably better (Table 3).
Table 3: Patient well-being compared to how they were feeling before implantation of the Carillon device (a survey completed one month after the procedure) (Woloszyn et al 2011)

<table>
<thead>
<tr>
<th>How are you feeling now compared to how you were feeling before the implantation of the Carillon device?</th>
<th>n = 13</th>
</tr>
</thead>
<tbody>
<tr>
<td>Considerably worse</td>
<td>0% (0/13)</td>
</tr>
<tr>
<td>Much worse</td>
<td>0% (0/13)</td>
</tr>
<tr>
<td>A bit worse</td>
<td>0% (0/13)</td>
</tr>
<tr>
<td>No change</td>
<td>0% (0/13)</td>
</tr>
<tr>
<td>A bit better</td>
<td>31% (4/13)</td>
</tr>
<tr>
<td>Much better</td>
<td>54% (7/13)</td>
</tr>
<tr>
<td>Considerably better</td>
<td>15% (2/13)</td>
</tr>
</tbody>
</table>

With regard to echocardiographic parameters, following the procedure significant improvements were observed for vena contracta (0.65 ± 0.04 before the procedure to 0.36 ± 0.03 directly after the procedure and 0.31 ± 0.03 one month after the procedure; P<0.001 for both differences) and EROA (0.28 ± 0.04 cm² before the procedure to 0.18 ± 0.02 cm² directly after the procedure (P<0.05) and 0.20 ± 0.02 cm² one month after the procedure (P<0.005)).

Lipiecki et al (2010) reported that in patients implanted with the Carillon device, a significant improvement in NYHA functional class (P<0.0001), walking distance in the 6MWT (P=0.0036), and quality of life (P=0.00012) was observed up to 12 months after the procedure (Table 4). In non-implanted patients however, no significant improvements in any of these functional parameters were observed at 6 or 12 months. In addition, this study reported that reductions in four quantitative functional mitral regurgitation measures ranged from 32-43% at 6 months for implanted patients; however, the specific measures were not identified and the authors did not report whether these reductions were statistically significant.
Table 4: Functional changes in implanted and non-implanted patients (Lipiecki et al 2010)

<table>
<thead>
<tr>
<th></th>
<th>6MWD (m)</th>
<th>NYHA Class</th>
<th>KCCQ points</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline 6 mo</td>
<td>Baseline 6 mo</td>
<td>Baseline 6 mo</td>
</tr>
<tr>
<td>Implanted (n=36)</td>
<td>302 ± 74</td>
<td>436 ± 208</td>
<td>427 ± 193</td>
</tr>
<tr>
<td></td>
<td>P=0.0036</td>
<td>P&lt;0.0001</td>
<td>P=0.00012</td>
</tr>
<tr>
<td>Non-implanted (n=17)</td>
<td>338 ± 83</td>
<td>322 ± 105</td>
<td>330 ± 139</td>
</tr>
<tr>
<td></td>
<td>P=0.915</td>
<td>P=0.135</td>
<td>P=0.655</td>
</tr>
</tbody>
</table>

All figures given are mean ± standard deviation. P-value by ANOVA, KCCQ: Kansas City Cardiomyopathy Questionnaire; 6MWD: 6-minute walk distance; NYHA: New York Heart Association.

The study by Reuter et al (2010) reported that in patients implanted with the Carillon device, regurgitant volume was reduced by 16.8 ± 21 ml between baseline and 6 months; however, the authors did not report whether this reduction was statistically significant. When patients were stratified according to functional mitral regurgitation grade, etiology of their functional mitral regurgitation, and sinus, valvuloplasty was shown to reduce regurgitant volume, and improve the walking distance in the 6MWT and quality of life between baseline and 6 months, in all patient subgroups (Table 5). The authors did not report whether these changes were statistically significant, but did state that patients in sinus rhythm with a non-ischaemic etiology to their functional mitral regurgitation improved the most.

Table 5: Change in haemodynamic and clinical parameters between baseline and 6 months in patients implanted with the Carillon device stratified according to FMR grade, etiology of FMR and rhythm (Reuter et al 2010)

<table>
<thead>
<tr>
<th></th>
<th>Regurgitant volume (ml)</th>
<th>6MWD (m)</th>
<th>KCCQ points</th>
</tr>
</thead>
<tbody>
<tr>
<td>FMR Grade</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2 + (n=11)</td>
<td>-28.5 ± 13</td>
<td>155.3 ± 249</td>
<td>19.8 ± 18</td>
</tr>
<tr>
<td>3 + - 4+ (n=25)</td>
<td>-13 ± 23</td>
<td>110.1 ± 183</td>
<td>25.7 ± 20</td>
</tr>
<tr>
<td>Etiology</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ischaemic (n=23)</td>
<td>-21.3 ± 24</td>
<td>71.1 ± 135</td>
<td>19.5 ± 21</td>
</tr>
<tr>
<td>Non-ischaemic (n=13)</td>
<td>-11.4 ± 18</td>
<td>192.5 ± 256</td>
<td>29.5 ± 15</td>
</tr>
<tr>
<td>Rhythm</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sinus (n=24)</td>
<td>-18.5 ± 22</td>
<td>143.9 ± 203</td>
<td>23.5 ± 17</td>
</tr>
<tr>
<td>A Fib (n=12)</td>
<td>-10.3 ± 19</td>
<td>63 ± 204</td>
<td>21.2 ± 17</td>
</tr>
</tbody>
</table>

All figures given are mean ± standard deviation. FMR: functional mitral; regurgitation; KCCQ: Kansas City Cardiomyopathy Questionnaire; 6MWD: 6-minute walk distance.
2012 Cost Impact

No studies evaluating the cost-effectiveness or cost impact of the Carillon Mitral Contour System were identified from the retrieved material.

2012 Ethical, Cultural or Religious Considerations

No issues were identified from the retrieved material.

2012 Other Issues

Of the three studies included in this update, one study explicitly stated that one of the authors was an employee of Cardiac Dimensions Inc, the company that manufactures the Carillon mitral contour system, but that none of the other authors had any conflicts of interest to declare (Woloszyn et al 2011). The other two included studies failed to provide any statement regarding potential conflicts of interest (Lipiecki et al 2010 and Reuter et al 2010).

There is potential patient overlap between Woloszyn et al (2011) and Jerzykowska et al (2010) which was included in the original 2010 summary, as both studies were conducted at the same institution. Similarly, there is potential patient overlap between Woloszyn et al (2011) and both of the studies presenting data from the TITAN trial (Lipiecki et al 2010 and Reuter et al 2010).

A recent case report by Bartkowiak et al (2011) described mitral valve repair in a patient who had previously undergone percutaneous annuloplasty. The 67 year old female patient, who had a history of heart failure, coronary artery disease and severe mitral regurgitation that had been previously treated with a Carillon device, was referred for a coronary artery bypass graft and retreatment for severe mitral regurgitation. The patient underwent a coronary artery bypass graft, and mitral regurgitation was corrected with a saddle ring; however, the authors reported that a few problems emerged during the operation. Specifically, they described a number of difficulties that they had anchoring ring sutures to the mitral annulus, which was caused by the protruding Carillon device. The ring was eventually stitched, the patient was weaned from bypass, and transoesophageal echocardiography showed a competent valve. The patient subsequently developed hypotension and extremely low vascular resistance that was resistant to vasoconstrictors, and died six days after surgery, due to multiorgan failure. The authors thought it unlikely that the operation contributed to the postoperative course. They suggested that percutaneous valve intervention may create a group of complicated surgical patients, and that there is still very little known about mitral function following implantation of a Carillon device, as well as subsequent mitral repair with the ring.
Searches of clinical trial registers indicate that there are currently no additional ongoing clinical trials evaluating the Carillon mitral contour system.

2012 SUMMARY OF FINDINGS
Few studies evaluating the safety and efficacy of the Carillon mitral contour system have been published, and there is likely to be significant patient overlap between those studies that have been published. A small case series study undertook a functional assessment of patients following percutaneous mitral valvuloplasty with the Carillon device. This study demonstrated a significant improvement in NYHA functional class, exercise capacity, and quality of life, one month after the procedure. In addition, echocardiographic parameters of mitral regurgitation, namely vena contracta and EROA, were also improved up to one month after the procedure. Similar improvements in patient outcomes following implantation of the Carillon device were observed in the TITAN trial, which compared implanted and non-implanted patients. In this trial, patients implanted with the Carillon device demonstrated a significant improvement in NYHA functional class, walking distance in the 6MWT, and quality of life, up to 12 months after the procedure; however, in non-implanted patients, no significant improvements in any of these outcomes were observed at 6 or 12 months. Safety outcomes were poorly reported in the included studies. The rate of MAEs at one month was 1.9% in the TITAN trial (implanted and non-implanted patients combined).

2012 HealthPACT Assessment
The evidence base for the Carillon mitral contour system is limited, and there is still uncertainty around the uptake of this and other comparator technologies for the treatment of mitral valve disease in Australian clinical practice. Therefore, HealthPACT have recommended that no further assessment of this technology is warranted. In addition, HealthPACT have recommended that a review of comparator treatments for mitral valve disease be conducted in 12-months.

2012 INCLUDED STUDIES
Total number of studies 3
Level III-2 interventional evidence 1
Level IV interventional evidence 2

2012 REFERENCES


PRIORITISING SUMMARY 2010

REGISTER ID S000118

NAME OF TECHNOLOGY CARILLON™ MITRAL CONTOUR SYSTEM™

PURPOSE AND TARGET GROUP THE CARILLON MITRAL CONTOUR SYSTEM IS FOR PATIENTS WITH FUNCTIONAL MITRAL REGURGITATION

STAGE OF DEVELOPMENT (IN AUSTRALIA)

☐ Yet to emerge
☐ Established
☐ Experimental
☐ Established but changed indication or modification of technique
☐ Investigational
☐ Should be taken out of use
☐ Nearly established

AUSTRALIAN THERAPEUTIC GOODS ADMINISTRATION APPROVAL

☐ Yes
☐ No
☒ Not applicable

INTERNATIONAL UTILISATION

<table>
<thead>
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<th>COUNTRY</th>
<th>LEVEL OF USE</th>
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<td>Trials Underway or Completed</td>
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<td>Germany</td>
<td>✓</td>
</tr>
<tr>
<td>Poland</td>
<td>✓</td>
</tr>
</tbody>
</table>

IMPACT SUMMARY

10 The Carillon™ Mitral Contour System™ (Cardiac Dimensions®, Washington USA) is a contouring device indicated for patients with mitral (valve) regurgitation. The device is positioned around the mitral valve via percutaneous access through the jugular vein (Schofer et al 2009). The Carillon Mitral Contour System (CMCS) provides an alternative, non-invasive intervention for patients classed as unfit for open heart surgery due to co-morbidities (Bach 2009). The CMCS is implanted by a cardiologist under general anaesthesia.
**2010 BACKGROUND**

Mitr al regurgitation (also known as functional mitral regurgitation (FMR)) is the backflow of blood from the left ventricle into the left atrium due to the incomplete closure of the mitral valve within the heart (Heart Failure Society of America (HFSA), 2010). MR occurs whilst the left ventricle contracts (systole), in order to pump blood into the systemic circulation. Deformities in the mitral valve, resulting in MR, can arise from a number of causes including mitral valve prolapse, damaged chordae tendineae, deterioration of the valve with age, prior heart attack (myocardial infarction), endocarditis (infection), congenital heart defects and rheumatic fever (Bach 2009, Mayo Clinic 2010). MR is a degenerative disorder and contributes to decreased heart function and therefore congestive heart failure (CHF).

Failure to medically or surgically correct MR can lead to chronic long term congestive heart failure (HFSA 2010). In contrast, acute MR (via sudden rupture of the chordae tendineae or papillary muscle) requires immediate attention and can result in cardiovascular collapse (shock) and death (HFSA 2010). Symptoms of chronic MR include shortness of breath, pulmonary oedema (fluid in the lungs), orthopnea (shortness of breath when lying down) and exercise intolerance (Mayo Clinic 2010). The clinical implications of MR can be divided into two categories, namely, haemodynamic or functional. Haemodynamic parameters quantify the severity of MR via ECG (Helmcke et al 1987, Schofer et al 2009). Functional parameters for measuring the severity of MR include the New York Heart Association (NYHA) Classification of MR (see Table 1), six minute walk distance (6MWD) test and the Kansas City Cardiomyopathy Questionnaire (Bach 2009, Schofer et al 2009). All measure the overall impact of decreased heart function on quality of life, exercise tolerance and clinical symptoms of MR.

Traditional treatment for MR consists of medical (pharmacological) treatment (with diuretics, ACE inhibitors/angiotensin two receptor blockers and/or beta blockers) as well as surgical replacement of the mitral valve with a prosthesis, or placement of an annuloplasty ring (Bach 2009, e-Medicine 2010). Surgically placed annuloplasty rings aim to decrease the diameter of the mitral valve, in an attempt to increase the probability of complete closure of the mitral valve (during systole) (Bach 2009). However, significant co-morbidities prevent surgical intervention (open heart surgery) in a large proportion of patients with MR (Bach 2009, HFSA 2010, Mayo Clinic 2010). As a result, percutaneous (non-surgical) interventions have been developed and include percutaneous transvenous mitral annuloplasty (PTMA) as well as the Carillon Mitral Contour System. Percutaneous therapies may also be used as an adjuvant therapy to conventional medical (pharmacological) intervention.
Table 1: NYHA Classification of MR Severity

<table>
<thead>
<tr>
<th>Class</th>
<th>Patient Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Class I (Mild)</td>
<td>No limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, or dyspnea (shortness of breath).</td>
</tr>
<tr>
<td>Class II (Mild)</td>
<td>Slight limitation of physical activity. Comfortable at rest, but ordinary physical activity results in fatigue, palpitation, or dyspnea.</td>
</tr>
<tr>
<td>Class III (Moderate)</td>
<td>Marked limitation of physical activity. Comfortable at rest, but less than ordinary activity causes fatigue, palpitation, or dyspnea.</td>
</tr>
<tr>
<td>Class IV (Severe)</td>
<td>Unable to carry out any physical activity without discomfort. Symptoms of cardiac insufficiency at rest. If any physical activity is undertaken, discomfort is increased.</td>
</tr>
</tbody>
</table>

The CMCS is a metal contouring system designed to decrease the annular diameter of the mitral valve (Cardiac Dimensions 2010). It functions in a similar manner to an annuloplasty ring, as decreased mitral diameter increases the probability of complete closure of the valve during systole. Placement of the CMCS is achieved via percutaneous access through the jugular vein to the mitral valve. The metal contour system is then anchored proximally and distally in order to decrease the diameter of the mitral valve. The procedure is performed by a Cardiologist under general anaesthesia. Possible complications include death, myocardial infarction (MI), cardiac perforation necessitating catheter based or surgical intervention, device embolisation, or device failure.

2010 CLINICAL NEED AND BURDEN OF DISEASE

According to the AIHW 2007-08 data there were 2,826 principle diagnoses of non-rheumatic mitral valve disorders (including mitral insufficiency, mitral prolapse and mitral stenosis). The current prevalence of MR within Australia is estimated to be 11203 people (Hanson 2010, Australian Bureau of Statistics 2010). In addition, patients with dilated cardiomyopathy and congestive heart failure may also possess mitral valve deformities, however; specific data indicating the prevalence of MR within these patient populations was not available. In the Framingham Study (USA) conducted in 1999 the prevalence of MR increased from 0.3% to 11.2% in men and 0% to 2.3% in women from age groups 40 to 83 years of age (Singh et al 1999).

2010 DIFFUSION

The Carillon Contour System (CMCS) received the CE Mark of approval on the 26th January 2009 (Bloomberg.com). The Carillon Contour System has not received Food and Drug Administration (FDA) or Therapeutic Goods Administration (TGA) approval (FDA 2010, TGA 2010).
2010 Comparators

Comparators include

- Prosthetic mitral valves such as the Carpentier-Edwards® Perimount Magna Mitral Pericardial Bioprostheses™ (Edwards Life Sciences®, USA), Starr-Edwards Silastic ball valve™ (Baxter International Inc®, USA), Medtronic Hall mitral valve™ (Medtronic Inc®, USA) and others (e-Medicine, 2010).
- Annuloplasty rings include the Rigid Saddle Ring with EZ Suture™ Cuff (St. Jude Medical®, USA), Adjustable Annuloplasty Ring™ (MitralSolutions®, USA), Memo 3D Annuloplasty Ring™ (Sorin Group®, USA) and others.
- Two percutaneous devices are currently available are the PTMA™ (Percutaneous Transvenous Mitral Annuloplasty) (Viacor®, USA) and the MitraClip™ (Abbott Laboratories®, USA) previously examined in Horizon Scanning Prioritising Summary 2006.

2010 Safety and Effectiveness Issues

Study description

Two case series were identified for inclusion, namely, Schofer et al (2009) and Jerzykowska et al (2010).

Schofer et al (2009) enrolled 48 patients (18 years of age and over) with FMR and moderate heart failure (it is unclear if the study was performed prospectively). Based on intent-to-treat analysis 30 of 46 received the device. The mean age of the patients implanted with the device was 64 (SD 9) years and included 26 males and 4 females. Patients were recruited. Haemodynamic baseline characteristics included a mean left-ventricle end diastolic diameter (LVEDD) of 6.7±0.75cm, mitral annular diameter (MAD) of 4.2±0.4cm and left-ventricle ejection fraction (LVEF) of 30±8%.

Functional baseline characteristics included a mean 6 minute walking distance (6MWD) of 307±87 metres and NYHA class of between II and IV. In addition, there had been a mean number of 1.2 (SD1.5) hospital admissions for heart failure (HF) per patient. All patients’ medication regimen was optimised throughout the study.

Prior to implantation an ECG was conducted to rule out significant organic mitral valve pathology and to quantify MR, according to ventricular size and left ventricular ejection fraction. Semi-quantitative measures were also determined (including VC, ERO, RV and FMR jet area to left atrial area ratio); and an independent ECG core laboratory reviewed all screening ECGs to qualify patients.

Safety was evaluated by the 30-day rate of major adverse events (AEs). Major AEs were defined as the composite end point of death, myocardial infarction (MI), cardiac perforation necessitating catheter based or surgical intervention, device embolisation, or the occurrence of surgery or percutaneous coronary intervention (PCI) related to device failure.
Assessment of effectiveness was divided into haemodynamic and clinical outcomes. Haemodynamic outcomes were measured using ECG and clinical outcomes included functional improvements (NYHA class, 6-minute walk distance and Kansas City Cardiomyopathy Questionnaire). Secondary outcomes included chest x-ray, ECG, cardiac enzymes and concurrent medications; and baseline variables were reassessed at one and 6 months.

Jerzykowska et al (2010) reports the outcomes of nine consecutive patients enrolled between July 2006 and June 2007, including eight men and one woman (mean age 58.56±6.3 years, range 48-67 years). All patients had been diagnosed with dilated cardiomyopathy (DCM), were classified as NYHA class III and class IV and seven patients had previous history of MI. In addition, the PISA method was used to determine the severity of MR and all patients had at least grade 2 MR. Baseline haemodynamic characteristics were determined by ECG prior to device implantation (see Table 2) and include semiquantitative measures of MR (VC, MR jet area to left atrial area ratio, ERO and RV). Functional outcomes of Carillon device implantation were measured using the NYHA classification system and 6MWD test at one month follow up.

**Safety**

Implantation was not attempted in five of the 18 (28%) patients who did not receive the Carillon device. Reasons included coronary sinus (CS) access-related dissection/perforation (n=3) and screen failure (n=2). In addition, the implant was recaptured in 13 patients, 3 of which experienced slipping of the distal anchor, precluding device delivery. Following this early experience the apex of the device was modified (twisted) to improve structural rigidity and anchoring. Only 1 patient was implanted with the original design. There were two major reasons for device recapture in the 10 patients who initially experienced successful deployment, namely, insufficient FMR reduction and coronary artery compromise. There was no evidence of late coronary compromise in any of the patients who received a permanent implant. Specifically, there were no hospitalisations for new MI or ECG changes suggestive of chronic device-related coronary compromise. In all 30 patients implanted with the device follow up radiographs were performed and none revealed device movement, loss of integrity or fracture.

Two patients withdrew from the study before the 30-day follow up. Six of the 46 (13%) patients (intent-to-treat) experienced a total of 7 major AEs, including one death, a rise in creatine kinase-MB (n=2) and CS perforation or dissection (n=3).

The one death occurred in a 56 year old man with a history of 3-vessel coronary artery disease, chronic renal insufficiency, and chronic obstructive pulmonary disease (COPD). One day after the procedure the patient had a repeat coronary
angiogram to evaluate a rise in his creatine kinase-MB level from 6 to 92 U/L. No significant change in the coronary anatomy was identified; however, the patient developed acute renal failure presumed to be due to contrast-induced nephropathy. This patient died of multi-system organ failure 22 days after the index procedure.

The two patients who experienced a rise in creatine kinase-MB (>3 times the upper limit) after the implant procedure had no accompanying ECG changes or clinical symptoms; and their postprocedure clinical course was uncomplicated. In one of the two patients the proximal anchor of the Carillon device was noted to cross the small side branch (<1mm) of the right coronary artery that ran in the atroventricular groove.

One of the three (33%) patients suffering CS perforation successfully underwent a dissection procedure and the complication resolved without any specific therapy. In one patient in whom the CS was perforated with a stiff guidewire, no therapy was needed, and there were no clinical sequelae with observation. Lastly, the third patient in whom the CS was perforated after advancement of a diagnostic catheter required pericardial drainage. Notably, two of the perforations occurred early in the study (first and fourth patients), and the resulting procedural insights prevented subsequent cases.

Jerzykowska et al (2010) reported that Carillon device implantation was attempted in 15 patients, and successful in 11 (74%) patients; however two were lost to follow up. Attempts to implant the Carillon device were terminated in four (of 15) (27%) patients due to lack of expected reduction in the MR jet (n=2) and unfavourable local coronary vessel anatomy precluding safe delivery of the device (due to compression of the left circumflex artery) (n=2). In all four patients the device was introduced into the coronary sinus, and the decision to withdraw was assessed by transoesophageal echocardiography (TEE). In two of the four patients device implantation was attempted twice, with a thrombus in the left atrial appendage found during TEE in one patient, and the other patient required initial coronary vessel dilatation and stenting. No further safety data was reported.

Effectiveness

Schofer et al (2009) recorded improvements in haemodynamic parameters as outlined in Table 2. Notably, follow up data is not available for six (20%) patients at 6 month follow up as 2 patients died, 1 patient received a transplant and 3 patients declined to return for the follow up visit.

Table 2: Improvements in haemodynamic properties following implantation of the Carillon device by Schofer et al (2009)

<table>
<thead>
<tr>
<th>Haemodynamic parameter</th>
<th>Baseline (n=30)</th>
<th>Follow up</th>
<th>p-value</th>
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Carillon Mitral Contour System for Mitral Regurgitation: September 2010

### Table 3: Improvements in haemodynamic parameters following Carillon device implantation in Jerzykowska et al (2010)

<table>
<thead>
<tr>
<th>Haemodynamic parameter</th>
<th>Baseline (n=15)</th>
<th>Follow up (1 month) (n=9)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>VC</td>
<td>0.66±0.1</td>
<td>0.35±0.1</td>
<td>P&lt;0.005</td>
</tr>
<tr>
<td>MR jet/LA</td>
<td>55±11.2</td>
<td>36±10.2</td>
<td>P&lt;0.005</td>
</tr>
<tr>
<td>ERO</td>
<td>0.25±0.1</td>
<td>0.24±0.1</td>
<td>NS</td>
</tr>
<tr>
<td>RV</td>
<td>33.1±11.8</td>
<td>32.3±7.8</td>
<td>NS</td>
</tr>
</tbody>
</table>

MR jet/LA area, mitral regurgitation jet area to left atrial area ratio; RV, regurgitation volume; ERO, effective regurgitation orifice area; VC, vena contracta; NS, not statistically significant.

The improvements in VC and MR jet/LA correspond to a reduction of MR severity by one grade according to the PISA method. Patients implanted with the CMCS showed an improvement in the 6MWD from 360 (SD75) metres (baseline) to 422 (SD91) metres at one month follow up. Finally, Jerzykowska et al (2010) reports an

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1 VC, vena contracta; is a measure of MR severity. The cross-sectional area of the vena contracta represents a measure of the effective regurgitant orifice area (ERO), which is the narrowest area of actual flow through the mitral valve (E-chocardiography Journal)..
improvement in NYHA class for all patients, however does not report the quantitative results.

2010 Cost Impact

No cost-utility analysis literature was identified for the CMCS. However, if the CMCS is effective in reducing MR without the need for open heart surgery, ongoing medical intervention and in patients with co-morbidities preventing surgical intervention, cost savings may be achieved for the health system.

2010 Ethical, Cultural or Religious Considerations

No issues were identified.

2010 Other Issues

Schofer et al (2009) was funded by Cardiac Dimensions Inc, Kirkland, Washington USA. Schofer et al (2009) conducted further analysis and refinement into the implantation procedure. It was found that there were two main reasons for unsuccessful implantation in the 18 of 30 patients (n=5/18 not attempted; n=13/18 recaptured). Firstly, the device was implanted on average more distal in the coronary sinus/great cardiac vein (CS/GCV). Secondly, during the tensioning process to create tissue plication, the CS anchor was pulled closer toward the CS ostium in the successfully implanted patients. Therefore, it is apparent that further investigation into the implantation methodology is required.

2010 Summary of Findings

Early peer reviewed literature indicates that the CMCS is feasible, safe and effective for the non-invasive treatment of MR. The complication rate across the two case series ranged from 0% (n=0/9) to 13% (n=6/46). Major complications included death (n=1), a rise in creatine kinase-MB (n=2) and CS perforation or dissection (n=3).

Statistically significant improvements in haemodynamic and functional measures of MR severity were also achieved. Schofer et al (2009) reported a reduction in VC, MR jet/LA, ERO and RV (all p<0.001); whilst Jerzykowska et al (2010) observed a reduction in VC and MR jet/LA (both p<0.005). Finally, Schofer et al (2009) demonstrated a functional improvement in NYHA class and 6MWD at 6 month follow up (both p<0.001). Attempts to implant the device were either terminated or abandoned in 5 of 18 (28%) patients (Schofer et al 2009) and 4 of 15 (27%) patients (Jerzykowska et al 2010). The device recapture rate ranged from 0% to 28% (n=13/46).

2010 HealthPACT Assessment
Based on the functional improvements experienced by patients implanted with the CMCS and the lack of high-quality evidence comparing these outcomes to those of the gold standard it is recommended that this technology be monitored for 12 months:

5 2010 NUMBER OF STUDIES INCLUDED
Total number of studies 2
Level evidence IV

2010 REFERENCES


2010 SOURCES OF FURTHER INFORMATION


2010 SEARCH CRITERIA TO BE USED