TREATMENT OF SECONDARY MITRAL REGURGITATION VIA PERCUTANEOUS ANNULOPLASTY

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Chairperson

Michael Haude[1]

Speakers

Christian Spaulding,[2] Stephan Fichtlscherer,[3] Christoph Hammerstingl[4]

1. Medical Clinic I, Neuss City Clinic, Lukas Krankenhaus GmbH, Neuss, Germany
2. European Hospital Georges Pompidou and INSERM U 970, Paris Descartes University, Paris, France
3. Department of Internal Medicine III / Division of Cardiology, University Hospital Frankfurt, Goethe University, Frankfurt, Germany
4. Heart Center, University of Bonn, Bonn, Germany

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MEETING SUMMARY

Functional mitral regurgitation (FMR) is a common occurrence in patients with heart failure (HF). FMR is associated with as much as a 2-fold increase in mortality, as well as in HF hospitalisations. Over the past 15 years, efforts to address FMR have focussed on the development of transcatheter devices that replicate the effect of annuloplasty; however, besides open heart surgery, optimal medical treatment remains the standard of care (SoC) for these patients. To date, the only CE-marked option available for clinical use as a transcatheter annuloplasty device is the CARILLON® Contour System® from Cardiac Dimensions. The efficacy demonstrated in clinical trials, implantation technique, and comprehensive patient treatment was discussed during the symposium at EuroPCR and is presented in detail in this article.

Overview of the CARILLON Mitral Contour Device and Clinical Data

Professor Christian Spaulding

FMR occurs in HF patients as a result of dilation of the heart's mitral annulus, which can be caused by either ventricular or atrial dilation. The mitral valve (MV) leaflets no longer seal adequately and the valve allows blood to regurgitate. This can lead to a dramatic reduction in cardiac output and exacerbates HF symptoms.

The current SoC is medical therapy, which has been shown to improve patient survival but not patient quality of life (QoL). Few patients with FMR are indicated for MV surgery, and of these 84% are often not referred or are denied treatment. This is therefore a huge clinical problem and an unmet need. To address this, a number of interesting devices have been developed; this presentation will describe the CARILLON device.

Implantation is a rapid procedure that can be completed in less than 40 minutes, with or without general anaesthesia. The implantation technique has a short learning curve in comparison with other devices. In 10-15% of cases the device may have an impact on blood flow in the coronary circumflex artery (Cx), which is assessed by coronary angiogram (CA) during implantation. In such cases, the CARILLON device can be removed and, if feasible, a second device placed in a different position (Figure 1).

The CARILLON system comprises a handle assembly, a 9 Fr delivery catheter, and the permanently implanted device. Additionally a marker catheter is used. The marker catheter contains marker bands spaced at 1 cm intervals in order to measure vein length and diameter for implant size selection. The implants consist of distal and proximal anchors (nitinol and titanium) joined with a ribbon connector (nitinol). The distal anchor is secured in the great cardiac vein by expanding the anchor in the vein and locking it in place with the delivery catheter. The pressure applied on the vein wall by the expanded and locked anchor enables secure positioning. Manual tension is applied to the delivery system, which pulls the proximal anchor towards the coronary sinus ostium, plicates the periannular tissue of the MV, which improves leaflet coaptation, and thus reduces regurgitant flow. The proximal anchor is deployed and locked in the coronary sinus by retracting the delivery catheter and advancing an inner locking sheath.

Three prospective, controlled, multicentre trials have assessed the safety and efficacy of the CARILLON device: AMADEUS,[1] TITAN,[2] and TITAN II.[3] All studies included patients with dilated ischaemic or non-ischaemic cardiomyopathy; moderate-to-severe FMR 2+ to 4+, with an ejection fraction of <40%; and who were New York Heart Association (NYHA) Class II-IV with a 6-minute walk distance (6MWD) test result of 150-450 m.

Click here to access the CARILLON device animation

Figure 1: Animation demonstrating implantation of the CARILLON device.

Patients needed to be stable on HF medication and there were no anatomical exclusions — the study enrolled all comers.

The primary endpoint was the same for each study: the 30-day rate of major adverse events (MAEs), with the following secondary endpoints: haemodynamic changes (up to 1 year), FMR quantification, left ventricle dimensions, functional changes (up to 2 years), 6MWD, NYHA class, and QoL (up to 1 year) as measured by the Kansas City Cardiomyopathy Questionnaire (KCCQ).

The TITAN study compared patients implanted with the CARILLON device with those who did not receive the device, due to a reduction of blood flow in the Cx necessitating removal of the device[2] or due to a <1 Grade acute reduction in mitral regurgitation (MR), as required by the study protocol. In comparison, TITAN II was a single-arm study of patients who received the device.[3] Baseline demographic results for the TITAN (n=53) and TITAN II (n=30) studies showed an average age of approximately 62 years for TITAN and 70.5 years for TITAN II. Most of the patients were NYHA Class III (>90% in each study) with MR Grade >3 (84.5% for TITAN; 64% for TITAN II).[2,3]

Safety results from both studies demonstrated no MAEs after 30 days that could be attributable to the device. There was one death (1.9%) in the TITAN study, due to nephropathy and renal failure occurring several days after the procedure, and one death (2.8%) in the TITAN II study due to a non-cardiac cause; neither event was attributed to the device. No patients showed the following MAEs: myocardial infarction, cardiac perforation, device embolisation, surgery, or percutaneous coronary intervention related to the device.

Echocardiography results from the TITAN study showed a significant reduction in MR for implanted patients (Figure 2a). This change occurred over time and continued to improve up to a year after implantation of the device. Left ventricle reverse modelling occurred in patients with the implant versus those without (Figure 2b).

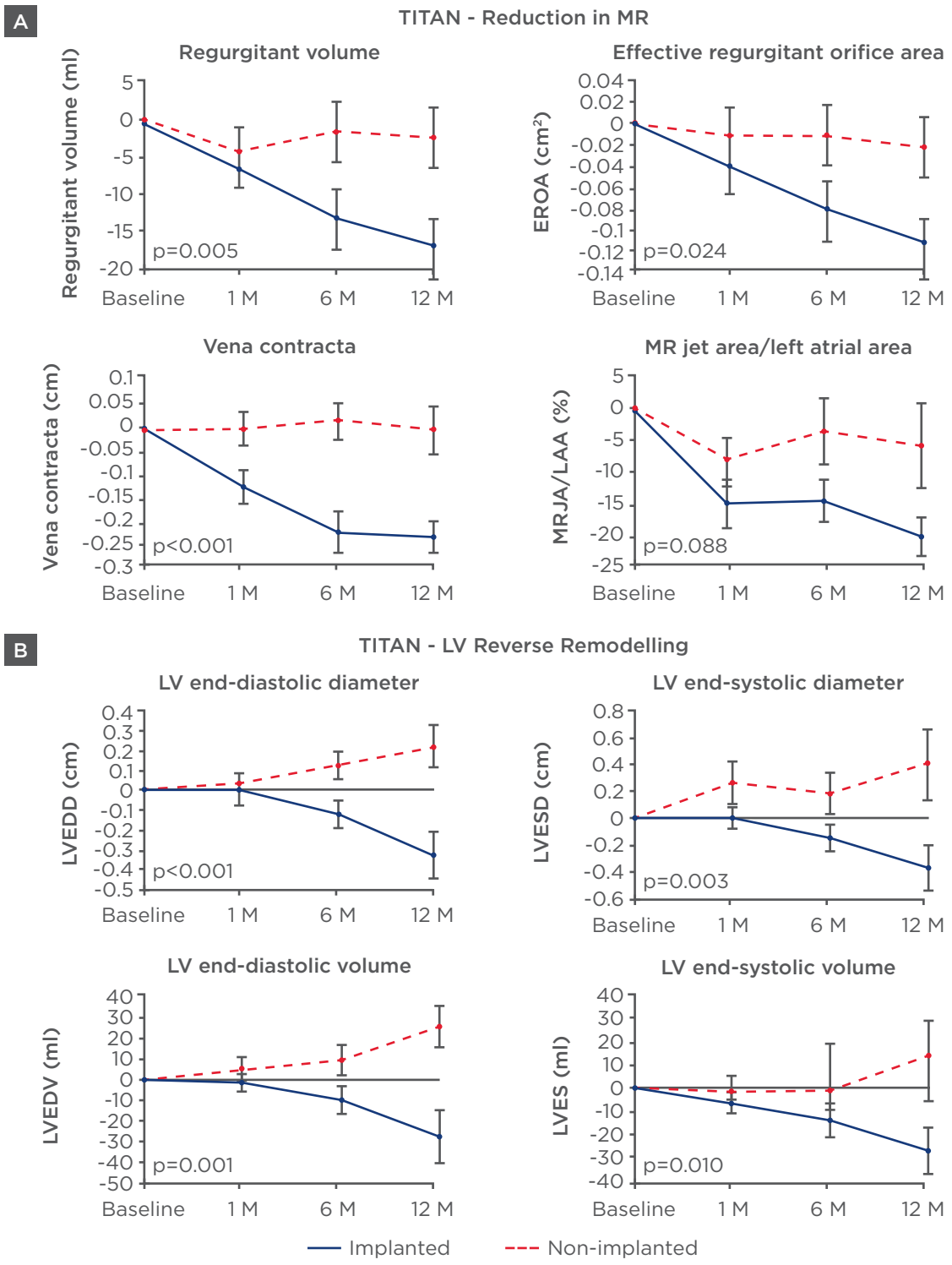

Figure 2: Results from the TITAN study.[2]

Echocardiographic changes in functional mitral regurgitation (MR) severity and left ventricular dimensions between implanted (n=36) and non-implanted (n=17) patients. Statistical significance was calculated by comparing the difference between the two groups from baseline to 12 months. A) Reduction in MR severity as assessed by changes in regurgitant volume, effective regurgitant orifice area, vena contracta, and MR jet area/left atrial area. B) Left ventricle (LV) reverse remodelling assessed during both systole and diastole.

EROA: effective regurgitation orifice area; MRJA/LAA: mitral regurgitation jet area/left atrial area. LVEDD: left ventricular end-diastolic diameter; LVESD: left ventricular end-systolic diameter; LVEDV: left ventricular end-diastolic volume; LVESV: left ventricular end-systolic volume.

Reproduced with permission from Siminiak T et al. Treatment of functional mitral regurgitation by percutaneous annuloplasty: results of the TITAN Trial. Eur J Heart Fail. 2012;14(8):931-8.

Patients without the device experienced additional left ventricular dilatation. In addition, patients with the device experienced improvements in their 6MWD test results and in NYHA class, resulting in a full class reduction.

After three successful trials involving a total of more than 100 patients, the manufacturer has initiated a double-blind, multicentre study (REDUCE FMR; NCT02325830) in Australia and Europe to further assess the benefits of the CARILLON device in this patient population. This study compares patients implanted with the CARILLON device versus patients receiving medical treatment as per current HF guidelines. Patients initially randomised to the control group of this study may be offered the CARILLON device once they have completed the protocol-defined follow-up period. The inclusion criteria are the same as for the TITAN/TITAN II studies; 120 patients will be randomised 3:1 to the device plus an optimal medical regimen of heart failure therapy (optimal medical management [OMM]) versus remaining on OMM alone. The study includes a 1-year follow-up period, with the primary endpoint assessing the change in regurgitant volume at 12 months. In addition to REDUCE FMR, a three-centre pilot study of 30 patients is under way in which patients will receive either the CARILLON device or the MitraClip.[4]

In conclusion, results from the TITAN studies demonstrate that effective and safe reduction of FMR with the CARILLON device is feasible. REDUCE FMR is a double-blind, randomised study that will compare the CARILLON device plus OMM with OMM alone.

Discussion and audience interaction

The following questions were taken from the audience and addressed by the panel:

Is the CARILLON device indicated for patients with severe FMR or is it just used for those with moderate/moderate-to-severe FMR? Can the device be used in patients with MR resulting from prolapse or a torn leaflet, or is this technique reserved for patients with HF? The delegate asking the question also asked whether regurgitation is assessed during the procedure.

Prof Spaulding answered that the trials included patients with FMR Grade 2. Prof Haude added that use of the CARILLON device is indicated for patients with FMR and that it should not be used in patients with primary leaflet diseases or significant MV prolapse. He added that the MitraClip procedure aims to reduce regurgitation during the procedural surgery; however, MR reduction occurs over time with the CARILLON device.

Do you use the CARILLON device for severe MR?

Prof Haude answered that the device has been used for all grades of MR and, in his experience, patients with MR Grade 2+ benefit the most from the device. Very sick NYHA Class IV patients with severe MR often do not respond to treatment irrespective of the intervention. Prof Spaulding added that patients obtain greater benefit when the device is placed earlier in the course of their treatment, and he recommends not waiting until a patient has revisited the intensive care unit for the fourth, fifth, or sixth time.

Is there a way to monitor the effects of the CARILLON device during the implantation procedure? Can you see any changes immediately after implanting?

Implanters will often measure the vena contracta while the MV is plicated during the procedure in order to assess the acute impact of the CARILLON device. As previously noted, there is probably a reverse remodelling process that continues to improve the results over a 6-12 month period.

Practical Application of Percutaneous Annuloplasty: Case Review

Professor Stephan Fichtlscherer

The CARILLON device is available in different length anchor sizes in order to align with patient anatomical assessments prior to implantation (Figure 3).

A patient case was described in real time using a video to show details of the implantation procedure (Figure 4).

A CA precedes implantation of the device in order to determine the relationship between the Cx, the right coronary artery (RCA), and the great coronary sinus. A marker catheter is first inserted in order to determine the size of the proximal and distal anchors required for each individual patient and the length of the vein.

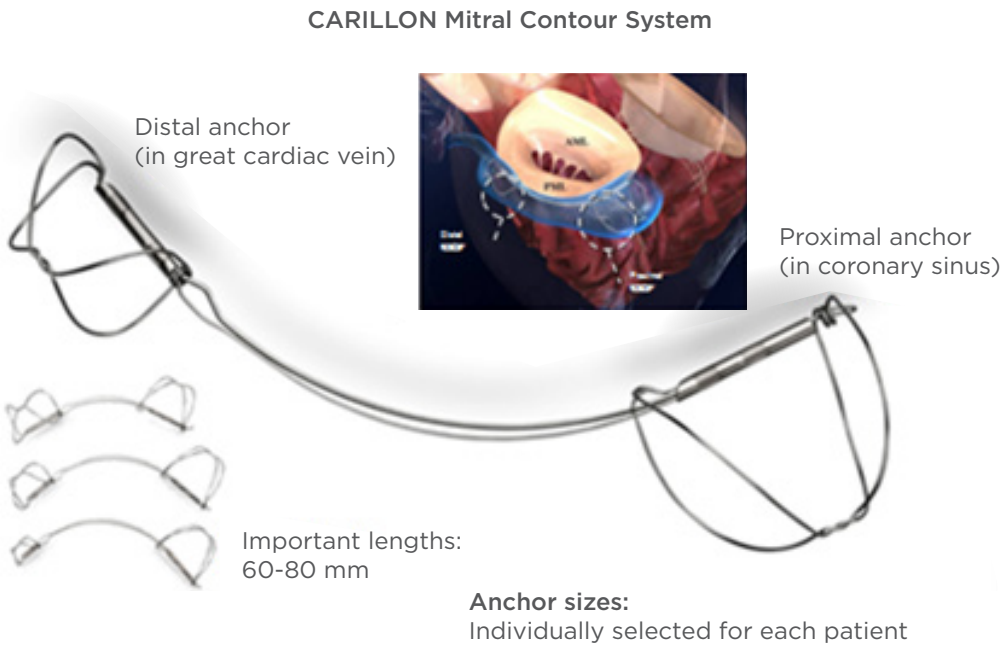

Figure 3: The CARILLON Mitral Contour System.

While the procedure can be performed without anaesthesia, Prof Fichtlscherer stated that in his hospital the procedure is performed with anaesthesia and intubation so that a transoesophageal echocardiogram (TOE) can be performed during implantation. Under TOE, the anchoring system is tensioned in order to reshape the mitral annulus. Successful implantation is determined using echocardiographic assessment, and the device decouples if satisfactory blood flow is confirmed in the Cx. In addition, the RCA is checked for any occlusion or damage.

Prof Fichtlscherer concluded his presentation by stating that he finds the CARILLON device to be effective, with 80% of patients demonstrating an improvement of one NYHA class, and patients demonstrating a 50% reduction in MR overall. He added that the device has an excellent safety profile together with a short learning curve. Lastly, he noted that the CARILLON device is a flexible technology allowing subsequent adjunctive therapy to be implanted, such as the MitraClip, valves, or cardiac resynchronisation therapy (CRT) leads.

Discussion and audience interaction

Although the CARILLON device does not occlude the coronary sinus, allowing future insertion of a CRT probe, what should be done for patients who already have a CRT probe in the coronary sinus?

Prof Fichtlscherer replied that he would not implant a CARILLON device in such patients, as removal of the CRT leads is possible but not recommended to ensure patient safety. He added that some centres have in fact removed a CRT lead in order to allow for implantation of a CARILLON device; however, this is not indicated at this time.

Is constriction of the Cx during the procedure mechanical or physiological, and how often can the constriction be alleviated by the use of nitroglycerin?

Prof Fichtlscherer replied that, from his experience, this is seen in around 10% of patients and acknowledged that this is a very important point. He added that sometimes pulling on the device impacts the Cx, which results in vasoconstriction of the vessel, and he recommended administering nitroglycerin or verapamil followed by a wait of up to 10 minutes to allow the constriction to subside. He added that a small percentage of these patients would not respond to the medication, and that the device would need to be recaptured and a second device placed in a different position.

CARILLON as a Part of the Heart Failure Treatment Plan

Doctor Christoph Hammerstingl

FMR affects 20-60% of patients with a reduced left ventricular ejection fraction (LVEF), depending

on the definition of FMR.[5] Guidelines state that patients with an effective regurgitation orifice area (EROA) ≥20 mm^2 have FMR of sufficient severity to impact their prognosis and should receive treatment.[6] This is in contrast to primary or degenerative MR in which the cut-off is ≥40 mm^2.

Indeed, it has even been reported that FMR Grade 2+ has an impact on prognosis.[7] In addition, the discrepancy between EROA calculated using the proximal isovelocity surface area (PISA) method and the EROA determined by direct measurement suggests that FMR is often underestimated using PISA-calculated EROA, and that more patients should receive treatment at an earlier stage in their disease. Implantation of the CARILLON device was described as previously presented. It was emphasised that substantial improvements in MR following implantation could take months.[2,3]

Correct timing of implantation should be taken into consideration, as HF is a progressive condition. In patients for whom interventional therapy for MV regurgitation is being considered, guidelines state that improvements should be sought initially via CRT (in select patients) and by optimising medical therapy for a period of 6 months. However, clinical data have shown that improvement in FMR is seen only in approximately half of CRT patients, and they typically have a worse prognosis if they are aged over 75 years, are high-risk with NYHA Class III-IV, or have severely reduced LVEF (≤25%) or chronic renal failure.[8,9] Therefore, applying a stepwise approach and allowing evaluation time between treatments may not be appropriate in such a frail patient population.

Prof Hammerstingl concluded that his approach is to first assess the severity of HF together with the pathophysiology of the underlying heart disease, and to determine the FMR severity. If the coronary status does not indicate that the patient requires a coronary artery bypass graft and medical therapy has been optimised as far as possible, then in the highest-risk patients who are still highly symptomatic with severely depressed LVEF a multimodal treatment plan should be undertaken in which the CARILLON device is implanted first, then the CRT is implanted where necessary with a short waiting time.

Click here to access case study video

Figure 4: Video of patient case showing real-time implantation of the CARILLON device.

Discussion and audience interaction

When a patient is equally suitable for the MitraClip or the CARILLON device, which should they receive first?

Prof Hammerstingl replied that this is unclear at present and that both devices should be discussed with the patient in order for them to reach an informed choice. Prof Haude replied that his recommendation would be the CARILLON device due to its ease of use, high safety profile, and efficacy. Prof Fichtlscherer commented that some patients, particularly those with a large left atrium (LA), small ventricles, or greatly dilated annuli, would benefit from receiving the CARILLON device first. Prof Hammerstingl agreed that anatomical issues should be taken into consideration and if the LA is really large then difficulties will arise in using the MitraClip, and these patients represent better candidates for the CARILLON system. Prof Spaulding added that in the EVEREST II study[10] there were very few patients with FMR who were actually included, so perhaps there are insufficient data regarding MitraClip use in patients with FMR. He mentioned that ongoing studies are assessing the MitraClip in patients with FMR.

Summary

Professor Michael Haude

In conclusion, the CARILLON Mitral Contour System is the only CE-marked option currently designed for transcatheter mitral annuloplasty in patients with FMR. The procedure is simple, effective, and easy to learn. Clinical data demonstrate promising efficacy outcomes and the CARILLON device allows for future adjunctive therapies. Further research will refine patient selection for receipt of the CARILLON device and determine the ideal time for implantation. Clinical and commercial experience to date is more than 350 implanted CARILLON devices.

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