Mitral valve repair with a device for artificial chordal implantation at 2 years

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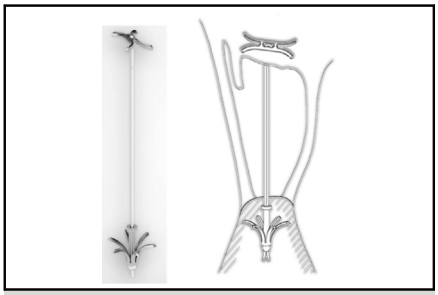
ABSTRACT

Objectives: This study examines the early and midterm safety, efficacy, and durability of mitral valve repair for primary mitral regurgitation (MR) using the ChordArt device (CoreMedic) for chordal replacement.

Methods: Five patients with symptomatic severe primary degenerative MR due to isolated central posterior leaflet prolapse/flail were treated with the ChordArt device in a transseptal surgical approach and followed prospectively with periodical clinical and echocardiographic assessments for 2 years.

Results: Reduction of MR immediately after the implantation of artificial chords was achieved in all patients showing no or trace MR (<1+/4+). In all patients, MR <1+ was maintained during 24 months of follow-up. No dehiscence, detachment, or dislocation of the implanted ChordArt devices was observed. Transthoracic echocardiography showed that left ventricle end diastolic diameter significantly decreased during the whole follow-up period in comparison to baseline condition, especially at discharge and 1-month follow-up. Left ventricle end systolic diameter also significantly decreased during the whole follow-up period in comparison to baseline condition. Left atrial volume significantly decreased during the follow-up period in comparison to discharge. No major adverse events, as defined per protocol, were observed during the intervention or during the follow-up period.

Conclusions: The ChordArt device allows successful treatment of primary degenerative MR due to posterior mitral leaflet prolapse or flail, with a good safety profile and promising immediate clinical and echocardiographic benefits that are confirmed up to 24 months. (JTCVS Open 2021;8:280-9)



ChordArt implant (CoreMedic).

CENTRAL MESSAGE

Chordal replacement with ChordArt is safe, efficient, and durable up to 2 years' follow-up.

PERSPECTIVE

Transseptal approaches for chordal replacement could represent an ideal tool for early treatment of MR, especially if annular dilatation is not yet present.

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The ChordArt System (CoreMedic) is a newly developed device designed for the quick and reliable implantation of artificial mitral chords to treat degenerative mitral regurgitation (MR) through a standard sternotomy, a minimally invasive surgical approach, or ultimately with a percutaneous transcatheter approach.[1] Recently published clinical experience in a pilot study with 5 patients confirmed that the device implantation under direct view is feasible and reproducible with low rates of complications in 1-year follow-up.[1] Herein, we present the midterm safety, efficacy, and durability of the ChordArt device implanted on previously included 5 patients.

Primary aim of this first in human study is to evaluate feasibility of the CordArt device in 5 patients. Secondary aim is to evaluate cardiac remodelling using ultrasonographic parameters, left ventricular ejection fraction (LVEF), left ventricular end systolic volume (LVESD), left ventricular end diastolic volume (LVEDD), and left atrium volume.

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Abbreviations and Acronyms

EDD = end diastolic diameter
ESD = end systolic diameter
GLS = global longitudinal strain
LVEF = left ventricular ejection fraction
LVEDD = left ventricular end diastolic diameter
LVESD = left ventricular end systolic diameter
MAE = major adverse event
MR = mitral regurgitation
MV = mitral valve
NYHA = New York Heart Association
TEE = transesophageal echocardiograph
TTE = transthoracic echocardiograph

METHODS

Study Design and Oversight

The ChordArt System Study for the Treatment of Mitral Regurgitation due to Leaflet Prolapse or Flail (CHAGALL) (ClinicalTrials.gov ID: NCT03581656) trial is a prospective, single-center, single-arm, non-randomized clinical trial designed to test the efficacy and safety of the ChordArt device. This is an interim analysis of the first 5 patients with protocol-specified clinical and echocardiographic follow-up conducted at baseline, discharge, 1, 12, and 24 months. These patients were enrolled from April to August 2018 in Vilnius Heart Surgery University Hospital, Vilnius, Lithuania, and the study was sponsored by the manufacturer of the ChordArt device (CoreMedic GmbH). The study protocol was approved by the national authorities and the ethics committee (Vilnius regional biomedical research ethics committee approval No. 2018-01-09 Nr. 158200-18-980-484). All patients provided written informed consent before enrollment. The study protocol has been uploaded as an Online Data Supplement.

Patient Selection

Seven patients were enrolled in the study. On screening visit, 2 patients did not fulfill the inclusion and/or exclusion criteria. Patient enrollment and disposition status are presented using consolidated standards of reporting trials diagram (Figure E1).

Five patients, aged 18 years or older with symptomatic severe primary degenerative MR due to isolated central posterior leaflet prolapse/flail with LVEF >25% and LVESD <55 mm were enrolled according to the protocol. All patients were candidates for surgical mitral valve (MV) repair according to current guidelines,[2-4] and to the judgment of the patient screening committee. Key exclusion criteria were: asymptomatic patients with primary degenerative MR; secondary (functional) MR due to annulus dilatation (leaflet-to-annulus index >1.4); anterior or bileaflet MV prolapse, as well as paracommissural prolapse/flail or any type of disease with the presence of significant leaflet or annular calcifications (anatomical type C and D of MV prolapse); severe LV systolic dysfunction (LVEF <25% and/or LVEDD >6.5 cm); life expectancy <1 year due to noncardiac conditions; New York Heart Association (NYHA) functional class IV; concomitant aortic or tricuspid disease that required treatment; a history of previous cardiac operation; severe pulmonary hypertension (systolic pulmonary artery pressure >70 mm Hg); and renal insufficiency defined as creatinine level >200 μmol/L (2.25 mg/dL). Full inclusion and exclusion criteria are available at ClinicalTrials.gov ID: NCT03581656.

Study Protocol

Transesophageal echocardiography (TEE) and transthoracic echocardiography (TTE) were performed in all patients. Anatomic feasibility of MV morphology was determined by the screening committee. Echocardiography was analyzed unblinded by a core lab (Academic Core Lab Ultrasound-based Cardiovascular Imaging, Comprehensive Heart Failure Center) using ImageArena4 (Tomtec Imaging Systems). The MV was analyzed in the periprocedural TEE from a 3-dimensional volume taken before the intervention using the 4D MV-Assessment 2 software package (Tomtec Imaging Systems). From the same TEE, left ventricular global longitudinal strain (GLS), as well as LVEDD and LVESD were measured, and LVEF was calculated using the semiautomated 4D LV-Analysis 3 software package. Severity of MR was quantified with the use of semiquantitative and quantitative assessment, and graded as none or trace, mild, moderate, or severe, by using integrative criteria specified by the American Society of Echocardiography and European Society of Cardiology.[2,5] The 2-dimensional TTE was performed before operation; before hospital discharge; and at 1, 12, and 24 months after the ChordArt device placement. The LVEF, as well as GLS, LVEDD, and LVESD, were measured with TTE, according to American Society of Echocardiography chamber quantification guidelines.[6]

Operative Technique

The ChordArt device implantation was performed under 2- and 3-dimensional TEE guidance under cardiopulmonary bypass through a standard sternotomy as previously described.[1] In brief, the ChordArt device enables implantation of premeasured artificial chordae using polytetrafluoroethylene sutures to replace the ruptured or elongated MV chordae and restore MV function and adequate leaflet coaptation. All patients were prepared for cardiac surgery according to the respective standard of care. Selection of the ChordArt length was based on preoperative TEE, as previously described.[7] After grasping the prolapsing segment with the ChordArt device, puncture of the leaflet was performed 3 to 4 mm from the free edge with the needle tip of the system. Thereafter, the target papillary muscle (PM) was punctured with the same tip, and the distal anchor was delivered. The device was then retrieved, and when the proximal anchor has reached the atrial surface of the leaflet, it was released anchoring the prolapsing leaflet segment. Finally, the grasper was opened to release the leaflet. If multiple chordae were required to restore MV function, steps were repeated. Concomitant procedures included complete ring annuloplasty in all subjects (ring sizes 30, 32, and 38 mm were used), according to surgeon's preference and the local standard of care. Procedures were performed by a team of senior interventional cardiologist and cardiac surgeons.

Statistical Methodology

Categorical variables are presented as count with percentages, whereas continuous variables are expressed as mean ± standard deviation (range) or mean with 95% CI. Due to pilot nature of the study and lack of statistical power (due to small sample size) no hypothesis testing was performed in this study. All data were analyzed using R version 4.0.2. (R Foundation for Statistical Computing).

RESULTS

Five consecutive male patients (mean age 63 ± 11 years; range, 47-76 years) presented with severe degenerative MR (ie, MR 4+) due to isolated prolapse of the posterior mitral leaflet. At the time of enrolment, mean LVEF obtained with TEE was 62% ± 6% (range, 56-68), and 61% ± 4% (range, 55-65) obtained with TTE. Four patients had NYHA functional class II, whereas 1 patient had NYHA

TABLE 1. Baseline demographic, clinical, and preoperative echocardiograph characteristics of the study population

Variable	All (N = 5)
Age (y)	63 ± 11
Male gender	5 (100)
BMI	27.5 ± 3.8
Hypertension	3 (60)
Diabetes	0 (0)
Smoking	0 (0)
Hyperlipidemia	0 (0)
Family history	0 (0)
LVEF-TEE (%)	62 ± 6
LVEF-TTE (%)	61 ± 4
LVEDD (mm)	61 ± 3
LVESD (mm)	41 ± 3
GLS (%)	20.62 ± 3.2
NYHA functional class II	4 (80)
NYHA functional class III	1 (20)

Values are presented as mean ± standard deviation or as (%). *BMI*, Body-mass index; *LVEF*, left ventricle ejection fraction; *TEE*, transesophageal echocardiography; *TTE*, transthoracic echocardiography; *LVEDD*, left end-diastolic diameter; *LVESD*, left end-systolic diameter; *GLS*, global longitudinal strain; *NYHA*, New York Heart Association functional status.

functional class III status. Baseline demographic characteristics, clinical and preoperative echocardiographic characteristics of these patients are presented in Table 1. All patients underwent MV repair with successful implantation of 1 or more artificial chordae with the ChordArt device (length, 14 mm in P2 and anterolateral PM, 1 mm [in P2 and postero-medial PM]). Severe MR was corrected with the implantation of 2 artificial chords in 4 patients, and with 1 artificial chord in 1 patient.

Efficacy Outcomes

Reduction of MR immediately after the implantation of artificial chords was achieved in all patients showing no or trace MR (<1+/4+) (Figure 1). In all patients, MR <1+ was maintained during 24 months' follow-up (Figures 1 and 2). No dehiscence, detachment, or dislocation of the implanted ChordArt devices was observed.

Transthoracic echocardiography showed that LVEF decreased at discharge (15%-18% relative decrease) in comparison to baseline condition, and almost retrieved to baseline value 1 month after the procedure (Figure 3, *A*, and Table E1). At 12- and 24-months' follow-up, LVEF did not significantly change in comparison to baseline and 1-month value (Figure 3, *A*, and Table E1). Similar changes were observed for GLS (Figure 3, *B*, and Table E1).

LVEDD decreased during the whole follow-up period in comparison to baseline condition, especially at discharge and 1-month follow-up (Figure 3, *C*, and Table E1). LVESD also decreased during the whole follow-up period in comparison to baseline condition, with initial mild increase at discharge (Figure 3, *D*, and Table E1). LA volume decreased during the follow-up period in comparison to discharge (no baseline measurement done). Figure E2 shows changes in echocardiographic parameters in each individual patient.

Safety Outcomes

No major adverse events (MAEs) as defined per protocol were observed, neither during the intervention, nor during

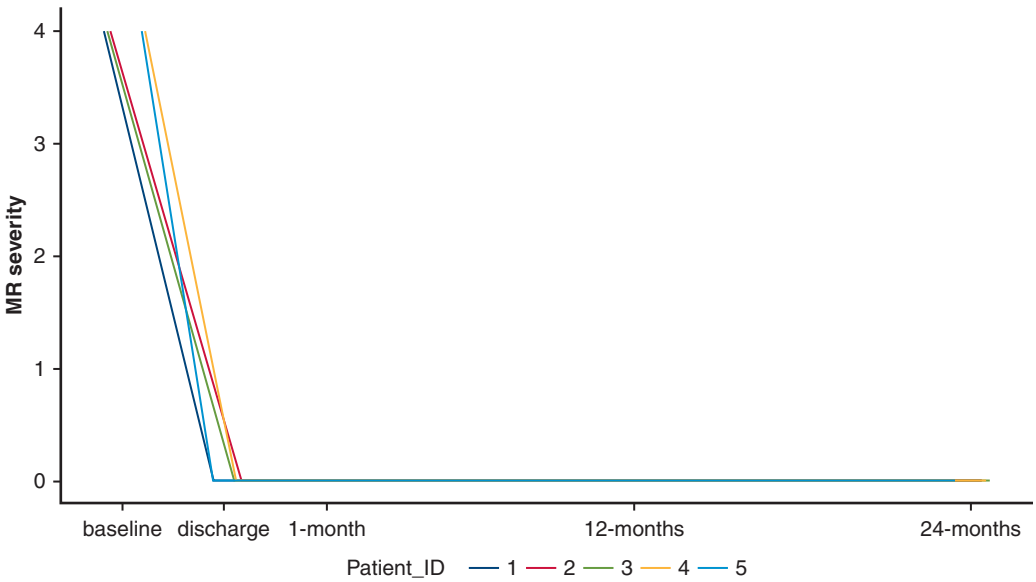

FIGURE 1. Mitral regurgitation (*MR*) severity at baseline, discharge, 1-, 12-, and 24-months' follow-up. The *curves* show excellent valve function following the procedure with no or trivial MR with persistent good results up to 2 years' follow-up.

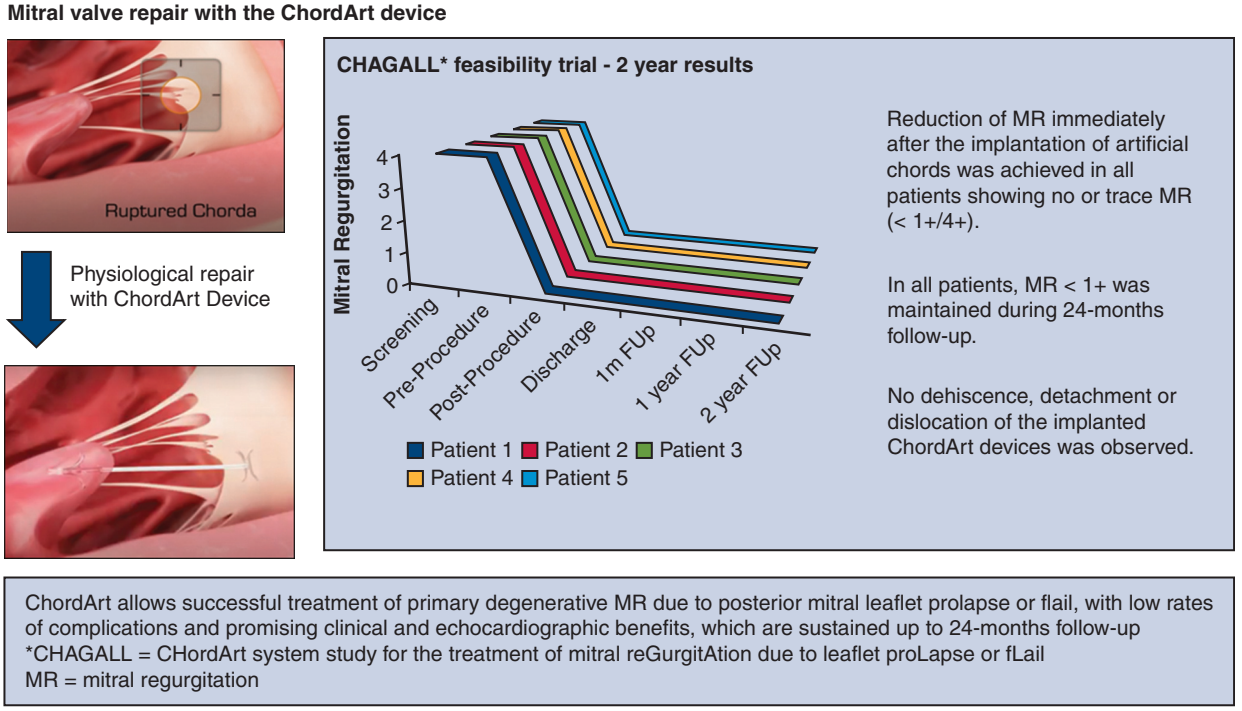

FIGURE 2. Mitral valve repair with the ChordArt device (CoreMedic) and results up to 24 months postoperatively. *Left*, The *picture* shows a ruptured chord on the posterior leaflet as the reason for severe mitral regurgitation (*MR*) (*top*). An artificial chord has been implanted using the automatic ChordArt device (*bottom*) with a proximal anchor in the tip of the papillary muscle and the distal anchor into the posterior leaflet (both leave a minimal footprint in the native mitral valve). *Right*, the implantation of ChordArt device was successful in all patients and allowed very stable results in term of the excellent function of the reconstructed mitral valve and the absence of any detachment or dislocation of the new device. *CHAGALL*, The ChordArt System Study for the Treatment of Mitral Regurgitation due to Leaflet Prolapse or Flail.

the follow-up period. Four AEs were recorded during the periprocedural phase: epigastric pain, clonus after extubation, respiratory infection, and paroxysmal atrial fibrillation (successfully treated by cardioversion). These AEs were considered probably related to the procedure. One serious AE was recorded at 3-month follow-up (paroxysmal atrial fibrillation successfully treated by cardioversion). All AEs were resolved without sequelae and none of the events were considered device-related. No MAEs or MAEs related to the study devices were observed during the follow-up period up to 24 months. In all patients, MR <1+ was maintained during 24 months of follow-up during which no dehiscence, detachment, or dislocation of the implanted ChordArt devices was observed (Figure 2).

DISCUSSION

The main finding of the present report is that surgical mitral repair using the ChordArt device to repair prolapse caused by elongated/ruptured native chordae is safe and that the chordal anchoring mechanism is durable up to 2 years, with stable MR reduction, in absence of any AEs related to the device.

In the past, mitral repair with chordal replacement has been associated with excellent results in terms of MR reduction and durability in patients undergoing surgery for severe degenerative MR, providing reproducible and long-term durable results in different clinical and anatomical settings, including complex mitral anatomy and minimally invasive approach.[8,9]

More recently, chordal replacement has been shown to be noninferior to the conventional resection MV repair approach, being associated with a better mobility of the repaired leaflet and with comparable results in terms of efficacy and durability.[10-12]

Potentially, the respect more than resect technique offers a better physiological MV repair compared with resection techniques, being associated with lower transvalvular gradients, improved MV area, better preserved leaflet mobility, and increased leaflet coaptation.[13,14] Although these supposed advantages have never been confirmed in a large randomized study, there is no doubt that chordal replacement is an essential part in the armamentarium of surgical MV repair that allows a nearly physiologic MV reconstruction and can be applied to almost any pathology and at any phase of degenerative MR.[15] Because this technique represents the current and most likely also the future standard of care in degenerative MR repair, there is an increasing interest in developing reliable, durable, and easy-to-perform

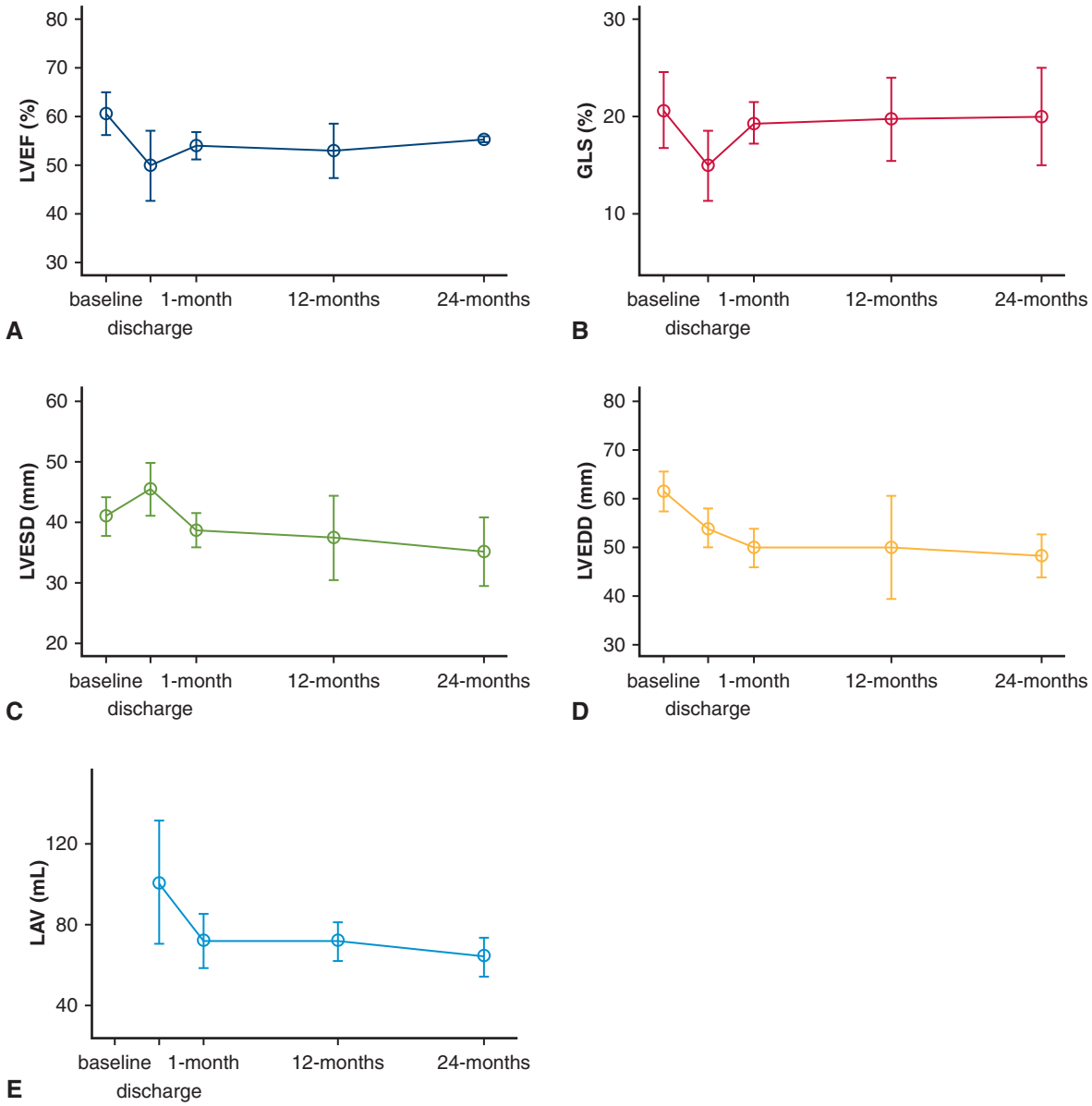

FIGURE 3. Ultrasound parameters (multigraph) at baseline, discharge, 1 month, 12 months, and 24 months: A, Left ventricle ejection fraction obtained with transthoracic echocardiography (*LVEF*-TTE). B, Global longitudinal strain (*GLS*). C, Left ventricle end-systolic (*LVESD*). D, End-diastolic diameter (*LVEDD*). E, Left atrial volume (*LAV*). *Lines* represent mean (95% CI).

transcatheter-based methods to perform durable and effective chordal replacement.

There are mainly 2 groups of patients who could ideally profit from a catheter-based chordal replacement system, which confirms the large clinical need:

- Patients with degenerative MR who are presenting with high risk for conventional surgery due to advanced age, frailty, and/or comorbidities: These patients are at the moment largely treated with percutaneous edge to edge technique, which has been associated with favourable results, but has the big limitation to reduce the chance of valve repair (either surgical or transcatheter) in case of failure; moreover, the edge-to-edge concept is effective in reducing MR, but represents by definition a negotiation between MR reduction and increase of valve gradient due to reduced valve area (especially in patients with extended pathology). In addition, because the edge-to-edge technique does neither preserve a full leaflet mobility nor stabilizes the mitral annulus, the technique cannot be considered a physiological repair; and

- Patients with single segment flail in the early phase of the disease, in whom the annulus is not yet dilated: In this subset of patients, the use of a device that can provide a physiological repair by leaving a small footprint on the valve itself is extremely appealing. Different from edge-to-edge techniques, chordal replacement does not reduce the further possibilities of a successful valve repair, which can be performed in case of residual or recurrent MR. This early treatment approach could be justified even in younger and operable patients (proven that it is safe) because it is minimally invasive and would not preclude the success of repair surgery.

The present study shows that, after the initial feasibility and safety report from Weber and colleagues,[1] chordal replacement with ChordArt is safe and durable up to 2 years. There were no changes with respect to the MR function during follow-up (all patients have no or trace MR, unchanged after discharge), suggesting that optimal early results remain stable up to 24 months.

Although 2 years cannot be considered a long-term follow-up and all the patients had concomitant surgical annuloplasty, the most important observation of this study is that no detachment, dehiscence, or dislocation occurred, suggesting that the implant is stable and durable. As time goes by, the fibrotic process will most probably strengthen the healing process and further stabilize the attachment of the device on the leaflet and also in the PM. All patients experienced positive reverse remodelling of the LV and left atrium, as expected after successful MV repair.

Nowadays, there is a strong interest to move from surgical and transapical procedures toward percutaneous (via femoral vein) and transseptal procedures and different devices are in the preclinical testing phase.[7,16-18] Final preclinical studies to test feasibility of transseptal ChordArt implantation are ongoing and it will enter the clinical phase of development soon.

The feasibility of concomitant, combined transcatheter chordal repair and annuloplasty has been reported and this could represent the future gold standard for high-risk patients.[19] But at the moment, the absence of annuloplasty represents among the main limitations of all the transcatheter leaflet repair devices, including chordal implantation. It is known from the surgical experience that the presence of annuloplasty is associated with improved durability and overall better outcomes. As already mentioned, the small footprint following ChordArt repair easy allows further surgical or transcatheter repair (like annuloplasty) and could represent an ideal tool for early treatment, especially if annular dilatation is not present yet.

Limitations

The present study represents the first-in-man clinical experience with direct view antegrade surgical implantation of artificial chordae with ChordArt device to correct MR due to posterior mitral leaflet prolapse or flail. Therefore, only preliminary conclusions can be drawn regarding the short- and long-term durability of this new procedure. The number of patients is limited and no control group is available. Only descriptive statistics with 95% CIs are presented. No statistical analysis has been performed due to the limited number of treated patients and exploratory (ie, pilot) nature of the study.

CONCLUSIONS

The procedure with the ChordArt device is feasible, with low rates of complications at 2-year follow-up and promising clinical and echocardiographic benefits. Further studies on a larger patient population are required to confirm short- and long-term efficacy and safety of the device. A transcatheter system for a percutaneous, transseptal treatment approach represents the natural evolution of the technique and will enter the clinical phase of development soon.

Webcast

You can watch a Webcast of this AATS meeting presentation by going to: https://aats.blob.core.windows.net/media/21%20AM/AM21_A24/AM21_A24_04%20-%20Thierry-Pierre%20Carrel.mp4.

Conflict of Interest Statement

Dr Taramasso receives consultancy fees from Abbott, Boston Scientific, 4tech, Shenqi Medical, Simulands, MTEx, Occlufit, Mitraltech, and CoreMedic; as well as speaker fees and institutional Educational Grant from Edwards Lifescience. Drs Weber, Carrel, and Vogel disclose a financial relationship with CoreMedic. All other authors reported no conflicts of interest.

The *Journal* policy requires editors and reviewers to disclose conflicts of interest and to decline handling or reviewing manuscripts for which they may have a conflict of interest. The editors and reviewers of this article have no conflicts of interest.

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Key Words: chordal repair, mitral valve repair, mitral regurgitation

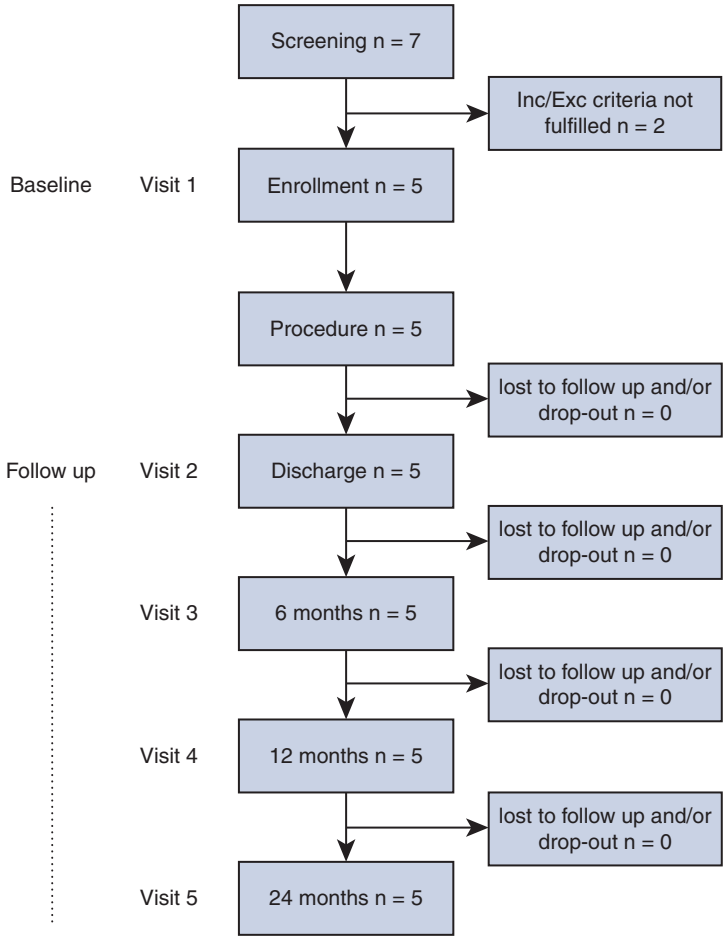

FIGURE E1. Consolidated standards of reporting trials diagram.

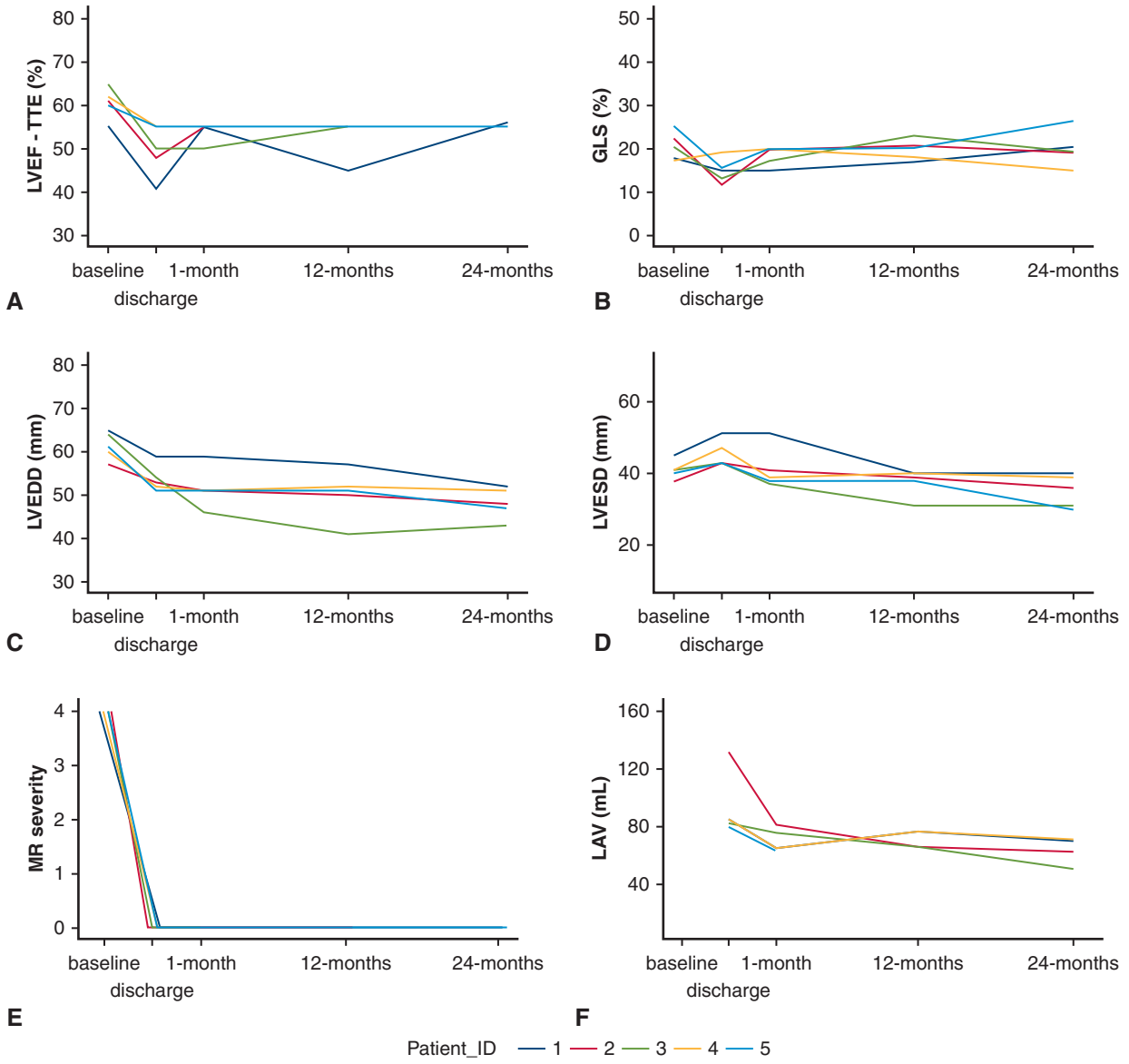

FIGURE E2. Ultrasound parameters at baseline, discharge, 1 month, 12 months and 24 months per patient: A, Left ventricle ejection fraction obtained with transthoracic echocardiography (*LVEF-TTE*). B, Global longitudinal strain (*GLS*). C, Left ventricle end-diastolic (*LVEDD*). D, End-systolic diameter (*LVESD*). E, Mitral regurgitation (*MR*) severity. F, Left atrial volume (*LAV*). *Lines* represent the values of examined ultrasound parameter in each time point per patient.

TABLE E1. Echocardiographic parameters and New York Heart Association (*NYHA*) functional status at baseline and during follow-up

Parameter	Baseline	Discharge	1 mo	12 mo	24 mo
LVEF-TTE	61 (56-65)	50 (43-57)	54 (51-57)	53 (47-59)	55 (55-56)
LVEF-TEE	62 (55-69)	–	–	–	–
GLS	20.6 (16.7-24.6)	14.9 (11.3-18.5)	19.3 (17.2-21.5)	19.7 (15.4-24.0)	20.0 (15.0-25.0)
LVEDD	61.4 (57.4-65.4)*	53.8 (49.9-57.7)	49.8 (45.8-53.7)	50.0 (39.4-60.6)	48.2 (43.8-52.6)
LVESD	41.0 (37.8-44.2)*	45.4 (41.0-49.8)	38.8 (36.0-41.5)	37.5 (30.6-44.4)	35.2 (29.6-40.8)
LAV	–	100.8 (70.2-131.4)	72.0 (58.5-85.5)	71.7 (62.1-81.4)	64.0 (54.6-73.4)
MR 4+/1+	5/0	0/5	0/5	0/5	0/5
NYHA functional class II or III	4/1	2/3	4/1	5/0	5/0

Values are presented as mean (95% CI) or count/total. *LVEF-TTE*, Left ventricle ejection fraction obtained with transthoracic echocardiography; *LVEF-TEE*, left ventricle ejection fraction obtained with transesophageal echocardiography; *GLS*, global longitudinal strain; *LVEDD*, left ventricle end-diastolic diameter; *LVESD*, left ventricle end-systolic diameter; *LAV*, left atrial volume; *MR*, mitral regurgitation. *TEE.