Title

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Journal

JACC Cardiovascular Interventions, 15(12)

ISSN

1936-8798

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Publication Date

2022-06-01

DOI

10.1016/j.jcin.2022.04.013

Peer reviewed

HHS Public Access

Author manuscript

JACC Cardiovasc Interv. Author manuscript; available in PMC 2023 June 27.

Published in final edited form as:

JACC Cardiovasc Interv. 2022 June 27; 15(12): 1249–1263. doi:10.1016/j.jcin.2022.04.013.

Transcatheter Mitral Cerclage Ventriculoplasty: From Bench to Bedside

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Abstract

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Background: Transcatheter mitral valve repair is beneficial in patients with mitral regurgitation (MR), left ventricular dysfunction and persistent symptoms despite maximally tolerated medical therapy.

Objective: To evaluate safety and feasibility of Transcatheter Mitral Cerclage Ventriculoplasty in patients with MR and either heart failure with reduced ejection fraction (HFrEF) or preserved ejection fraction (HFpEF), and subjects with prior edge-to-edge repair but persistent or recurrent symptomatic MR.

Methods: The NHLBI Transcatheter Mitral Cerclage Ventriculoplasty Early Feasibility Study (NCT03929913) was an Investigator-initiated prospective multicenter study. The primary endpoint was technical success measured at exit from the catheterization laboratory. Follow-up included heart failure quality-of-life assessments, and serial imaging with echocardiography and cardiac computed tomography.

Results: Nineteen subjects consented and underwent cerclage, 63% with HFrEF and 37% with HFpEF, with ischemic cardiomyopathy in 26% and non-ischemic in 74%. There were no procedural deaths, strokes or transient ischemic attacks, or other major cardiovascular adverse events. The primary endpoint was met in 17/19 subjects. Cerclage induced a sustained reduction in mitral regurgitant volume (−41%) and effective orifice area (−33%) after a median 337days. Cerclage resulted in improvements in six-minute walking distance (+78m) and Kansas City Cardiomyopathy Questionnaire Overall Summary Score (+22) at 30 days that were maintained after a median 265 days. New complete heart block developed in 6/17 subjects. Three deaths occurred on post-procedure day 79, 159 and 756 respectively, unrelated to cerclage.

Conclusions: Transcatheter Mitral Cerclage Ventriculoplasty resulted in significant and sustained improvements in mitral regurgitation, and in heart failure quality of life assessments.

CONDENSED ABSTRACT

The NHLBI Transcatheter Mitral Cerclage Ventriculoplasty Early Feasibility Study (NCT03929913) was an Investigator-initiated prospective multicenter study in patients with mitral regurgitation and heart failure with reduced ejection fraction (HFrEF) or preserved ejection fraction (HFpEF). The primary endpoint was technical success measured at exit from the catheterization laboratory. Nineteen subjects underwent cerclage. There were no major cardiovascular adverse events. The primary endpoint was met in 17/19 subjects. Complete heart block developed in 6/17 subjects. Cerclage induced reduction in mitral regurgitant volume and effective orifice area, and large and sustained improvements in heart failure quality of life assessments.

Keywords

Secondary mitral regurgitation; Transcatheter ventriculoplasty; Heart failure; Ventricular repair; Transcatheter annuloplasty; Cardiomyopathy

INTRODUCTION

Surgical mitral valve repair in the setting of secondary mitral regurgitation (MR) due to left ventricular (LV) or left atrial dilation and dysfunction typically involves implantation

of an annuloplasty ring or band to bring the malcoapting – but otherwise normal – mitral leaflets together(1,2). However, since there is limited evidence that surgical mitral valve repair improves survival in symptomatic patients with secondary MR, surgery only received a Class 2b recommendation in the latest guidelines(3). In contrast, transcatheter edge-to-edge repair (TEER) has been shown to improve survival, hospitalization, symptoms, and quality of life in selected patients with MR, LV dysfunction and persistent symptoms despite maximally tolerate guideline directed medical therapy(4) and received a Class 2a recommendation. Compared to TEER, transcatheter ventriculoplasty may have incremental benefit because in addition to improving leaflet coaptation, it alters cardiac geometry which may encourage reverse left ventricular and/or atrial remodeling(5). Herein we report the results of the National Heart, Lung, and Blood Institute Division of Intramural Research (NHLBI DIR) Early Feasibility Study of Transmural Systems' Transcatheter Mitral Cerclage Ventriculoplasty using a percutaneous, circumferential, reversible ventriculoplasty device implanted via the internal jugular approach in patients ill-suited or ineligible for TEER.

METHODS

Pre-clinical experiments

Cerclage was conceived at NHLBI DIR(6). Human testing of a prototype device was performed in Korea(7). The Transcatheter Mitral Cerclage Ventriculoplasty (TMCV) device tested herein was a dedicated system developed through a collaboration between NHLBI DIR and Transmural Systems (Andover, MA) under a Small Business Innovation Research (SBIR) contract. Experiments were performed on 14 Yorkshire swine for device development, which are not described further herein. Subsequently, cerclage was performed in 9 swine (mean bodyweight 51kg) under Good Laboratory Practice (GLP) conditions for U.S. Food and Drug Administration (FDA) Investigational Device Exemption license submission. These GLP experiments are described in the Supplemental Materials.

Study design and oversight

The NHLBI DIR Transcatheter Mitral Cerclage Ventriculoplasty Early Feasibility Study (NCT03929913) was an Investigator-initiated, prospective multicenter study. FDA granted Investigational Device Exemption for the study. A central Institutional Review Board (Advarra) approved the study protocol. The NHLBI Data and Safety Monitoring Board provided study oversight. NHLBI was the data coordinating center. All subjects consented in writing. Representatives from the manufacturer attended all cerclage procedures but did not participate in the study design, data collection, analysis, or report.

To ensure data integrity, all case report forms were independently verified with source data on-site or remotely using electronic medical records, clinical events were independently monitored, and all echocardiography and computed tomography (CT) images were analyzed by central core laboratories. An independent Clinical Event Committee adjudicated the primary endpoint of technical success, the secondary endpoint of procedural success, and all deaths. The investigators attest to data integrity and NHLBI has custody of all data.

Subjects

Key inclusion and exclusion criteria for the study are summarized in Table 1. In brief, candidates with MR and heart failure with reduced ejection fraction (HFrEF) who were ill-suited or ineligible for TEER, or subjects with MR and heart failure with preserved ejection fraction (HFpEF) were eligible to participate. Candidates with prior TEER but persistent or recurrent symptomatic MR were eligible provided the TEER procedure was performed at least 30 days before. The protocol was changed mid-trial to broaden eligibility to subjects with HFrEF and mild or greater MR with LVEF ≤50% and NYHA class III or IV symptoms. This change was implemented after early observations suggested clinical benefit in subjects with HFrEF even in the absence of significant MR reduction immediately post-implantation. Figure 1 summarizes the study design.

Transcatheter mitral cerclage ventriculoplasty device and procedural steps

The TMCV device applies circumferential compression to the base of the LV. The device lies entirely within the right sided circulation, is fully percutaneous and reversible until final locking, and implantation is guided by fluoroscopy. The device comprises a tether implant (Figure 2, Panel A) and a wishbone-shaped lock (Figure 2, Panel A). If preprocedural CT suggests that the circumflex artery may be entrapped, then a tether with a rigid arch-like coronary protection element is selected (Figure 2, Panel B-C). Online Videos 1 and 2 demonstrate key procedure steps. The device is introduced via the right internal jugular vein through an 18Fr sheath. The coronary sinus is cannulated and a balloon-tipped guide catheter (8Fr Cello Balloon Guide Catheter, Medtronic, Minneapolis, MN) is inflated to pressurize the coronary sinus and obtain coronary venograms (Figure 3, Panel A). Alongside this guide catheter and through the same internal jugular sheath, an inflated balloon-wedge end-hole catheter is used navigate through the tricuspid valve to the pulmonary artery ensuring traversal through the major orifice of the tricuspid valve and absence of chordal or moderator band entanglement. This catheter is exchanged for a conforming snare (Figure 1, Panel D) that expands to appose the right ventricular outflow tract (RVOT) endocardial surface. Through the coronary sinus guide catheter, a septal perforator vein that tracks towards the RVOT snare is selected and engaged using an 0.014” coronary guidewire and microcatheter. A stiff 0.014” guidewire (Astato XS 20, Asahi, Tokyo, Japan) with a 30–40° angled distal tip is used to traverse the remaining interventricular septum, re-enter the RVOT and is captured in the snare (Figure 3, Panel B). The ensnared guidewire is externalized through the internal jugular sheath. The TMCV tether is crimped to the back end of the guidewire and pulled through the coronary sinus, interventricular septum, RVOT, tricuspid valve and back out the sheath until both ends are externalized. A double-barreled detangling catheter is advanced over both limbs of the tether to ensure no twisting/wrapping, and the rigid coronary protection element is positioned over the entrapped circumflex artery if needed. The wishbone lock (Figure 2, Panel E) is advanced over both limbs of the tether into position (Figure 3, Panel C). The tether is then cinched to the desired tension and locked under transesophageal echocardiography (TEE) guidance. The ends of the suture are severed with a cutter. The lock lies within the right atrium with one limb in the coronary sinus and the other limb through the anteroseptal commissure of the tricuspid valve. The rigid coronary protection element prevents compression of the entrapped circumflex artery (Figure 3, Panel D). Online Videos 1 and 2 summarize key procedure steps.

Study endpoints

Modified Mitral Valve Academic Research Consortium (MVARC) definitions(8) were used to determine endpoint success. The primary endpoint of the study was technical success, measured at exit from the catheterization laboratory. All of the following must be present: (1) Alive; (2) Successful deployment and correct final positioning of a single intended TMCV. Repositioning and recapture of the device, if needed, is not classified as failure; (3) Retrieval of the TMCV delivery system; (4) Absence of cerclage-related coronary artery compression and absence of additional procedure such as percutaneous coronary intervention (PCI) to relieve coronary artery compression; and (5) No additional unplanned or emergency surgery or reintervention related to the TMCV or delivery system.

The secondary endpoint of the study was procedural success. This endpoint was measured at 30 days. All of the following must be present: (1) Technical success; (2) No TMCV device-related Serious Adverse Device Effects, defined as VARC-2 life-threatening bleeding, or major vascular or cardiac complications related to the TMCV requiring unplanned reintervention or surgery. Such reinterventions were directly related to the valve. Pacemaker implantation, for example, was consistent with procedural success.

Exploratory endpoints included in-hospital or 30-day death, stroke, life-threatening bleeding, major vascular complications, major cardiac structural complications, stage 2 or 3 acute kidney injury, new conduction block requiring permanent pacemaker implantation, coronary compression or myocardial infarction requiring intervention, repeat surgery or transcatheter intervention, correct device placement, device delivery failure, device structural failure, tamponade, damage to native mitral structures, endocarditis, residual mitral regurgitation, and mitral valve gradient ≥5mmHg. Additional exploratory endpoints included heart failure quality-of life assessments, six-minute walking distance, heart failure hospitalization, and change in cardiac chamber volumes. Subjects self-administered the 23-question Kansas City Cardiomyopathy Questionnaire (KCCQ-23)(9) at four timepoints.

Imaging

Baseline, 30-day and 6-month contrast-enhanced, time-resolved CT were reconstructed at 5% to 10% intervals with <1.0-mm slice thickness. Transthoracic and/or transesophageal echocardiograms were performed at baseline, intra-procedure, discharge, 30 days and 6 months. All echocardiograms and CT images were analyzed at central core laboratories.

Statistical analysis

Subjects were analyzed as ‘intention-to-treat’ and ‘treated’. The treated group was further stratified according to heart failure phenotype (HFrEF vs. HFpEF). Statistical comparisons use paired datapoints to avoid survivorship bias. We do not correct for multiple comparisons because of the exploratory nature of the data. New York Heart Association (NYHA) functional class was analyzed as change among all subjects in the status (class I-II vs. class III-IV) from baseline to 30 days or latest timepoints, using an exact McNemar’s test. Change in the continuous variables were assessed by a Wilcoxon signed rank test. All analyses were performed using R v4.1.1 (https://www.R-project.org/). Results are reported as mean

± standard deviation if normally distributed or as median (interquartile range). A *p* value of 0.05 was considered statistically significant.

RESULTS

Pre-clinical device testing

Cerclage was successful in 9/9 GLP animals with implantation of a single TMCV device in the intended position. Coronary artery compression was not observed in any animal. At necropsy, the TMCV device was partially covered by tissue at 30 days and completely covered at 90 days. These pre-clinical experiments are described further in the Supplemental Materials.

Subject characteristics

Nineteen subjects consented and underwent a cerclage procedure between May 2019 and February 2021, despite COVID-19-related delays. Figure 1 summarizes study enrollment. Baseline characteristics are summarized in Table 2. Twelve (63%) had HFrEF and 7 (37%) had HFpEF. All subjects with HFrEF had Carpentier Functional Classification Type I and all subjects with HFpEF had Type IIIb. The etiology of cardiomyopathy was ischemic in 5 (26%) and non-ischemic in 14 (74%). Supplemental Table 1 summarizes medications at baseline. Hypotension limited use of heart failure medications in 11 subjects. Seventeen (89%) were ill-suited or ineligible for TEER due to excessive leaflet gap (21%), broad/multiple MR jets (79%), leaflet restriction (32%) or ejection fraction >50% (37%). No subject had mitral annular calcification or excessive leaflet calcification. Eight were enrolled after a protocol change that allowed subjects with HFrEF and less-than-severe MR after early observations suggested meaningful heart failure quality-of-life benefits in subjects with HFrEF even in the absence of significant MR reduction in the cath lab. In consultation with FDA, the inclusion criteria were modified to allow enrollment of subjects with mild or greater MR with LVEF ≤50% and NYHA class III or IV symptoms.

Although presence of LV pacing leads in the coronary sinus was not an absolute exclusion criterion, none of the enrolled subjects had LV leads in place. Only one subject with persistent symptomatic MR after TEER was enrolled.

Procedure details and clinical outcomes

The primary endpoint of technical success was met in 17/19 subjects. Cerclage was aborted in one subject because cinching caused compression of the left anterior descending artery (LAD). The intramyocardial trajectory appeared to be too close to the LAD and caused vessel kinking as tension was applied. Compression resolved immediately upon release of device tension. The TMCV device was removed from the body in its entirety without complication. The subject completed 30-day follow up and then elected to return two months later, at which time cerclage was performed successfully with a different intramyocardial trajectory. Cerclage was aborted without complication in a second subject because a suitable intramyocardial trajectory could not be found, presumed to be due to scarring/fibrosis at the base of the heart from prior surgical aortic valve replacement. The

subject underwent TEER 3 months later. Fluoroscopy time was 73±22min and sheath-to-hemostasis time was 192±57min.

The secondary endpoint of procedural success was met in 16/19 subjects. The three exceptions were the two subjects in whom technical success was not met and a third in whom the TMCV device fractured losing tension sometime between hospital discharge and 30-day follow up. There were no complications related to device fracture other than loss of efficacy. Specifically, the device did not migrate or embolize after fracture and did not interfere with tricuspid valve function. Hereto forth, these 3 subjects are referred to as the 'untreated' group and the remaining 16 subjects as the 'treated' group for subgroup comparisons. Supplemental Table 7 summarizes invasive hemodynamics at baseline and immediately after cerclage, which showed no significant change in any parameter.

Quality of life and heart failure

To prevent survival bias, only paired data are presented. Six-minute walking distance increased significantly at 30 days and remained increased upon latest assessment after a median 265 days (Figure 4, Supplemental Figures 2 and 3). Six-minute walking distance increased irrespective of HFrEF or HFpEF phenotype and increased by 100m in 7/16 'treated' subjects after cerclage, compared with 0/3 'untreated' subjects.

There was a significant improvement in NYHA class at 30 days (p<0.0001) and at latest assessment (p=0.001)(Figure 5, Supplemental Figure 4). At 30 days among 'treated' subjects, NYHA functional class improved ≥1 grade in 14/16 (88%), and ≥2 grades in 4/16 (25%). At latest assessment, NYHA functional class improved ≥1 grade in 11/16 (69%) and ≥2 grades in 8/16 (50%), compared with 0/3 'untreated' subjects after median 253 days.

KCCQ Clinical Summary and Overall Summary scores increased at 30 days and at latest assessment after a median of 268 days (Figure 4, Supplemental Figures 5 and 6). Medication classes and doses did not change over time, nor did brain natriuretic peptide levels (HFpEF: baseline 1078pg/mL (878,1278) vs. latest assessment 1448pg/mL (884, 1660), p=0.6; HFrEF: baseline 2513pg/mL (242, 5881) vs. latest assessment 1404pg/mL (180,4051), p=0.8).

Adverse events

There were no procedural deaths, strokes or transient ischemic attacks, major vascular complications, periprocedural myocardial infarctions, nor major or life-threatening bleeding events. Three subjects had heart failure hospitalizations on post-procedure days 30, 64, and 150 respectively. Three subjects died, on post-procedure days 79, 159 and 756 respectively. All three had undergone successful TMCV and met the primary endpoint of technical success. All three deaths were adjudicated to be related to other comorbidities and/or progression of underlying disease, and unrelated to cerclage.

New complete heart block developed in 6/17 subjects (35%) within 48hrs of cerclage (Supplemental Figure 4). Two had a pre-existing cardiac implantable electronic device (CIED) and 4 underwent implantation of a new device (pacemaker in 1, cardioverter defibrillator in 1, and cardiac resynchronization therapy in 2). Only one subject underwent

invasive electrophysiological study which indicated supra-Hisian block. New complete heart block was not predicted by baseline electrocardiogram characteristics or heart failure phenotype. At 30 days, 4/6 were pacing dependent and 2/6 were intermittently paced.

In 2 additional subjects with HFrEF and pre-existing conduction disturbance (atrial fibrillation and left bundle branch block, respectively), planned CIED was deferred until after cerclage to avoid risk of lead entrapment/dislodgement. Both subsequently underwent uncomplicated CIED implantation (cardioverter defibrillator on day 2 and cardiac resynchronization therapy on day 79, respectively).

Cardiac CT findings

There was no evidence of erosion or migration of the TMCV device by CT at any follow-up timepoint. Acutely, cerclage displaced the posterior left atrial wall anteriorly (Figure 3, Panel F). Cerclage induced a significant and sustained change in the geometry of the basal left ventricle, as intended. The cerclage perimeter was reduced 21% versus baseline ($p<0.001$), which was more pronounced among subjects with HFrEF. This corresponded with a sustained 20% reduction in mitral annular area ($p=0.002$), which was also more evident among subjects with HFrEF. The annular reductions were comparable in all dimensions (septal-lateral, inter-commissural, and inter-trigonal). Although the coronary sinus and mitral annulus commonly lie apart, cerclage reduced the distance between them by 46% at latest assessment ($p=0.001$). There was no correlation between coronary sinus-to-annulus distance and any outcome.

Cerclage did not consistently reduce left or right ventricle end-systolic or end-diastolic volumes but did appear to arrest further dilatation (Figure 6). Cerclage did induce a significant and sustained reduction in left atrial but not right atrial volume indices. There was a trend towards improvement in right ventricle ejection fraction but not in LV ejection fraction (Figure 6).

Echocardiography findings

Cerclage induced a sustained reduction in mitral regurgitant volume (−41%) and effective regurgitant orifice area (−33%) after a mean 274 days and a maximum 807 days. Table 3 and Supplemental Figure 3 summarize key echocardiography findings at baseline, 30 days, and latest assessments, and stratified according to heart failure phenotype. Cerclage did not induce a transmitral gradient and did not induce tricuspid regurgitation. There was no change in left ventricular global longitudinal strain (data not shown).

DISCUSSION

The key findings of this Investigator-initiated Early Feasibility Study were: 1) Cerclage was safe with high technical and procedural success; 2) Cerclage led to significant reduction in mitral regurgitation, and appeared to prevent further cardiac chamber dilation in subjects ill-suited or ineligible for TEER; 3) Cerclage led to large improvements in quality-of-life metrics including NYHA class, six-minute walking test and Kansas City Quality of Life Questionnaire scores at 30 days that were maintained at latest assessment; 4)

Improvements were most evident in subjects with HFrEF and in subjects with non-ischemic cardiomyopathy.

Cerclage appears to be safe with no important procedural complications observed in this early experience. To operators, the most unfamiliar step of the cerclage procedure is selecting a septal perforator vein branch of the coronary sinus and traversing the myocardium to re-enter the RVOT. Nonetheless, the technical success rate was high. Cerclage was aborted without complication in two subjects. These two cases confirm that cerclage is fully reversible and removable in its entirety even after cinching and locking, which we consider to be a major advantage of the technology. This contrasts with other transcatheter annuloplasty or ventriculoplasty systems (e.g., Cardioband, Edwards Lifesciences, Irvine, CA or Accucinch, Ancora Heart, Santa Clara, CA), which rely on intramyocardial anchors that cannot be retrieved once deployed.

In contrast to TEER, it is not clear whether acute reduction in MR by echocardiography is a useful parameter to determine immediate success with transcatheter annuloplasty/ventriculoplasty devices. Although we did observe significant reduction in objective measures of MR at 30 days and beyond (Table 3), we found severity of MR by intraprocedural TEE to be less useful. Relatedly, we did not observe significant changes in invasive hemodynamics immediately after cerclage. Rather, device tension and geometric change (specifically anterior displacement of the posterior left atrial wall/mitral annulus) appeared to be more useful parameters in the cath lab. In hindsight, excessive tension was applied in early subjects to try to achieve significant MR reduction by TEE. This excessive tension likely led to TMCV device fracture in one subject. Fracture led to loss of device effectiveness but no other complications.

We observed significant and sustained reduction in objective echocardiographic parameters of mitral regurgitation with cerclage in all heart failure phenotypes. We did not observe significant change in cardiac chamber dimensions. However, absence of progressive chamber dilation may be a signal for treatment effect. Indeed, although TEER achieved significant MR reduction in the COAPT (Cardiovascular Outcomes Assessment of the MitraClip Percutaneous Therapy for Heart Failure Patients with Functional Mitral Regurgitation) trial, progressive left ventricular dilation continued, albeit at a slower rate than in the control arm(10).

We believe that cerclage has several potential advantages over other ventriculoplasty/annuloplasty devices. For example, in contrast to coronary sinus compression devices, cerclage is circumferential. In contrast to direct annuloplasty devices, cerclage has no LV blood contact. In contrast to anchor-based ventriculoplasty, cerclage imposes extrinsic compression with even load distribution that is not susceptible to anchor failure. The findings from this Early Feasibility Study should be interpreted in the context of other studies of patients with heart failure and secondary MR, although not all comparator studies report paired data which introduces risk of survival bias. Cerclage resulted in substantial improvement in NYHA class with 95% of subjects in class III-IV at baseline and 84% in class I-II at 30 days (16% in class III-IV). Cerclage resulted in substantial improvement in KCCQ-Overall Summary score of +25.5 at 30 days and +28.4 at latest assessment (median

255 days) compared to baseline. In comparison, TEER using the Mitraclip (Abbott Vascular, Santa Clara, CA) in the COAPT trial resulted in smaller improvements in KCCQ-Overall Summary score of +16.9 at 30 days and +18.5 at 6 months compared to baseline(11). While TEER did not impact 6-minute walking distance in COAPT (−4.6m, 12 months compared to baseline), cerclage resulted in a clinically meaningful increase (+81.2m, median 255 days compared to baseline).

Interestingly, these large quality-of-life improvements were observed even in patient groups that did not appear to derive much benefit from TEER in previous studies. The left ventricular end-diastolic volume index (LVEDVi) of HFrEF patients in the cerclage trial was 135.9mL/m^2 which is very similar to the device group of MITRA-FR (Percutaneous Repair with the MitraClip Device for Severe Functional/Secondary Mitral Regurgitation) trial(12) and a 'dilated left ventricle' subgroup from the COAPT trial (13) (LVEDVi 136.2mL/m^2 and 127.6mL/m^2, respectively). In this phenotype, increase in KCCQ-Overall Summary score at 12 months/latest assessment was +28.4 vs. +18.4 (cerclage vs. COAPT) and increase in 6-minute walking distance was +81.2m vs. +25.0m vs. +39.0m (cerclage vs. MITRA-FR vs. COAPT). Rather, the quality-of-life improvements achieved with cerclage were comparable or superior to those reported for other transcatheter annuloplasty/ventriculoplasty devices. Increase in KCCQ-Overall Summary score at 6 months/latest assessment was +28.4 vs. +24.5 for cerclage vs. Accucinch(14), respectively, and increase in 6-minute walking distance was +81.2m vs. +49.1m vs. +57.0m for cerclage vs. Accucinch vs. Cardioband(15), respectively. Quality-of-life improvements were smaller with a 'partial' annuloplasty device (Carillon, Cardiac Dimensions, Kirkland, WA) which had an increase in 6-minute walking distance of +24m and in KCCQ-Overall Summary score of +12 at 12 months compared to baseline(16). Together, these data point to an important treatment signal for annuloplasty/ventriculoplasty devices in patients with HFrEF that may be attributable to geometric change above and beyond MR reduction alone, and that circumferential – rather than partial – ventriculoplasty imparting substantial geometric change may be better. Further trials are needed to confirm whether an edge-to-edge approach or annuloplasty/ventriculoplasty approach is preferable in patients with heart failure and MR.

We observed the greatest quality-of-life improvements in subjects with HFrEF and in subjects with non-ischemic cardiomyopathy. However, even though we did not observe significant left atrial remodeling in subjects with HFpEF, we did observe decrease in NYHA class, and increases in KCCQ-Overall Summary score, KCCQ-Clinical Summary score and 6-minute walking distance at 30 days. Encouragingly, these improvements were maintained at median 350 days follow-up, which we believe warrants further investigation, as pharmacological and device treatment options remain extremely limited for patients with HFpEF(17).

There was a relatively high rate of CIED utilization in this early experience. Cerclage was associated with new complete heart block in 6 subjects, of whom 2 had prior CIED and 4 required a new CIED. Two additional subjects had CIED implanted after cerclage for other (pre-existing) indications. It is possible that excessive TMCV tension in some subjects may have contributed to development of heart block and CT analysis suggested that more apical and posterior myocardial trajectories may be associated with less heart block. Most

enrolled subjects had HFrEF for which cardiac resynchronization therapy and implantable cardioverter defibrillators both have Class I recommendations(17), therefore high CIED utilization may be expected. Indeed, in the COAPT trial almost 40% of subjects in the TEER arm had prior CIED.

Limitations

This was an Early Feasibility Study focused on safety and technical feasibility, but also to better define the target patient phenotype for this therapy. For this reason, the inclusion criteria were intentionally designed to enroll subjects with varied phenotypes. Effectiveness endpoints were exploratory. We recognize that the sample size was small. However large treatment effects can be evident even in small sample sizes. We believe that there are many lessons to be learned from Early Feasibility Studies, not only specific to the device in question, but also to inform future study design for other innovative devices targeting patients with the same disease. The small sample size limited statistical sub-group comparisons. Larger studies are needed to confirm which patient phenotypes are most likely to benefit from cerclage (e.g., HFrEF vs. HFpEF, or non-ischemic vs. ischemic cardiomyopathy) and to evaluate impact on clinical outcomes such as mortality and heart failure hospitalizations. Although the study protocol allowed for enrollment of patients with failed TEER, ultimately only one such subject was enrolled. This precludes meaningful exploration of efficacy of cerclage after failed TEER.

CONCLUSIONS

In this Early Feasibility Study, transcatheter mitral cerclage ventriculoplasty was safe with high technical and procedural success. Cerclage resulted in significant and sustained improvements in mitral regurgitation, and in heart failure quality of life assessments.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

ACKNOWLEDGEMENTS

The authors would like to thank collaborators at Transmural Systems; E. Collins, V. Wilson, S. Thompson, J. James, and K. Pitts, the site Research Coordinators; S. Sidenko and C. Brenneman from the echo core lab; S. Ivusic, P. Pullen, and A. Idriss from the Clinical Trials Database support team; V. Matveev from the Data Monitor; H. Garcia-Garcia, K. Kuku and colleagues from the Clinical Events Adjudication Committee; W. Schenke and K. Lucas for support with preclinical experiments; J. Bourque and colleagues from the Data Safety Monitoring Board; and J.H. Kim, one of the co-inventors of the procedure, for thoughtful insights.

Funding:

Supported by NHLBI Division of Intramural Research (Z01-HL006040) and by NHLBI SBIR contract (HHSN268201500008C) to Transmural Systems.

Disclosures:

TR is a consultant and physician proctor for Edwards Lifesciences; and Medtronic; is a Medtronic advisory board member; and has an equity interest in Transmural Systems.

TR and RJL are co-authors on patents, assigned to NIH, on cerclage-related devices.

VCB and ABG receive institutional research support from Abbott Vascular, Ancora Heart, Edwards Lifesciences, Gore Medical, Jena Valve, Medtronic, Polares Medical, Transmural Systems, 4C Medical; receive consulting fees from Abbott Vascular, Edwards Lifesciences, and Medtronic; and have equity interest in Transmural Systems.

JRF is a physician proctor for Edwards Lifesciences and Medtronic.

PTG receives institutional research support from Edwards, Medtronic and Abbott Vascular

ABBREVIATIONS AND ACRONYMS

CIED	Cardiac implantable electronic device
HFpEF	Heart failure with preserved ejection fraction
HFrEF	Heart failure with reduced ejection fraction
LV	Left ventricle
LVOT	Left ventricular outflow tract
MR	Mitral regurgitation
RVOT	Right ventricular outflow tract
TAPSE	Tricuspid annular plane systolic excursion
TEE	Transesophageal echocardiography
TEER	Transcatheter edge-to-edge repair
TMCV	Transcatheter mitral cerclage ventriculoplasty
TTE	Transthoracic echocardiography

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PERSPECTIVES

WHAT IS KNOWN?

Transcatheter mitral valve repair appears beneficial in patients with mitral regurgitation (MR), left ventricular dysfunction and persistent symptoms despite maximally tolerated guideline directed medical therapy.

WHAT IS NEW?

Transcatheter annuloplasty/ventriculoplasty may have incremental benefit because in addition to improving leaflet coaptation, it alters cardiac geometry which may retard or even reverse left ventricular and/or atrial remodeling.

WHAT IS NEXT?

Transcatheter annuloplasty/ventriculoplasty may be of benefit in patients with heart failure and persistent symptoms but who do not meet criteria for advanced therapies such as left ventricular assist device or transplant.

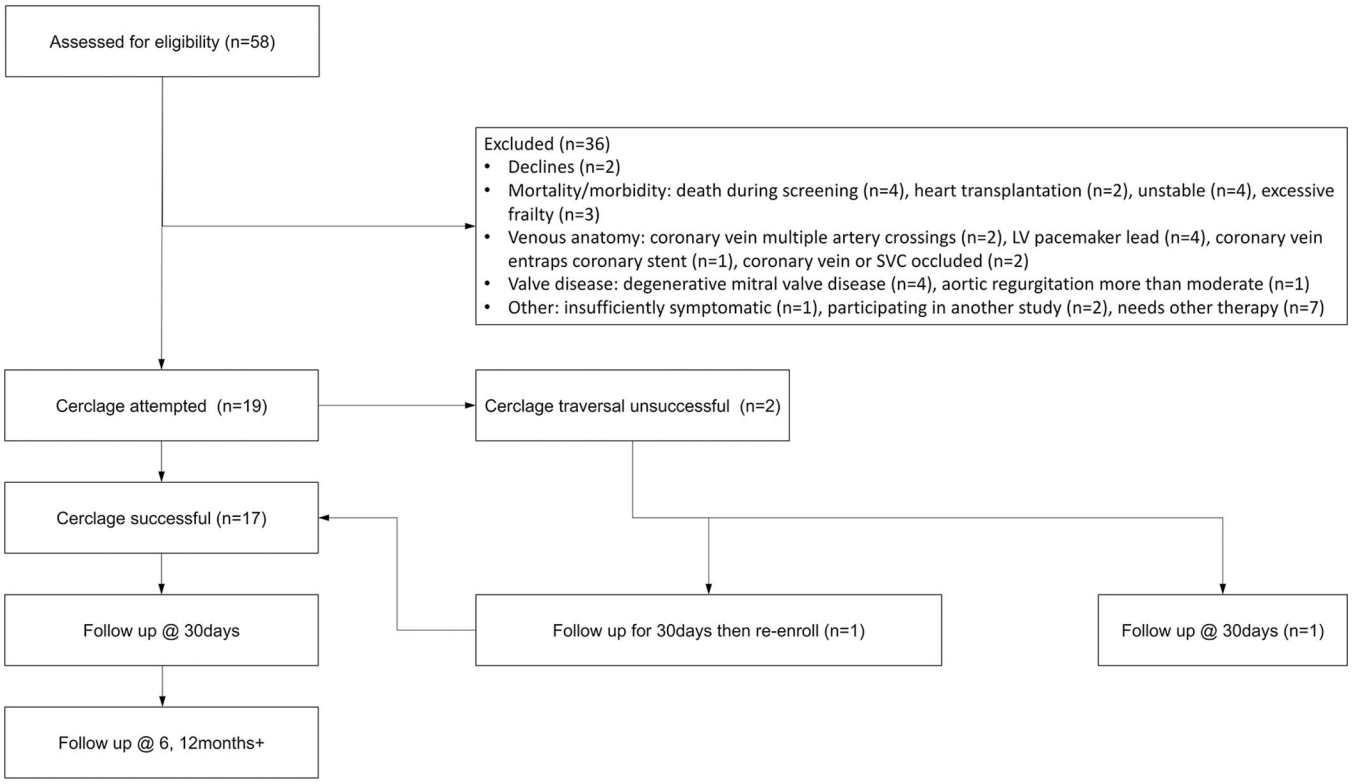


Figure 1 –. Study design

LV: left ventricle; SVC: superior vena cava.

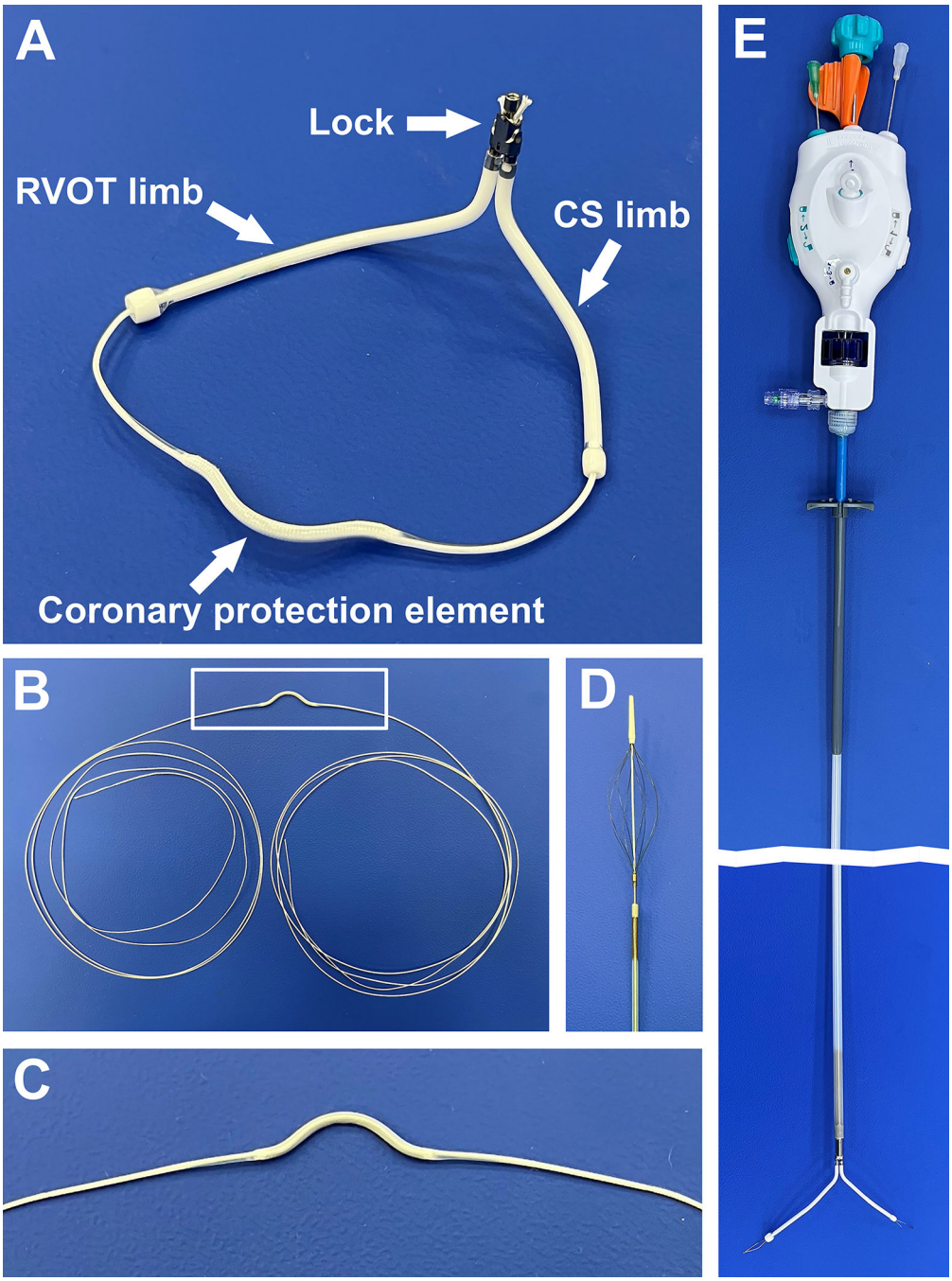


Figure 2 –. Transcatheter mitral cerclage ventriculoplasty device

The Transmural Systems transcatheter mitral cerclage ventriculoplasty device. (A) Complete transcatheter mitral cerclage ventriculoplasty (TMCV) device incorporating wishbone lock with coronary sinus (CS) and right ventricular outflow tract (RVOT) limbs, and tether with rigid coronary protection element. (B) Tether incorporating coronary protection element. (C) Magnified image of coronary protection element corresponding to white box in (B). (D) Expandable right ventricular outflow tract snare. (E) Wishbone lock delivery system with proximal handle to adjust tether tension and to open and close lock.

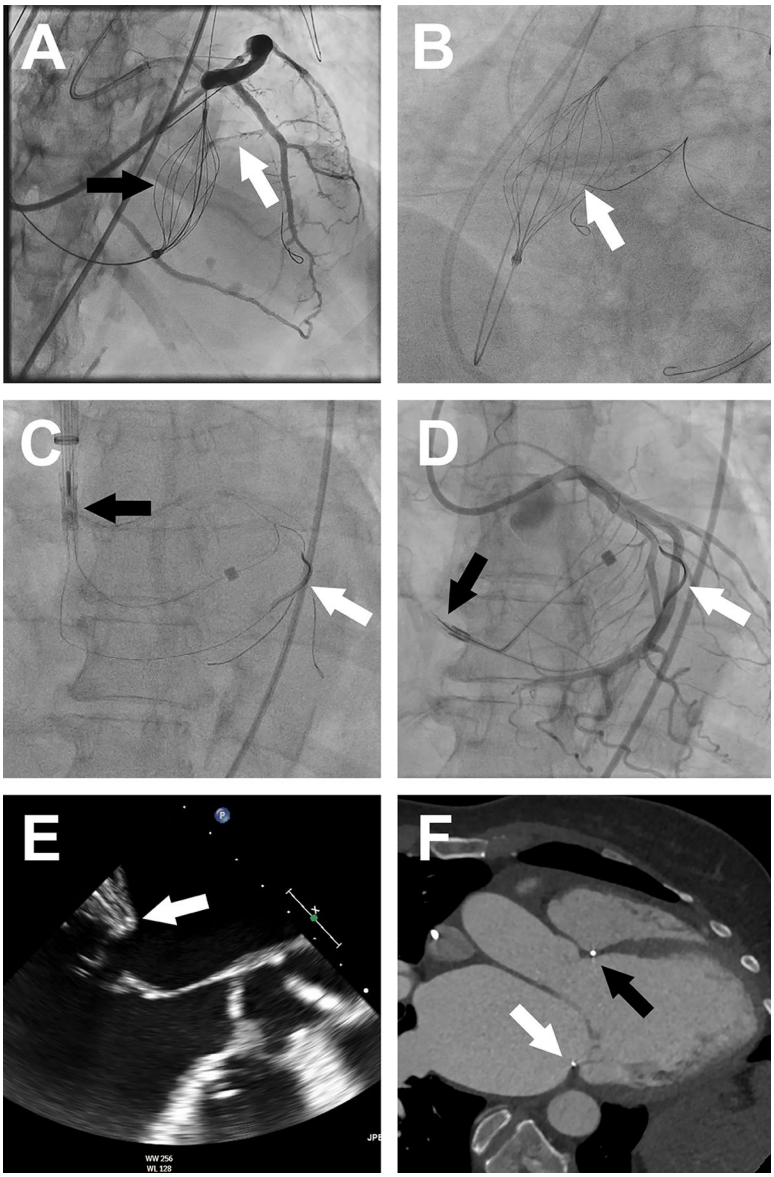


Figure 3 –. Representative cerclage procedure

(A) Coronary sinus venogram with balloon-tipped guide catheter to pressurize the coronary sinus. Black arrow: snare in right ventricular outflow tract (RVOT). White arrow: target septal perforator vein. (B) 0.014” guidewire with 30-degree angled distal tip inside microcatheter to navigate into the septal perforator vein, through the myocardium and re-enter the RVOT where guidewire is captured by the snare. (C) Permanent implant consists of tether with rigid coronary protection element (white arrow) over which a wishbone lock (black arrow) is advanced with one limb in the coronary sinus and the other through the tricuspid valve to the RVOT. (D) After tensioning, the tether is cut (black arrow). Coronary angiography demonstrates no compression of the entrapped left circumflex artery (white arrow). (E) Transesophageal echocardiography demonstrates ‘shelf’ (white arrow) of anteriorly displaced posterior annulus created by the tensioned coronary sinus limb of the transcatheter mitral cerclage ventriculoplasty (TMCV) device. (F) Computed tomography

after cerclage demonstrates ‘shelf’ (white arrow) created by the tensioned TMCV device. Black arrow indicates the TMCV within the interventricular septum.

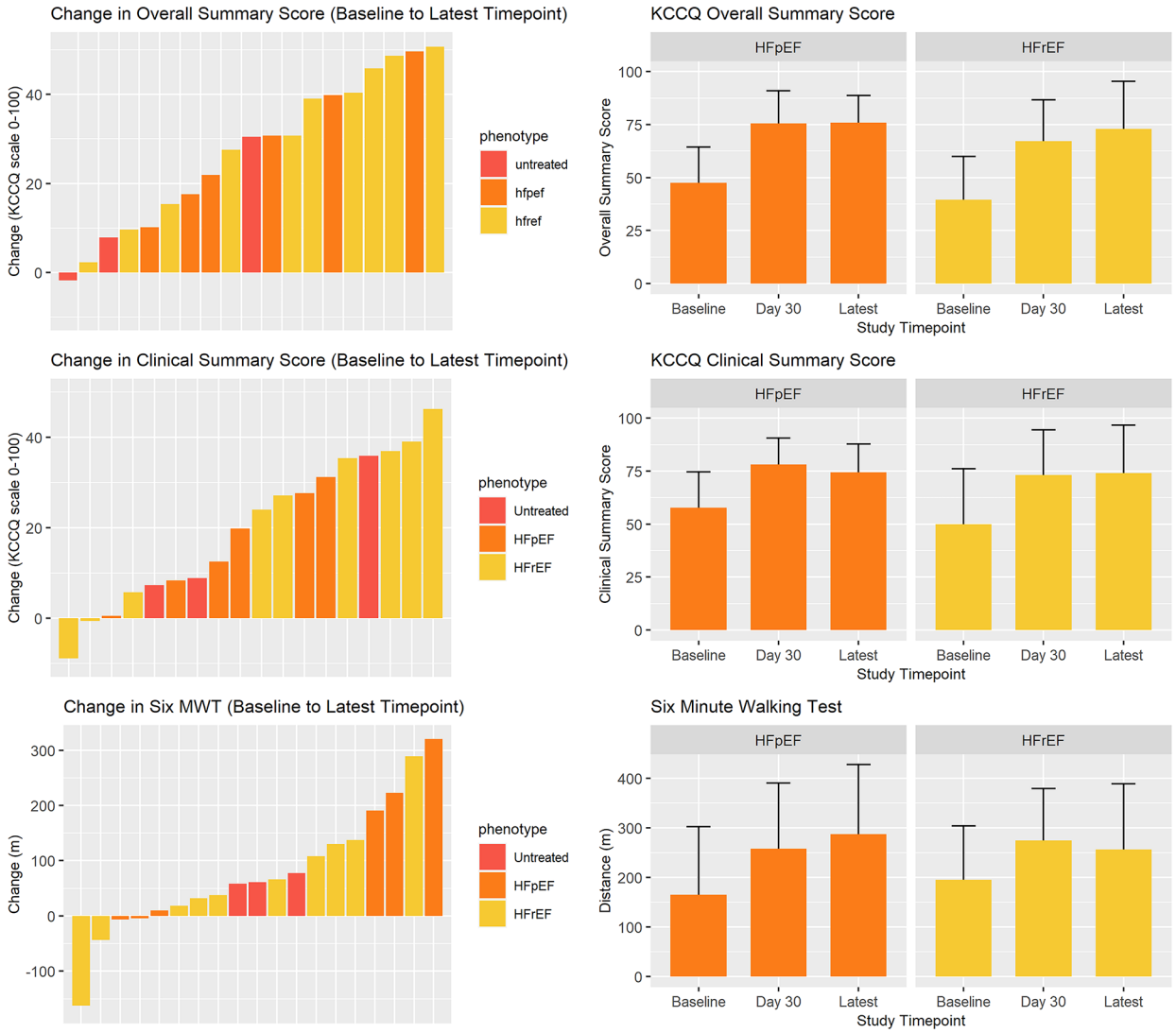


Figure 4 –. Quality-of-life assessments

Asymmetry of waterfall plots demonstrates that improvement occurred in most subjects. Means with standard deviation error bars are shown in the right-side panels. HFpEF: Heart failure with preserved ejection fraction; HFrEF: heart failure with reduced ejection fraction; KCCQ: Kansas City Cardiomyopathy Questionnaire; Six MWT= Six-minute walk test.

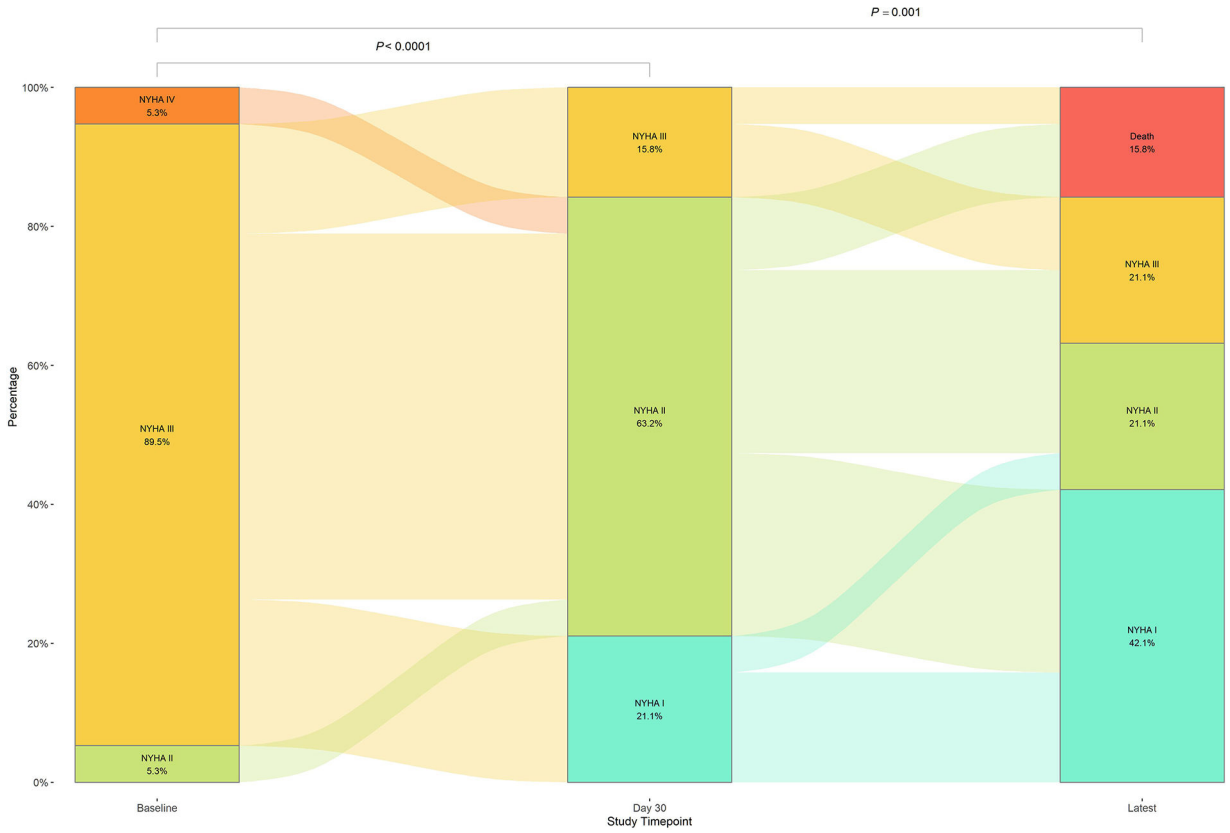


Figure 5 –. NYHA functional class among all subjects (n=19)

Modified NYHA class among all subjects (N=19) using paired datapoints to avoid survivorship bias. NYHA: New York Heart Association. The alluvial plot tracks NYHA class changes for subjects between timepoints.

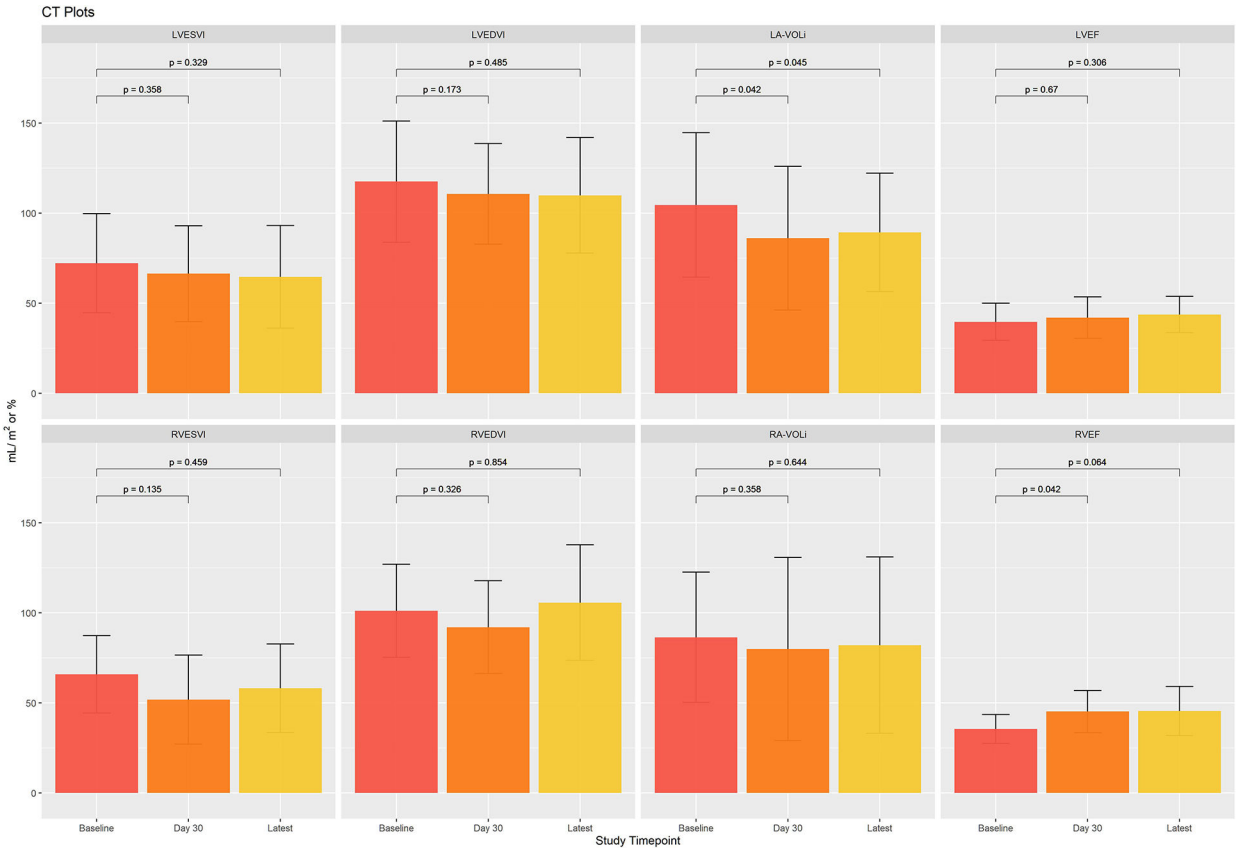
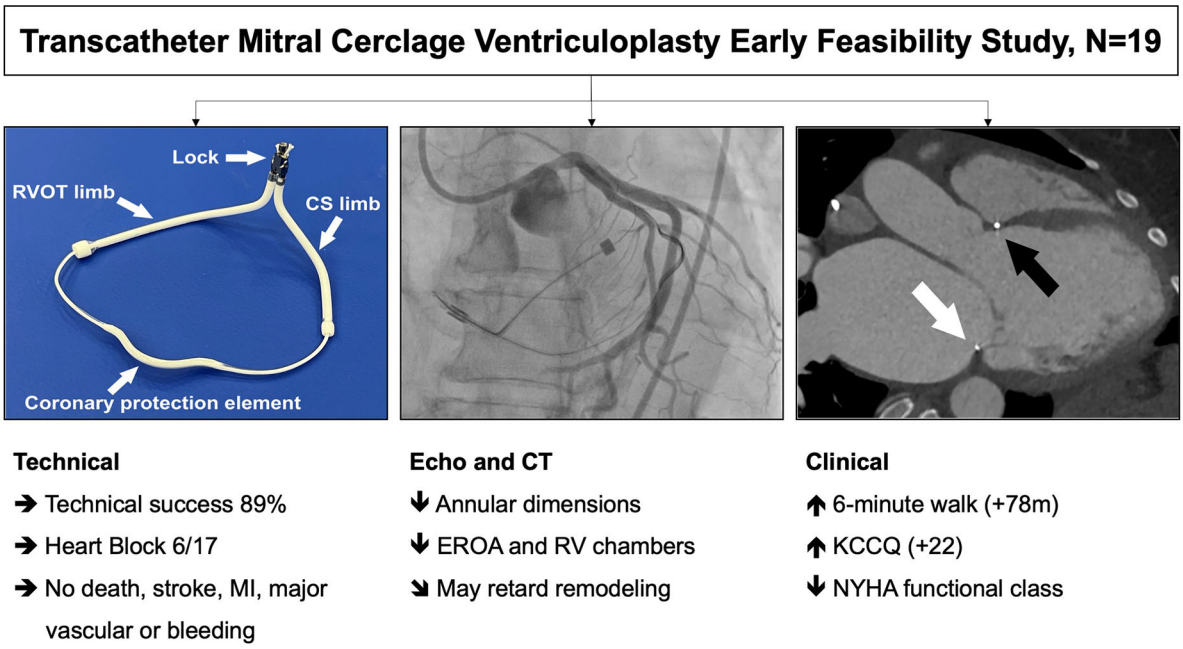


Figure 6 –. CT imaging findings

Means with standard deviation error bars are shown. LA-VOLi: left atrial volume index; LVEDVI: left ventricle end-diastolic volume index; LVEF: left ventricle ejection fraction; LVESVI: left ventricle end-systolic volume index; RA-VOLi: right atrial volume index; RVEDVI: right ventricle end-diastolic volume index; RVEF: right ventricle ejection fraction; RVESVI: right ventricle end-systolic volume index. *p* value <0.05 was considered statistically significant.



Central Illustration:
Summary of findings of the NHLBI and Transmural Systems transcatheter mitral cerclage ventriculoplasty early feasibility study.

Table 1 –

Key inclusion and exclusion criteria

Key inclusion criteria	Key exclusion criteria
1. Age ≥21 years 2. Symptomatic functional mitral valve regurgitation: a. Mild or greater mitral valve regurgitation, LVEF ≤50%, and NYHA class III-IV heart failure * b. Moderate or greater mitral valve regurgitation and NYHA II-IV heart failure, irrespective of LV systolic function 3. On optimal medical therapy for at least 1 month 4. LVEF ≥20% assessed by echocardiography, CT, or CMR 5. Suitable coronary venous anatomy for TMCV based on pre-procedural cardiac CT or invasive coronary venogram 6. If present, TEER was performed at least 30 days previously	1. Prior cardiac implanted electronic devices likely to be entrapped by TMCV device (but candidates with coronary sinus LV pacing or RV defibrillation leads that are not likely to be entrapped by cerclage, evident on baseline CT or invasive coronary venogram, are eligible to participate). 2. Intended concurrent structural heart procedure, such as aortic or tricuspid valve intervention 3. Single-leaflet TEER detachment, if present

CMR: cardiac magnetic resonance; CT: computed tomography; LV: left ventricle; LVEF: left ventricle ejection fraction; NYHA: New York Heart Association; RV: right ventricle; TEER: transcatheter edge-to-edge repair; TMCV: transcatheter mitral cerclage ventriculoplasty.

* Reflects protocol change implemented mid-trial to broaden eligibility to subjects with HFrEF and less than severe mitral regurgitation.

Table 2 –

Baseline characteristics

	Total, N=19
Age	73 (65, 82)
Sex, female	12 (63%)
STS Predicted Risk Mortality at 30 days	3.3 (2.6, 5.0)
Obesity, body mass index >30	7 (37%)
Diabetes	
None	12 (63%)
Diet-controlled	1 (5.3%)
Oral agent	3 (16%)
Insulin-dependent	3 (16%)
Smoking	
Current	3 (16%)
Prior	10 (53%)
Pulmonary disease	2 (11%)
Home oxygen	1 (5.3%)
Estimated glomerular filtration rate,ml/min/1.73 m2	60 (46, 60)
Chronic renal insufficiency, stage IV or V	2 (11%)
End-stage renal disease on hemodialysis	1 (5.3%)
Hypertension	16 (84%)
Coronary artery disease	9 (47%)
Prior percutaneous coronary intervention	3 (16%)
Prior myocardial infarction	5 (26%)
Peripheral vascular disease	2 (11%)
Prior stroke	2 (11%)
Prior transient ischemic attack	4 (21%)
Atrial fibrillation	
None	8 (42%)
Paroxysmal	7 (37%)
Persistent >1 week	2 (11%)
Permanent	2 (11%)
Oral anticoagulation	11 (58%)
Permanent pacemaker in situ	2 (11%)
Implantable cardioverter defibrillator in situ	3 (16%)

Data are presented as n (%) or median (interquartile range). STS: Society of Thoracic Surgeons.

Table 3 –

Echocardiography

		EROA, cm^2	MR volume by PISA, mL	MR severity grade[a]	Mitral gradient, mmHg	TR severity grade[b]	TR peak velocity, m/ s
All (n=19)	**Baseline**	0.26 (0.23, 0.3)	46.5 (35.5, 57.5)	3 (2.5, 3.5)	2.7 (1.7, 4.0)	1 (1, 2)	2.8 (2.4, 3.1)
	30 days	0.17 (0.11, 0.24)	26.5 (20.3, 37.8)	2 (1.5, 3)	3.0 (1.9, 3.6)	1 (1, 2)	2.9 (2.5, 3.1)
	p value †	0.002*	0.002*	0.002*	0.80	0.78	0.37
	Latest	0.16 (0.13, 0.20)	26.5 (21.5, 32.7)	2.5 (1.5, 3)	3.0 (1.8, 3.4)	1 (1, 2)	2.9 (2.5, 3.2)
	***p* value** †	0.001*	<0.001*	0.005*	0.53	0.18	0.62
Treated (n=16)	**Baseline**	0.23 (0.22, 0.28)	37.3 (34.5, 56.0)	3 (2.5, 4)	2.3 (1.5, 3.0)	1 (1, 2)	2.7 (2.4, 3.1)
	30 days	0.12 (0.11, 0.18)	25.0 (18.9, 27.5)	2 (1, 2)	2.0 (1.5–3.6)	1 (1, 2)	2.8 (2.5, 3.1)
	***p* value** †	0.001*	0.004*	0.002*	0.76	0.48	0.42
	Latest	0.16 (0.14, 0.18)	25.0 (20.7, 31.1)	2.5 (1.5, 3)	2.3 (1.4, 3.0)	1 (1, 2)	2.8 (2.5, 3.2)
	***p* value** †	0.002*	<0.001*	0.009*	0.58	0.28	0.70
Untreated (n=3)	**Baseline**	0.33 (0.31, 0.33)	56.0 (54.5, 58)	3 (3, 3.5)	3.9 (3.1, 4.1)	1 (1, 1)	3.1 (3.1, 3.1)
	30 days	0.36 (0.31, 0.36)	61.0 (49.0, 61.3)	3 (3, 3.5)	3.4 (3.2, 4.4)	2 (2, 2)	3.2 (3.2, 3.2)
	***p* value** †	0.75	1.0	1.0	1.0	1.0	1.0
HFrEF (n=12)	**Baseline**	0.23 (0.21, 0.27)	35.7 (30.1, 52.8)	3.5 (3, 4)	3.0 (1.5, 4.5)	1 (1, 1)	2.9 (2.3, 3.1)
	30 days	0.18 (0.13, 0.22)	27.5 (20.1, 35.5)	1.5 (1, 2.5)	2.9 (2.0, 3.6)	1 (1, 1)	2.7 (2.2, 3.2)
	***p* value** †	0.06	0.031*	0.020*	0.55	1.0	0.84
	Latest	0.16 (0.13, 0.18)	28.0 (22.9. 32.0)	2.5 (1, 3)	2.7 (1.9, 3.5)	1 (1, 2)	3.0 (2.7, 3.2)
	***p* value** †	0.03*	0.004*	0.06	0.59	0.57	0.83
HFpEF (n=7)	**Baseline**	0.25 (0.23, 0.28)	40.0 (37.0, 54.0)	3 (2.5, 3.5)	2.0 (1.5, 2.5)	2 (1, 2)	2.5 (2.4, 2.8)
	30 days	0.11 (0.1, 0.12)	21.0 (20.0, 25.0)	2 (2, 2)	1.8 (1.4, 2.5)	2 (1, 2)	2.8 (2.8, 2.9)
	***p* value** †	0.031*	0.06	0.034*	0.88	0.35	0.44
	Latest	0.15 (0.14, 0.16)	22.0 (20.5, 28.3)	2.5 (2, 2.5)	1.8 (1.3, 2.4)	2 (1, 3)	2.5 (2.5, 2.7)
	***p* value** †	0.06	0.06	0.09	0.79	0.42	1.0

Latest echocardiogram performed at median 337 days after cerclage. EROA: effective regurgitant orifice area; MR: mitral regurgitation; PISA: proximal isovelocity surface area.

[a] MR severity grade scale: 0 – None or Trace; 1 – Mild; 1.5 – Mild-Moderate; 2 – Moderate (2+); 2.5 – Moderate (2+ to 3+); 3 – Moderate (3+); 3.5 – Moderate-Severe; 4 – Severe.

[b] TR severity grade scale: 0 – None; 1 – Mild; 2 – Moderate; 3 – Severe.

[†] *p* values refer to comparisons with baseline and use paired datapoints to avoid survivorship bias. All results reported as median (interquartile range).

[*] denotes statistical significance.