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Off-Pump Transapical Implantation of Artificial Neo-Chordae to Correct Mitral Regurgitation

The TACT Trial (Transapical Artificial Chordae Tendinae) Proof of Concept

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Objectives The goal of this study was to evaluate the safety and performance of the NeoChord DS1000 system (NeoChord, Inc., Minneapolis, Minnesota).

Background There is an increasing interest in transcatheter mitral valve (MV) treatment. The NeoChord DS 1000 system enables off-pump beating heart transapical MV repair with implantation of artificial neo-chordae.

Methods Patients with severe mitral regurgitation (MR) due to isolated posterior prolapse were included in this TACT (Transapical Artificial Chordae Tendinae) trial. All patients were scheduled for off-pump transapical implantation of neo-chordae.

Results Thirty patients at 7 centers were enrolled. Major adverse events included 1 death due to post-cardiotomy syndrome and concomitant sepsis and 1 minor stroke with the patient fully recovered at the 30-day follow-up visit. Additional patients experienced procedural major adverse events related to a reoperation or conversion to standard of care. Acute procedural success (placement of at least 1 neo-chord and reduction of MR from 3+ or 4+ to ≤2+) was achieved in 26 patients (86.7%). In 4 patients neo-chordae were not placed for technical and/or patient-specific reasons. These patients underwent intraoperative (3 patients) or post-operative (1 patient) standard MV repair. At 30 days, 17 patients maintained an MR grade ≤2+. Four patients who developed recurrent MR were successfully treated with open MV repair during 30-day follow-up. Results improved with experience: durable reduction in MR to ≤2+ at 30 days was achieved in 5 (33.3%) of the first 15 patients and 12 (85.7%) of the last 14 patients.

Conclusions Off-pump transapical implantation of artificial chordae to correct MR is technically safe and feasible; however, it yields further potential for improvement of efficacy and durability. (Safety and Performance Study of the NeoChord Device [TACT]; NCT01777815) (J Am Coll Cardiol 2014;63:914–9) © 2014 by the American College of Cardiology Foundation

Surgical mitral valve (MV) repair with the use of artificial neo-chordae for Carpentier type II pathology has proven excellent short- and long-term results (1–6). A newly developed device (NeoChord DS1000 system, NeoChord, Inc., Minneapolis, Minnesota) facilitates transapical implantation of neo-chordae to correct mitral regurgitation (MR) on the beating heart without cardiopulmonary bypass (7). This approach may be of special value to correct degenerative MR for prolapse; however, clinical applicability has not yet been investigated. After thorough pre-clinical and first-in-man application the investigation of this new treatment was performed (7–9). We herein report on the very early results of the TACT (Transapical Artificial Chordae Tendinae) study.

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Methods

Study design and endpoints. A prospective, multicenter, single-arm study with pre-defined endpoints was performed to evaluate the safety and performance of the NeoChord

DS1000 system (Fig. 1, Table 1). Patients were seen at 30 days post-procedure for study endpoints.

Patient selection. Patients with severe MR due to isolated Carpentier type II prolapse of the posterior MV leaflet and no annulus dilation (NeoChord, Inc.), with an indication for surgery confirmed according to guidelines, were included in the trial (1,10). Key exclusion criteria included secondary MR, severe left ventricular dysfunction (left ventricular end-diastolic diameter >6.5 cm), anterior or bileaflet MV prolapse, permanent atrial fibrillation, and concomitant cardiac disease with an indication for surgical treatment.

Ethics approval. Informed consent was obtained from all patients prior to surgery. All patients were informed about the first-in-human nature of this study. Ethics committee approval was granted by the respective institutional review boards. Leading ethics committees were Aarhus (Denmark), Leipzig (Germany), Turin (Italy), and Vilnius (Lithuania).

Operative setup. Patients were prepared for surgery according to the respective standard of care (SOC) of each participating center. SOC general anesthesia was performed and SOC equipment was available in all cases if necessary. In all patients the safety net strategy was chosen using femoral lines for potential cardiopulmonary bypass cannulation. Cell saver with blood retransfusion was prepared for use in all patients.

Surgical technique. The NeoChord procedure was performed under 2-dimensional and 3-dimensional transesophageal echocardiographic guidance through a standard transapical access as previously described (Fig. 2) (7). In brief, the NeoChord DS 1000 device enables implantation of neo-chordae using polytetrafluoroethylene sutures to the prolapsing MV leaflet. After grasping of the MV leaflet tissue with 2 grippers, embedded color-sensible fiber optics allow for verification of sufficient tissue grasping. Piercing and fixation with subsequent retraction of the neo-chordae are realized using a special needle. After a girth hitch knot is tied and slid to the leaflet, the 2 free ends of the suture are then fixed on the left ventricular apex at a defined length for correction of leaflet prolapse (Fig. 3). Procedures were performed by 6 senior surgeons in cooperation with two lead surgeons (proctor).

Abbreviations and Acronyms

APS = acute procedural success
MR = mitral regurgitation
MV = mitral valve
PML = posterior mitral leaflet
SOC = standard of care

Data acquisition. Data were prospectively collected by the respective study coordinator at each participating center. Pre- and post-operative echocardiography core laboratory analysis was performed (Mayo Clinic, Rochester, Minnesota). The trial was monitored by an independent contract research organization. A Clinical Events Committee reviewed and adjudicated all serious adverse events.

Statistical analysis. Data are presented as descriptive statistics where the distribution (number and percent) is reported for each level of the categorical response along with the 95% exact confidence interval. Summary statistics (n, mean, median, SD, minimum, and maximum) are reported for continuous variables.

Results

Patient characteristics. A total of 30 patients at 7 centers were enrolled in the TACT trial. All patients presented with severe MR due to isolated prolapse of the posterior mitral leaflet (PML). Relevant patient variables as well as concomitant diseases are depicted in Table 2.

Procedure refinements. Two procedure refinements were introduced during the conduct of the trial: 1) the use of multiple neo-chordae per procedure (introduced after 2 patients received implants); and 2) the revision of the left ventricular access to a posterolateral approach (introduced after 15 patients received implants). Therefore data will be presented in the following cohorts:

- **Entire cohort:** all patients enrolled (n = 30)
- **Multiple suture cohort:** patients in whom multiple sutures were recommended (n = 28)
- **Posterolateral cohort:** patients undergoing implantation with a posterolateral apical access (n = 15)

Figure 1 NeoChord DS1000 Device for Transapical Off-Pump Implantation of Artificial Chordae Tendinae

(A) The NeoChord DS1000 device (NeoChord, Inc., Minneapolis, Minnesota) which contains a handle for steering purpose, the needle, which is advanced through the mitral valve leaflet tissue, and a long shaft with the grasping mechanism on the very tip. **(B)** The associated device monitor, which contains fiber optics that reflect the respective tissue color (red for blood, white for mitral valve leaflet tissue) within the graspers to verify a successful leaflet grasp. The device has proven user-friendliness and efficacy within this initial clinical trial.

Table 1 Study Endpoints for Safety and Performance of the NeoChord DS1000 Device* for Treatment of Mitral Regurgitation Due to Isolated Posterior Leaflet Prolapse

Primary safety endpoints (30 days)	Major adverse events • Death • Myocardial infarction • Reoperation for failed surgical repair • Nonelective cardiovascular surgery to treat an adverse event • Procedural ventilation >48 h • Procedure-related transfusion of >2 U blood product • Stroke • Renal failure • Deep wound infection • New onset of permanent atrial fibrillation • Septicemia
Primary performance endpoints (30 days)	• Rate of patients maintaining mitral regurgitation reduction grade ≥2

*Trademark of NeoChord, Inc., Minneapolis, Minnesota.

Safety. Eight (26.7%) patients experienced at least 1 major adverse event (MAE) during the first 30 days (Table 3). Six patients underwent conversion to successful SOC MV repair: 2 patients experienced early dehiscence of neo-chordae as both received implantation of just 1 neo-chord. These early dehiscences resulted in procedure modification 1 (single to multiple neo-chordae). Two additional patients experienced early dehiscence and were converted to SOC. Two patients did not have acute procedural success (APS) and were converted to SOC (1 intraoperative and 1 post-operative).

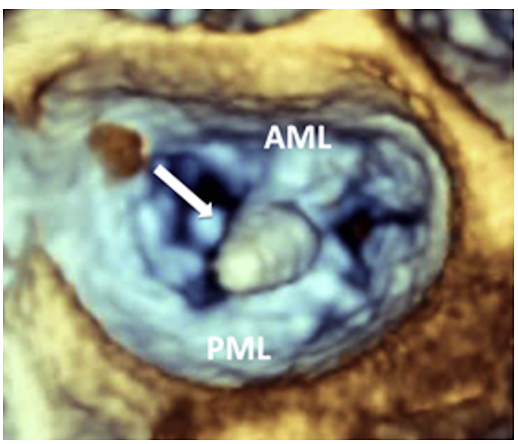

Figure 2 Intraoperative Imaging With 3-Dimensional Transesophageal Echocardiography

This intraoperatively taken 3-dimensional transesophageal echocardiography image depicts the very tip of the NeoChord DS1000 device (NeoChord, Inc., Minneapolis, Minnesota) **(arrow)** within the mitral valve orifice. The grasping mechanism, which can be identified as the accentuation on the tip, is facing the posteromedial commissure. Three-dimensional echocardiography imaging is especially valuable for identification of the prolapsing segment of the mitral valve as well as for intraoperative navigation of the device. AML = anterior mitral leaflet; PML = posterior mitral leaflet.

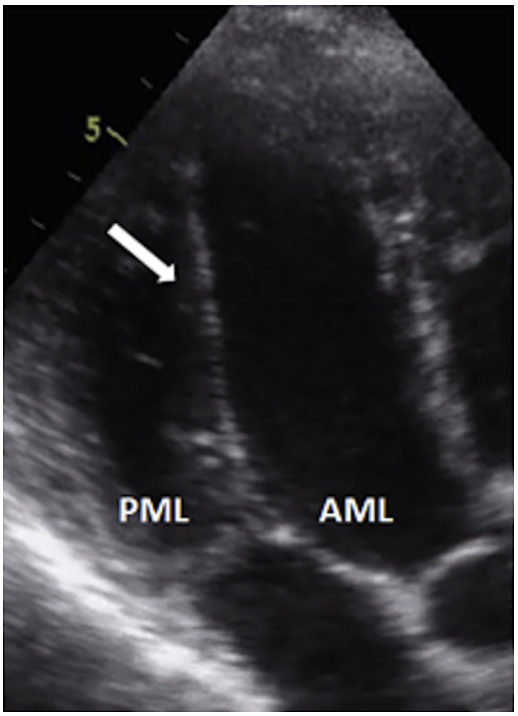

Figure 3 Artificial Chordae Tendinae 6 Months After Implantation

Six-month follow-up transthoracic control echocardiography in a patient who underwent successful transapical off-pump implantation of neo-chordae to correct posterior mitral leaflet prolapse is shown. The artificial neo-chord can be identified as the string **(arrow)** from the left ventricular apex toward the coaptation zone between the PML and AML. Echocardiographic control exams at 6 months post-operation underline the intermediate-term durability of this innovative repair technique. Abbreviations as in Figure 2.

One patient died within 30 days due to post-cardiotomy syndrome and concomitant sepsis. This patient was an 82-year-old female with significant comorbidities who developed recurrent MR on post-operative day 4. One patient (3.3%) experienced perioperative minor stroke with full recovery at the 30-day follow-up visit. Of note, no patient experienced intraoperative hemodynamic deterioration and/or resuscitation.

Acute procedural success. APS, defined as placement of at least 1 neo-chord and reduction of MR to ≤2+, was achieved in 26 patients (86.7%). In 4 patients, neo-chordae were not placed for technical or patient-specific reasons, and thus these patients underwent subsequent successful MV repair (Fig. 4). In 2 other patients, neo-chordae dehisced under minimal tensioning load due to poor tissue quality; both patients were intraoperatively converted to SOC. In 1 patient 2 neo-chordae were successfully deployed; however, a perforation of the PML dictated intraoperative conversion. In 1 patient, multiple attempts to place neo-chordae were unsuccessful and conversion to SOC was

Table 2 Baseline Data of the 30 Patients in the TACT

Age, yrs	63.5 ± 11.9
Female	12 (40.0)
BMI, kg/m^2	25.7 ± 3.7
LVEF, %	59 ± 5
MR grade 3+	3 (10.0)
MR grade 4+	27 (90.0)
PML prolapse	30 (100)
PML chordae rupture and/or chordae elongation	30 (100)
NYHA functional class II	13 (43.3)
NYHA functional class III	17 (56.6)
Hyperlipidemia (medically treated)	3 (10.0)
Arterial hypertension	16 (53.3)
Coronary artery disease	1 (3.3)
Prior myocardial infarction	0 (0)
Prior percutaneous coronary intervention	2 (6.7)
Intermittent atrial fibrillation	3 (10.0)
Prior stroke	0 (0)
Pulmonary hypertension	10 (33.3)
COPD	1 (3.3)
Diabetes mellitus	3 (10.0)
Malignancy	3 (10.0)

Values are mean ± SD or n (%).
BMI = body mass index; COPD = chronic obstructive pulmonary disease; LVEF = left ventricular ejection fraction; MR = mitral regurgitation; NYHA = New York Heart Association; PML = posterior mitral leaflet.

performed 7 days post-procedure. All 4 patients received successful MV repair (Fig. 4). With the procedural modifications in the last 15 patients (posterolateral cohort), APS reached 100% (Table 4).

30-day results. The 30-day follow-up visits have been completed on all patients. At 30 days, 17 of 29 (58.6%) maintained performance success. Of these 17 patients, 12 (71%) have maintained an MR grade ≤1+. One patient had an indeterminate result at the 30-day visit and is therefore not included in the 30-day success rate. The overall success rate improved with each additional suture placed (Fig. 5).

Discussion

The TACT trial shows the feasibility, safety, and efficacy of off-pump transapical implantation of neo-chordae using the NeoChord DS1000 system to correct MR.

Concept. The concept of off-pump transapical implantation of neo-chordae to the mitral leaflet with apical fixation has been introduced and evaluated in pre-clinical trials (9). The technology is based on 2 principles: 1) the very broad and excellent experience with surgical implantation of neo-chordae using expanded polytetrafluoroethylene sutures; and 2) the secure and standardized transapical left ventricular access (4,6,9,11,12).

The DS1000 device includes potential advantages over conventional open MV repair. The technology enables resuspension of a prolapsed PML under physiological conditions on the beating heart without the use of cardiopulmonary bypass and its inherit risks of morbidity and mortality. As shown herein, perioperative morbidity and mortality using the DS1000 system are low despite the very early stage of development and clinical application.

Clinical results. MAEs related to an intra- or post-operative conversion to SOC. There was 1 death due to post-cardiotomy syndrome, concomitant sepsis, and multi-organ failure. This multimorbid patient, however, who was on inotropic support before the procedure, was considered a high-risk candidate. During surgery, anatomical challenges further complicated the case, and in retrospect the inclusion of this patient was rated as selection failure. Additional morbidity of the procedure was low, with 1 transient stroke. Prolonged post-operative respiratory support was necessary in only 1 patient (the same patient who died). The majority of patients were extubated within 3 h post-operatively. The amount of procedure-related transfusion was very reasonable.

Learning curve. Through the course of the study, APS, durability, and safety significantly improved. As previously mentioned, 2 procedure refinements (1 and 2) were introduced during the conduct of the trial. We explain the

Table 3 MAEs in the Entire Patient Cohort as Well as in the Latter 15 Patients Who Underwent Implantation Through a Posterolateral Approach

	Entire Cohort (n = 30)	Posterolateral Approach (n = 15; Patients #16 to #30)
Any MAE	8 (26.7)	1 (6.7)
Death (post-cardiotomy syndrome with subsequent sepsis)	1 (3.3)	0 (0.0)
Reoperation for failed repair*	6 (20.0)	1 (6.7)
Procedure-related transfusion >2 U of blood	5 (16.7)	1 (6.7)
Procedural ventilation >48 h	1 (3.3)	0 (0.0)
Stroke (transient)	1 (3.3)	0 (0.0)
Myocardial infarction	0 (0.0)	0 (0.0)
Nonelective cardiovascular surgery	0 (0.0)	0 (0.0)
Renal failure	0 (0.0)	0 (0.0)
Deep wound infection	0 (0.0)	0 (0.0)
New onset of permanent atrial fibrillation	0 (0.0)	0 (0.0)
Septicemia	0 (0.0)	0 (0.0)

Values are n (%). *One patient was intraoperatively converted to standard of care, but adjudicated as a major adverse event (MAE) because the standard of care procedure required a modification. Numbers are not mutually exclusive because 1 patient can experience more than 1 MAE.

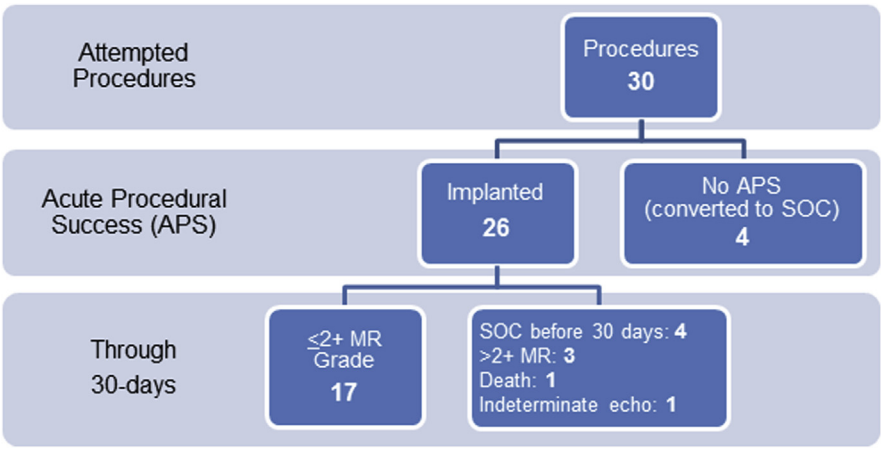

Figure 4 The TACT Study Flow Chart

A flow chart of the Transapical Artificial Chordae Tendinae (TACT) trial is depicted. From a total of 30 attempted procedures, 26 were performed successfully, whereas in 4 patients there was no APS achieved. Early echocardiographic follow-up identified mitral regurgitation (MR) graded as 2+ or less in 17 patients. Despite the acute/late conversion to standard of care (SOC) in 4 of 4 patients the overall success rate is acceptable with regard to the procedural aspects. Long-term durability, however, remains unknown.

observed improvements as the following: 1) the equal distribution of mechanical stress on MV leaflet tissue and polytetrafluoroethylene sutures when using multiple neo-chordae; and 2) the reduction of mechanical stress due to the posterolateral fixation of neo-chordae.

Special consideration was given to optimal patient selection with regard to MV leaflet morphology. Initially, only patients with narrow prolapsing segments were considered to be suitable; however, these patients have shown an even higher difficulty with secure grasping and placement of neo-chordae. In consequence, patients with a wide P2 and/or P3 prolapse were identified as most suitable, and best results were achieved in these patients with regard to acute and durable reduction of MR.

Perspective. Despite the encouraging results of this study using the new NeoChord DS1000 device, the SOC for patients with secondary MR is and will remain surgical open MV repair (1,3,6,11). Catheter-based and innovative approaches may represent a significant potential for innovation to treat MV disease in the future; however, they so far only reflect a niche in clinical practice and are generally accepted to offer palliation rather than treatment.

The NeoChord approach, however, with its promising initial results, may become a treatment option in patients with isolated MV leaflet prolapse: the physiological approach, the low invasiveness, and the effective reduction of MR at a very low operative risk may be used in the very early disease process of primary MR.

Therefore, however, the somewhat preliminary results of this study need to be completed, especially with regard to durability in a large clinical surveillance study.

Study limitations. This study represents the first-in-man clinical experience with transapical off-pump implantation of neo-chordae to correct MR and thus only preliminary conclusions can be drawn from the results. The determination of the exact positioning, length adjustment, and neo-chordae tensioning depends exclusively on the ability and training of the operator and echocardiographer. The exact fixation of neo-chordae on the posterolateral wall is of special interest because it has improved the APS as well as durability; thus, special and extensive training is inevitable.

Conclusions

MV repair for PML prolapse with off-pump transapical implantation of neo-chordae is safe and feasible from a procedural point of view. Further investigation is needed to assess durability and long-term outcome.

Table 4 Post-Procedure MR ≤2+ and 30-Day MR ≤2+ Results for the Entire Cohort of Patients, Patients Who Underwent Implantation of Multiple Neo-Chordae, and Patients Who Underwent the Procedure Using a Posterolateral Approach on the Cardiac Apex

	Entire Cohort (n = 30)			Multiple Sutures (n = 28)			Posterolateral (n = 15)		
Parameter	n/N	%	95% CI	n/N	%	95% CI	n/N	%	95% CI
Post-procedure MR ≤2+	26/30	86.7	69.3–96.2	24/28	85.7	67.3–96.0	15/15	100	78.2–100.0
30-day MR ≤2+*	17/29	58.6	39.0–76.5	17/27	63.0	42.3–80.6	12/14	85.7	57.2–98.2

*One patient with an indeterminate mitral regurgitation (MR) grade at 30 days is excluded from the 30-day results.
CI = confidence interval.

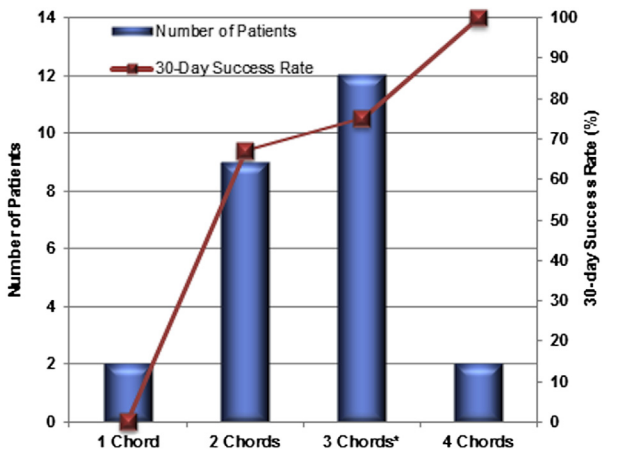

Figure 5 **Acute Procedural Success Rate in Relation to the Number of Implanted Artificial Chordae**

Within the course of the TACT trial, 2 procedure refinements were introduced: the use of multiple neo-chordae per procedure and the revision of the left ventricular apical assess site toward the posterolateral wall. The impact of the use of multiple neo-chordae on the 30-day success rate in patients undergoing off-pump transapical mitral valve repair is shown herein: the more neo-chordae implanted, the higher the 30-day success rate. Although adequate data are lacking, this may well be attributed to the decreased forces applied to each single neo-chord in this multiple neo-chordae approach.

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