European Journal of Cardio-Thoracic Surgery 54 (2018) 460–466
doi:10.1093/ejcts/ezy064 Advance Access publication 5 March 2018

ORIGINAL ARTICLE

Cite this article as: Colli A, Manzan E, Aidietis A, Rucinskas K, Bizzotto E, Besola L *et al.* An early European experience with transapical off-pump mitral valve repair with NeoChord implantation. Eur J Cardiothorac Surg 2018;54:460–6.

An early European experience with transapical off-pump mitral valve repair with NeoChord implantation†

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Received 6 September 2017; received in revised form 19 January 2018; accepted 24 January 2018

Abstract

OBJECTIVES: Transapical off-pump NeoChord repair is a novel minimally invasive surgical procedure to treat degenerative mitral valve regurgitation. The aim was to evaluate 1-year clinical results of the NeoChord procedure in a consecutive cohort of patients.

METHODS: Between February 2013 and July 2016, 213 patients were enrolled in the NeoChord Independent International Registry. All patients presented severe mitral regurgitation due to flail/prolapse of 1 or both leaflets, and they all completed postoperative echocardiographic assessment up to 1 year. We identified the primary end point as composed of procedural success, freedom from mortality, stroke, reintervention, recurrence of severe mitral regurgitation, rehospitalization and decrease of at least 1 New York Heart Association functional class at 1-year follow-up. We also compared outcomes according to the anatomical classification (Type A: isolated central posterior leaflet disease; Type B: posterior multisegment disease; Type C: anterior, bileaflet, paracommissural disease with/without leaflet/annular calcifications).

RESULTS: The median age was 68 years (interquartile range 56–77), and the median EuroSCORE II was 1.05% (interquartile range 0.67–1.76). The number of Type A, B and C patients was 82 (38.5%), 98 (46%) and 33 (15.5%), respectively. Procedural success was achieved in 206 (96.7%) patients. At 1-year follow-up, overall survival was 98 ± 1%. Composite end point was achieved in 84 ± 2.5% for the overall population and 94 ± 2.6%, 82.6 ± 3.8% and 63.6 ± 8.4% in Type A, Type B and Type C patients, respectively ($P < 0.0001$).

CONCLUSIONS: These results demonstrate that the NeoChord procedure is safe, effective and reproducible. Clinical and echocardiographic efficacy is maintained up to 1 year with significant differences among the anatomical groups. Specific anatomical selection criteria are necessary to achieve stable results.

Keywords: Mitral valve repair • NeoChord • Transapical • Echo guided • Off-pump • Registry

INTRODUCTION

Mitral valve repair (MVr) is the preferred surgical treatment for severe mitral regurgitation (MR) due to leaflet prolapse [1]. Conventionally, MVr is performed with the patient in cardioplegic arrest to allow exposure of the mitral valve (MV). However, this approach prohibits visualization of physiological leaflet closure, thus making it difficult to determine the appropriate neochordae length. Within the growing era of percutaneous treatments for valvular heart disease, the transapical NeoChord repair procedure was developed to overcome this possible

†Presented at the 53rd Annual Meeting of the Society of Thoracic Surgeons, Houston, TX, USA, 24 January 2017.

limitation [2, 3]. The procedure is performed using the NeoChord DS1000 Artificial Chordae Delivery System (NeoChord, Inc., St. Louis Park, MN, USA) under direct 2D and 3D transoesophageal echocardiography (TOE) guidance [4]. Recently published clinical experience has confirmed early safety and efficacy of this procedure [2, 3].

Herein, we present the early and 1-year results of the first NeoChord multicentre, International Independent Registry (NIIR) study.

MATERIALS AND METHODS

All consecutive patients who underwent MVr with the NeoChord procedure were enrolled in this retrospective multicentre study between February 2013 and July 2016 in 7 hospitals in Europe (3 in Italy, 2 in Germany, 1 in Lithuania and 1 in Poland). No patient was excluded from the current study. All enrolled patients had indications for surgical MVr due to degenerative MR according to current guidelines [1]. An additional inclusion criterion was the presence of a consistent overlap of tissue to obtain a potential postoperative coaptation length of 3–5 mm. The evaluation of the potential coaptation was based on an eyeball judgement of the surgeon due to the lack of precise predefined echocardiographic measurements during the initial clinical experience. Exclusion criteria were the presence of active endocarditis and functional MR (Carpentier's Types I and III) or mixed disease.

Outcome definitions were based on the Mitral Valve Academic Research Consortium (MVARC) guidelines [5]. The primary endpoint was composed of (i) procedural success (defined as the placement of at least 2 neochordae and mild or less MR at the end of the procedure) and (ii) freedom from death, stroke, structural or functional failure of the MVr (MR more than moderate), unplanned interventions related to the procedure or device, cardiac-related rehospitalization or worsening New York Heart Association (NYHA) functional class at 1 year and at each follow-up time.

A secondary analysis was performed by comparing the primary end point among the anatomical groups (A, B and C) defined according to the conventional MV surgery as follows [1]. Patients were stratified according to the preoperative 3D TOE assessment of MV morphology: 'Type A', isolated central posterior leaflet prolapse/flail; 'Type B', posterior multisegment prolapse/flail and 'Type C', anterior, bileaflet or paracommissural disease with or without leaflet and annular calcifications.

Data monitoring was performed by 3 investigators (E.M., E.B. and L.B.). Clinical and echocardiographic follow-up was performed at discharge, 30 days, 6 months and 1 year after the NeoChord procedure. All patients completed postoperative echocardiographic assessment up to 1 year. Postoperative MR was assessed with transthoracic echocardiograms independently by each centre's investigators according to the following American Society of Echocardiography (ASE) modified criteria [6]. MR severity was graded as absent/trace, mild, moderate or severe based on a combination of semi-quantitative (vena contracta width: mild <3 mm, moderate = 3–6 mm, severe ≥7 mm; pulmonary vein flow: mild = systolic dominance, moderate = systolic blunting, severe = systolic flow reversal) and quantitative parameters (regurgitant volume: mild <30 ml, moderate = 31–59 ml, severe ≥60 ml as well as effective regurgitant orifice area: mild <0.2 cm^2, moderate ≥0.2 ≤0.4 cm^2, severe >0.4 cm^2).

Operative technique

The NeoChord repair is performed with the patient under general anaesthesia. Access to the left heart is achieved through a left lateral minithoracotomy in the 5th intercostal space. Two purse-string sutures are placed 2–4 cm posterolateral from the apex of the left ventricle to pass in between the papillary muscles. After ventriculotomy, the NeoChord DS1000 device (NeoChord, Inc.) is inserted in the left ventricle, and 2D and 3D-TOE imaging is used to guide the device to the prolapse/flail leaflet and implant the neochordae. When the proper number of neochordae needed to correct MR has been implanted, they are tensioned under direct TOE control. Finally, the tensioned neochordae are secured to the left ventricular (LV) epicardium using Teflon pledgets [7].

Statistical considerations

Baseline and demographic categorical variables were expressed as percentages, while quantitative variables were expressed as medians (first and third quartiles, interquartile range). Survival curves were obtained by means of the Kaplan–Meier analysis, and statistical differences among the anatomical groups (Type A, B and C) were determined by the log-rank Mantel–Cox test. A *P*-value <0.05 was considered to be significant. SPSS statistical software was used (IBM SPSS Statistics, version 24.0. Armonk, NY, USA).

RESULTS

Patient characteristics

In the NIIR, 213 patients were enrolled. The median age was 68 years (interquartile range 56–77), and the mean EuroSCORE-II was 1.8 ± 2.5%. Baseline characteristics are presented in Table 1.

Early outcomes

Procedural outcomes are summarized in Table 2. Procedural success was achieved in 206 (96.7%) patients. In 4 cases, an acute recurrence of severe MR was observed after the completion of the procedure due to leaflet rupture at the level of the implanted neochordae. These patients were converted to conventional MV surgery (2 repairs and 2 replacements). In the other 3 patients, neochordae implantation was not technically feasible. No intraoperative deaths occurred. Nine (4.2%) patients presented minor bleeding (1–2 blood units transfused), 3 (1.4%) patients presented major bleeding (≥3 blood units transfused), 5 (2.3%) patients presented extensive bleeding (≥4 blood units transfused), of whom only 3 (1.4%) patients required surgical revision. Four (1.9%) high-risk patients died within the first 30 postoperative days (Fig. 1). All deaths were considered procedure related because apical rupture, sudden cardiac death, acute respiratory failure and multiorgan failure are known complications of surgical interventions. Additional early complications are presented in Table 2.

At discharge, of the 206 alive and successfully treated patients, MR was absent/trace in 85 (41.3%) patients, mild in 93 (45.1%) patients, moderate in 25 (12.1%) patients and severe in 3 (1.5%)

Table 1: Patient demographics and preoperative echocardiographic data

	Median (I–III quartile), *n* (%) or mean ± SD
Age (years)	68 (56–77)
Male	153 (71.8)
EuroSCORE II (%)	1.8 ± 2.5
STS-PROM MV repair score (%)	1.5 ± 2.1
Arterial hypertension	126 (59.1)
Chronic obstructive pulmonary disease	20 (9.4)
Diabetes mellitus Type II	13 (6.1)
Associated ischaemic cardiomyopathy	32 (15)
Previous cardiac Surgery	11 (5.2)
Previous percutaneous coronary intervention	17 (8)
Previous stroke	1 (0.5)
Malignancy	23 (10.8)
Glomerular filtration rate (ml/min)	75.8 (55.3–98.5)
NYHA functional class	
I	14 (6.6)
II	92 (43.2)
III	101 (47.4)
IV	6 (2.8)
MR grade	
Absent/trace	
Mild	
Moderate	
Severe	213 (00)
Leaflet involvement	
Posterior mitral leaflet	193 (90.6)
Anterior mitral leaflet	11 (5.2)
Bileaflet	9 (4.2)
Leaflet prolapse	74 (34.7)
Leaflet flail	139 (65.3)
Anatomical MV type	
A	82 (38.5)
B	98 (46)
C	33 (15.5)
Left ventricular ejection fraction (%)	60 (55–66)
≤30	0 (0.0)
31–55	31 (14.5)
>55	182 (85.5)
Left ventricular end-diastolic volume (ml/m^2)	60 (66–92)
<70	41 (19.2)
70–100	156 (73.2)
>100	16 (7.6)
Systolic pulmonary artery hypertension (mmHg)	35 (28–45)
≤25	65 (30.5)
26–35	62 (29.1)
36–45	43 (20.2)
>45	43 (20.2)
Tricuspid regurgitation	
Absent	69 (32.4)
Mild	116 (54.5)
Moderate	28 (13.1)

MR: mitral regurgitation; MV: mitral valve; NYHA: New York Heart Association; SD: standard deviation; STS-PROM: Society of Thoracic Surgeons Predicted Risk of Mortality.

Table 2: Procedural and 30-day outcomes

	Median (I–III quartile) or *n* (%)
Neochordae in place (*n*)	4 (3–4)
0	1 (0.5)
2	8 (3.8)
3	73 (34.3)
4	79 (37.1)
5	34 (16)
6	12 (5.6)
7	3 (1.4)
8	2 (0.9)
9	1 (0.5)
Neochordae implantation attempts (*n*)	4 (3–5)
Operative time (min)	130 (120–155)
Conversion to conventional surgery	4 (1.9)
MV repair	2 (0.9)[a]
MV replacement	2 (0.9)
Procedural ECMO support	6 (2.8)
Procedural IABP support	1 (0.5)
Access site complications	4 (1.9)
Bleeding	17 (8)
Minor	9 (4.2)
Major	3 (1.4)
Extensive	5 (2.3)
Surgical revision for bleeding	3 (1.4)
Ventricular fibrillation	2 (0.9)
Mechanical ventilation time (h)[b]	3 (1–4)
0 (extubation in operative room)	45 (21.5)
≤3	78 (37.3)
4–6	66 (31.6)
>6	20 (9.6)
Hospital stay (days)[b]	8 (7–9)
Discharge[b]	
Home	101 (48.3)
Rehabilitation centre	105 (50.2)
In-hospital deaths	3 (1.6)
Procedural success	206 (96.7)
Transient ischaemic attack[b]	1 (0.5)
Stroke[b]	
Acute myocardial infarction[b]	2 (1)
Vascular complications[b]	1 (0.5)
Acute kidney injury[b]	14 (6.7)
Stage I (creatinine increase >150–199%)	9 (4.3)
Stage II (creatinine increase >200–299%)	3 (1.4)
Stage III (creatinine increase >300%)	2 (1)
Need for CVVH	2 (1)
Conduction disturbances[b]	17 (8.1)
Transient	17 (8.1)
Permanent	
Need for permanent PM implantation	
New-onset atrial fibrillation[b]	47 (22.5)
Paroxysmal	40 (19.2)
Persistent	7 (3.3)
Pericardial effusion[b]	8 (3.8)
Minor	7 (3.3)
Major	1 (0.5)
Pleural effusion[b]	86 (41.1)
Minor	84 (40.1)
Major	2 (1)
Wound dehiscence[b]	14 (6.7)
Sepsis[b]	3 (1.4)

[a]One patient died in hospital after conventional reintervention.
[b]Postoperative outcomes are calculated on a population of 209 patients (excluding 4 cases of intraoperative conversion to conventional surgery).
CVVH: continuous venovenous haemofiltration; ECMO: extracorporeal membrane oxygenation; IABP: intra-aortic balloon pump; MV: mitral valve; PM: pacemaker.

patients. One patient with severe MR underwent reintervention (MV replacement).

At 30 days, of the 205 patients who reached this follow-up time, MR was absent/trace in 84 (41%) patients, mild in 73 (35.6%) patients, moderate in 35 (17.1%) patients and severe in 13 (6.3%) patients (Fig. 2). Among patients with severe MR, 3 underwent conventional MV surgery (1 MVr, 2 MV replacement)

and 4 NeoChord reoperation (retensioning). Technical failure mechanisms are summarized in Table 3.

Six-month and 1-year outcomes

No additional deaths occurred out to 1 year. At 6-month follow-up, MR was absent/trace in 68 (34.3%) patients, mild in 85 (43%) patients, moderate in 31 (15.7%) patients and severe in 14 (7%) patients. Seven patients with severe MR underwent conventional MV reintervention (2 MVr, 5 MV replacement). At 1-year follow-up, MR was absent/trace in 60 (31.4%) patients, mild in 84 (44%) patients, moderate in 32 (16.7%) patients and severe in 15 (7.9%) patients (Fig. 2). Of the patients with severe MR, 5 underwent a conventional MV reoperation (1 MVr, 4 MV replacement). At 6-month and 1-year follow-up, the actuarial rate of patients meeting the composite primary end point was 88.3 ± 2.2% and 84 ± 2.5%, respectively (Fig. 3A).

Anatomical analysis

Patients were stratified into 3 groups based on preoperative MV anatomy in order to assess the impact of morphology on NeoChord repair outcomes. Eighty-two (38.5%) patients were classified as 'Type A', 98 (46%) as 'Type B' and 33 (15.5%) as 'Type C'. A significant difference was observed in the primary end point at 6 months among the anatomical groups: 'Type A', 95 ± 2.4%; 'Type B', 86.7 ± 3.4%; 'Type C', 76 ± 7.5% and at 1 year 'Type A', 94 ± 2.6%; 'Type B', 82.6 ± 3.8% and 'Type C' 63.6 ± 8.4% ($P < 0.001$) (Fig. 3B). MR severity over time according to the anatomical subgroup analysis is presented in Fig. 4. Consort flow diagram is presented in Fig. 5.

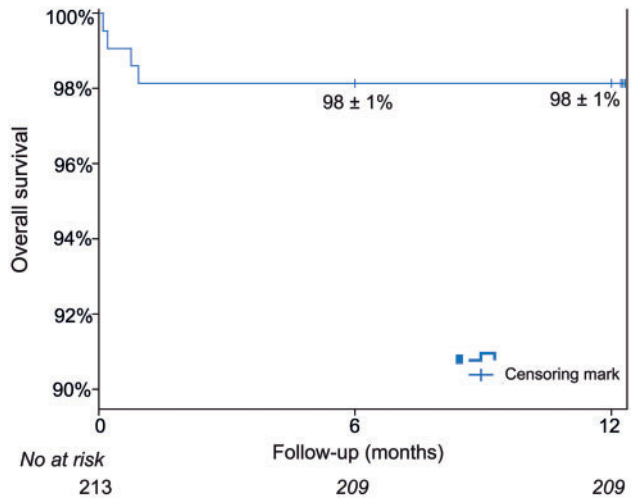

Figure 1: Overall survival.

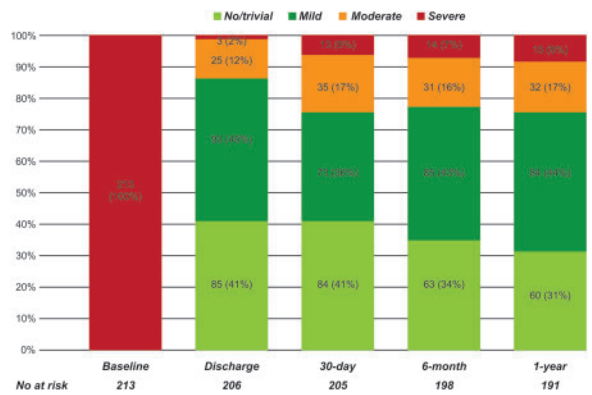

Figure 2: Overall degree of mitral regurgitation at baseline, discharge, 30-day, 6-month and 1-year follow-up.

DISCUSSION

This report describes the largest multicentre clinical experience with the NeoChord repair procedure after its initial evaluation with the Transapical Artificial Chordae Tendinae (TACT) trial to treat symptomatic degenerative MR [8]. Patients with all types of prolapse/flail of 1 or both MV leaflets were included; only pathophysiological and anatomical exclusion criteria were used.

Our results with the NeoChord repair procedure have several important implications. This study demonstrates the feasibility of a new, less invasive cardiac procedure, which employs a minithoracotomy approach without cardiopulmonary bypass, aortic cross-clamping or cardioplegic arrest. The procedure is technically mature and standardized. The successful placement of 2 or more neochordae was achieved in 96.7% of patients and resulted in a significant reduction of MR severity. Furthermore, in cases where a NeoChord repair was not successful, the patient was easily and safely converted to conventional on-pump surgery. No additional risk associated with surgical revision was introduced upon conversion due to the absence of pericardial adhesions or leaflet modifications.

An excellent safety profile for the NeoChord procedure was achieved. Overall survival at 1 year was 98%; only 4 high-risk patients died during the study period. The rate of procedural and 30-day complications was also low if we consider the novelty of the procedure and its learning curve phase. NeoChord repair outcomes demonstrate clinical benefits in the treated cohort. The primary end point for this study considered both procedural outcomes (e.g. reduction in MR) and improvement in clinical status (e.g. NHYA functional classification, number of cardiac-related rehospitalizations). At 1 year, the rate of achieving the primary end point was 84 ± 2.5%. The majority of the patients experienced both a reduction in MR severity and an improvement in the NYHA functional class.

Today, as suggested by Suri *et al.* [9], early referral allows the treatment of patients presenting leaflet disease without enlarged LV volumes. Early treatment, resulting in restoration of valve competence, removes the haemodynamic burden of volume overload, which leads to dilatation of the annulus and deterioration of LV function. Both quality of life and longevity are improved as a result [10, 11]. The NeoChord repair procedure provides a treatment option that does not require cardioplegic arrest and is less invasive than the conventional MVr. The present results demonstrate that the NeoChord procedure can be a viable alternative to conventional surgery for a subset of patients with MR in an early phase of the disease when it is limited to the leaflets and not extended to the annulus and/or LV.

Despite the positive results observed, however, we stress that it is necessary to refine the NeoChord procedure

Table 3: Mechanism of technical failure

Pt (type)	Reintervention	MR mechanism	Technical error
Pt 1 (Type A)	Intraoperative conversion (MVr)	Leaflet rupture at the level of the NeoChord implantation	Multiple attempts of neochordae implantation due to inadequate placement
Pt 2 (Type B)	Intraoperative conversion (MVR)	Leaflet rupture at the level of the NeoChord implantation	Multiple attempts of neochordae implantation due to inadequate placement
Pt 3 (Type C)	Intraoperative conversion (MVR)	Leaflet rupture at the level of the NeoChord implantation	Multiple attempts of neochordae implantation due to inadequate placement
Pt 4 (Type C)	Intraoperative conversion (MVr)[a]	Leaflet rupture at the level of the NeoChord implantation	Multiple attempts of neochordae implantation due to inadequate placement
Pt 5 (Type B)	MVR	AML native chordal rupture	Inappropriate MV crossing
Pt 6 (Type B)	No[a]	AML native chordal rupture	NeoChord implantation not technically feasible Compassionate procedure
Pt 7 (Type B)	No[a]	AML native chordal rupture	NeoChord implantation not technically feasible Compassionate procedure
Pt 8 (Type C)	No[a]	Heavy calcified valve Paracommissural disease	NeoChord implantation not technically feasible Compassionate procedure
Pt 9 (Type A)	Retensioning	Relative NeoChord elongation	Inappropriate NeoChord overtensioning to prevent acute LV reductive remodelling
Pt 10 (Type A)	Retensioning	Relative NeoChord elongation	Inappropriate NeoChord overtensioning to prevent acute LV reductive remodelling
Pt 11 (Type C)	Retensioning	Relative NeoChord elongation	Inappropriate NeoChord overtensioning to prevent acute LV reductive remodelling
Pt 12 (Type B)	Re-NeoChord	AML native chordal rupture	Inappropriate MV crossing
Pt 13[b] (Type A)	MVRe with Carillon	Annulus dilation	No concomitant annuloplasty
Pt 14 (Type B)	MVR	AML native chordal rupture	Inappropriate MV crossing Too anterior LV entry site
Pt 15 (Type C)	MVR	AML native chordal rupture	Inappropriate MV crossing Too anterior LV entry site

[a]Patient died in hospital.
[b]Today, this would have been a case of COMBO (combination of transcatheter therapies), but due to the fact that at that time, COMBO procedures were not considered, we have classified this case as a failure.
AML: anterior mitral leaflet; LV: left ventricular; MR: mitral regurgitation; MV: mitral valve; MVR: mitral valve replacement; MVr: mitral valve repair; Pt: patient.

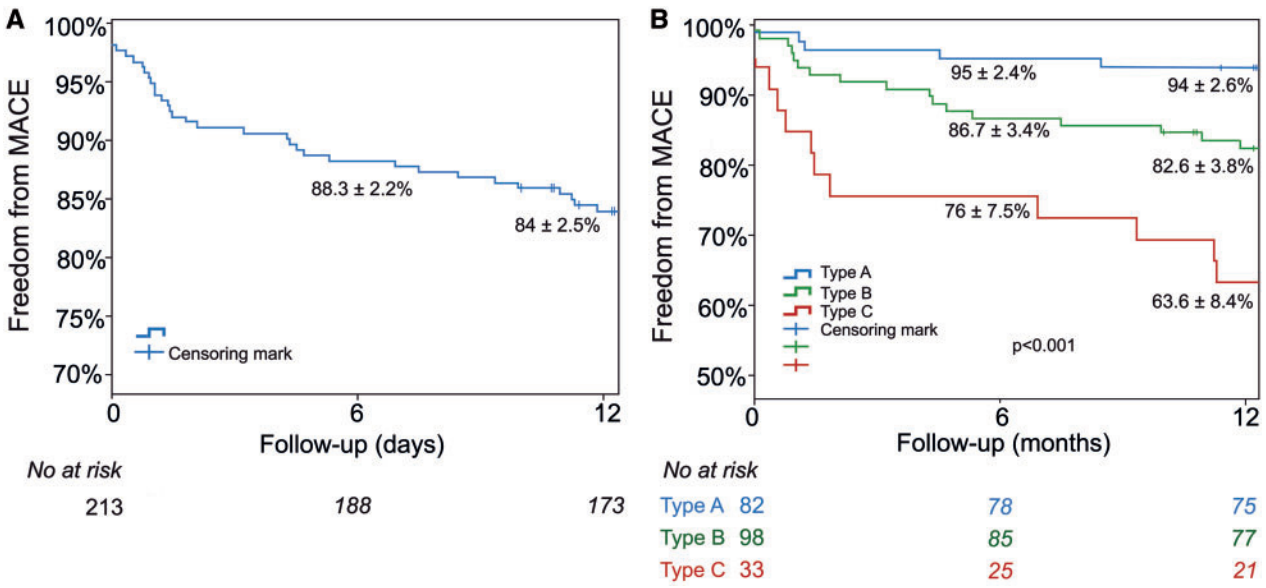

Figure 3: Freedom from composite end point (MACE) overall (**A**) and according to the morphological classification (**B**). 'Type A': isolated central posterior leaflet prolapse/flail; 'Type B': posterior multisegment prolapse/flail and 'Type C': anterior, bileaflet or paracommissural disease with/without leaflet and/or annular calcifications. MACE: major adverse composite endpoint.

selection criteria including more objective echocardiographic parameters that reflect the previously expressed concept of the disease limited to MV leaflets. In this regard, we recently presented the leaflet-to-annulus index, which identifies the quantity of over-riding leaflet that should represent the final coaptation length. It has been demonstrated that the leaflet-to-annulus index correlates with a residual MR ≤mild at 1-year follow-up when it was >1.25 [12].

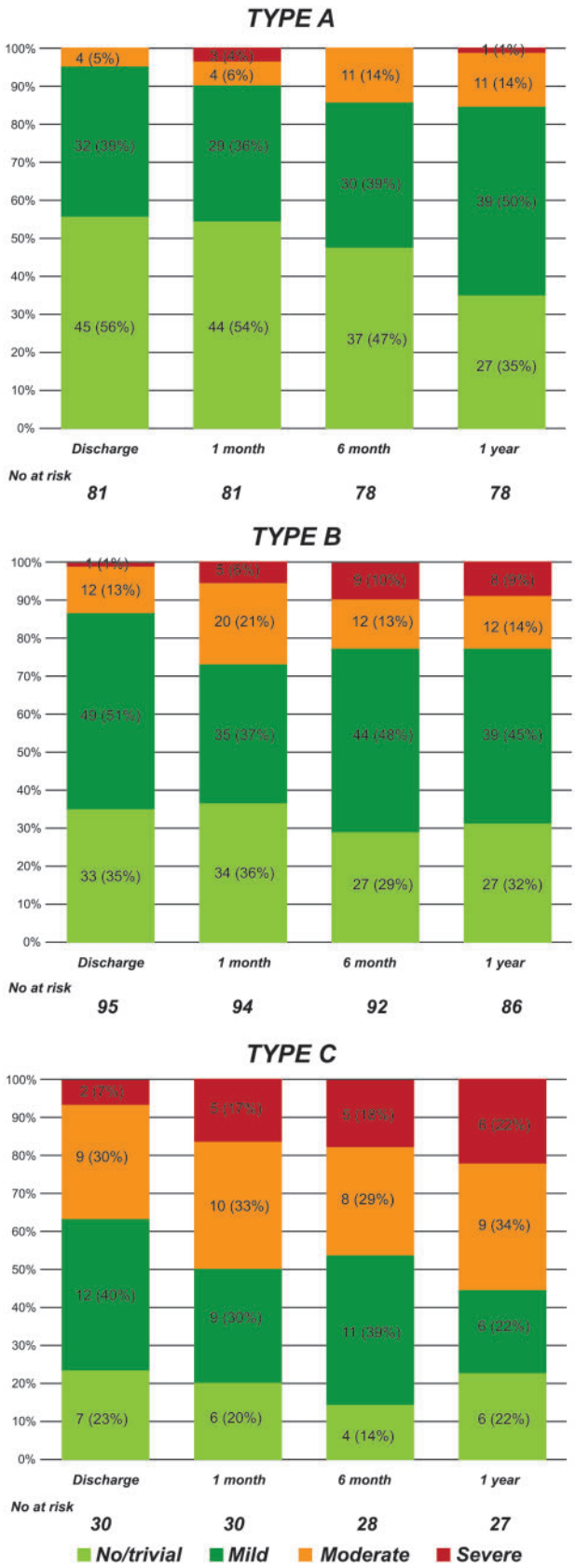

Figure 4: Degree of mitral regurgitation at baseline, discharge, 30-day, 6-month and 1-year follow-up according to the morphological classification. 'Type A': isolated central posterior leaflet prolapse/flail; 'Type B': posterior multisegment prolapse/flail; 'Type C': anterior, bileaflet or paracommissural disease with/without leaflet and/or annular calcifications.

The present study has also explored the impact of MV morphology on the stability of the surgical result at follow-up. The 'surgically derived' morphological classification identified 3 subsets of patients who presented a low, mild and moderate risk of procedural failure. This information is of paramount importance for the identification of anatomical selection criteria for procedure suitability. It is noteworthy that patients presenting isolated central posterior leaflet diseases and multisegment disease (Type A and B) experienced a similar outcome than traditionally observed in conventional MVr in real-world practice and slightly poorer results than centres of excellence [13]. Interestingly, we have recently observed a significant improvement in clinical results of patients presenting anterior leaflet flail/prolapse after having modified the surgical technique. We have extensively implanted neochordae on all the anterior leaflet segments, not only the diseased ones. The purpose of this modification is to create a 'new anterior subvalvular apparatus' able to adequately distribute the tension that each neochord should manage with respect to the anterior leaflet surface, which covers at least two-thirds of the MV annulus area [14].

We should point out that the present results are biased by the initial learning curve that each centre had to face with a new procedure. This learning curve entails acquisition of new technical skills for device manipulation, LV navigation, leaflet grasping and neochordae tensioning. It also requires a change in the surgeon's mindset in treating MV, moving from a direct and/or video-assisted MV visualization in open-heart surgery or a fluoroscopic-guided MV visualization in transcatheter procedures, to the new field of live 4D-TOE-guided NeoChord procedure.

Today, NeoChord, Inc. has developed and started to use a new *ex vivo* biosimulator and *in vitro* simulator which will be used to train surgeons before they start active clinical practice. The training tools provide the surgeon with the perfect balance between a safe and a fast acquisition of the above-mentioned 'new skills' needed to perform the NeoChord procedure. We think that these new tools will significantly improve clinical results and accelerate the worldwide adoption of this new therapeutic procedure with significant benefit for patients.

Limitations

Several limitations need to be acknowledged. Although this study represents the largest multicentre experience reported to date, the total number of procedures is still small. Additionally, the retrospective design of this study is a classical limitation together with the absence of a single core echo lab for imaging assessment. To diminish the potential impact of this bias, we have applied a stricter definition of the moderate MR group with respect to the ASE guidelines. It should be noted that after this study began, the morphological and echocardiographic patient selection criteria for suitability of the NeoChord repair procedure were refined [2, 9]. Therefore, some patients of Group C included in this registry would no longer be considered suitable for the procedure (e.g. paracommissural prolapse/flail, presence of annulus or leaflets calcifications). A larger number of patients and longer follow-up are needed to assess the definitive value of this therapeutic approach.

CONCLUSIONS

This study demonstrates the safety and clinical benefits of the NeoChord repair are sustained up to 1-year follow-up as measured

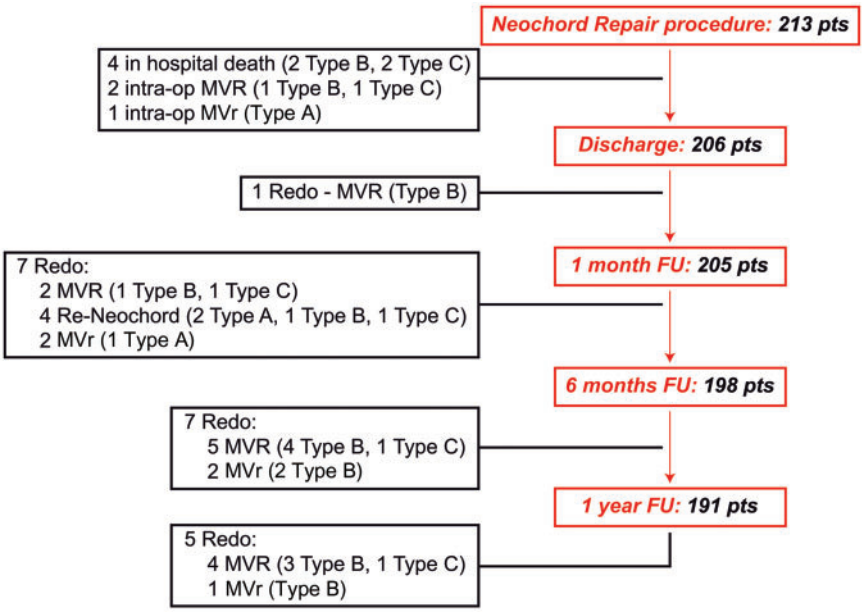

Figure 5: The CONSORT flow diagram. FU: follow-up; MVR: mitral valve replacement; MVr: mitral valve repair.

by the composite end point. Given the low complication rate and high surgical success rate, the NeoChord repair procedure should be considered a possible therapeutic option to treat patients presenting posterior leaflet prolapse/flail (Type A and B anatomies) and anterior leaflet disease if adequate MV tissue over-riding is present. In cases of paracommissural disease and/or calcifications of the annulus/leaflets, the NeoChord repair is not recommended. Future detailed echocardiographic studies with larger and longer series of patients—studies that are already ongoing—will lead to more precise identification of anatomical indications for isolated ringless NeoChord procedures and COMBO (combination) transcatheter MV repair procedures that will combine leaflet and annular therapies [15].

ACKNOWLEDGEMENTS

The authors thank Eta Beta Grafica, Reggio Emilia, Italy, for editing the figures.

Conflict of interest: Andrea Colli, Erica Manzan, Laura Besola, Eleonora Bizzotto and Gino Gerosa received travel grants from NeoChord, Inc. Andrea Colli, Demetrio Pittarello, Audrius Aidietis, Kristof Wrobel, Vilius Janusauskas, Agne Drasutiene, Mauro Rinaldi, Stefano Salizzoni were proctoring for NeoChord, Inc.

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