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Treatment of Heart Failure With Associated Functional Mitral Regurgitation Using the ARTO System

Initial Results of the First-in-Human MAVERIC Trial (Mitral Valve Repair Clinical Trial)

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ABSTRACT

OBJECTIVES MAVERIC (Mitral Valve Repair Clinical Trial) reports the safety and efficacy of the ARTO system in patients with symptomatic heart failure and functional mitral regurgitation (FMR).

BACKGROUND The ARTO system percutaneously modifies the mitral annulus to improve leaflet coaptation in FMR.

METHODS The MAVERIC trial is a prospective, nonrandomized first-in-human study. Key inclusion criteria were systolic heart failure New York Heart Association functional classes II to IV, FMR grade ≥2+, left ventricular (LV) ejection fraction ≤40%, LV end-diastolic diameter >50 mm and ≤75 mm. Exclusion criteria were clinical variables that precluded feasibility of the ARTO procedure. Primary outcomes were safety (30-day major adverse events) and efficacy (MR reduction, LV volumes, and functional status).

RESULTS Eleven patients received the ARTO system, and there were no procedural adverse events. From baseline to 30 days, there were meaningful improvements. Effective regurgitant orifice area decreased from 30.3 ± 11.1 mm^2 to 13.5 ± 7.1 mm^2 and regurgitant volumes from 45.4 ± 15.0 ml to 19.5 ± 10.2 ml. LV end-systolic volume index improved from 77.5 ± 24.3 ml/m^2 to 68.5 ± 21.4 ml/m^2, and LV end-diastolic volume index 118.7 ± 28.6 ml/m^2 to 103.9 ± 21.2 ml/m^2. Mitral annular anteroposterior diameter decreased from 45.0 ± 3.3 mm to 38.7 ± 3.0 mm. Functional status was 81.8% New York Heart Association functional class III/IV improving to 54.6% functional class I/II. At 30 days, there were 2 adverse events: 1 pericardial effusion requiring surgical drainage; and 1 asymptomatic device dislodgement.

CONCLUSIONS The ARTO system is a novel transcatheter device that can be used safely with meaningful efficacy in the treatment of FMR. (Mitral Valve Repair Clinical Trial [MAVERIC]; NCT02302872) (J Am Coll Cardiol Intv 2015;8:1095–104)

Percutaneous treatment of functional mitral regurgitation (FMR) is an important therapeutic target and remains an unmet clinical need in the field of adult structural heart disease. Mitral regurgitation (MR) can arise from abnormalities of the valve itself (primary MR), but more commonly, it is a consequence of underlying ischemic or nonischemic left ventricular (LV) dysfunction, which

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ABBREVIATIONS AND ACRONYMS

AP = anteroposterior

CS = coronary sinus

CT = computed tomography

EROA = effective regurgitant orifice area

FMR = functional mitral regurgitation

GCV = great cardiac vein

LA = left atrium

LV = left ventricle

MR = mitral regurgitation

TEE = transesophageal echocardiographic

results in restricted leaflet motion and inadequate leaflet coaptation (functional or secondary MR). Moderate-to-severe MR is present in up to 74% of inpatients and 45% of outpatients with systolic heart failure, and the presence of FMR is associated with a higher mortality rate than for patients without FMR (1). Despite the use of guideline-directed medical therapy for systolic heart failure, quality of life and survival remain poor in patients with concomitant FMR (2). Small randomized clinical trials of patients with ischemic MR undergoing coronary artery bypass surgery with and without MR correction have shown improved LV remodelling and functional capacity in the MR correction group (3,4). However, many patients with moderate-to-severe FMR have significant comorbidities and are not routinely offered surgery in clinical practice (5).

Percutaneous therapies have the potential to allow treatment of FMR in patients who are not currently offered surgery. Although other transcatheter technologies currently exist, there remain concerns with technical complexity, safety, and efficacy. The ARTO (MVRx Inc., Belmont, California) system is a catheter-based system designed to treat FMR. The mechanism of the device consists of a suture that connects interatrial-septal and coronary sinus anchors. This suture is tensioned in order to shorten the anteroposterior (AP) diameter of the mitral annulus, thereby improving mitral leaflet coaptation and reducing FMR. We previously reported that this system was effective in ameliorating FMR in an ovine tachycardia model, and we subsequently performed successful temporary transcatheter implantation in 2 patients before planned mitral valve surgery (6,7). In this paper, we report the first-in-human 30-day primary outcome measures of safety and efficacy for 11 patients treated with the latest generation of the ARTO device.

METHODS

Patients were enrolled at a single institution (Pauls Stradins Clinical University Hospital, Riga, Latvia) between October 2013 and May 2014. A local heart team consisting of a cardiologist, cardiac surgeon, and heart failure specialist evaluated all patients, and they were deemed to be at high surgical risk due to underlying comorbidities and would not be offered surgery as part of routine clinical care. All patients provided informed consent and the MAVERIC (Mitral Valve Repair Clinical Trial) protocol was approved by the institutional ethics committee.

Key inclusion criteria for the trial included the following: age 21 to 85 years, inclusive; New York Heart Association functional classes II to IV systolic heart failure of any etiology; FMR grade ≥2+; LV ejection fraction ≤40%; LV end-diastolic diameter >50 mm and ≤75 mm; and transseptal puncture feasibility. Key exclusion criteria consisted of the following: femoral or internal jugular vein unable to accommodate a 16-F introducer sheath; structural abnormality of the mitral valve (e.g., flail, prolapse, or leaflet calcification); significant mitral annular calcification; hemodynamic instability (systolic pressure <90 mm Hg without afterload reduction, cardiogenic shock, need for inotropic support or intra-aortic balloon pump); previous mitral valve surgery or valvuloplasty or any currently implanted prosthetic valve or ventricular assist device; history of rheumatic heart disease; any atrial septal defect or patent foramen ovale associated with clinical symptoms; any atrial septal aneurysm; serum creatinine >2.5 mg/dl or dialysis dependence; platelet count $<100 \times 10^3$ cells/mm^3; any active infection, endocarditis, or intracardiac thrombus; percutaneous coronary intervention or surgery anticipated within the 6-month follow-up period following the investigational procedure; life expectancy <1 year.

The primary safety outcome was the major adverse event rate at 30 days post-procedure. Major adverse events were defined as stroke, myocardial infarction, death, any device-related surgery, and any events (even if unforeseen in the study planning) that the events committee might consider major. The primary efficacy outcome was FMR grade and change from baseline to 30 days evaluated by 2-dimensional transthoracic echocardiogram. Other evaluations obtained included functional status, left ventricular volume and function indices, and procedural details. Follow-up to 3 years post-procedure is planned. Successful device placement was defined as successful delivery of the device including retrieval of all catheters and no procedural device-related major adverse events. Procedure time was defined as the time from first guidewire introduction to last catheter removal.

All echocardiographic and clinical data were monitored and analyzed by an independent core laboratory (Cardiovascular European Research Centre, Massy, France). Echocardiographic grading of MR severity at baseline and follow-up was performed in accordance with current American Society of Echocardiographic guidelines, and MR was graded on a traditional 0 to 4+ scale (8). Because FMR differs