Heart failure (HF) is a major cause of mortality and morbidity in developed countries. In the past 2 decades, improvements in drug therapy and the widespread use of implantable cardioverter-defibrillators and cardiac resynchronization therapy devices has improved the prognosis of HF patients. However, morbidity and mortality rates remain high, with an estimated 5-year mortality rate exceeding 50% coupled with significant rehospitalization rates. Several transcatheter implantable devices have recently emerged in an attempt to improve the prognosis and quality of life of such patients.

We reviewed the current literature on interventional chronic HF. The review focus on the description of the devices and main procedural characteristics, patient eligibility, procedural results, and clinical outcomes associated with such devices. This article will focus only on mechanical transcatheter structural heart interventions for treating chronic HF. Devices used for percutaneously delivering biological therapies and interventions for acute HF fall beyond the scope of this article.

Left Ventricular Restoration Devices

Several surgical and device-based therapies have emerged in an attempt to reverse LV remodeling by restoring normal LV architecture and reducing LV volumes and wall stress. Among these surgical therapies, the most commonly used is the endoventricular circular patch plasty or Dor procedure, which consists of excluding the akinetic septal and apical ventricular regions by performing aneurysm resection with the insertion of a circular pericardial patch. Although this procedure showed promising results in multicenter registries, the only randomized trial—Surgical Treatment for Ischemic Heart Failure (STICH)—failed to demonstrate differences in the composite end point of death and rehospitalization for cardiac causes between surgical ventricular restoration + coronary artery bypass graft versus coronary artery bypass graft alone. However, some subgroups, experienced significant benefits with surgical ventricular restoration.

In this regard, the parachute device (Cardiokinetix, Inc, Menlo Park, CA) emerged as a percutaneous device with the purpose of excluding the dysfunctional area of the LV, leading to a geometric reconfiguration and corresponding reductions in LV volumes. It consists of a ventricular partitioning device composed of a self-expanding nitinol frame, an expanded polytetrafluoroethylene occlusive membrane, and a distal atraumatic (pebax polymer) foot (Figure 1). The nitinol frame is shaped like an umbrella with 16 struts. The tip of each strut ends in a 2-mm anchor. The device is available in expanded nominal diameters of 65, 75, 85, and 95 mm.

The device is self-expandable and is deployed by retracting the delivery catheter. Full expansion of the parachute device is facilitated by inflating a low-pressure contrast-filled 6-mL balloon with a nominal diameter of 24 mm until the anchors are fully expanded and in contact with the LV wall (Figure 1). The procedure is performed under local anesthesia and is guided angiographically and via transthoracic echocardiography.

Patients selected for device implantation had a history of anterior myocardial infarction, resulting in ante-ro-apical akinesia or dyskinesia, left ventricular ejection fraction (LVEF) <40%, and chronic HF (New York Heart Association [NYHA] class II–IV), despite optimal medical therapy. Although transthoracic echocardiography remains the initial imaging tool, the importance of multimodality image techniques, including cardiac computed tomography has become relevant for patient selection.

The first-in-man experience with the parachute device included 39 patients. The primary end point was successful device delivery and deployment without the occurrence of device-related major adverse cardiovascular events at 6 months, and this was observed in 74% of the patients. There were no cases of ventricular perforation or stroke. At 12-month follow-up, patients improved their NYHA class (from 2.5±0.6 at baseline to 1.3±0.6 at 12 months P<0.001) and there was a significant reduction in left ventricular end-systolic and left ventricular end-diastolic volumes (from 93.6±4.1 mL to 79.5±3.6 mL and from 127.2±4.2 mL to 110.4±4.6 mL, all P<0.001). However, changes in 6-minute walk test (6MWT) were not statistically significant (from 359±20 m to 375±26 m, P=0.19). Costa et al recently reported the 3-year follow-up of this initial cohort of patients. NYHA class improved in 52% of patients, did not change in 33%, and worsened in 15%. The combined 3-year incidence of death or HF hospitalization was 38.7%. Improvements in LV volume indices were sustained through the 3-year follow-up.

After this initial experience, cardiac computed tomography exams were added to the preprocedural workup to improve patient selection. The Parachute III postmarket European study, including 100 patients, showed a procedural success...
rate of 97% (Abraham W. HFSA meeting 2014). Procedural or device-related events at 1-year follow-up (primary safety end point) occurred in 7% of the patients, and all of these were related to vascular access complications (partially related to the use of 14 or 16F delivery catheters). At 1-year follow-up, 65% of the patients were classified as NYHA I or II, echocardiography data showed significant reductions in left ventricular end-diastolic and left ventricular end-systolic volumes (P<0.0001), and there was a significant increase in exercise capacity as evaluated by 6MWT (P<0.01; Figure 2). Menon et al.10 performed a substudy focusing on the volumetric and regional function changes associated with the parachute device using computed tomography. The computed tomography was performed at baseline and at 6-month follow-up. This study showed that although the device did not achieve the complete isolation of the apical segment of the LV, it was effective in both, excluding the dyskinetic myocardium and reducing the volume of the dynamic compartment at follow-up.

Of note, a pathological study of 7 explanted devices (autopsy or heart transplantation) showed fractures of the foot and nitinol struts in those devices implanted >300 days before.11 Although no adverse events were associated with the device fracture, these findings led to modifications of the composite material to improve durability.

In summary, available data supports the feasibility and safety of the parachute device as a novel concept of minimally invasive ventricular restoration therapy. Definitive device efficacy will be determined by the ongoing Parachute IV trial12 (clinicaltrials.gov#NCT01614652). This trial will randomly (1:1) assign 478 patients with NYHA class III-IV ischemic HF, including a total of 21 sheeps (14 received the device, 7 controls). The device implantation was associated with a persistent decrease in LA pressure, improved LVEF, and lower mortality, with no changes in right atrial or pulmonary artery pressure. Patent left-to-right shunt was documented in all devices over the entire duration of the study (12 weeks).17

The first patient was treated in October 2013, and data from the first 6 patients treated with this device have been recently reported.18 All patients had chronic systolic HF (LVEF <40%), were in NYHA class ≥II despite optimal medical treatment, and had a pulmonary capillary wedge pressure ≥15 mmHg. The V-Wave device was successfully implanted in all patients with no complications. At hospital discharge, patients were treated with aspirin and oral anticoagulation (for a period of 3 months in those patients with no other indications for anticoagulant therapy). No device-related adverse events occurred. One patient experienced gastrointestinal bleeding related to warfarin at 2 months postprocedure, and another patient with LVEF of 15% and a history of ventricular arrhythmias had several episodes of symptomatic ventricular tachycardia requiring hospitalization and ablation therapy 5 weeks postprocedure. This patient continued to deteriorate in the ensuing weeks after hospitalization and finally died of terminal HF.

At 1-month follow-up, transesophageal echocardiography showed patent left-to-right atrial shunt in all patients. No thrombus or device migrations were documented. At 3-month follow-up, there were significant improvements in PWCP, quality of life, and 6MWT (P<0.05 for all; Table 1). There were no significant changes between baseline and 3 months in LVEF, telediastolic LV diameter, left atrial volume, prohormone of brain natriuretic peptide values, mitral regurgitation (MR) grade, or right arterial pressure (Table 1).

Data from the first patient with HF and preserved LVEF treated with the V-Wave device were recently presented (Rodés-Cabau J, TCT 2014). The procedure was performed successfully with no complications, and the patient had significant improvements in NYHA class, quality of life, 6MWT distance, and prohormone of brain natriuretic peptide values at 3-month follow-up.

Therefore, data from these 2 first-in-man experiences showed that the creation of a left-to-right shunt with the implantation of the interatrial septal device or v-wave systems is safe, feasible, and seems to be associated with good
short-term clinical and hemodynamic outcomes. Larger trials are required to confirm these early findings.

**Renal Denervation**

Catheter-based radiofrequency renal artery denervation has been developed as a new potential treatment for resistant hypertension.19 However, the only blinded, sham-controlled, appropriately powered study of renal denervation conducted to date, the SYMPLECTICITY HTN-3 study, failed to show differences in the primary and secondary efficacy end points (change in office systolic blood pressure at 6 months and change in ambulatory blood pressure at 6 months, respectively).20 Despite these controversial results, renal denervation’s effects are not limited to pressure-lowering applications. Thus, renal denervation is thought to be useful in HF patients with low and preserved LVEF because of its inhibitory effects on the renin–angiotensin system.

In a randomized study including 64 patients (46 treated with bilateral renal denervation and 18 controls, all of them with resistant hypertension), renal denervation with the Symplicity or Flex ablation catheters (Ardian [now Medtronic], Palo Alto, CA) significantly reduced interventricular septal thickness and LV mass index. LV filling pressures and LVEF significantly improved in the treatment group.22 Schirmer et al23 showed that in patients undergoing renal denervation, the improvement in LV structure and function may be independent of changes in blood pressure and heart rate. This study enrolled 66 patients with resistant hypertension. LV hypertrophy and diastolic function improved 6 months after renal denervation, without significant relation to blood pressure or heart rate reductions. In a first-in-man experience, including 7 nonhypertensive patients with chronic systolic HF (Renal Artery Denervation in Chronic HeartFailure [REACH] Pilot study), renal denervation was performed without complication, and it was associated with significant improvements in symptoms and distance walked at the 6MWT (P=0.03) and reduction in loop diuretic doses (P=0.046) at 6-month follow-up. Interestingly, no significant changes in blood pressure, heart rate of renal function were observed (Figure 4).24 Preliminary data suggest a potential benefit of renal denervation for treating patients with chronic HF, irrespective of the presence of hypertension. After this initial experience, several trials using renal denervation in HF are currently ongoing.25 The Renal Sympathetic Denervation for patients with Chronic Heart Failure (RSD4CHF) trial (clinicaltrials.gov#NCT01790906) is expected to include 200 symptomatic patients (100 treated with renal denervation and 100 controls) with NYHA II-IV and severe systolic dysfunction (LVEF≤35%). The primary end point will be all-cause mortality and cardiovascular events at 24-month follow-up.

**Implantable Hemodynamic Monitoring**

Several strategies for measuring intrathoracic impedance26 or RV pressure have been proposed to reduce HF readmissions by detecting early evidence of HF decompensation. However, no randomized clinical trials have shown a reduction in HF hospitalizations with these approaches.27,28 In an attempt to more accurately assess the hemodynamic status of HF patients, several implantable hemodynamic monitoring devices have been developed.
Pulmonary Artery Pressure Monitors

The pulmonary artery pressure monitoring system (CardioMEMS, St Jude Medical, Minnesota, MN) consists of an implantable HF sensor, a delivery catheter, an electronic monitoring unit with a barometer, and a database in a secure website (Figure 5). The sensor is a coil and a pressure-sensitive capacitor encased in a hermetically sealed silica capsule covered by silicone, which is implanted in the distal pulmonary artery. It is powered by an external antenna containing no batteries or internal power source. A wired loop made from PTFE-coated nitinol wire is attached to each end to prevent sensor distal embolization. Pressure changes from inside the pulmonary artery are transmitted wirelessly by using an external antenna. This external electronic unit is held against the patient’s side or back in the area of the sensor, allowing device calibration and daily waveform recording. The data are finally transmitted by telephone line to a website.

After first-in-man and feasibility studies,31 the prospective randomized CardioMEMS Heart Sensor Allows Monitoring of Pressure to Improve Outcomes in NYHA Class III Heart Failure Patients (CHAMPION) trial evaluated the efficacy of this device in 550 patients with chronic HF. All patients received the CardioMEMS HF sensor and were randomized before discharge to receive HF management guided by hemodynamic information from the sensor (treatment group n=270) or traditional HF standard of care (control group n=280). Antithrombotic treatment consisted of anticoagulation therapy in the presence of AF or dual antiplatelet therapy in the absence of AF.

Sensor implantation was attempted in 575 patients and achieved in 550 (95.7%). Fifteen serious adverse events were registered, 8 device-related or system-related complications (1%), and 7 procedure-related adverse events. No pressure-sensor failures were registered.

The primary efficacy end point of HF-related hospitalizations within 6 months follow up occurred in 84 patients in the treatment group and in 120 in the control group (hazard ratio =0.72, 95% confidence interval [CI] 0.60–0.85, P=0.0002). During a mean follow up of 15 months, a 37% relative risk reduction in HF-related hospitalization was observed in the treatment group (158 versus 254, hazard ratio =0.63, 95% CI 0.52–0.77; P<0.0001). No differences were found regarding survival rates (94% versus 93%, hazard ratio =0.77, 95% CI 0.40–1.51; P=0.45; Figure 5).

The results of a prespecified subgroup analysis of CHAMPION focusing on patients with preserved LVEF (n=119, mean LVEF=51%) also showed a significant reduction in HF hospitalizations at 6-month follow up, representing a 46% reduction compared with the control group (incidence rate ratio 0.54, 95% CI 0.38–0.70; P<0.0001).

Based on results of CHAMPION study, the FDA recently approved the CardioMEMS HF System for patients in NYHA Class III who have been hospitalized for HF in the previous year.

Left Atrial Pressure Monitoring

The permanent implantable left atrial pressure monitoring system (HeartPOD, Savacor, Inc, a subsidiary of St Jude Medical, Inc, Minneapolis, MN) consists of an implantable sensor lead coupled with a subcutaneous antenna coil, a patient advisory module, and the clinician’s personal computer software (Figure 6). The sensor module is located at the distal of the lead implanted into the atrial septum oriented to the LA by a transeptal puncture technique using femoral or axillary/subclavian venous access. It comprises a 3x7 mm hermetically sealed sensor module with a titanium pressure sensing membrane and circuitry for measuring and sending data on LA pressure, temperature, and intracardiac electrograms. LA pressure is calculated by subtracting the absolute pressure obtained by the implant from an atmospheric reference measured by a pressure sensor located in the patient advisory module. The implant is powered and interrogated through the skin by 125-kHz radiofrequency wireless transmissions from the patient advisory module. The patient advisory module is able to store ≥3 months of data if 6 waveforms are acquired each day.

After first-in-man experience with 8 patients,33 the Hemodynamically Guided Home Self-Therapy in Severe
Heart Failure Patients (HOMEOSTASIS I) trial included 40 patients with chronic HF. Study device was successfully implanted in all patients, and no major adverse events were recorded at 6 weeks (primary safety end point). Two late ischemic strokes were registered. Mean daily left atrial pressure was lower during LA pressure-guided (15 mm Hg) versus nonguided (18 mm Hg) therapy ($P=0.003$). The incidence of death or acute decompensated HF at 3-month follow-up was less frequent during LA pressure guidance (hazard ratio =0.16 [95% CI, 0.04–0.68], $P=0.012$). Significant improvement in

| Table 1. Atrial Shunt Devices: Baseline and Short-Term Clinical and Hemodynamic Data |
|-----------------------------------|-----------------|-----------------|-----------------|-----------------|
|                                  | IASD Device (n=11) | V-WAVE Device (n=6) |
|                                  | Baseline | 30d. FU | P Value | Baseline | 90d. FU | P Value |
| NYHA III-IV, % patients          | 100%     | 45%     | N/A     | 100%     | 0%      | N/A     |
| LVEF, %                          | 57±9*    | N/A     | N/A     | 32 [20–35]| 33 [20–35]| NS |
| QoL: MLWHF                       | 56 [17–78] | 30 [9–68] | 0.005 | N/A | N/A | N/A |
| QoL: KCCQ                        | N/A      | N/A     | N/A     | 40 [39–41] | 70 [47–75] | 0.009 |
| mPCWP, mm Hg                     | 19 [6–25] | 13 [9–18] | 0.005 | 20 [18–22] | 14 [11–14] | 0.018 |
| CI, L/(min/m²)                   | 2.3 [1.6–3.3]| N/A | N/A | 2.2 [2.2–2.4]| 2.5 [2.4–2.6]| NS |
| $Q_p/Q_s$                        | N/A      | N/A     | N/A     | 1.0 [0.9–1.0] | 1.1 [1.1–1.2] | 0.04 |

Values are presented as median [range] or mean±SD. 6MWT indicates 6-minute walk test; CI, cardiac index; FU, follow-up; IASD, interatrial septal device; KCCQ, Kansas City Cardiomyopathy Questionnaire; LVEF, left ventricular ejection fraction; MLWHF, Minnesota living with heart failure; mPAP, mean pulmonary artery pressure; mPCWP, mean pulmonary capillary wedge pressure; N/A, not available; NS, not significant; NT-proBNP, N-terminal prohormone of brain natriuretic peptide; NYHA, New York Heart Association functional class; and QoL, quality of life.
NYHA class (Δ −0.7±0.8, \(P=0.001\)) and LVEF (Δ7%±10%, \(P=0.001\)) were also observed.

After these positive preliminary data, a prospective randomized trial (LAPTOP-HF) including 730 patients with chronic HF and NYHA class III was designed to demonstrate a reduction in HF decompensation and hospitalizations with invasive LA pressure guidance. However, this trial was prematurely terminated because of a higher incidence of serious adverse events in the implant group, most of them linked to peri-procedural complications.34

Percutaneous Interventions in Functional Mitral Regurgitation

Functional MR is a common comorbidity in HF, affecting >50% of patients with LVEF<40%, and it is associated with high mortality and poor clinical outcomes.35

Mitral valve surgical interventions have been associated with excellent outcomes for treating patients with degenerative MR,36 but long-term benefits of surgical treatment of functional MR remain unclear.7 In addition, the surgical treatment of functional MR has been associated with increased perioperative morbidity and mortality, and this may have negatively influenced patient referral. Therefore, the development of new percutaneous and less invasive techniques for treating functional MR may represent an important therapeutic advance in the HF field.

Figure 4. The REACH-Pilot study (n=7).24 Changes from baseline to 6 months after renal denervation in systemic (systolic and diastolic) pressures (A), 6-minute walk test (B), and loop diuretic doses (C and D).

Percutaneous Edge-to-Edge Repair: The MitraClip System

The MitraClip (Abbott, Menlo Park, CA) device is a 4-mm-wide cobalt chromium and covered-polyester implant with 2 arms that are opened and closed by control mechanisms on the clip delivery system (Figure 7). The 2 arms have an open span of ≈2 cm in the grasping position. There is a U-shaped gripper in the inner portion of the clip that matches up to each arm and helps to stabilize the leaflets from the atrial aspect as they are captured during closure of the clip arms. Leaflet tissue is secured between the closed arms and each side of the gripper and the clip is then closed and locked to achieve and maintain leaflet coaptation. The clip is positioned using a clip delivery system, which is passed through a 24F guide catheter previously placed in the left atrium using a standard transeptal approach. The procedure is performed under general anesthesia and is guided by fluoroscopic and transeosophageal echocardiography imaging. Adequate MR reduction is considered as a grade 2+ or less, measured by echocardiography (Figure 7). If this MR degree is not achieved with one device, the clip may be repositioned, removed, or a second device could be implanted. After the procedure, patients are treated with aspirin 325 mg daily for 6 months and clopidogrel 75 mg daily for 30 days.39

To date, >20000 patients have been treated with the MitraClip system worldwide. The FDA has recently approved
the device for the treatment of degenerative MR, but increasing experience exists on the treatment of functional MR in patients with chronic HF.

Treatement of Functional MR With the MitraClip System: Observational Studies

Several observational studies have focused on the evaluation of the use of the MitraClip device for the treatment of functional MR, and their main results are summarized in Table 2. Overall, a total of 553 patients have been included in these studies. Hospital/30-day mortality was 3.6%, and a successful result (MR ≤ 2+) at discharge) was obtained in 89% of the patients (from 80% to 96%). After a follow-up ranging from 7 to 14 months, all cause mortality rate was 19%, (ranging from 13% to 22%), most (80%) patients were in functional class I or II, and MR remained <2+ in 85% of the patients at risk.

Treatement of Functional MR With the MitraClip System: The EVEREST II Randomized Trial

The Endovascular Valve Edge-to-Edge repair Study (EVEREST) II trial is the only randomized trial to date comparing the use of the MitraClip system with surgical mitral repair. Details of the design and results of the study have been provided elsewhere. Briefly, a total of 279 patients with 3+ or 4+ MR were randomly assigned in a 2:1 ratio to percutaneous mitral valve repair (184 patients) or mitral valve surgery (95 patients).

At 12-mo follow-up, the rates of the primary efficacy end point (freedom from death, repeat surgery, or mitral regurgitation 3+ or 4+) were 55% in the percutaneous group and 73% in the surgery group (P=0.007), mainly because of a higher rate of surgery for mitral dysfunction in the percutaneous group (20% versus 2.2% in the surgery group). Major adverse events at 30 days occurred in 15% of patients in the percutaneous-repair group and 48% of patients in the surgery group (P<0.001). In both groups, improvements in left ventricular size, NYHA class, and quality of life measures were documented.

In EVEREST II, patients with functional MR comprised 27% of the study population. Compared with those with degenerative MR, patients with functional MR were at higher risk and had a higher prevalence of coronary artery disease, atrial fibrillation, and cerebrovascular disease. In a nonpre-specified subgroup analysis, a significant interaction was found between patients with functional MR compared with those with degenerative MR. Although 1-year mortality rates were higher in
patients with functional MR (7.9% versus 1% in degenerative MR), compared with surgery, percutaneous repair was more beneficial in the functional MR patients than in patients with degenerative MR. Thus, among patients with functional MR, the primary efficacy end point at 1-year follow-up occurred in 54% of patients in the percutaneous group versus 50% of patients in the surgery group, compared with 56% and 82%, respectively, in the degenerative MR group (P value for interaction =0.02) (Figure 8). At 4-year follow-up, the statistical interaction regarding pathogenesis remained significant.46

Data at 5-year follow-up according to MR pathogenesis were recently presented (Dr Saibal Kar, EuroPCR 2014) and are summarized in Table 3.

**Treatment of Functional MR With the MitraClip System: Future Randomized Studies**

Three randomized trials are currently comparing the use of the MitraClip system versus medical treatment in patients with functional MR. A summary of the sample size, main inclusion criteria, and primary end points of these trials is shown in Table 4.

In summary, several studies have shown the safety, feasibility, and preliminary efficacy of the MitraClip system for treating patients with HF and significant functional MR. Three ongoing randomized trials will provide definitive data on the efficacy of this treatment strategy for reducing rehospitalisation and mortality rates compared with medical treatment. Demonstrating a positive effect of percutaneous mitral repair in such patients would represent a major paradigm shift in the treatment of HF.

**Percutaneous Annuloplasty**

Several percutaneous devices have been designed in the last years aimed at being an alternative to surgical annuloplasty in high-risk patients.

**Indirect Annuloplasty**

The rationale of this approach is to reduce the mitral annular perimeter by placing a device that increases tension in the coronary sinus. Although coronary sinus cannulation is feasible, safe, and routinely used in other invasive cardiology procedures, several percutaneous annuloplasty systems have failed mainly because of safety issues. The Viacor PTMA device (Viacor, Wilmington) is no longer available because of device-related adverse events, including late fatal coronary sinus laceration,47 and the MONARC system (Edwards Lifesciences, Irvine, CA) was also suspended because of high rate of device-related adverse events.48

The Carillon Mitral Contour System (Cardiac Dimension, Inc, Kirkland, WA) received CE mark approval in 2011 and is the only device currently using the coronary sinus approach for the treatment of MR. The Carillon device is a fixed-length double anchor implant with mirror-image hoop-shaped helical anchors that is implanted via internal jugular vein access (Figure 9).

Following results of the CARRILLON Mitral Annuloplasty Device European Union Study (AMADEUS) trial,50 a second generation of the Carillon device was tested in the Transcatheter Implantation of Carillon Mitral Annuloplasty Device (TITAN) study.51 This trial included 53 patients, 36 patients underwent permanent implant of the device, and 17 patients in whom the device had to be recaptured for clinical reasons and served as a comparison group. At 12-month follow-up, patients who received the Carillon system showed significant reduction in regurgitant jet area/left atrium area, regurgitant volumes, effective orifice area, and vena contracta at 6 months (all P<0.05). Although no device-related adverse events were reported in TITAN, the device could not be successfully implanted in 32% of the patients because of aforementioned reasons. Results from the TITAN II study were recently presented (Dr Horst Sievert, PCR London Valve 2014). The study included 43 patients and showed similar benefits to TITAN, but with a much higher rate of successful device implantation (83%). Despite these encouraging results, some issues concerning the system were observed. Of note, in both AMADEUS and TITAN, wire fractures were detected in several patients at follow-up.51 In spite of these fractures, there...
were no related clinical manifestations or adverse events. A new generation device was recently developed after technical improvements, which should further prevent wire fractures. The redesigned device was used in TITAN II trial, but data assessing wire fractures have not been reported yet.

Direct Annuloplasty

The purpose of these technologies is to reproduce surgical annuloplasty by cinching directly the mitral annulus by sutures, anchors, or similar devices. Although some issues regarding this approach remain challenging (annulus

Table 2. MitraClip Experience for the Treatment of Functional Mitral Regurgitation: Nonrandomized Trials

<table>
<thead>
<tr>
<th>Study</th>
<th>No of Patients</th>
<th>Age, Years</th>
<th>LVEF, %</th>
<th>Risk Score, %, Logistic EuroScore</th>
<th>Procedural Success, %</th>
<th>Need for ≥2 Devices, %</th>
<th>Residual MR ≤2+ at Discharge, %</th>
<th>Mortality at 30 Days/in Hospital,*</th>
<th>Mean/ Median† FU, Months</th>
<th>NYHA I-II at FU, %</th>
<th>LVEF at FU, %</th>
<th>Residual MR ≤2+ at FU, %</th>
<th>All Cause Mortality/CV Death‡ at FU, %</th>
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<td>27±9</td>
<td>30±19</td>
<td>96</td>
<td>49</td>
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<td>52</td>
<td>68±9</td>
<td>28±10</td>
<td>22±5</td>
<td>98</td>
<td>79</td>
<td>90</td>
<td>0*</td>
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<td>84</td>
<td>35±11</td>
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<td>87</td>
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<td>13†</td>
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<td>73±10</td>
<td>42±12</td>
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<td>96</td>
<td>39§</td>
<td>88</td>
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<td>12</td>
<td>81</td>
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</table>

CV indicates cardiovascular; FU, follow-up; LVEF, left ventricular ejection fraction; MR, mitral regurgitation; N/A, not available; and NYHA, New York Heart Association functional class.

*In-hospital mortality.
†Median Follow-Up.
‡Cardiovascular death.
§Global data from 351 patients, including 105 patients with degenerative mitral regurgitation.
calcification, possible leaflet damage, and circumflex artery proximity), several devices have recently emerged.

The Mitralign device (Mitralign, Tewksbury; Figure 9) uses a transfemoral retrograde approach to place a 13.5 Fr guide catheter on the posterior side of the left ventricle and 2 wires in the mitral annulus. Pairs of pledgets connected with a suture are delivered across the annulus at the medial and lateral edges of the posterior leaflets to create an arch cinching the annulus circumference. A prospective feasibility and safety trial to obtain CE mark has been completed after the recruitment of 61 patients. Preliminary data using the first generation of the Mitralign device were recently presented (Dr Nicking, TVT 2014), showing a decrease in MR degree ($\leq 2+$ in 55% of patients at 12-month follow-up) and improvements in ventricular measurements, valve dimensions, NYHA class, and quality of life.

The Accucinch annuloplasty system (Guided Delivery System, Santa Clara; Figure 9) uses also a retrograde transfemoral route to implant a series of anchor elements to circumferentially cinch the posterior annulus, from trigone to trigone. First-in-man experience was recently presented (Dr Starksen, TVT 2013). Data from the first patient at 6-month follow up evidenced reductions in MR degree, LV volumes, and N-terminal prohormone of brain natriuretic peptide, as well as improvement in NYHA class.

In addition to the aforementioned devices, energy-mediated annuloplasty systems have also been proposed. The rationale of these devices is to reduce annular length by applying heat energy to the mitral annulus causing scarring and shrinkage. Two systems, the QuantumCor (QuantumCor, San Clemente, CA) system and the ReCor (Recor Medical, Ronkonkoma, New York, NY) devices, are under preclinical evaluation.

**Cinching Devices**

The MVRx System (MVRx Inc; Figure 9) uses a transseptal approach to position a sutureless annuloplasty band similar to a surgical band. A sequence of multiple anchors is previously implanted from the anterolateral to the posteromedial commissure. Results from the CardioBand CE Mark study, including 29 patients with functional MR grade $\geq 2+$ and NYHA class III-IV, were recently presented (Dr Francesco Maisano, PCR London Valves 2014). The device was successfully implanted in all patients with no device-related major adverse events. Intraoperative transesophageal echocardiography showed an average 20% septolateral diameter reduction. Among 11 patients with 6-month follow-up data, 92% had $\leq 2+$ MR degree and 81% were in NYHA class I or II.

![Figure 8. EVEREST II trial results. Differences in the primary end point (freedom from death, mitral valve surgery, and mitral regurgitation $\geq 3+$) at 1- and 4-year follow-up according to MR pathogenesis (functional versus degenerative).](http://circinterventions.ahajournals.org/)

Table 3. EVEREST II Trial: 5-Year Follow-Up Data According to MR Etiology

<table>
<thead>
<tr>
<th></th>
<th>Degenerative MR</th>
<th>Functional MR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Freedom from mortality</td>
<td>89% [78%–95%]</td>
<td>86% [60%–96%]</td>
</tr>
<tr>
<td>Freedom from MV surgery or reoperation</td>
<td>69% [55%–80%]</td>
<td>96% [62%–100%]</td>
</tr>
<tr>
<td>MR grade $\leq 2+$</td>
<td>81%</td>
<td>100%</td>
</tr>
<tr>
<td>NYHA class $\leq 2$</td>
<td>95%</td>
<td>97%</td>
</tr>
<tr>
<td>LVEDV reduction, mL</td>
<td>-31.7</td>
<td>-49.2</td>
</tr>
<tr>
<td>LVESV reduction, mL</td>
<td>-5.6</td>
<td>-8.8</td>
</tr>
</tbody>
</table>

LVEDV indicates left ventricular end-diastolic volume; LVESV, left ventricular end-systolic volume; MR, mitral regurgitation; MV, mitral valve; and NYHA, New York Heart Association functional class.
placing a device in the septal wall connected by a bridge with another device placed in the great cardiac vein. Thirty-day follow-up results of the first-in-man study (Mitral Valve Repair Clinical [MAVERIC] trial), including 11 patients, were recently presented (Dr Martin Thomas, PCR London Valves 2014). Two procedure-related events were reported: one pericardial effusion requiring surgical drainage and one great cardiac vein anchor dislocation requiring surgical mitral valve replacement. Significant MR reduction (<2+ in all patients with successful procedure) and NYHA class improvement at 30 days were observed. The Phase II of the Maverick trial which is expected to enrol 30 patients is currently ongoing.

Transcatheter Mitral Valve Replacement

Given the complexity of the mitral anatomy, the development of transcatheter mitral valve replacement devices has not been comparable to the exponential development of transcatheter aortic valve replacement devices. Despite this, many systems have been tested in preclinical trials, and first-in-man data are available from 4 transcatheter mitral valve systems: the CardiAQ valve54 (CardiAQ Valve Technologies, Inc, Irvine, CA, transfemoral and transapical systems), the Tiara valve 55 (Neovasc, Inc, Richmond, British Columbia, Canada), the Fortis TVM56 (Edwards Lifesciences, Irvine, CA), and the Tendyne valve57 (Tendyne Inc, Minneapolis, MN; Figure 10).

**Table 4. MitraClip System for the Treatment of Functional Mitral Regurgitation: Ongoing Randomized Trials**

<table>
<thead>
<tr>
<th></th>
<th>COAPT</th>
<th>RESHAPE</th>
<th>MITRA-FR</th>
</tr>
</thead>
<tbody>
<tr>
<td>ClinicalTrials.gov Identifier</td>
<td>NCT01626079</td>
<td>NCT01772108</td>
<td>NCT01920698</td>
</tr>
<tr>
<td>Design/location</td>
<td>Multicentre and randomized; US</td>
<td>Multicentre and randomized; EU</td>
<td>Multicentre and randomized; France</td>
</tr>
<tr>
<td>No of patients</td>
<td>430</td>
<td>800</td>
<td>288</td>
</tr>
<tr>
<td>Control group</td>
<td>Optimal standard of care therapy</td>
<td>Optimal standard of care therapy</td>
<td>Optimal standard of care therapy</td>
</tr>
<tr>
<td>NYHA class</td>
<td>≥II</td>
<td>≥III</td>
<td>≥II</td>
</tr>
<tr>
<td>LVEF, %</td>
<td>≥20%−≤50%</td>
<td>≥15%−≤40%</td>
<td>≥15%−≤40%</td>
</tr>
<tr>
<td>LV measure</td>
<td>LVESD ≤70 mm</td>
<td>LVEDD ≥55 mm</td>
<td></td>
</tr>
<tr>
<td>Other inclusion criteria</td>
<td>≥1 HF hospitalization in previous 12 mo, and NT-proBNP ≥1500 pg/mL or BNP ≥300 pg/mL</td>
<td>≥1 HF hospitalization in previous 12 mo, or NT-proBNP ≥1400 pg/mL or BNP ≥350 pg/mL</td>
<td>≥1 HF hospitalization in previous 12 mo</td>
</tr>
<tr>
<td>FMR grade definition</td>
<td>≥3+</td>
<td>Moderate-to-severe or severe mitral regurgitation</td>
<td>Severe mitral regurgitation: regurgitation volume &gt;30 mL/beat and a regurgitant orifice area &gt;20 mm²</td>
</tr>
<tr>
<td>Primary safety end point</td>
<td>Composite of SLDA, device embolizations, endocarditis or MS requiring surgery, and any device-related complications requiring nonelective cardiovascular surgery.</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>Primary efficacy end point</td>
<td>Recurrent heart failure HF hospitalizations</td>
<td>Composite of all-cause mortality and recurrent HF hospitalizations</td>
<td>Composite of all-cause mortality and recurrent HF hospitalizations</td>
</tr>
</tbody>
</table>

COAPT indicates Cardiovascular Outcomes Assessment of the MitraClip Percutaneous Therapy for Heart Failure Patients With Functional Mitral Regurgitation; EU, European Union; HF, heart failure; LV, left ventricle; LVESD, left ventricular end-systolic diameter; MITRA-FR, Multicentre Study of Percutaneous Mitral Valve Repair MitraClip Device in Patients With Severe Secondary Mitral Regurgitation; NT-proBNP, N-terminal prohormone of brain natriuretic peptide; NYHA, New York Heart Association functional class; RESHAPE-HF, Randomized Study of the MitraClip Device in Heart Failure Patients With Clinically Significant Functional Mitral Regurgitation; and US, United States.

**Figure 9. Percutaneous mitral annuloplasty devices.**

A, Carrillon Mitral Contour device. B, Mitraling device. C, Accucinch device (Adapted from Feldman et al49 with permission of the publisher. Copyright ©2011, American College of Cardiology Foundation. Authorization for this adaptation has been obtained both from the owner of the copyright in the original work and from the owner of copyright in the translation or adaptation.) D, Cardioband System (Courtesy of Valtech Cardio Ltd, Or-Yehuda, Israel). E, MVRx System.

**Transcatheter Mitral Valve Replacement**

Given the complexity of the mitral anatomy, the development of transcatheter mitral valve replacement devices has not been comparable to the exponential development of transcatheter aortic valve replacement devices. Despite this, many systems have been tested in preclinical trials, and first-in-man data are available from 4 transcatheter mitral valve systems: the CardiAQ valve54 (CardiAQ Valve Technologies, Inc, Irvine, CA, transapical and transapical systems), the Tiara valve55 (Neovasc, Inc, Richmond, British Columbia, Canada), the Fortis TVM56 (Edwards Lifesciences, Irvine, CA), and the Tendyne valve57 (Tendyne Inc, Minneapolis, MN; Figure 10).
Although transcatheter mitral valve replacement is still in an early development stage, it is expected that this technology will become a major player in the treatment of MR in the coming years among those patients considered at high or prohibitive surgical risk.

Conclusions
Several transcatheter structural heart interventions for chronic HF currently exist, including a variety of mechanistic approaches, such as LV partition, creation of an atrial septal communication, renal denervation, continuous invasive hemodynamic monitoring, and percutaneous mitral valve repair/replacement/annuloplasty for functional MR. The preliminary results associated with most of these interventions have been promising, with significant improvements in symptoms, quality of life, functional status, and hemodynamics. However, data from the majority of these technologies are restricted to observational studies, including a limited number of patients. Larger randomized studies will be needed to provide definite data on the efficacy of these new devices for the treatment of HF. Importantly, adherence to evidence-based medical and device therapies remain the cornerstone therapy for HF. So, the efficacy of new devices should be tested within patients with optimized HF management according to current treatment guidelines. Ultimately, proving the benefits of these structural heart disease interventions on top of optimal medical treatment for harder end points, such as HF decompensation or mortality, may represent a major paradigm shift in the management of patients with chronic HF.

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References


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