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Covered CP Stent for Treatment of Right Ventricular Conduit Injury During Melody Transcatheter Pulmonary Valve Replacement

Results From the PARCS Study

See Editorial by Hainstock

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BACKGROUND: High-pressure balloon and stent angioplasty are frequently necessary to prepare the dysfunctional right ventricular outflow tract conduit before transcatheter pulmonary valve replacement (TPVR). Conduit injury can result, which may be catastrophic to the patient or prevent successful TPVR.

METHODS AND RESULTS: The PARCS trial (Pulmonary Artery Repair With Covered Stent) was a pivotal, prospective multicenter trial to evaluate the safety and efficacy of the NuMED Covered CP Stent (CCPS) for treatment of conduit injury occurring during TPVR. The study also evaluated immediate and short-term TPVR function in patients receiving covered stents. A total of 616 patients were consented; 120 (19.5%) had a wall injury identified and were treated with CCPS. Severe conduit injuries were uncommon (5%), but predictors for severe injury were not identified. Stenotic homografts had the highest incidence of injury (29%), compared with other conduit substrates. Among patients receiving CCPS implant, 96% required no further therapy for conduit injury, and 94% underwent TPVR at that procedure. Only 2 patients (1.6%) required urgent surgery for conduit injury, despite CCPS implant. There were few CCPS-related complications. TPVR function was similar between CCPS and non-CCPS groups at follow-up.

CONCLUSIONS: Conduit injury during TPVR is common, although severe injury is rare. The CCPS was a safe and effective treatment for right ventricular outflow tract conduit injury during preparation for TPVR, allowing nearly all patients to complete the procedure without identifiable impact on valve performance.

CLINICAL TRIAL REGISTRATION: URL: https://www.clinicaltrials.gov. Unique identifier: NCT01824160.

Key Words: allografts ■ methods ■ patients ■ pulmonary valve ■ wounds and injuries

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WHAT IS KNOWN

- Important conduit injury can occur during ultrahigh pressure angioplasty.
- Ultrahigh pressure angioplasty is often required to dilate conduits effectively for transcatheter pulmonary valve replacement.
- Conduit injury, once identified, could preclude further dilation of the conduit out of concern for extension of the area of injury.
- Stenting of the conduit before valve implantation improves the durability of the implanted valve.
- Covered stents have been used in the vascular space to isolate areas of injury.

WHAT THE STUDY ADDS

- No stent, covered or uncovered, at the time of this clinical trial was approved for use in the right ventricular outflow tract in the United States. This article reports the results of covered stent use for conduit injury as part of the multicenter clinical trial.
- The article describes the frequency and severity that conduit injury was identified in the study population with an analysis of possible risk factors.
- Severe conduit injury was found to be rare but unpredictable. The covered stent was effective in either treating or mitigating this problem.
- The article demonstrated that the vast majority of patients, even with identified conduit injury, was able to complete the valve replacement procedure.
- The covered stent did not interfere with Melody valve function at short-term, 6-month, follow-up.

Right ventricular outflow tract (RVOT) reconstruction with a valved conduit or bioprosthetic pulmonary valve placement is necessary during surgical repair of a substantial subset of patients with congenital heart disease. All valved RVOT substrates, regardless of type, have been associated with functional deterioration, with between 50% and 80% requiring replacement by 10 years.[1,2] Moreover, RVOT dysfunction may be associated with substantial patient morbidity and even mortality.

Transcatheter RVOT conduit rehabilitation using high-pressure angioplasty with or without stent placement has been utilized to delay or defer the need for surgical pulmonary valve replacement.[3–5] An injury within the wall of the conduit is likely to occur with any successful conduit dilation, although minor injuries may not be clinically relevant or recognized with angiography. Successful RVOT conduit angioplasty often requires the use of ultrahigh pressure noncompliant balloons to effectively relieve the stenosis but with a higher rate of recognized conduit injury (≤33%).[5] The vast majority of these injuries was not associated with hemodynamic compromise.[5] Introduction of the Melody transcatheter pulmonary valve (TPV; Medtronic, Inc, Minneapolis, MN) led to more frequent percutaneous conduit rehabilitation because cardiologists could effectively treat both stenosis and insufficiency, without the need for open-heart surgery.[6–8] However, despite growing clinical experience with the use of balloon-expandable stents in the pretreatment of conduit stenosis for valve implantation, at the time of Melody TPV approval, no stent was Food and Drug Administration approved in the US market for use in the RVOT, with clinicians instead relying on off-label use of various large-diameter biliary stents.[7–12] Melody TPV implants, without stent reinforcement of the conduit before valve implant, have been associated with a high rate of progressive valve deformity and stent fracture leading to valvular dysfunction.[7,8,10,12–15] In fact, long-term follow-up suggests that a single stent, placed before valve implant, may be inadequate for long-term protection of the valve from deformity and dysfunction.[14] Further, conduit wall injury is a known complication of isolated or serial balloon angioplasty of the RVOT conduit.[5] Although bare metal stents may provide some reinforcement of a damaged conduit wall, they are not likely to allow for safe, continued dilation of an injured RVOT conduit that has not been fully prepared (eg, left with hemodynamically important residual stenosis) for TPV replacement (TPVR), and they are not anticipated to be effective in treating catastrophic conduit injuries.

The Covered CP Stent (CCPS; NuMED, Inc, Hopkinton, NY) is a balloon-expandable, large-diameter, covered stent whose construction and applications for vascular wall injury, tears, or leak have been reported previously.[12,13,16–19] Experience with the CCPS outside of the United States is extensive and has included its routine use in the prestenting process for valve implantation. The European experience has suggested that this practice may reduce the clinical impact of conduit injury.[12] Some US centers did have access to the CCPS as participants in the COAST (Coarctation of the Aorta Stent Trial) and could apply for emergency use if an unexpected RVOT wall injury occurred. Non-COAST centers could apply for a single-patient compassionate use exemption if they felt a patient was at high risk for conduit injury.[20] This pooled experience suggested that the CCPS could be used effectively to repair conduit injury and allow operators to proceed with Melody TPVR. Given this encouraging but anecdotal dataset, clinicians, regulators, and the manufacturer all favored the development of a clinical trial to evaluate the safety and effectiveness of the CCPS in the treatment of conduit injury during preparation for Melody TPVR.

METHODS

The PARCS trial (Pulmonary Artery Repair With Covered Stents) was a prospective, multicenter, single-arm pivotal clinical trial. Forty US centers participated in either the pivotal

trial (22 centers) or the continued access protocol, which immediately followed the pivotal trial during Food and Drug Administration submission. The data and analysis presented herein have not been published previously. Anonymized data from the pivotal trial have been made publicly available at https://www.clinicaltrials.gov. Additional anonymized data from the continued access study are available on request from the corresponding author.

The goal of the PARCS study was to evaluate safety and efficacy of the CCPS to treat conduit injury during preparation for Melody TPVR. Specific aims were to establish that the CCPS can acutely repair a conduit injury, allow for additional conduit preparation without further injury, and that this therapy would not adversely affect Melody TPV implantation or valve performance. These data would be used to support Food and Drug Administration premarket approval of the CCPS to repair RVOT injury during TPVR. The Johns Hopkins Institutional Review Board approved the trial, and all participating institutions received local Institutional Review Board approval before participation. All participating institutions were required to be certified Melody TPV implant centers. The pivotal trial was completed with the enrollment of 50 patients treated with CCPS therapy. The Continued Access Trial was completed when an additional 70 patients were enrolled.

The CCPS is a platinum stent (NuMED, Inc, Hopkinton, NY) covered by an expandable sleeve of expanded poly tetrafluoroethylene, attached at etched ends of the stent with a cyanoacrylate adhesive. It is designed to have ≤20% shortening at a maximal diameter of 22 mm. The CCPS was available in lengths from 22 to 45 mm. Centers in the PARCS protocol were supplied with CCPS premounted on NuMED BiB (balloon in balloon) catheters at lengths of 34, 39, and 45 mm. A range of balloon catheters was supplied in 14- to 22-mm diameters.

Table 1 summarizes inclusion and exclusion criteria. Participating sites were asked to consent all prospective on-label Melody TPV candidates for enrollment in PARCS. Written informed consent was obtained before the procedure, but actual enrollment eligibility was established during the catheterization. Table 2 details the definition and severity of conduit injury from category 0 (no injury) to category 3 (uncontained). If an injury was identified, the implanting physician could enroll the patient and proceed with CCPS use. For the pivotal trial, angiography and echocardiography core labs were established at nonparticipating institutions. The core labs independently evaluated the imaging studies for injuries treated with CCPS to confirm reported findings from trial centers. A Data and Safety Monitoring Board was established to adjudicate all adverse events (AEs).

Table 1. Inclusion and Exclusion Criteria

Precatheterization inclusion criteria
Patient meets institutional criterion for placement of Melody TPV
Patient size adequate to receive Melody TPV implantation via venous access using the Ensemble transcatheter delivery system
RV-PA conduit original size >16 mm diameter
Patient age between 7 and 75 y
Catheterization inclusion criteria
Angiographic evidence for RV-PA conduit injury including dissection, aneurysm, pseudoaneurysm, injuries, or rupture
Recognition and treatment of conduit injury may occur before, during, or after implantation of the Melody TPV
Conduit injury related to prior intervention, identified angiographically before conduit dilation is performed during the Melody implant procedure, can be eligible for CCPS implantation and study inclusion
Precatheterization exclusion criteria
Patient size too small for transvenous placement of the Melody TPV
Bloodstream infection, including endocarditis
Pregnancy
Prisoners and adults lacking the capacity to give consent
Catheterization exclusion criteria
Conduit size is not suitable (too small or too large) for a Melody TPV
Risk of coronary compression has been identified
Lack of angiographic evidence for RV-PA conduit injury
Prophylactic use of study CCPS is prohibited
Vessel injury occurring in either the right or left branch pulmonary arteries
If injury to branch pulmonary arteries occurs during the catheterization and covered stent usage is indicated, Emergency Use guidelines must be employed

CCPS indicates covered CP stent; RV-PA, right ventricle to pulmonary artery; and TPV, transcatheter pulmonary valve.

Catheterization Procedure

The catheterization procedures were performed following institutional routine clinical practice for the evaluation and treatment of patients for TPVR. A standardized study protocol was not established. Data acquired included hemodynamic measurements, gradients before intervention, severity of conduit calcification (defined in the protocol with grades 0–3), and the initial RVOT measurements by angiography. Interventional data, including angioplasty and bare metal stent placement (balloon size and inflation pressure), were recorded. If no conduit wall injury occurred during the procedure, the patient was considered a screen failure. If at any point during the procedure, including before intervention, the implanting physician identified an area of wall injury, the patient could be enrolled in the PARCS protocol. The severity of the conduit wall injury (Table 2) was recorded based off the measurements of the angiogram identifying the injury. A CCPS could then be selected and implanted. Follow-up angiography was performed, and assessment of conduit wall injury was again performed. If wall injury persisted, additional CCPS could be utilized and continued intervention performed at the discretion of the implanter. At the completion of the procedure, residual wall injury, TPV placement and function, final hemodynamics, and angiography were assessed.

Follow-Up

To evaluate whether there was an association between CCPS use and hemodynamic outcome, postprocedural and follow-up data were collected. This included clinical and echocardiographic findings at 6-month follow-up. A core lab reviewer interpreted all procedural angiograms, as well as follow-up echocardiograms. Screen fail patients were not followed longitudinally.

Table 2. Conduit Injury as the Indication for Covered CP Stent—Severity Definitions

Category 0
No injury or conduit wall injury: no contrast seen extending outside of, or extravasating (leaking) outside of, the longitudinal plane of the vascular lumen.
Category 1
Contained injury: small collection of contrast seen extending outside of the longitudinal plane of the vascular lumen less than or equal to half the diameter of the adjacent conduit, indicating the occurrence of an aneurysm, pseudoaneurysm, or well-contained injury. This category can also be used to describe the unlikely occurrence of a dissection with contrast held in a contained space within the conduit lumen.
Category 2
Partially contained injury: large collection of contrast seen outside the wall of the RV-PA conduit greater than half the diameter of the adjacent conduit.
Category 3
Uncontained conduit injury: extravasation of contrast into the mediastinum or pleural cavity.

Adverse Events

AEs were collected at the time of the procedure, predischarge from the hospital, and at 6-month follow-up. They were categorized as (1) not serious, (2) somewhat serious, or (3) serious. The definition of these criteria has been published previously.[16,18]

Statistical Analysis

Case report forms submitted by the participating institutions and the core lab data were analyzed. Continuous data were summarized using mean (SDs) and median (ranges) or categorical data as counts (percentage). Normal assumption was tested using the Kolmogorov-Smirnov method and histogram of the data. The Student *t* test was used to compare the difference between 2 groups of patients with or without conduit injury, whereas the Mann-Whitney *U* test was used for nonnormally distributed data. Multiple variables were evaluated to identify associations with conduit injury. Univariate analysis was considered for predictors of conduit injury. All results were considered statistically significant at $P \leq 0.05$. SAS v9.4 (SAS Institute, Cary, NC) was used for all calculations.

RESULTS

Incidence and Risk Factors for Wall Injury

The pivotal trial was active between January 1, 2013, and September 11, 2014; the continued access trial was active between October 1, 2014, and May 10, 2016. During the study, 50 of 254 (19.7%) pivotal trial subjects and 70 of 362 (19.3%) continued access subjects received CCPS implantation on protocol for conduit injury identified during the procedure. Table 3 lists the enrolled patient diagnoses and characteristics.

Based on the overall rates of study consent and CCPS implantation, the incidence of RVOT conduit injury receiving treatment with a CCPS was 19.5% (120 of 616), which was consistent across both pivotal and continued access cohorts. Table 3 compares conduit and procedural characteristics for patients who had identified conduit injury with placement of a CCPS and those who did not.

Although patients with a homograft represented 68% of the total cohort, they represented 86% of the treated injuries. Homografts had a high incidence of treatment at 29% (103 of 355), regardless of type: pulmonary homografts, 28.3%; aortic homografts, 31.8%; and unspecified homografts, 29.3%.

Procedural data are displayed in Table 4. Recognized wall injury was more common with smaller original conduit diameter. Mean conduit diameter at implant was 20 mm in the stented group, whereas the mean was 22 mm in the nontreated group ($P<0.01$). Patients with recognized wall injury also had a smaller minimum conduit diameter by angiography before intervention (10.5 versus 14.6 mm; $P<0.01$), and this reflected a

Table 3. Diagnoses and Characteristics of Enrolled Patients

Patient Diagnoses	Pivotal Trial (Total n=50)	Continued Access (Total n=70)
Primary cardiac diagnosis		
Aortic stenosis	13 (26%)	15 (21%)
DORV	1 (2%)	8 (11%)
Pulmonary atresia	…	4 (6%)
TOF	26 (52%)	23 (33%)
TGA	2 (4%)	6 (9%)
Truncus arteriosus	7 (14%)	9 (13%)
Other	1 (2%)	5 (7%)
Sex		
Men	28 (56%)	40 (57%)
Women	22 (44%)	30 (43%)
Age, y	17 (6–44)	16 (7–49)
Age group, y		
<10	5 (4%)	7 (10%)
10–13	11 (17%)	19 (27%)
14–17	12 (29%)	14 (20%)
18–29	18 (28%)	19 (27%)
>30	4 (4%)	11 (16%)
Weight, kg	57.9 (19–116)	61.6 (19.3–108.6)

Data are presented as n (%) or median (range). DORV indicates double outlet right ventricle; TGA, transposition of the great arteries; and TOF, tetralogy of Fallot.

Table 4. Comparison of Conduit and Procedural Characteristics With and Without Injury

Variable	Conduit Injury (n=120)	No Conduit Injury (n=473)	*P* Value
Implant conduit diameter, mm	20 (18–23)	22 (19–25)	<0.01
Conduit diameter subgroups, mm (n=566)			
≤15 (25)	6 (24%)		
16–18 (112)	38 (34%)		
19–21 (142)	32 (22%)		
≥22 (287)	40 (14%)		
Conduit type, n (%)	n (percentage of total group)	n (percentage of total non)	
Homograft injury incidence: 29%	103 (86)	252 (53)	
Contegra injury incidence: 10%	5 (4)	41 (9)	
Bioprosthesis injury incidence: 3%	1 (1)	24 (5)	
Minimum angiographic conduit diameter, mm	10.5±3.4	14.6±4.4	<0.01
Angiographic minimum subgroups, mm (n=552)			
≤8 (65)	32 (49%)		
8.1–12 (146)	47 (32%)		
12.1–14 (106)	24 (23%)		
14–18 (148)	10 (7%)		
≥18.1 (87)	3 (3%)		
Largest balloon size used, mm	18 (16–20)	20 (18–22)	<0.01
Balloon (mm) at injury/original diameter	0.95±0.25	0.96±0.20	0.459
Balloon (mm) at injury/minimum angiographic diameter	1.89±0.53	1.57±0.53	<0.01
Minimum angiographic diameter/implant diameter	0.54±0.19	0.68±0.20	<0.01
Maximum balloon inflation pressure, atm	13.6±4.7	12.5±6.1	0.20
Baseline RV/aortic pressure ratio	0.72±0.21	0.68±0.23	0.09
Baseline peak RVOT gradient, mm Hg	64.6±24.8	57.6±22.8	0.005

Mean±SD, n (%), or median (interquartile range). Twenty-seven entries did not record original conduit size. Forty-one entries did not record minimal angiographic diameter. RV indicates right ventricle; and RVOT, right ventricular outflow tract.

greater reduction from implant diameter. There was an inverse relationship to baseline angiographic diameter, with wall injury meeting study criteria, occurring in 49% of patients in the smallest baseline diameter subgroup (≤8 mm) but only 7% in the 14- to 18-mm subgroup, and 3% in conduits ≥18 mm. Conduit injury that was treated with CCPS was significantly related to the ratio of angioplasty balloon diameter to minimum conduit diameter but not to the ratio of balloon diameter to original conduit diameter. The CCPS group also had a higher baseline peak RVOT gradient.

Although the majority (107 of 120) were identified after therapeutic balloon angioplasty, 6 injuries with CCPS placement were identified before any intervention, representing preexisting injury or chronic degenerative change in the conduit wall. The remaining 7 patients were identified following bare metal stent implant.

Severity of Injury

The severity of conduit injury was defined angiographically and verified by the core laboratory (Table 2). Of the 120 conduit injuries, 3 were uncategorized, 1 was deemed not injured by core lab evaluation, and the remaining 116 cases included category 1 (48%), category 2 (44%), and category 3 (5%) injuries. This generated an incidence of potentially life-threatening conduit injury (category 3) of ≈1% of the total consented population. The characteristics, treatment, and outcome of the 6 patients with uncontained injuries are shown in Table 5.

Success of Covered Stent Therapy

After placement of the CCPS, 95% of patients were determined to have either no residual injury (category 0, 68%) or mild injury judged unlikely to require any further intervention (category 1, 27%; Figure 1). Residual category 2 (2%) and category 3 (2%) injuries were uncommon. Intervention across an injury, including CCPS angioplasty, did carry risk of extending the injury outside the protective margin of the initial CCPS, with potential for worsening in severity, requiring further intervention (Figure 2A through 2D). This extension of injury was identified only 1 time within the trial. Final evaluation after completion of TPVR was consistent with the post-CCPS but pre-TPVR assessment; placement of the TPV (also inherently a covered stent) raised the percentage of category 0 (no residual injury) to 79% within the overall total.

Of the 6 patients with uncontained injuries (category 3), 4 were effectively treated with CCPS, resulting in category 0 (n=3) or category 1 (n=1) injuries, and did not require urgent surgery. One of these patients did have an effective seal of the injury with CCPS but was identified to have a minor stent malposition and did not proceed to TPV. This patient was instead referred for elective surgical pulmonary valve replacement. The CCPS was removed at surgery. Two patients demonstrated persistent category 3 injury after CCPS implant and were taken urgently to surgery for repair. Despite the need for urgent surgery, both implanting physicians described CCPS implants as potentially lifesaving, by reducing the rate of bleeding and contributing to improved patient stability during the transition to surgical repair.

Table 5. Severe (Category 3) Conduit Injuries (n=6)

	Conduit Type	No. of CCPS	Category Residual Leak	Disposition	Minimum Diameter (Original)	Calcium Grade	Balloon Sizes Before Injury
1	Aortic homograft	1 (minor malposition)	0	Elective surgery	12 (22)	1	14, 16, 18
2	Pulmonic homograft	1	3	Urgent surgery	9 (19)	NR	14
3	Aortic homograft	1	3	Urgent surgery	NR (17)	3	12, 14, 16, 18
4	Aortic homograft	2	1	TPV	11 (19)	3	10, 12, 14, 16, 18
5	Pulmonic homograft	1	0	TPV	9.6 (22)	0	14, 18
6	Aortic homograft (Figure 1A through 1D)	3	0	TPV	9.5 (17)	3	12, 14, 16

CCPS indicates covered CP stent; NR, not recorded; and TPV, transcatheter pulmonary valve.

Stent-Related AEs

AEs that specifically related to the CCPS and its implantation were uncommon. One serious (stent malposition) and 1 somewhat serious (stent embolization) AE occurred (both in the same patient who is described above). A device usage issue was identified whereby the expanded poly tetrafluoroethylene covering separated from the stent during attempts to load the CCPS device into the delivery sheath. This was identified before deployment; the stent was removed and replaced with a new CCPS without consequence to the patient.

TPVR After CCPS for Conduit Injury

Ninety-four percent (113 of 120) of patients receiving CCPS therapy completed the TPVR procedure with implantation of a Melody TPV, despite the wall injury. Of the 7 patients in whom a TPV was not placed, 2 underwent urgent or emergency surgery (1.6%) for persistent category 3 injury and ongoing bleeding. The remaining 5 were successfully treated for conduit injury, but did not receive a TPV during that procedure, at the discretion of the operator. Although specific case details were limited on the case report forms, one of these explained that an RVOT stent remained somewhat loose, so although hemodynamically stable, further intervention was not undertaken, and the patient was referred for surgery. Two described technical difficulties with further intervention between sheath size and angulation, and 1 was deferred electively for endothelialization before further intervention and valve placement. The final deferment was based on the discovery of right ventricular muscle bundles causing persistent subconduit obstruction, despite intervention, so a surgical referral was made.

Acute and Short-Term Follow-Up of Melody Valve Function With CCPS Therapy

Immediate post-TPVR echocardiographic data demonstrated a mean RVOT conduit gradient of 10.6±6.2 mm Hg for the pivotal trial cohort (n=48) and 10.2±5.2

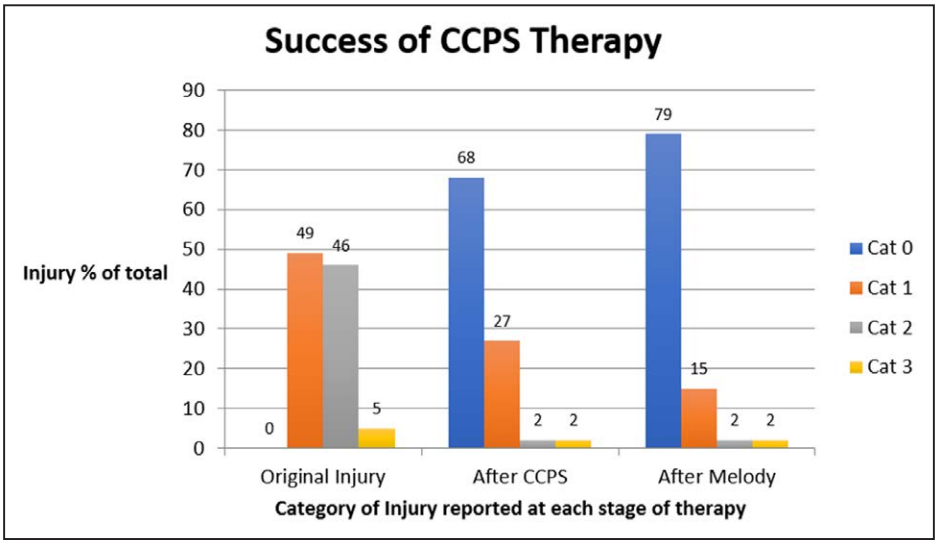

Figure 1. Category of injury before and after covered CP stent (CCPS) and Melody valve placement.
Patients were separated at the time of identified injury by category (0–3), columns listed in order and separated by color. At identification, most were category 1 and 2 (49% and 46%) with 5% category 3. After CCPS placement, 68% converted to category 0 and 27% to category 1 with only 2% each for category 2 and 3. After Melody implant, 79% were category 0, 15% category 1, with still 2% each for category 2 and 3. Cat indicates category.

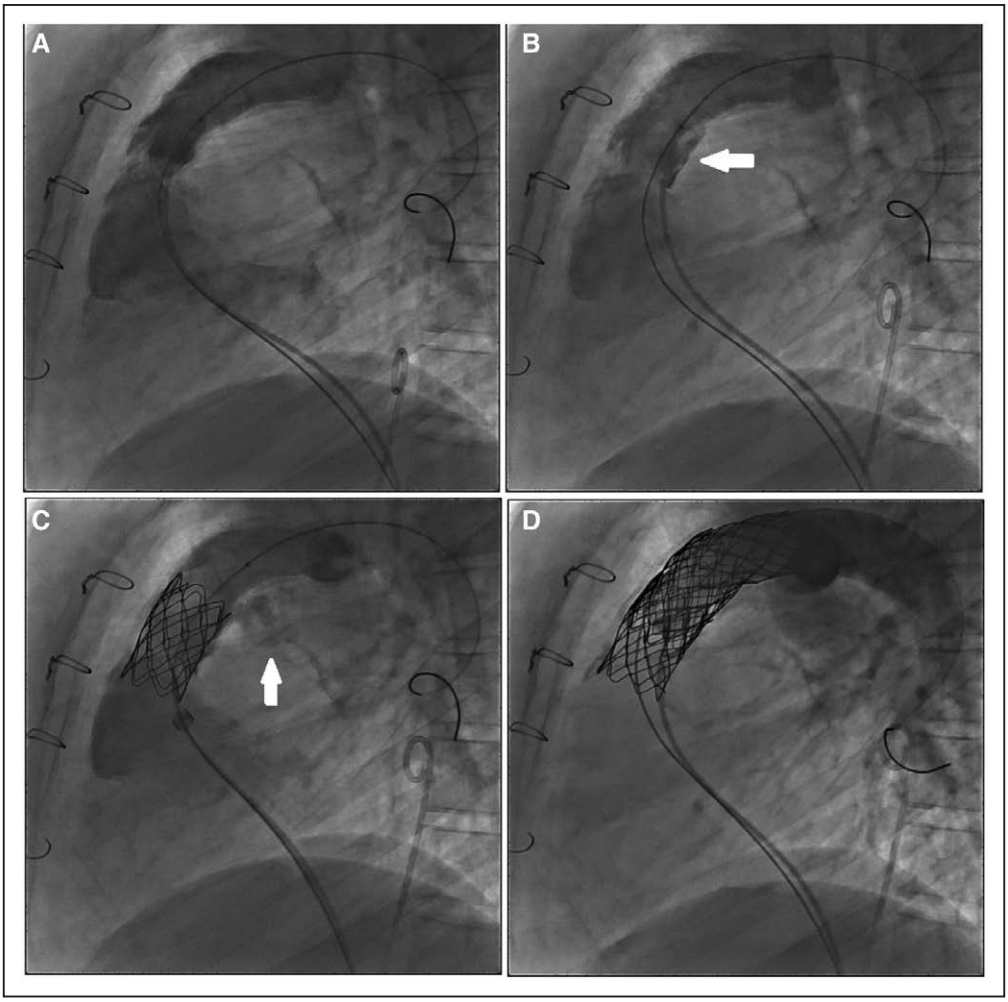

Figure 2. Evolution of injury with covered CP stent (CCPS) therapy.
Images represent patient number 6 from Table 5. **A**, Lateral angiography before injury. **B**, Category 1 wall injury with linear contrast stasis within a flap (arrow) of the posterior wall of the conduit. **C**, Extension of the injury after placement of the CCPS showing uncontained contrast (arrow) extravasating posterior to conduit wall, which defines a category 3 tear. **D**, Final angiogram with 3 CCPS and Melody valve in place with no residual injury, category 0.

mm Hg for the continued access trial cohort (n=65). Melody TPV regurgitation was none-to-trivial in 95% of patients, mild in 3%, and not recorded in 2%. For patients with 6-month follow-up data available, including an echocardiogram (n=80), RVOT mean gradient was 12.4±5.1 mm Hg in the pivotal cohort (n=39) and 12.4±6 mm Hg in the continued access cohort (n=34), among those with these data reported. Pulmonary regurgitation was none or trivial in 91.5% and mild in 8.5%. These 6-month follow-up data for Melody valve function in patients receiving CCPS therapy compared favorably to published data on Melody valve function without CCPS, such as the US clinical trial.[7] No patient required RVOT conduit or valve surgery within the 6-month follow-up period.

DISCUSSION

In the PARCS trial reported herein, we found an incidence of RVOT conduit injury that was treated with CCPS implant of 19.5% among consented patients. CCPS implants successfully treated 95% of conduit injuries with either no or minimal residual conduit wall injury. Perhaps of equal importance, CCPS implants also converted 4 of 6 uncontained injuries to no or minimal injury, resulting in only 2 patients (0.3% of the consented cohort) requiring urgent or emergent cardiac surgery for persistent bleeding. Melody TPVR was successfully performed in 94% of the enrolled cohort, and TPV function was not adversely affected by placement within the CCPS substrate, with 6-month follow-up data comparing favorably with other previously published cohorts.[7,13] CCPS-related AEs were uncommon.

Prior reports investigating the incidence of conduit injury have reported variable results. Bishnoi et al[20] found a significantly lower incidence of conduit injury (6%) than reported here, based on review of the Melody TPV US Investigational Device Exemption and postapproval studies. It is notable, although, that injuries, short of rupture, were not defined or identified in

the Investigational Device Exemption trial, and in the absence of CCPS availability for operators participating in those trials, mild conduit injury without a specific indication for therapy may not have been specifically addressed. In a single-center retrospective review, Peng et al[4] found an incidence of conduit injury of just 2.5%, without catastrophic injury, although these data came from an era before TPV or covered stent availability. Further, the use of ultra-noncompliant balloons, known to increase both the efficacy and risk of angioplasty in resistant lesions,[5] was less common in that series when compared with the current approach to conduit preparation before Melody TPVR.

A number of circumstances may account for the discrepant rates of conduit injury between the PARCS trial and prior studies that reported conduit injury. First, in the US Melody TPV Investigational Device Exemption trial, severity of conduit injury was not defined,[7] and it is possible that investigators only reported injuries that were felt to be clinically relevant (eg, moderate-to-large injuries or injuries with hemodynamic implications). This could have led to a systematic underreporting of the true incidence of conduit injury in that population, as defined by the PARCS criteria. Further, analysis of the compassionate or emergency use RVOT conduit CCPS data (from the COAST study) is complicated by the lack of a scientific study design and absence of an overall potential study population to provide a denominator for the incidence calculation. Retrospective review of homograft angioplasty by Hainstock et al identified a rate of conduit injury that is comparable with the incidence reported in the present study. They noted an overall incidence of any recognizable injury of 22% and as high as 33% when the population of homografts dilated with ultra-noncompliant balloons was selectively analyzed.[5] A subanalysis of the PARCS data reported here yielded an overall incidence of conduit injury of 19.4%, with homografts having the highest incidence at 29.1%. Lastly, although the PARCS trial protocol directed that consent be obtained from all patients undergoing catheterization with the intent to perform TPVR, not all sites were compliant with this intent. A limited retrospective inquiry across all study sites documented that consent was inconsistently obtained in patients perceived by the local investigator to be at low risk for conduit injury (eg, those with existing bioprosthetic valves planned for valve-in-valve TPVR or those with conduit insufficiency but no conduit stenosis). This practice served to artificially reduce the total consented study population, increase the percentage of consented patients with conduit stenosis as substrate, and underrepresent low-risk TPV candidates, all potentially serving to inflate the reported incidence of conduit injury in this trial. The follow-up survey indicated that homograft patients were consistently consented, suggesting that the subgroup analysis within this high-risk cohort is accurate.

Furthermore, the correlation between incidence of CCPS-treated conduit injury reported herein with the prior large retrospective analysis of RVOT angioplasty is consistent, suggesting that for the stenosis and mixed-indication population, the overall incidence of recognized conduit injury may be as high as 20%, with homografts associated with a risk of ≈30%. Severely obstructed conduits with small initial starting diameters are at the greatest risk, with nearly half (49%) developing an injury if the baseline angiographic diameter was ≤8 mm.

CCPS therapy proved to be effective in the treatment of wall injury during TPVR. Only 2 patients (1.6%) with a conduit injury required urgent surgical conversion, and 94% of patients with conduit injury went on to undergo successful TPVR. Although the high success rate in repairing conduit injury is ideal, there were a large number of mild conduit injuries identified and treated in this study that may not have required any further intervention. This study, unlike the Melody Investigational Device Exemption trial, defined injuries specifically (Table 2) and required investigators to identify and grade any injury, which could lead to a bias to treat. It is possible that many of these minor conduit injuries would not have negatively impacted or prevented TPVR or progressed to become important had they not been excluded with CCPS therapy. That said, the potential to convert an existing conduit injury into a hemodynamically destabilizing hemorrhage (if not excluded) during further angioplasty or conduit stenting is real, and that risk is not defined. New injuries and the extension of minor injuries were both observed after further intervention, including CCPS placement, in the PARCS study (Figure 1).

Although there may be debate surrounding specific treatment of minor conduit injury, adequate treatment of large or uncontained and potentially catastrophic conduit injuries is not in dispute and potentially represents the difference between mortality and mild morbidity. Thus, the performance of the CCPS in the setting of severe injury is paramount to judge the effectiveness of the device. After the development of catastrophic conduit injury (5% of the injury population or 1% of the total study population), CCPS implant effectively sealed the leak and stabilized the patient in 4 of 6 subjects, fully repairing the injury in 3, and was effective in sealing the leak in a fourth, although the patient was still referred for elective surgery because of minor stent malposition. CCPS was not able to mitigate the need for urgent surgery in 2 subjects. As discussed previously, the operators in both cases reported that in the absence of CCPS therapy, these patients might well have died in the catheterization laboratory because of overwhelming hemorrhage. Thus, although not adequate to fully repair the catastrophic conduit injury, CCPS implant was able to partially seal the injury, reduce the rate of

blood loss, and contribute to a satisfactory clinical outcome in both patients.

The PARCS trial identified risk factors for conduit injury, such as conduit type, smaller baseline angiographic diameter, and higher RVOT gradient. These factors have consistently been found to increase risk in prior studies.[5,7,14] However, we were not able to identify patient or procedural characteristics associated with the risk of different injury categories (ie, minor injury versus catastrophic injury). Category 3 injuries developed in 5 of 6 subjects following a conservative approach to serial balloon conduit angioplasty, with an initial balloon diameter selected that was near the minimal baseline angiographic conduit diameter. Further, 5 of 6 patients developed the category 3 injury before performing angioplasty at the original conduit implant diameter. These findings are not consistent with the hypothesis that severe conduit injuries result from an aggressive ratio of starting balloon diameter to initial conduit diameter or overdilation of the conduit beyond its nominal implant diameter.

In addition to its role in excluding conduit wall injury, the CCPS otherwise functions as an additional right ventricular outflow tract support (prestent), without interfering in the ability to implant a Melody TPV or in the function of the TPV immediately after implant or at follow-up. Given that routine prestenting has been documented to reinforce the conduit and reduce the incidence of Melody TPV stent fracture, thus preserving TPV function in follow-up, prestenting before valve implant has become part of standard practice during conduit preparation.[14] A specific protocol for prestenting was not included in this trial, and bare metal stents may have been, and often were, used in conjunction with CCPS for both seal and additional radial strength. The excellent preservation of valve function at 6-month follow-up cannot be attributed to a single CCPS because some cases used >1 CCPS, potentially in combination with bare metal stents at the discretion of the implanting physician. Minor stent fractures may have occurred and not been known to the investigators because routine radiographic or fluoroscopic follow-up was not required. However, major stent fractures are associated with a high incidence of valve dysfunction,[14] which was not seen. The favorable clinical and noninvasive evaluation of the valve in follow-up was reassuring that the use of the CCPS did not interfere with valve function. Reports from European operators have advocated for prophylactic covered stent use in the prestenting of RVOT conduits to both reinforce the conduit wall and guard against the potential for conduit injury, as the conduit is dilated at ultrahigh pressure.[12] Prophylactic use was specifically prohibited as part of the present protocol and thus was not evaluated. Empirical CCPS implantation in the RVOT conduit before dilation to the intended TPV implant diameter eliminates the ability to dynamically assess the impact of conduit dilation on adjacent structures (eg, coronary compression testing) before permanent conduit dilation. Although potentially reducing the incidence of conduit injury, this approach raises concern for a potential increase in irreversible aortic root deformation and coronary artery compression.[7,9,12,21–23] In the absence of a prospective trial of prophylactic CCPS implantation before complete conduit dilation, the authors urge caution in considering this approach.

In summary, the PARCS trial data demonstrated what most congenital interventional cardiologists might have presumed, which is that the vast majority of conduit injuries occur during angioplasty are small and not compromising. However, catastrophic conduit rupture is both rare and unpredictable. Whether small conduit injuries are at increased risk of extension to a potentially catastrophic injury with further dilation was not assessed in this study and remains unknown. The use of CCPS is associated with a low risk of AEs, is acutely effective in repairing small injuries, and may be lifesaving in the setting of a rare but catastrophic injury. Further, use of CCPS does not impede Melody TPV implant in the same procedure nor does it affect TPV function in short-term follow-up.

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