

Intermediate Outcomes in the Prospective, Multicenter Coarctation of the Aorta Stent Trial (COAST)

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Background—The Coarctation of the Aorta Stent Trial (COAST) was designed to assess the safety and efficacy of the Cheatham Platinum stent when used in children and adults with native or recurrent coarctation. Acute outcomes have been reported. We report here follow-up to 2 years.

Methods and Results—A total of 105 patients underwent attempted implantation, with 104 successes. There were no procedural deaths, serious adverse events, or surgical intervention. All patients experienced immediate reduction in upper-to lower-extremity blood pressure difference with sustained improvement to 2 years. Rates of hypertension and medication use decreased from baseline to 12 months and remained largely unchanged at 2 years. Six aortic aneurysms have been identified: 5 were successfully treated with covered stent placement, and 1 resolved without intervention. Stent fractures were noted in 2 patients at 1 year and 11 patients at 2 years, with evidence of fracture progression. To date, only larger stent diameter was associated with stent fracture. Twelve additional fractures have occurred after 2 years. No fracture has resulted in loss of stent integrity, stent embolization, aortic wall injury, or reobstruction. Nine reinterventions occurred in the first 2 years for stent redilation and address of aneurysms, and 10 additional reinterventions occurred after 2 years.

Conclusions—The Cheatham Platinum stent is safe and associated with persistent relief of aortic obstruction. Stent fracture and progression of fracture occur but have not resulted in clinically important sequelae. Reintervention is common and related to early and late aortic wall injury and need for re-expansion of small-diameter stents.

Clinical Trial Registration—URL: <http://www.clinicaltrials.gov>. Unique identifier: NCT00552812.

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Coarctation of the thoracic aorta (CoA) is a relatively common form of congenital cardiovascular disease and may occur in isolation or in association with more complex cardiac malformations. The preferred method of treatment of CoA depends on the individual anatomy, patient size, and nature of the lesion. In larger children and adults, endovascular therapy with either balloon angioplasty or stent placement is commonly preferred over surgery. Although balloon angioplasty typically results in favorable acute results, it is associated with a higher rate of both recurrent obstruction and aortic wall injury than stent therapy.^{1,2} As a result, stent placement is usually preferred when patient size and CoA anatomy are suitable. However, there are no US Food and Drug Administration–approved stents for use in the aorta, and in this absence, large-diameter stents approved for other applications have been used off label. In an effort to fill this void, in 1996, NuMED (Hopkinton, NY) began development of a platinum-iridium stent intended for use in the aorta. The Cheatham Platinum (CP) stent was designed to have rounded

ends to lessen the risk of aortic wall injury and ≈20% shortening at a maximal diameter of 22 mm. The Coarctation of the Aorta Stent Trial (COAST) began in 2007 and was designed to assess the safety and efficacy of the CP stent when used in CoA in children and adults with either native or recurrent obstruction. Short-term outcomes have been reported.³ We report here the follow-up to 24 months and beyond.

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Methods

Details of the COAST study design were reported previously.^{3,4} Briefly, COAST is a prospective, multicenter, single-arm clinical study involving 19 pediatric cardiology centers in the United States (<http://www.clinicaltrials.gov>; identification number, NCT00552812). The protocol for COAST received approval under an Investigational Device Exemption from the US Food and Drug Administration on August 3, 2007. The study received Institutional Review Board approval from all participating institutions, and subjects provided

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written informed consent. The study includes patients with native or recurrent CoA treated by physicians at the participating institutions. Table 1 summarizes inclusion and exclusion criteria.

Treatment Protocol

After baseline anatomic and physiological assessment, patients underwent initial compliance testing and sizing with the use of predilation with a low-pressure (2–4 atm) balloon inflation. The nominal diameter of this balloon was selected to dilate the CoA to no more than the smaller diameter of the distal transverse arch or the aorta at the diaphragm, without exceeding 4 times the minimal CoA diameter. If the dilation balloon waist was <80% of the maximum balloon diameter (eg, <12 mm waist on a 15-mm-diameter balloon in a patient with a 15-mm transverse arch), the aorta was labeled noncompliant, and patients were excluded from CP stent implantation. Those not excluded underwent implantation of a CP stent delivered on a NuMED balloon-in-balloon catheter. Because of the known risk of aortic wall complications during CoA intervention, NuMED covered CP stents (CCPSs) were made available to study centers for use in the event of aortic wall injury (AWI). Data on patients receiving a CCPS are included in this report for safety outcomes. These patients were then enrolled in the COAST II trial of aortic covered stents (<http://www.clinicaltrials.gov>; identification number, NCT01278303) for subsequent evaluation of efficacy and long-term outcomes. Decisions about AWI, patient safety, and the need for CCPS implantation were made by the implanting physician at the time of the procedure. Subsequent determinations about the extent of AWI during implantation procedures were adjudicated by the core laboratory, and final determinations may have differed from those of the implanting physician. Hemostatic mechanisms were not stipulated in the trial protocol and were therefore at the discretion of the interventional cardiologist. Similarly, decisions about antihypertension medication administration and modification were not specified in the study protocol and were left to the discretion of the primary physician. Finally, decisions about reintervention were at the discretion of the cardiologists caring for the patient and were not specified or guided by the trial protocol.

Follow-Up

Follow-up evaluations were performed before discharge and at 1, 6, 12, 24, 48, and 60 months after the procedure. Magnetic resonance imaging (MRI) or computed tomography (CT) imaging was performed at 12- and 24-month follow-up intervals to look for AWI. Biplane cine-fluoroscopic examination of the stent(s) was also

obtained at 12, 24, 48, and 60 months after implantation to look for stent fractures. All procedural angiograms, MRIs, and fluoroscopic images were reviewed by the core laboratories.

Outcome Variables

Four primary outcome variables were defined: 2 efficacy outcomes (reduction in upper-to lower-extremity systolic blood pressure measurements and hospital length of stay) and 2 safety outcomes (occurrence of any serious or somewhat serious adverse event attributed to the stent or implantation and occurrence of paradoxical hypertension), which were defined previously. In each case, outcomes for patients treated with the CP stent were compared with prespecified performance guidelines derived from studies of patients treated with surgery. These initial results have been published.³ In follow-up analysis, we also explored the effects of CoA stenting on systemic hypertension and antihypertension medication use. Blood pressures were recorded as the average of 3 measurements in each extremity, as reported previously⁴; ambulatory and exercise blood pressure assessment was not performed. Because of a broad range of subject ages, we used sex- and age-specific blood pressure norms in patients <18 years of age to define a dichotomous outcome of systemic arterial hypertension (>95th percentile).⁵ For patients ≥18 years of age, we used systolic and diastolic levels of 140 and 90 mm Hg, respectively, to define hypertension. In addition, this report includes an analysis of stent fracture and integrity. For this purpose, loss of stent integrity was defined a priori as a decrease in stent diameter ≥20% in either the maximal or minimal measurement in any radiographic projection compared with immediately after implantation, complete circumferential or longitudinal stent fracture, embolization of any portion of the stent, or protrusion of the stent through the aortic wall. Other adverse events were classified as not serious, somewhat serious, or serious, as previously defined.³

Statistical Analysis

Descriptive statistics are presented as mean±SD or median (minimum–maximum). Bivariate comparisons of preimplantation and postimplantation catheterization data and subsequent blood pressures were performed with the paired *t* test. Comparison of means or proportions between populations were performed by unpaired *t* test or Wilcoxon rank-sum test based on distribution and the Fisher exact test, respectively. Multivariable analysis of dichotomous outcome variables was performed with logistic regression. Analysis of time-dependent occurrences was presented graphically with Kaplan-Meier plots and analyzed statistically by the log-rank test. Predictors of time-dependent outcomes such as reintervention were obtained from Cox proportional hazards modeling.

Results

Between 2008 and 2010, 168 patients provided consent for participation in the trial. Of these, 55 were excluded on the basis of prespecified criteria. Five were perceived to have AWI during predilation, received CCPS, and were transferred to the COAST II trial. One patient withdrew consent before his procedure, and 2 others who were not specifically excluded from participation by the protocol were withdrawn because the primary physician felt that treatment with alternative therapy was preferable for safety reasons (Figure 1).

Short-Term Results

Short-term results were published previously and are summarized in Table 2. Of the 105 patients who underwent attempted implantation, a CP stent was successfully placed across the CoA in 104 (Figure 2). Stent therapy was effective, with significant improvements noted in CoA pressure gradients in the cardiac catheterization laboratory, which was confirmed by cuff blood pressure assessment at the 1-month

Table 1. COAST Trial Inclusion and Exclusion Criteria

Inclusion Criteria	Exclusion Criteria
Precatheterization	
Native or recurrent aortic coarctation	Age >60 y
Weight <35 kg	Bloodstream infection
Cuff blood pressure difference or catheter-measured systolic coarctation gradient of 20 mm Hg	Connective tissue disorders, including Marfan syndrome, Turner syndrome, or inflammatory aortitis
	Prior stent placement
	Aortic aneurysm
	Pregnancy
	Subject lacking ability to consent
Catheterization	
Coarctation involving the aortic isthmus or first segment of the descending thoracic aorta	Coarctation involving curved region of aorta, transverse arch, or beyond mid thoracic aorta
Coarctation found to be compliant on pre-stent balloon dilation	Anatomic location precluding safe stent placement
Patency of at least 1 femoral artery	Complete aortic atresia

COAST indicates Coarctation of the Aorta Stent Trial.

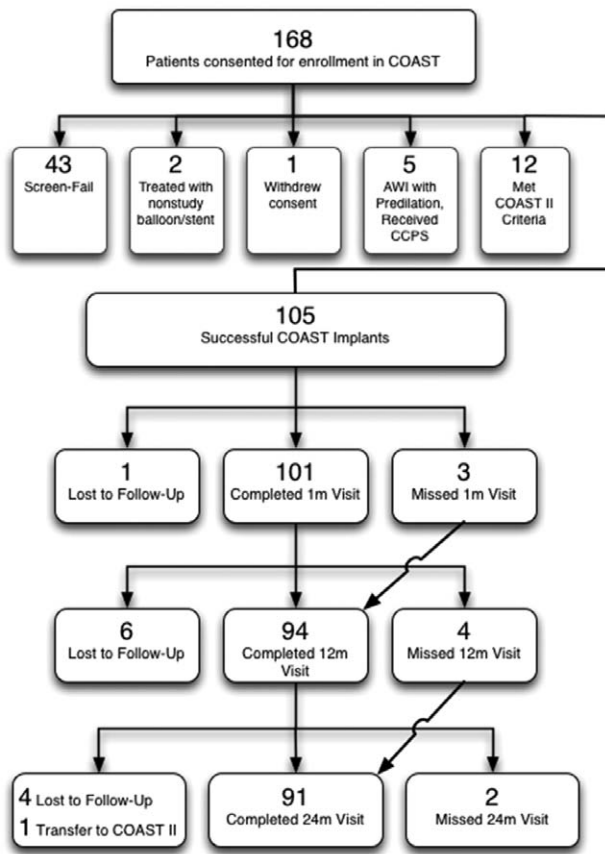


Figure 1. Coarctation of the Aorta Stent Trial (COAST) flow diagram. AWI indicates aortic wall injury; and CCPS, covered Cheatham Platinum stents.

follow-up evaluation. The average hospital length of stay was 1.0 ± 0.3 days. There were no procedural deaths or serious adverse events. Somewhat serious adverse events occurred in 8 patients (7%). Immediate postprocedural paradoxical hypertension, which was categorized separately from somewhat serious events, occurred in 8 patients (7%).

Mid-Term Follow-Up

Relief of Aortic Obstruction

As noted above and summarized in Table 2, all patients experienced an immediate reduction in upper- to lower-extremity

Table 2. Cardiac Catheterization Data Before and After CP Stent Placement

	Before Implantation	After Implantation	P Value
Ascending aorta systolic pressure, mm Hg	109±22	107±20	0.22
Descending aorta systolic pressure, mm Hg	80±17	105±20	<0.001
Average ascending to descending aorta systolic pressure difference, mm Hg	29±14	2±4	<0.001
Average minimal luminal diameter, mm	7.9±2.7	14±3	<0.001

Values are mean±SD. CP indicates Cheatham Platinum.

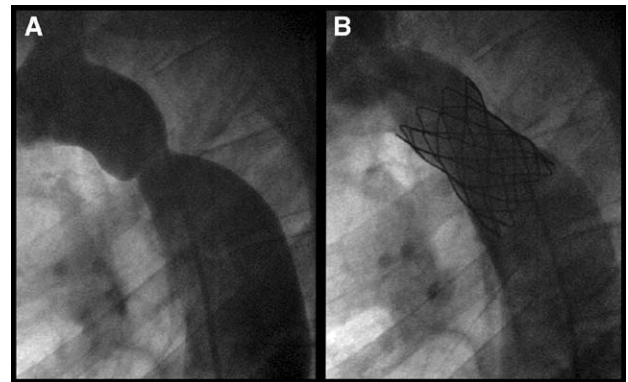


Figure 2. Aortic angiography before (A) and after (B) Cheatham Platinum stent implantation.

blood pressure difference (from 29 ± 14 to 2 ± 4 mmHg), with an average decrease in blood pressure gradient of 27 ± 14 mmHg. There was sustained improvement at the 1-month follow-up visit at which 99% had a blood pressure difference <20 mmHg, and 94% were <15 mmHg. Ninety-four patients (89% of those who had a CP stent implanted under the study protocol) returned for the 1-year follow-up evaluation, and 91 (86%) returned for the 2-year evaluation. Sustained improvement in upper-extremity systolic blood pressure and upper- to lower-extremity systolic pressure differences was observed at 12 and 24 months (Table 3). The primary efficacy outcome of this study, the mean reduction in systolic blood pressure difference from baseline (preintervention) to 12 months, was 30 ± 22 mmHg.

Systemic Arterial Hypertension and Antihypertension Medication Use

Overall trends in systemic arterial hypertension and antihypertension medication use are given in Figure 3. At baseline and in the setting of an average 29-mmHg pressure difference from upper to lower extremity, 63 patients (61%) demonstrated a right arm blood pressure meeting the criteria for systolic hypertension. An additional 17 patients (16%) had a normal blood pressure on ≥1 antihypertensive medications. At 12 months, with an average upper- to lower-extremity systolic blood pressure difference of -1 ± 15 mmHg, 19% of patients remained hypertensive and 28% continued to receive antihypertension medications, proportions that remained relatively stable at 24 months. Diastolic hypertension was uncommon: 10% of patients at baseline and 1% and 3% at 12 and 24 months after stent placement. Persistent systemic hypertension at 12 and 24 months after implantation was associated with higher baseline upper-extremity blood pressure and residual blood pressure difference but not sex or age at intervention (Table 4).

At baseline, 40 patients (38%) were on at least 1 antihypertension medication. At 12 months after implantation, 20 of these patients (50%) had stopped (n=17) or decreased the number of (n=3) antihypertension medications, whereas 10 (25%) remained on the same number of medications, 6 (15%) were started on medication, and 4 (10%) had a new medication added. At 24 months, 5 additional patients had either decreased the number of (n=1) or discontinued (n=4) antihypertensive medications, and 1 had increased

Table 3. Blood Pressures and Upper- to Lower-Extremity Systolic Pressure Differences

	Baseline (n=104)	At 12 mo (n=91)	At 24 mo (n=88)
Upper-extremity SBP, mm Hg	140±16	123±12	122±14
Lower-extremity SBP, mm Hg	110±16	123±15	125±16
Systolic blood pressure difference, mm Hg	29±17	-1±15	-3±15
Pressure difference <20 mmHg, n (%)		82 (90)	85 (90)
Pressure difference <15 mmHg, n (%)		76 (84)	79 (90)

Values are mean±SD when appropriate. SBP indicates systolic blood pressure.

the number of medications. Sixty-five patients (74%) were receiving no medications, 13 (15%) were receiving 1 medication, and 10 (11%) were receiving ≥2 medications directed at blood pressure control. Continued use of any antihypertensive medication at 12 and 24 months was associated with older age at stent implantation but not sex, baseline upper-extremity systolic blood pressure, or residual blood pressure gradient, Table 4.

Stent Fracture and Integrity

Immediate postimplantation fluoroscopy demonstrated no stent fractures. Fluoroscopic imaging at 1 year was obtained in 93 patients and identified no stent fracture in 91 (98%). Two patients had multiple stent fractures noted without evidence of reobstruction or loss of integrity. Fluoroscopic imaging at 2 years was obtained in 90 patients. Of the 2 patients with stent fractures noted at 12 months, both had additional stent fractures noted at 24 months, and there were 9 additional patients with new stent fractures noted. Three involved fracture of a single strut, whereas 6 involved fracture of multiple struts. Factors related to stent fracture included larger CoA minimal luminal diameter and postimplantation minimal stent diameters. Association with postimplantation maximal stent diameter and the ratio of postimplantation minimal to maximal stent diameters was weaker and statistically

nonsignificant, and no association with additional parameters, including stent lot number, length, or other clinical parameters, was apparent (Table 5). Follow-up imaging beyond 24 months is ongoing but remains incomplete. To date, a total of 23 stents have had identified fractures. No stent fracture has resulted in loss of stent integrity, stent embolization, or identified AWI, and stent fracture was not associated hemodynamic reobstruction as assessed by blood pressure gradients. No patient had stent fracture stated as a reason for reintervention.

Aortic Wall Injury

During initial cardiac catheterization, 2 patients developed small aortic aneurysms after compliance testing. One of these patients received a CCPS. The other had no additional therapy, and the aneurysm was not apparent on a CT study the following day or on subsequent imaging. Four patients developed minor localized vascular injury during compliance testing and received a CCPS at the decision of the implanting physician. These patients were enrolled in the COAST II trial. Subsequent review by the core laboratory classified these injuries as confined vascular tears, not dissections or aneurysms. One additional patient developed a minor localized vascular tear during compliance testing but did not receive a CCPS. The tear was monitored and covered by a bare metal CP stent, and no subsequent AWI was noted.

Of the 91 patients with comprehensive aortic imaging (CT or MRI) at 1 year, 1 was noted to have a large aneurysm at the margin of the previously implanted CP stent. This patient underwent a repeat cardiac catheterization for implantation of a CCPS. Although imaging beyond 24 months remains incomplete, 3 patients who underwent planned cardiac catheterization for stent re-expansion at 30, 45, and 50 months after implantation were found to have small stent-related aneurysms that were not apparent on routine MRI/CT imaging obtained before cardiac catheterization (Figure 4). These patients were treated with CCPS implantation and enrolled in the COAST II trial.

Reintervention

There were no surgical interventions related to the CoA or stent. As discussed above, 5 patients had CCPS implantations before CP stent implantation. Four patients underwent transcatheter reintervention within 24 months after initial implantation. Three of these 4 patients underwent re-expansion of the CP stent at 12, 13, and 21 months either as part of an intentionally staged approach or to compensate for somatic growth. As described above, 1 additional subject

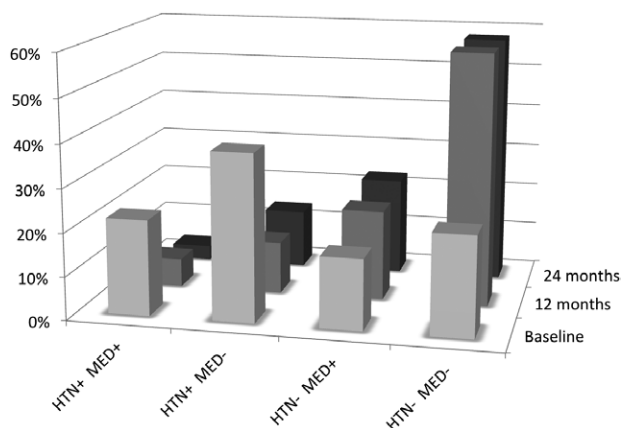


Figure 3. Trends in systemic arterial hypertension and antihypertension medication use. HTN indicates systemic arterial hypertension (>95% for age); and MED, the use of any medication directed at controlling blood pressure, with + signifying a presence and – signifying an absence. For example, HTN+ and MED+ is the group of patients who continue to have hypertension despite receiving blood pressure medication, and HTN– MED+ is the group of patients without hypertension while still receiving medication directed at controlling blood pressure.

Table 4. Factors Associated With Persistent Systemic Arterial Hypertension and Antihypertension Medication Use

	At 12 mo		At 24 mo	
	Odds Ratio (95% CI)	P Value	Odds Ratio (95% CI)	P Value
Factors associated with persistent systemic arterial hypertension				
Male sex	0.72 (0.17–2.98)	0.65	2.42 (0.47–12.40)	0.29
Age at implantation	0.96 (0.89–1.02)	0.19	1.00 (0.94–1.05)	0.83
Baseline systolic blood pressure	1.06 (1.01–1.12)	0.01	1.04 (1.00–1.08)	0.07
Residual blood pressure gradient	1.07 (1.02–1.12)	<0.05	1.05 (1.00–1.09)	0.04
Factors associated with any antihypertension medication use				
Male sex	1.70 (0.54–5.35)	0.37	3.16 (0.81–12.31)	0.10
Age at implantation	1.06 (1.01–1.11)	0.02	1.08 (1.02–1.13)	<0.05
Baseline systolic blood pressure	1.02 (0.99–1.06)	0.16	1.01 (0.97–1.04)	0.74
Residual blood pressure gradient	1.02 (0.99–1.06)	0.16	1.02 (0.98–1.05)	0.39

CI indicates confidence interval.

had a large aortic aneurysm noted on the 12-month MRI and underwent CCPS placement at 15 months. In preliminary follow-up beyond 24 months, 10 additional patients have undergone transcatheter reintervention. Seven returned to the cardiac catheterization laboratory for re-expansion of the CP stent. Of these, 6 had redilation of the existing stent, and 1 had redilation with an additional bare metal stent placed. As noted above, 3 patients were taken to the cardiac catheterization laboratory with the intent to redilate the existing stent and had small aortic aneurysms noted during angiography, and all 3 underwent CCPS placement and enrollment in COAST II. No AWI has been noted as a result of stent redilation after initial implantation. Overall freedom from reintervention is demonstrated in Figure 5. Among demographic and procedural variables, AWI, lower patient weight,

and smaller final stent diameter at initial implantation were associated with reintervention (Table 6).

Arterial Access Sites and Lower-Extremity Blood Pressures

As noted in the short-term outcomes study, somewhat serious procedural access complications occurred in 2 patients, with 1 large groin hematoma and 1 femoral arteriovenous fistula requiring surgical repair. Although loss of lower-extremity pulses was not reported and no patient complained of symptoms referable to peripheral arterial insufficiency, we analyzed differences in lower-extremity blood pressures to assess for subclinical obstructive peripheral arterial injury. We defined the development of systolic pressure difference of 10% to 19% lower in the leg used for stent delivery compared with the contralateral leg as suspicious for mild femoral artery injury and >20% lower as suggestive of important arterial injury. With these criteria, 13 patients had evidence of pre-existing femoral artery injury, 2 of whom appeared to have important arterial injury and 9 of whom had smaller blood pressure differences suspicious for arterial injury. At 1 month, 13 patients had what appeared to be new arterial injury, with 3 suggestive of important arterial injury and 10 suspicious for arterial injury. At 12 months, 6 of the patients suspected of having new femoral artery injury related to stent implantation had stable blood pressure differences between the lower extremities, whereas 6 others with relatively mild blood pressure differences appeared improved, and 1 did not have 12-month measurements available. Apparent arterial injury was not related to patient age or to the diameter of the balloon used for stent delivery (used as a surrogate for sheath size). Finally, hemostasis was assisted (Perclose, n=8; Prostar, n=51; or Syvek Patch, n=3) in 16 patients (15%), and there was no relationship between any type of assisted hemostasis and subsequently identified femoral artery injury.

Table 5. Analysis of Factors Associated with Stent Fracture at 24 Months After Implantation

	Stent Fracture (n=11)	No Stent Fracture (n=85)	P Value
Age, y	21±10	21±11	0.95
Male sex, %	73	68	0.78
Primary indication, n			0.21
Native coarctation	4	43	
Recurrent coarctation	7	33	
Coarctation minimum diameter, mm	9.8±2.0	7.6±2.7	0.01
Minimum stent diameter at implantation, mm	16.4±2.6	14.2±2.5	0.01
Maximum stent diameter at implantation, mm	17.8±2.7	16.2±2.7	0.09
Minimal to maximal stent ratio	0.92±0.06	0.88±0.07	0.07

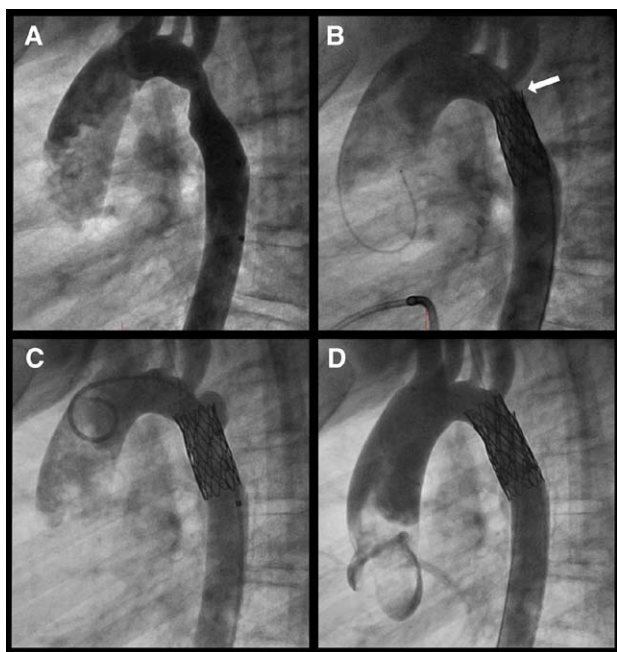


Figure 4. Aortic angiograms before (A) and after (B) Cheatham Platinum (CP) stent implantation for coarctation of the thoracic aorta. Although no aortic wall injury (AWI) was apparent at the time of implantation, a portion of the stent is seen protruding against the posterior wall of the aorta (arrow). Subsequent cardiac magnetic resonance imaging did not conclusively demonstrate AWI (not shown); however, at cardiac catheterization for intended stent re-expansion, an aneurysm was noted in this area (C). A covered CP stent was implanted (D), and the patient was transferred to the Coarctation of the Aorta Stent Trial II (COAST II) trial.

Discussion

Clinical and Hemodynamic Outcomes and Reintervention Rates

Short-term reductions in upper- to lower-extremity blood pressure measurements were sustained in later follow-up after CP stent implantation, with >90% of patients having pressure differences of <15 mmHg. Reintervention does occur. To date, 13%

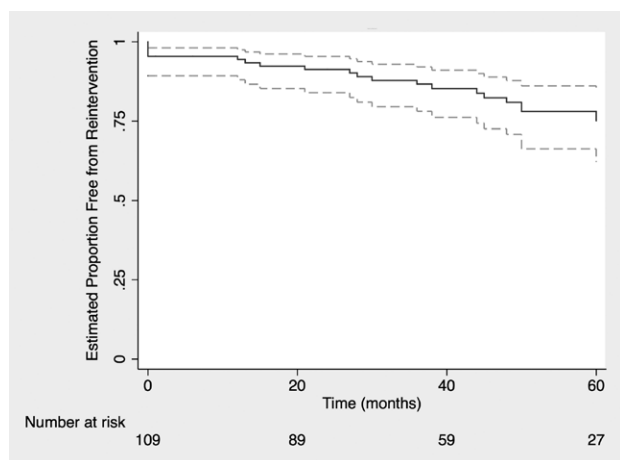


Figure 5. Estimated freedom from reintervention with 95% confidence intervals (dashed lines). One hundred ten patients were initiated along the study protocol. Five received covered Cheatham Platinum stents after predilation as a result of perceived aortic wall injury. One patient was lost to follow-up early; the remainder form the analysis cohort.

(14 of 105) of COAST patients have returned to the catheterization laboratory after CP stent implantation for stent redilation; however, none required additional therapy because of stent fracture or the development of excessive intimal hyperplasia. Twelve of these patients returned to the catheterization laboratory for stent redilation as part of a plan for staged therapy or related somatic growth, whereas 1 patient returned to the catheterization laboratory after routine follow-up MRI indicated the presence of a moderate-sized aneurysm. With these acknowledgments, the rate of unplanned reintervention in this cohort is lower than, but in the range of, the most recent and largest reported cohort of coarctation stenting by the Congenital Cardiovascular Interventional Study Consortium (CCISC).⁶ Other reports have suggested variable reintervention rates,^{1,2,7-11} but a more granular interpretation of these is confounded by heterogeneous subject populations, incomplete follow-up, and frequently unclear distinctions between planned and unplanned reinterventions. Similarly, comparison of this rate with historical surgical results must include the acknowledgment of selection bias with respect to anatomy, age at repair, and many other variables.¹ With this important caveat, reintervention after surgical repair of CoA appears to vary widely, depending on subject size, anatomy, era, and technique of repair.¹²⁻¹⁹ Except in unusual situations, there are no planned surgical reinterventions. In contrast, planned reintervention on endovascular stents, either as a part of a staged approach to severe arch obstruction or as a part of stent therapy in growing patients, is well documented.^{1,20-24} Second, and sometimes third, procedures are considered by some to be part of the tradeoff in selected high-risk and younger patients in avoidance of surgery. The prevalence of this practice is unknown, but small and probably increasing proportions of published cohorts include this population of patients. Appropriate concern has been expressed about the use of endovascular stents in smaller patients with potential for somatic and aortic growth.^{25,26} Although stent redilation is considered by many to be safe and effective, its role in stent fracture^{7,10} and the limits of safe expansion beyond an additional 2 to 3 mm have not been well characterized.^{20,23,27} In addition, the importance of patients lost to follow-up evaluation and care takes on added significance when residual or growth-related reobstruction is ensured by this approach. Forty-three of patients (41%) in this cohort had stents implanted at an age <15 years or diameters <14 mm, factors that have been associated with need for redilation owing to somatic growth,² and 10 patients had final minimal stent diameters of ≤ 11 mm. To date, 10 patients in the present series have returned to the cardiac catheterization laboratory for intended redilation of the CP stent, 3 of whom had covered stent placement for newly identified AWI prior to re-expansion. Inference from this small cohort should be done with caution, but neither stent fracture nor new AWI has been observed in the short term as a result of stent redilation. The long-term outcome of these patients and the remaining cohort of patients with smaller-diameter stent implants will need to be followed up closely before this practice can be recommended.

Hypertension

The prevalence of systemic arterial hypertension in the general population varies on the basis of both genetic and modifiable risk factors. As a segment of this broader population, patients with a history of CoA are confronted with both these baseline risks and

Table 6. Univariable Predictors of Reintervention

	Hazard Ratio (95% CI)	P Value
Weight, kg	0.97 (0.94 – 0.99)	0.02
Native-type coarctation	0.38 (0.12 – 1.22)	0.10
Decrease in stent minimum diameter, mm	2.10 (1.50 – 2.90)	<0.01
Aortic wall injury	8.08 (2.86 – 22.8)	<0.01

CI indicates confidence interval.

additional and probably interacting factors attendant to their CoA history. Both surgery and transcatheter therapy for CoA reduce systemic blood pressure and antihypertensive medication use, at least in the short term and midterm,^{1,6,14,15,26,28} but it is clear that patients with repaired CoA remain at high risk for hypertension even in the face of adequate anatomic surgical or transcatheter repair.^{7,14,15,19,26,29} In the present cohort, before stent implantation, 77% of patients were either hypertensive or on antihypertensive medications. At 12 months after implantation, only 42% were either hypertensive or on antihypertensive medications, a proportion of which remained fairly stable at 24 months. Baseline blood pressure and residual arch obstruction were associated with persistent hypertension (with or without medication use) at 12 and 24 months, despite modest rates of both planned reintervention and more aggressive medication administration. In contrast, persistent medication use was consistently associated with older age at intervention, likely reflecting a more complex interplay of population and patient-specific factors, perhaps colored by provider tendencies toward medication use in older patients, factors beyond the scope of our analysis. Nevertheless, if the primary goals of addressing CoA are preservation of ventricular systolic and diastolic function, reduction of systemic hypertension, and a reduction in the need for long-term antihypertension medication use, then these findings suggest that early intervention and reintervention for residual obstruction may provide favorable outcomes. More conclusive recommendations require a more focused study design to evaluate the role of timing of intervention on late blood pressure and clinical outcomes.

Stent Fracture

Fracture of endovascular stents is a known complication of stenting procedures, and although frequently asymptomatic, stent fracture can be associated with stent fragment embolization, vascular reobstruction, and vascular injury. Although stent fractures have been observed after CoA stenting,^{2,7,10,22,30,31} historically, their frequency has seemed to be lower than observed rates in other vascular territories such as right ventricle-to-pulmonary artery conduits and pulmonary arteries in which the mechanical stressors and risk factors for fracture are more thoroughly understood. In the present cohort, although no stent fractures were observed immediately after stent placement, we have observed some degree of stent fracture in 23 subjects during follow-up, with evidence of progression of stent fractures from single to multiple struts. The biomechanics of stent fracture have been reviewed,^{31,32} and although fracture has been noted anecdotally after stent redilation, the risk factors for stent fracture in the aorta are otherwise poorly characterized. In this cohort, we could find no association with stent length, subject age, native or recurrent CoA, or other clinical parameters.

However, stent fracture was more common with larger preimplantation and postimplantation coarctation and stent diameters. There are a number of possible explanations for this finding. It is possible that larger implant diameters serve as an indicator of more compliant aortas and that the adjacent highly pulsatile vessel wall imparts a greater cyclic stress to aortic stents than less compliant aortic walls, resulting in structural fatigue. It may also be that the in situ radial strength of these stents varies with their expanded diameter in a clinically important manner. Finally, because the CP stent is manually mounted on the delivery balloon, variables involved in this process may affect stent durability. Larger balloons entail a larger mass of pliable material on which the stent is mounted. It is possible that manual crimping of the stent onto these balloons results in application of irregular stresses that effect stent longevity. To date, no patient with stent fracture has experienced stent embolization, and stent fracture has not been associated with identified AWI or hemodynamic reobstruction. In response to these findings, the recommended fluoroscopic follow-up of the COAST cohort has been extended, and further analysis is ongoing.

Aortic Wall Injury

AWI, including dissection, aneurysm, or rupture, is a known complication of both angioplasty and stent therapy for CoA and is observed in the short term during initial intervention and in later follow-up.^{2,7,10,33} There is some evidence that acute AWI is more likely to occur with smaller initial coarctation diameters, with larger ratios of balloon to minimal aortic diameter, and when stent placement is preceded by balloon angioplasty,^{1,34} whereas predictors of late AWI are less well understood. Although several patients in this study received CCPS therapy at the discretion of their interventional cardiologist, we observed acute AWI, both small aortic aneurysms, in only 2 patients, a rate similar to prior publications.^{1,6,7,34} All late (after initial cardiac catheterization) AWI in this cohort consisted of aortic aneurysms, which were identified in 4 patients. It is notable that only one of these, a large aneurysm, was apparent by MRI; the other 3 were small, not identified by screening MRI or CT and found only during follow-up cardiac catheterization. Although it seems plausible that these aneurysms could have developed in the short interval between imaging and repeat cardiac catheterization, the sensitivity of MRI and CT for small aneurysms should also be questioned. Because it is composed of a platinum-iridium alloy, the CP stent generally causes less imaging artifact on MRI than traditional steel stents, but 1 aneurysm was also missed by CT imaging. Routine angiographic and hemodynamic reassessment after 12 months after stenting has been advocated in the past,³⁵ but this practice appears uncommon in the absence of other indications for repeat cardiac catheterization. Although the significance of these small aortic aneurysms is not known, until proven otherwise, it seems prudent to approach them as clinically important. All aortic aneurysms in this cohort were treated with covered stent placement. Prior published rates of late AWI after CoA stenting range from 0% to 6%, but follow-up imaging rates in these series were only 11% to 54%, so a reliable estimate of the true incidence of AWI in this situation must be considered unknown.^{1,7,33} Only 2 recent prospective studies reported >96% follow-up imaging.^{10,36} Both studies reported low rates of late aneurysms, but both include

significant proportions of covered stent use. The finding that at least 1 late aneurysm in this series was adjacent to the ends of the stents is also biased by the availability and use of covered stents for early AWI and by the fact that the study excluded patients with near-atretic CoAs, a population that may be at higher risk for AWI. Nevertheless, these findings serve as a reminder that although covered stents may confer some protective effect in selected populations,^{21,36,37} they are unlikely to prevent all AWI associated with COA stenting.

Arterial Access Injury

Although no patient was identified as symptomatic, we identified a modest number of patients with lower-extremity blood pressure differences concerning for pre-existing femoral artery injury. We presumed this to be attributable to prior cardiac catheterizations, although our estimate should be considered conservative because femoral artery patency was a prerequisite for this trial. We also found an equal number of patients with evidence of new femoral artery injury. Unfortunately, this study was not designed to detect or provide a complete analysis of this complication, and the use of lower-extremity blood pressures has limitations. Nevertheless, it is important to recognize that although femoral artery injury related to catheter-based therapies or arterial access in infancy is well known, it may also occur in the older child and adult and deserves closer attention.

Limitations

This study documents the early to midterm outcome of the CP stent in a selected cohort of patients under a defined prospective protocol, but there are limitations to these findings. In an attempt to provide a systematic and consistent protocol for endovascular stenting of CoA, the generalizability of our findings may be limited, and our findings may not apply as well or at all to other stents, patient groups, or implantation protocols. For example, rates of reintervention and AWI may differ for a variety of reasons, including the use of predilation, more severe lesions obstruction, and institution-specific approaches to CoA in smaller children and adults. Likewise, stent fracture rates and consequences may differ if implantation is performed in curved regions of the aorta. In addition, although this study was designed to demonstrate the safety and efficacy of the CP stent in CoA, it was not designed to fully evaluate late clinical outcomes or other potentially important aspects of CoA stenting. Therefore, although some information has been gleaned about CP stent fracture rates in this location, many unanswered questions remain. As additional data become available, some of these questions will be answered, but some may not.

Conclusions

Use of the CP stent in children and adults with CoA is safe and associated with persistent relief of aortic obstruction up to 2 years after implantation. Early and late aortic aneurysms occur, both within and at the margins of the stent, and require long-term vigilance. In this regard, CT imaging may be more sensitive than MRI for smaller aneurysms. Stent fractures occur, can progress over time, and appear to be associated with stent implantation size. However, to date, no stent fracture has been associated with reobstruction or stent embolization. The mechanism of this association and additional risk factors for stent fracture require further evaluation.

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References

- Forbes TJ, Kim DW, Du W, Turner DR, Holzer R, Amin Z, Hijazi Z, Ghasemi A, Rome JJ, Nykanen D, Zahn E, Cowley C, Hoyer M, Waight D, Gruenstein D, Javois A, Foerster S, Kreutzer J, Sullivan N, Khan A, Owada C, Hagler D, Lim S, Canter J, Zellers T, CCISC Investigators. Comparison of surgical, stent, and balloon angioplasty treatment of native coarctation of the aorta: an observational study by the CCISC (Congenital Cardiovascular Interventional Study Consortium). *J Am Coll Cardiol*. 2011;58:2664–2674. doi: 10.1016/j.jacc.2011.08.053.
- Butera G, Manica JL, Marini D, Piazza L, Chessa M, Filho RI, Sarmento Leite RE, Carminati M. From bare to covered: 15-year single center experience and follow-up in trans-catheter stent implantation for aortic coarctation. *Catheter Cardiovasc Interv*. 2014;83:953–963. doi: 10.1002/ccd.25404.
- Ringel RE, Vincent J, Jenkins KJ, Gauvreau K, Moses H, Lofgren K, Usmani K. Acute outcome of stent therapy for coarctation of the aorta: results of the Coarctation Of The Aorta Stent Trial. *Catheter Cardiovasc Interv*. 2013;82:503–510. doi: 10.1002/ccd.24949.
- Ringel RE, Gauvreau K, Moses H, Jenkins KJ. Coarctation of the Aorta Stent Trial (COAST): study design and rationale. *Am Heart J*. 2012;164:7–13. doi: 10.1016/j.ahj.2012.04.008.
- National High Blood Pressure Education Program Working Group on High Blood Pressure in Children and Adolescents. The fourth report on the diagnosis, evaluation, and treatment of high blood pressure in children and adolescents. *Pediatrics*. 2004;114:555–576.
- Holzer R, Qureshi S, Ghasemi A, Vincent J, Sievert H, Gruenstein D, Weber H, Alday L, Peirone A, Zellers T, Cheatham J, Slack M, Rome J. Stenting of aortic coarctation: acute, intermediate, and long-term results of a prospective multi-institutional registry: Congenital Cardiovascular Interventional Study Consortium (CCISC). *Catheter Cardiovasc Interv*. 2010;76:553–563. doi: 10.1002/ccd.22587.
- Qureshi AM, McElhinney DB, Lock JE, Landzberg MJ, Lang P, Marshall AC. Acute and intermediate outcomes, and evaluation of injury to the aortic wall, as based on 15 years experience of implanting stents to treat aortic coarctation. *Cardiol Young*. 2007;17:307–318. doi: 10.1017/S1047951107000339.
- Chessa M, Carozza M, Butera G, Piazza L, Negura DG, Bussadori C, Bossone E, Giamberti A, Carminati M. Results and mid-long-term follow-up of stent implantation for native and recurrent coarctation of the aorta. *Eur Heart J*. 2005;26:2728–2732. doi: 10.1093/eurheartj/ehi491.
- Hamdan MA, Maheshwari S, Fahey JT, Hellenbrand WE. Endovascular stents for coarctation of the aorta: initial results and intermediate-term follow-up. *J Am Coll Cardiol*. 2001;38:1518–1523.

10. Chakrabarti S, Kenny D, Morgan G, Curtis SL, Hamilton MC, Wilde P, Tometzki AJ, Turner MS, Martin RP. Balloon expandable stent implantation for native and recurrent coarctation of the aorta—prospective computed tomography assessment of stent integrity, aneurysm formation and stenosis relief. *Heart*. 2010;96:1212–1216. doi: 10.1136/hrt.2009.170928.
11. Johnston TA, Grifka RG, Jones TK. Endovascular stents for treatment of coarctation of the aorta: acute results and follow-up experience. *Catheter Cardiovasc Interv*. 2004;62:499–505. doi: 10.1002/ccd.20071.
12. Presbitero P, Demarie D, Villani M, Perinetti EA, Riva G, Orzan F, Bobbio M, Morea M, Brusca A. Long term results (15–30 years) of surgical repair of aortic coarctation. *Br Heart J*. 1987;57:462–467.
13. Kappetein AP, Zwinderman AH, Bogers AJ, Rohmer J, Huysmans HA. More than thirty-five years of coarctation repair: an unexpected high relapse rate. *J Thorac Cardiovasc Surg*. 1994;107:87–95.
14. Clarkson PM, Nicholson MR, Barratt-Boyes BG, Neutze JM, Whitlock RM. Results after repair of coarctation of the aorta beyond infancy: a 10 to 28 year follow-up with particular reference to late systemic hypertension. *Am J Cardiol*. 1983;51:1481–1488.
15. Hager A, Kanz S, Kaemmerer H, Schreiber C, Hess J. Coarctation Long-Term Assessment (COALA): significance of arterial hypertension in a cohort of 404 patients up to 27 years after surgical repair of isolated coarctation of the aorta, even in the absence of restenosis and prosthetic material. *J Thorac Cardiovasc Surg*. 2007;134:738–745. doi: 10.1016/j.jtcvs.2007.04.027.
16. McElhinney DB, Yang SG, Hogarty AN, Rychik J, Gleason MM, Zachary CH, Rome JJ, Karl TR, Decampoli WM, Spray TL, Gaynor JW. Recurrent arch obstruction after repair of isolated coarctation of the aorta in neonates and young infants: is low weight a risk factor? *J Thorac Cardiovasc Surg*. 2001;122:883–890. doi: 10.1067/mtc.2001.116316.
17. Fenchel G, Steil E, Seybold-Epting W, Seboldt H, Apitz J, Hoffmeister HE. Repair of symptomatic aortic coarctation in the first three months of life: early and late results after resection and end-to-end anastomosis and subclavian flap angioplasty. *J Cardiovasc Surg (Torino)*. 1988;29:257–263.
18. van Heurn LW, Wong CM, Spiegelhalter DJ, Sørensen K, de Leval MR, Stark J, Elliott MJ. Surgical treatment of aortic coarctation in infants younger than three months: 1985 to 1990: success of extended end-to-end arch aortoplasty. *J Thorac Cardiovasc Surg*. 1994;107:74–85—discussion 85–6.
19. Brown ML, Burkhart HM, Connolly HM, Dearani JA, Cetta F, Li Z, Oliver WC, Warnes CA, Schaff HV. Coarctation of the aorta: lifelong surveillance is mandatory following surgical repair. *J Am Coll Cardiol*. 2013;62:1020–1025. doi: 10.1016/j.jacc.2013.06.016.
20. Zanjani KS, Sabi T, Moysich A, Ovroutski S, Peters B, Miera O, Kühne T, Nagdyman N, Berger F, Ewert P. Feasibility and efficacy of stent redilatation in aortic coarctation. *Catheter Cardiovasc Interv*. 2008;72:552–556. doi: 10.1002/ccd.21701.
21. Bruckheimer E, Dagan T, Amir G, Birk E. Covered Cheatham-Platinum stents for serial dilation of severe native aortic coarctation. *Catheter Cardiovasc Interv*. 2009;74:117–123. doi: 10.1002/ccd.21923.
22. Thanopoulos BD, Giannakoulas G, Giannopoulos A, Galdo F, Tsaoussis GS. Initial and six-year results of stent implantation for aortic coarctation in children. *Am J Cardiol*. 2012;109:1499–1503. doi: 10.1016/j.amjcard.2012.01.365.
23. Duke C, Rosenthal E, Qureshi SA. The efficacy and safety of stent redilatation in congenital heart disease. *Heart*. 2003;89:905–912.
24. Butera G, Gaio G, Carminati M. Redilatation of e-PTFE covered CP stents. *Catheter Cardiovasc Interv*. 2008;72:273–277. doi: 10.1002/ccd.21609.
25. Mullins CE. Inappropriate stents: primary cause of failure of stent redilatation in coarctation of the aorta. *Catheter Cardiovasc Interv*. 2008;72:557–558. doi: 10.1002/ccd.21786.
26. Morgan GJ, Lee KJ, Chaturvedi R, Bradley TJ, Mertens L, Benson L. Systemic blood pressure after stent management for arch coarctation implications for clinical care. *JACC Cardiovasc Interv*. 2013;6:192–201. doi: 10.1016/j.jcin.2012.10.009.
27. McMahon CJ, El-Said HG, Grifka RG, Fraley JK, Nihill MR, Mullins CE. Redilatation of endovascular stents in congenital heart disease: factors implicated in the development of restenosis and neointimal proliferation. *J Am Coll Cardiol*. 2001;38:521–526.
28. Vohra HA, Adamson L, Haw MP. Does surgical correction of coarctation of the aorta in adults reduce established hypertension? *Interact Cardiovasc Thorac Surg*. 2009;8:123–127. doi: 10.1510/icvts.2008.185736.
29. Cohen M, Fuster V, Steele PM, Driscoll D, McGoon DC. Coarctation of the aorta: long-term follow-up and prediction of outcome after surgical correction. *Circulation*. 1989;80:840–845.
30. Golden AB, Hellenbrand WE. Coarctation of the aorta: stenting in children and adults. *Catheter Cardiovasc Interv*. 2007;69:289–299. doi: 10.1002/ccd.21009.
31. Breinholt JP, Nugent AW, Law MA, Justino H, Mullins CE, Ing FF. Stent fractures in congenital heart disease. *Catheter Cardiovasc Interv*. 2008;72:977–982. doi: 10.1002/ccd.21742.
32. McElhinney DB, Marshall AC, Schievano S. Fracture of cardiovascular stents in patients with congenital heart disease: theoretical and empirical considerations. *Circ Cardiovasc Interv*. 2013;6:575–585. doi: 10.1161/CIRCINTERVENTIONS.113.000148.
33. Forbes TJ, Moore P, Pedra CA, Zahn EM, Nykanen D, Amin Z, Garekar S, Teitel D, Qureshi SA, Cheatham JP, Ebeid MR, Hijazi ZM, Sandhu S, Hagler DJ, Sievert H, Fagan TE, Ringwald J, Du W, Tang L, Wax DF, Rhodes J, Johnston TA, Jones TK, Turner DR, Pass R, Torres A, Hellenbrand WE. Intermediate follow-up following intravascular stenting for treatment of coarctation of the aorta. *Catheter Cardiovasc Interv*. 2007;70:569–577. doi: 10.1002/ccd.21191.
34. Forbes TJ, Garekar S, Amin Z, Zahn EM, Nykanen D, Moore P, Qureshi SA, Cheatham JP, Ebeid MR, Hijazi ZM, Sandhu S, Hagler DJ, Sievert H, Fagan TE, Ringwald J, Du W, Tang L, Wax DF, Rhodes J, Johnston TA, Jones TK, Turner DR, Pedra CA, Hellenbrand WE; Congenital Cardiovascular Interventional Study Consortium (CCISC). Procedural results and acute complications in stenting native and recurrent coarctation of the aorta in patients over 4 years of age: a multi-institutional study. *Catheter Cardiovasc Interv*. 2007;70:276–285. doi: 10.1002/ccd.21164.
35. Tanous D, Benson LN, Horlick EM. Coarctation of the aorta: evaluation and management. *Curr Opin Cardiol*. 2009;24:509–515. doi: 10.1097/HCO.0b013e328330cc22.
36. Sohrabi B, Jamshidi P, Yaghoubi A, Habibzadeh A, Hashemi-Aghdam Y, Moin A, Kazemi B, Ghaffari S, Abdolhazadeh Baghayi MR, Mahmoodi K. Comparison between covered and bare Cheatham-Platinum stents for endovascular treatment of patients with native post-ductal aortic coarctation: immediate and intermediate-term results. *JACC Cardiovasc Interv*. 2014;7:416–423. doi: 10.1016/j.jcin.2013.11.018.
37. Tzifa A, Ewert P, Brzezinska-Rajszyz G, Peters B, Zubrzycka M, Rosenthal E, Berger F, Qureshi SA. Covered Cheatham-Platinum stents for aortic coarctation: early and intermediate-term results. *J Am Coll Cardiol*. 2006;47:1457–1463. doi: 10.1016/j.jacc.2005.11.061.

CLINICAL PERSPECTIVE

The Coarctation of the Aorta Stent Trial (COAST) was designed to assess the safety and efficacy of the Cheatham Platinum stent when used in children and adults with native or recurrent coarctation. Analysis of acute outcomes previously documented no procedural deaths, serious adverse events, or surgical intervention. The clinical follow-up to 2 years is presented here, during which all patients experienced immediate and lasting relief of aortic obstruction. Rates of hypertension and medication use decreased from baseline to 12 months and remained largely unchanged at 2 years. During the follow-up, 6 aortic aneurysms have been identified: 5 were successfully treated with cover stent placement, and 1 resolved without intervention. Stent fracture has been identified at all time points, but no fracture has resulted in loss of stent integrity, stent embolization, aortic wall injury, or reobstruction. Reintervention appears common and is related to early and late aortic wall injury and the need for re-expansion of small-diameter stents.

Intermediate Outcomes in the Prospective, Multicenter Coarctation of the Aorta Stent Trial (COAST)

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