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

Running title: Meadows et al.; Intermediate Outcomes in COAST

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Abstract

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—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 cover stent placement, 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. 12 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 after 2 years.

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

Clinical Trial Registration Information—ClinicalTrials.gov. Identifier: NCT00552812.

Key words: coarctation of the aorta, stent, catheterization
Introduction

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 upon 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. While 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.\textsuperscript{1,2} As a result, stent placement is usually preferred when patient size and CoA anatomy are suitable. However, there are no FDA 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\textsuperscript{®} was designed to have rounded ends to lessen the risk of aortic wall injury and \textasciitilde20\% shortening at 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. Acute outcomes have been reported.\textsuperscript{3} We report here the follow-up to 24 months and beyond.

Methods

Details of the COAST study design were reported previously.\textsuperscript{3,4} Briefly, COAST is a prospective, multi-center, single-arm clinical study involving 19 pediatric cardiology centers in the United States (clinicaltrials.gov ID: NCT00552812). The protocol for COAST received approval under an Investigational Device Exemption (IDE) from the FDA on 8/3/2007. The
study received IRB approval from all participating institutions and subjects provided 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

Following baseline anatomic and physiologic assessment, patients underwent initial compliance testing and sizing utilizing 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 lesser 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 less than 80% of the maximum balloon diameter (e.g., less than 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 BIB® (balloon-in-balloon) catheter. Because of the known risk of aortic wall complications during CoA intervention, NuMED covered CP stents (CCPS) 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 (ClinicalTrials.gov ID: 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 anti-
hypertension 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 prior to discharge and at 1, 6, 12, 24, 48 and 60 months post-procedure. Magnetic resonance imaging (MRI) or commuted 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 post-implant to look for stent fractures. All procedural angiograms, MRI, and fluoroscopic images were reviewed by core laboratories.

Outcome Variables

Four primary outcome variables were defined: two efficacy outcomes (reduction in upper-to-lower extremity systolic blood pressure measurements, and hospital length of stay) and two 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 to pre-specified 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 anti-hypertension medication use. Blood pressures were recorded as the average of 3 measurements in each extremity, as reported previously;4 ambulatory and exercise blood pressure assessment was not performed. Because of a broad range of subject ages we utilized gender and age specific blood pressure norms in patients <18 years of
age to define a dichotomous outcome of systemic arterial hypertension (>95th percentile). For 18
years of age and over we used systolic and diastolic levels of 140 and 90mmHg, 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 either: 1. a decrease in stent
diameter ≥20% in either the maximal or minimal measurement in any radiographic projection,
compared with immediately post-implant; 2. complete circumferential or longitudinal stent
fracture; 3. embolization of any portion of the stent; or 4. protrusion of stent through the aortic
wall. Other adverse events were classified as: 1. not serious, 2. somewhat serious, or 3. Serious,
as previously defined.

Statistical Analysis

Descriptive statistics are presented as mean ± standard deviation or median (minimum -
maximum). Bivariate comparison of pre- and post-implantation catheterization data and
subsequent blood pressures were performed using the paired t-test. Comparison of means or
proportions between populations were performed by unpaired t-test or Wilcoxon rank-sum test
test based upon distribution, and Fisher’s 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 like reintervention were
obtained from Cox Proportional Hazards modeling.

Results

Between 2008 and 2010, 168 patients were consented for participation in the trial. Of these, 55
were excluded based upon pre-specified criteria. Five were perceived to have aortic wall injury
during predilation, received CCPS and were transferred to the COASTII 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.

**Acute Results**

Acute 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 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 post-procedural 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 blood pressure difference (from 29 ± 14 mmHg 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 where 99% had a blood pressure difference <20 mmHg, and 94% were <15mmHg. 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 of 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 (pre-intervention) to 12 months, was 30 ± 22 mmHg.

Systemic Arterial Hypertension and Anti-hypertension Medication Use

Overall trends in systemic arterial hypertension and anti-hypertension medication use are represented in Figure 3. At baseline, and in the setting of an average 29mmHg pressure difference from upper-to-low extremity, 63 patients (61%) demonstrated a right arm blood pressure meeting criteria for systolic hypertension. An additional 17 (16%) patients had a normal blood pressure on 1 or more anti-hypertensive medications. At 12 months, with an average upper-to-lower systolic blood pressure difference of -1 ±15mmHg, 19% of patients remained hypertensive and 28% continued to receive anti-hypertension 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 following stent placement. Persistent systemic hypertension at 12 and 24 months post-implant was associated with higher baseline upper extremity blood pressure and residual blood pressure difference, but not gender or age at intervention, Table 4.

At baseline, 40 (38%) patients were on at least one anti-hypertension medication. At 12 months after implant, 20 (50%) of these patients had stopped (n=17) or decreased the number (n=3) of anti-hypertension medications, while 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 (n=1) or discontinued (n=4) the number of anti-hypertensive medications, and 1 had increased the number of medications. Sixty-five patients (74%) were receiving no medications, 13 (15%) were receiving 1 medication, and 10 (11%) were receiving 2 or more medications directed at blood pressure control. Continued use of
any anti-hypertensive medication at 12 and 24 months was associated with older age at stent implantation but not gender, baseline upper extremity systolic blood pressure or residual blood pressure gradient, Table 4.

**Stent Fracture and Integrity**

Immediate post-implant 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, while 6 involved fracture of multiple struts. Factors related to stent fracture included larger CoA minimal luminal diameter and post-implantation minimal stent diameters. Association with post-implantation maximal stent diameter and the ratio of post-implantation minimal-to-maximal stent diameters was weaker and statistically nonsignificant, and there was no association apparent with additional parameters, including stent lot number, length or other clinical parameters, 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 aortic wall injury, 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 and 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 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. While imaging beyond 24 months remains incomplete; 3 patients who underwent planned cardiac catheterization for stent re-expansion at 30, 45 and 50 months post-implant were found to have small stent-related aneurysms that were not apparent on routine MRI/CT imaging obtained prior to cardiac catheterization. Figure 4. These patients were treated with CCPS implantation and enrolled in the COAST II trial.

Re-Intervention

There were no surgical interventions related to the CoA or stent. As discussed above, 5 patients had CCPS implantations prior to CP stent implantation. Four patients underwent transcatheter reintervention within 24 months after initial implant. Three of these 4 patients underwent re-expansion of the CP stent at 12, 13 and 21 months as part of either an intentionally staged approach or to compensate for somatic growth. As described above, one additional subject 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 brought 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 aortic wall injury 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 and smaller patient weight and final stent diameter at initial implantation were associated with reintervention, Table 6.

Arterial Access Sites and Lower Extremity Blood Pressures

As noted in the acute outcomes study, somewhat serious procedural access complications occurred in 2 patients, with 1 large groin hematoma and 1 femoral arteriovenous fistula, requiring surgical repair. While 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 10-19% lower in the leg used for stent delivery, compared to the contralateral leg, as suspicious for mild femoral artery injury and > 20% lower as suggestive of important arterial injury. Utilizing 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 lesser 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, while 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 the diameter of balloon utilized for stent delivery (used as a surrogate for sheath size). Finally, hemostasis was assisted (Perclose [8], Prostar [5] or Syvek Patch [3]) in sixteen (15%) patients, and there was no relationship between any type of assisted hemostasis and subsequently identified femoral artery injury.

Discussion

Clinical and hemodynamic outcomes and reintervention rates

Acute reductions in upper to lower extremity blood pressure measurements are sustained in later follow-up after CP stent implantation with >90% of patients having pressure differences of less than 15mmHg. Reintervention does occur. To date 13% (14/105) of COAST patients have returned to the catheterization lab 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 lab for stent redilation as part of a plan for staged therapy or related somatic growth, while one patient returned to the catheterization lab after routine follow up MRI indicated the presence of a moderate sized aneurysm. With these acknowledgements, 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 (CCISC). Other reports have suggested variable reintervention rates, 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 to historical
surgical results must include the acknowledgement of selection bias with respect to anatomy, age at repair and many other variables.\textsuperscript{1} With this important caveat, reintervention after surgical repair of CoA appears to vary widely, depending upon subject size, anatomy, era and technique of repair.\textsuperscript{12-19} Except in unusual situations there are no planned surgical reinterventions. In contrast, planned reintervention upon 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.\textsuperscript{1,20-24} Second, and sometimes third, procedures are considered by some to be part of the trade-off 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.\textsuperscript{25,26} While stent redilation is considered by many to be safe and effective, its role in stent fracture\textsuperscript{7,10} and the limits of safe expansion beyond an additional 2-3mm have not been well characterized.\textsuperscript{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 assured by this approach. Forty-three (41\%) of patients in this cohort had stents implanted at an age < 15 years or diameters < 14mm, factors that have been associated with need for redilation due to somatic growth,\textsuperscript{2} and 10 patients had final minimal stent diameters of $\leq 11$mm. To date 10 patients in the present series have returned to the cardiac catheterization laboratory for intended re-dilation 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 taken with caution, but neither stent fracture nor new AWI have been observed acutely as a result of stent re-dilation. The long-term outcome of these patients and the remaining cohort of patients with smaller diameter stent implants will need to be followed.
closely before this practice can be recommended.

**Hypertension**

The prevalence of systemic arterial hypertension in the general population varies based upon 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 as well as additional and probably interacting factors attendant to their CoA history. Both surgical and transcatheter therapy for CoA reduce systemic blood pressure and anti-hypertensive medication use, at least in the short and mid-term,\(^1,6,14,15,26,28\) 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, prior to stent implantation, 77\% of patients were either hypertensive or on anti-hypertensive medications. At 12 months post-implant, only 42\% were either hypertensive or on anti-hypertensive 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 utilization 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 upon late blood pressure and clinical outcomes.

Stent Fracture

Fracture of endovascular stents is a known complication of stenting procedures, and while 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, 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 where the mechanical stressors and risk factors for fracture are more thoroughly understood. In the present cohort, while no stent fractures were observed immediately following 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, and while anecdotally fracture has been noted 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 pre and post-implant 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 upon the delivery balloon variables involved in this process may affect stent durability. Larger balloons entail a larger mass of pliable material upon 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 aortic wall injury or hemodynamic reobstruction. In response to these findings the recommended fluoroscopic follow-up of the COAST cohort has been extended and further analysis is on-going.

**Aortic wall injury**

AWI, including dissection, aneurysm or rupture, is a known complication of both angioplasty and stent therapy for CoA, and is observed acutely during initial intervention as well as in later follow-up.\(^1,6,7,34\) There is some evidence that acute AWI is more likely to occur with smaller initial coarctation diameters, larger balloon to minimal aortic diameter ratios, and when stent placement is preceded by balloon angioplasty,\(^1,34\) whereas predictors of late AWI are less well understood. While 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 only found during follow-up cardiac catheterization. While 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 that traditional steel stents, but 1 aneurysm was also missed by CT imaging. Routine angiographic and hemodynamic reassessment after 12 months post-stenting has been advocated in the past,\(^35\) but this practice appears uncommon in the
absence of other indications for repeat cardiac catheterization. While 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 - 6%, but follow-up imaging rates in these series were only 11-54%, so a reliable estimate of the true incidence of AWI in this situation must be considered unknown. Only 2 recent prospective studies reported >96% follow-up imaging. Both studies reported low rates of late aneurysms, however both include significant proportions of covered stent use. The finding that at least one late aneurysm in this series were 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 to remind us that while covered stents may confer some protective effect in selected populations, 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 preexisting femoral artery injury. We presumed this to be due to prior cardiac catheterizations, although our estimate should be considered conservative since 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 while 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 mid-term 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 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 narrowing obstruction and institutional 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, while this study was designed to demonstrate 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. As such, while some information has been gleaned about CP stent fracture rates in this location there remain many unanswered questions. 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 implant. 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 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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Appendix: Participating Institutions and Principal Investigators: John Moore, MD - Rady Children’s Hospital and Health Center; Evan Zahn, MD - Miami Children’s Hospital; Thomas Jones, MD - Children's Hospital and Regional Medical Center; Doff McElhinney, MD and Lisa Bergersen, MD; Children’s Hospital Boston; William Hellenbrand, MD and Julie Vincent, MD, Children’s Hospital of New York, New York; Allison Cabalka, MD - Mayo Clinic; Frank Ing, MD - Texas Children’s Hospital; Thomas Forbes, MD - Children’s Hospital of Michigan; Jonathan Rome, MD - Children’s Hospital of Philadelphia; Michael Slack, MD - Children’s National Medical Center; Phillip Moore, MD - University of California San Francisco; Robert Beekman, MD - Cincinnati Children’s Hospital and Medical Center; Richard Ringel, MD - Johns Hopkins Children's Center; Jacqueline Kreutzer, MD - Children’s Hospital of Pittsburgh; Thomas Zellers, MD - Children’s Medical Center Dallas; Larry Latson, MD and Lourdes Prieto, MD - Cleveland Clinic Foundation; John Rhodes, MD - Duke University; Robert Vincent and Dennis Kim, MD - Children’s Healthcare of Atlanta; John Cheatham, MD - Nationwide Children’s Hospital.

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References:


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**Table 1.** COAST Trial Inclusion and Exclusion Criteria.

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<th>Pre-catheterization Inclusion Criteria</th>
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<tr>
<td>• Native or recurrent aortic coarctation</td>
<td>• Age &gt; 60 years</td>
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<td>• Weight &lt; 35 kg</td>
<td>• Bloodstream infection</td>
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<td>• Cuff blood pressure difference or catheter measured systolic coarctation gradient 20mmHg</td>
<td>• Connective tissue disorders, including Marfans, Turners or inflammatory aortitis</td>
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<td>• Prior stent placement</td>
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<td>• Aortic aneurysm</td>
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<td>• Pregnancy</td>
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<td>• Subject lacking ability to consent</td>
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<tr>
<th>Catheterization Inclusion Criteria</th>
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<td>• Coarctation involving the aortic isthmus or first segment of the descending thoracic aorta</td>
<td>• Coarctation involving curved region of aorta, transverse arch or beyond mid thoracic aorta</td>
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<tr>
<td>• Coarctation found to be compliant on pre-stent balloon dilation</td>
<td>• Anatomic location precluding safe stent placement</td>
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<td>• Patency of at least one femoral artery</td>
<td>• Complete aortic atresia</td>
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**Table 2.** Cardiac catheterization data before and after CP stent placement (means ± SD).

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<th>Pre-Implant</th>
<th>Post-Implant</th>
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<td>Ascending aorta systolic pressure, mmHg</td>
<td>109 ± 22</td>
<td>107 ± 20</td>
<td>0.22</td>
</tr>
<tr>
<td>Descending aorta systolic pressure, mmHg</td>
<td>80 ± 17</td>
<td>105 ± 20</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Average ascending to descending aorta systolic pressure difference, mmHg</td>
<td>29 ± 14</td>
<td>2 ± 4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Average minimal luminal diameter, mm</td>
<td>7.9 ± 2.7</td>
<td>14 ± 3</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>
Table 3. Blood pressures and upper to lower extremity systolic pressure differences (means ± SD).

<table>
<thead>
<tr>
<th></th>
<th>Baseline, n=104</th>
<th>12 Months, n=91</th>
<th>24 Months, n=88</th>
</tr>
</thead>
<tbody>
<tr>
<td>Upper extremity SBP, mmHg</td>
<td>140 ± 16</td>
<td>123 ± 12</td>
<td>122 ± 14</td>
</tr>
<tr>
<td>Lower extremity SBP, mmHg</td>
<td>110 ± 16</td>
<td>123 ± 15</td>
<td>125 ± 16</td>
</tr>
<tr>
<td>Systolic blood pressure difference, mmHg</td>
<td>29 ± 17</td>
<td>- 1 ± 15</td>
<td>- 3 ± 15</td>
</tr>
<tr>
<td>Number (%) with pressure difference &lt;20mmHg</td>
<td>82 (90%)</td>
<td>85 (90%)</td>
<td></td>
</tr>
<tr>
<td>Number (%) with pressure difference &lt;15mmHg</td>
<td>76 (84%)</td>
<td>79 (90%)</td>
<td></td>
</tr>
</tbody>
</table>

Table 4. Factors associated with persistent systemic arterial hypertension and anti-hypertension medication use.

<table>
<thead>
<tr>
<th>Factors associated with persistent systemic arterial hypertension</th>
<th>12 months</th>
<th>24 months</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Odds Ratio (95% CI)</td>
<td>p</td>
</tr>
<tr>
<td>Gender, male</td>
<td>0.72 (0.17 – 2.98)</td>
<td>0.65</td>
</tr>
<tr>
<td>Age at Implant, years</td>
<td>0.96 (0.89 – 1.02)</td>
<td>0.19</td>
</tr>
<tr>
<td>Baseline systolic blood pressure, mmHg</td>
<td>1.06 (1.01 – 1.12)</td>
<td>0.01</td>
</tr>
<tr>
<td>Residual blood pressure gradient</td>
<td>1.07 (1.02 – 1.12)</td>
<td>&lt;0.05</td>
</tr>
</tbody>
</table>

Factors associated with any anti-hypertension medication use

<table>
<thead>
<tr>
<th>Factors associated with any anti-hypertension medication use</th>
<th>Odds Ratio (95% CI)</th>
<th>p</th>
<th>Odds Ratio (95% CI)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender, male</td>
<td>1.70 (0.54 – 5.35)</td>
<td>0.37</td>
<td>3.16 (0.81 – 12.31)</td>
<td>0.10</td>
</tr>
<tr>
<td>Age at Implant, years</td>
<td>1.06 (1.01 – 1.11)</td>
<td>0.02</td>
<td>1.08 (1.02 – 1.13)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Baseline systolic blood pressure, mmHg</td>
<td>1.02 (0.99 – 1.06)</td>
<td>0.16</td>
<td>1.01 (0.97 – 1.04)</td>
<td>0.74</td>
</tr>
<tr>
<td>Residual blood pressure gradient</td>
<td>1.02 (0.99 – 1.06)</td>
<td>0.16</td>
<td>1.02 (0.98 – 1.05)</td>
<td>0.39</td>
</tr>
</tbody>
</table>
Table 5. Analysis of Factors Associated with Stent Fracture at 24 Months Post-Implant

<table>
<thead>
<tr>
<th></th>
<th>Stent Fracture, n=11</th>
<th>No Stent Fracture, n=85</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>21 ±10</td>
<td>21 ±11</td>
<td>0.95</td>
</tr>
<tr>
<td>Gender, male</td>
<td>73%</td>
<td>68%</td>
<td>0.78</td>
</tr>
<tr>
<td>Primary Indication</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Native coarctation</td>
<td>4</td>
<td>43</td>
<td>0.21</td>
</tr>
<tr>
<td>Recurrent coarctation</td>
<td>7</td>
<td>33</td>
<td></td>
</tr>
<tr>
<td>Coarctation minimum diameter, mm</td>
<td>9.8 ±2.0</td>
<td>7.6 ±2.7</td>
<td>0.01</td>
</tr>
<tr>
<td>Minimum stent diameter at implant, mm</td>
<td>16.4 ±2.6</td>
<td>14.2 ±2.5</td>
<td>0.01</td>
</tr>
<tr>
<td>Maximum stent diameter at implant, mm</td>
<td>17.8 ±2.7</td>
<td>16.2 ±2.7</td>
<td>0.09</td>
</tr>
<tr>
<td>Minimal to maximal stent ratio</td>
<td>0.92 ±0.06</td>
<td>0.88 ± 0.07</td>
<td>0.07</td>
</tr>
</tbody>
</table>

Table 6. Univariable Predictors of Reintervention.

<table>
<thead>
<tr>
<th></th>
<th>Hazard Ratio (95% CI)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight, kg</td>
<td>0.97 (0.94 – 0.99)</td>
<td>0.02</td>
</tr>
<tr>
<td>Native type coarctation</td>
<td>0.38 (0.12 – 1.22)</td>
<td>0.10</td>
</tr>
<tr>
<td>Decrease in stent minimum diameter, mm</td>
<td>2.10 (1.50 – 2.90)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Aortic wall injury</td>
<td>8.08 (2.86 – 22.8)</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

Figure Legends:

Figure 1. COAST Flow Diagram.

Figure 2. Aortic angiography prior to (A) and following (B) CP stent implantation.

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

**Figure 4.** Aortic angiograms prior to (A) and following (B) CP stent implantation for CoA. Although no 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 MRI did not conclusively demonstrate AWI (not shown), however, at cardiac catheterization for intended stent reexpansion an aneurysm was noted in this area (C). A CCPS was implanted (D) and the patient was transferred to the COASTII trial.

**Figure 5.** Estimated Freedom from Reintervention with 95% confidence intervals (dashed lines). 110 patients were initiated along the study protocol. Five received CCPS after predilation due to perceived AWI, 1 was lost to follow-up early on and the remainder form the analysis cohort.
Figure 1
Figure 4
Intermediate Outcomes in the Prospective, Multicenter Coarctation of the Aorta Stent Trial (COAST)
Jeffery Meadows, Matthew Minahan, Doff B. McElhinney, Kerry McEnaney and Richard Ringel on behalf of the COAST Investigators

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