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Roll-in Experience from the Cardiovascular Outcomes with Renal Atherosclerotic Lesions (CORAL) Study

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Introduction

The Cardiovascular Outcomes with Renal Atherosclerotic Lesions (CORAL) study is a multicenter randomized clinical trial examining whether renal artery stenting modifies the natural history for patients with atherosclerotic renal artery stenosis and hypertension or chronic kidney disease. In prior renal artery stent randomized studies(1, 2), concerns have been raised about the number and severity of procedural complications, failed procedures, and inclusion of subjects without clinically significant renal artery stenosis(3, 4). On the

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recommendation of the CORAL Interventional Management Committee (IMC) a roll-in qualification phase was adopted at each site prior to allowing investigators to participate in the randomized phase of the study. The purposes were: 1) to ensure the proficiency of the investigators; 2) to ensure that the study site could comply with proper renal angiographic methods and image submission requirements of the Angiographic Core Lab; and 3) to provide experience with the investigational short-tip renal Angioguard (Cordis, a Johnson and & Johnson Co, Warrenton, NJ) distal embolic protection device (DPD). The current work describes the experience and results from the roll-in phase of the CORAL Study.

Materials and Methods

Design

CORAL is a clinical trial registered with [ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT00081731) (NCT00081731). The CORAL roll-in experience is a nonrandomized cohort study. The study was designed by the study authors, and data was analyzed by statisticians at the data coordinating center under the direction of one of the authors (J.M.M.).

Site selection and Interventional Investigator Qualification

Clinical centers were screened by a multidisciplinary site selection committee consisting of an interventional radiologist (T.P.M.), an interventional cardiologist (K.A.R.), and a hypertensionologist (K.J.). Investigators were required to have prior experience with at least 25 renal artery stent procedures and board certification in either interventional radiology, interventional cardiology, or vascular surgery, and were required to designate a hypertensionologist at each site who would be responsible for medical management but was not an interventionalist. Before initiation of the study at each site, the protocol and informed consent documents were approved by the Institutional Review Board. Initially, to complete the roll-in phase, each clinical center investigator was required to successfully conduct two consecutive cases using the Angioguard® (Cordis, Inc., Warren, NJ) distal embolic protection device and the Genesis® stent (Cordis, Inc.). Since renal artery stenting was a common clinical procedure and all of our investigators had experience with it, the number of roll-in cases that were required was low and only done so that procedure and data compliance could be confirmed by the angiography core lab. Once approved, sites entered the randomization phase.

Patient population

The CORAL Study required participants to have one or more atherosclerotic renal artery stenoses of at least 60% in diameter as determined by an onsite investigator using either computer-generated or manual caliper measurements, with either a systolic blood pressure of at least 160 mm Hg while on two blood pressure medications from different classes of drugs or chronic kidney disease with an eGFR rate of less than 60 ml/minute/1.73m². Roll-in enrollment inclusion criteria included patients with an ARAS less than 2 cm in length, with the reference artery being between 3.5 mm and 8 mm in diameter. Initially, the CORAL Study required translesional pressure measurements for moderate diameter stenoses ($\geq 60\%$), and the use of a distal embolic protection device during stent placement.

Although renal artery stenting was common in clinical practice, translational pressure measurements and use of a distal embolic protection device were not routine.

Roll-in procedures

Two roll-in cases utilizing the Genesis® stent on the Aviator® balloon (Cordis, a Johnson & Johnson Co, Warren, NJ) and the Angioguard® (Cordis, a Johnson & Johnson Co) distal embolic protection device were to be performed. All renal artery stenosis $\geq 60\%$ in diameter were to undergo revascularization.

The CORAL Intervention Management Committee (IMC) made recommendations regarding the renal stent procedure. When recruitment began, simultaneous trans-lesional pressure measurements were required for lesions that measured $\geq 60\%$ but $<80\%$, with a threshold of 20 mm Hg systolic gradient for inclusion in the study. When trans-lesion pressure measurements were performed, no "pullback" pressures were accepted or included in the analysis. Simultaneous systolic, diastolic and mean pressure measurements proximal and distal to the lesion were obtained using either a 0.014 inch diameter pressure wire or a 3–4F catheter across the lesion. The exact method, i.e., device, catheter, or guide catheter or sheath used to acquire the simultaneous measurements was at the discretion of the site investigator. Pressure tracings from the measurements performed by site investigator were submitted to the Angiographic Core Laboratory for analysis.

Beginning with study protocol version 6.0, which became active during the fourth quarter of 2006, the requirements for trans-lesional pressure measurements and use of a DPD became optional (at the discretion of the operator), and thereafter, investigators were only required to perform one successful roll-in procedure with the Genesis® stent prior to entering the randomized phase of the study. Images were to be obtained pre- and post-intervention, and sent to the Angiographic Core Laboratory at the University of Virginia (UVA CORC; Alan H. Matsumoto, M.D., Principal Investigator) in DICOM format for blinded and unbiased evaluation. Specific parameters and data were evaluated and recorded on a case report form approved by the CORAL Study Steering Committee. The case report forms were then transmitted from the Angiographic Core Lab to the centralized Data Collection Center (Harvard Cardiovascular Research Institute, Donald Cutlip, M.D., Principal Investigator).

Clinical Endpoints

Roll-in participants had blood pressure measurements and serum creatinine levels obtained at baseline and at short-term follow-up (2–4 weeks) after the renal stent procedure. This interval was chosen to observe short-term differences in kidney function or blood pressure that might be attributable to the procedure. Office seated blood pressures were measured using standard methods(5) and creatinine levels were measured at the University of Minnesota Core Laboratory under the direction of Dr. Michael Steffes. Patients were contacted by phone or in person at 30 days and 9-months after the procedure and asked about the occurrence of any adverse events or a subsequent renal artery revascularization procedure.

Procedural Endpoints

Images were reviewed for the diagnostic quality of the images, the percent diameter stenosis before and after stenting using a validated quantitative vascular analysis program (QAngioXA software, Medis Medical Imaging, Leiden, the Netherlands), and the presence of an angiographic complication. Intra-procedural complications were rated as minor or major and were defined as follows:

- Minor: spasm of the renal artery or any of its branches
- Major: renal artery thrombus formation, embolus, dissection, perforation or occlusion of a branch or main renal artery or pseudoaneurysm

Site investigator-reported adverse events were collected at baseline, 2–4 weeks, 30-days and nine months. Adverse event data were examined to determine whether participants experienced any events that would be considered endpoints in the CORAL Study. The adverse events that were components of the primary endpoint in the CORAL Study were: myocardial infarction, stroke, congestive heart failure, progressive renal insufficiency, and death. Since roll-in participants were not part of the randomized study, these data were not independently adjudicated by a blinded endpoint committee.

Statistical Analyses

Study data are presented as continuous (mean $\pm$ s.d.) and categorical data. All analyses were performed using R version 2.10 (R Foundation for Statistical Computing, Vienna, Austria) and SAS version 9.2 (SAS, Cary, NC). Differences in continuous variables were analyzed using two-way ANOVA, and differences in proportions analyzed using a chi-square test. P-values of 0.05 were considered statistically significant. Kidney function, using serum creatinine levels and eGFR as calculated using the Modified Diet in Renal Disease (MDRD) formula, and systolic blood pressure were compared between the baseline assessment and at the short-term follow-up evaluation. Univariate and multiple regression analyses were done to examine baseline variables associated with stenosis severity and eGFR changes between the baseline and short-term follow-up. Site-reported adverse events up to 30 days and 9 months were examined, and cumulative and component events were compared between those in whom distal embolic protection was used and those who in whom it was not used. In the roll-in phase, the distal embolic protection device was provided by the study, and for these analyses all participants for whom a device was opened analyzed in the DPD group. Univariate and multiple regression analyses were done to examine the correlation between baseline variables and endpoints at 30 days and 9 months. Stenosis severity as reported by investigators and the angiographic core laboratory were also compared using Pearson's Product Moment Correlation.

Results

Population Characteristics

The first roll-in participant was enrolled in March 2005, and the last in November 2009. In the 109 participating centers, 239 patients underwent renal artery stenting during the roll-in phase of the CORAL Study. In total, 12 of 115 (10%) sites failed to initially qualify for the

randomized phase of the study because of performance and/or submission-related issues. Six of these sites were approved to proceed to the randomization phase of the study after additional cases were performed. The baseline characteristics of the roll-in participants are presented in Table 1.

Of 239 participants for whom arteriograms were received by the core lab, a total of 18 patients had angiograms that were deemed uninterpretable (15) or that had missing data regarding lesion location (3), resulting in 221 analyzable cases (221 of 239 or 92.5%).

Clinical outcomes

Kidney Function and Blood Pressure—Kidney function did not change after renal artery stenting from baseline to the short-term follow-up interval (Table 2; Figure 1). By univariate analysis (Table 3), none of the baseline variables correlated with the change in eGFR from baseline to follow-up at 2–4 weeks. A similar finding was observed using multivariable regression. Systolic blood pressure decreased by 15 ± 24 mm Hg at the short-term follow-up evaluation compared with baseline ($p<0.001$).

Site-reported Endpoint Events—By univariate and multivariate regression analysis, there were no baseline variables that significantly correlated with the occurrence of a site-reported endpoint up to 30-days after the procedure (Table 4). Through 9-months of follow-up, the presence of bilateral renal artery stenosis ($p=0.01$) and a prior history of stroke or transient ischemic attack (TIA) ($p=0.03$) correlated with subsequent development of study endpoints (Table 5a). By multiple regression analysis, these variables remained significant ($p=0.01$ and $p=0.05$, respectively), as was a history of CKD ($p=0.03$) (Table 5b).

Procedural outcomes

Adverse Events—There were 32 (17%) minor stent-related complications (spasm) and 28 (13%) major stent-related complications. Major procedural complications reported by the Angiographic Core lab included: dissection (11, 4.5%), embolus (9, 3.7%), occlusion (9, 3.7%), thrombus (3, 1.2%), vessel rupture (2, 0.8%), wire perforation of a branch artery (2, 0.8%), or pseudoaneurysm (1, 0.4%), (Table 6). There were 7 serious adverse events (7/40, 18%) at thirty days at 12 sites that required more than the minimum number of roll-in procedures, and 26/199 (13%) in the sites ($n=132$) that did not require more than the minimum number of roll-in procedures ($p=0.45$).

Stenosis Interpretation and Pressure Gradients

The average diameter stenosis for the most severe lesion by core lab analysis for each patient was $72\pm 12\%$ ($n=221$). Site interpretations of stenosis severity were higher than the core lab readings by mean $7\pm 2\%$. Of 221 arteries with both core lab and site readings available, there were 163 where the site reading was higher than the core lab reading, 57 where the core lab reading was higher than the site reading, and one measurement that was identical. The number of patients undergoing trans-lesion pressure measurements was 85 or 38% of the 221 analyzable cases. Using Pearson's correlation, the relationship between stenosis severity and the trans-lesion systolic pressure gradient was not statistically significant (0.18, $p=0.09$). The correlation with mean pressure gradient was borderline significant (0.21, $p=0.06$).

(Figure 2). By both univariate and multiple analyses there were no variables that correlated significantly with stenosis severity, but there were trends for both gender and highest pressure gradient recorded (Tables 7a and 7b).

Distal Embolic Protection

Of the 161 participants who were analyzed in the distal embolic protection group, there were nine who had the package opened but the device was not used. Of the 152 for whom the device was opened and used, the device was deployed successfully in 132. Of the 20 in whom the device could not be successfully deployed, 15 were due to inability to cross the lesion with the DPD and the remainder due to inability to achieve an adequate landing zone that would enable the device to be deployed and the stent placed.

At baseline there were no significant differences between patients treated with or without DPD with the exception that those patients treated without DPD were significantly more likely to have had a history of CKD ($p<0.001$). Use of a DPD was associated with 50 (34%) minor angiographic complications and 12 (8%) major complications as reported by the Angiographic Core Lab. There was no difference between patients treated with a DPD and those treated without a DPD with respect to either blood pressure ($p=0.716$) or eGFR ($p=0.783$) at 2–4 weeks follow-up. Through 30-days of follow-up, there were no site-reported endpoints in the group of patients treated without use of a DPD ($n=78$) and four reported endpoints in those that had a DPD used ($n=161$, 2.5%, $p=0.17$). Endpoints in the four patients who were treated with a DPD included two myocardial infarctions and three episodes of CHF (Table 8a). The 30-day incidence of any serious adverse event reported by sites was 15% (24/161) in the group in which a DPD was employed and 11.5% (9/78) in the group in which a DPD was not used ($p=0.55$). Of the individual SAEs reported, there were none that were significantly different between the DPD and no-DPD groups.

Through 9 months of follow-up, there were four site-reported endpoints in the group who underwent renal stenting without use of a DPD ($n=60$, 6.7%) and 12 site-reported endpoints in the DPD group ($n=121$, 9.9%, $p=0.47$) (Table 8b).

Discussion

In the CORAL study, the roll-in phase was done to qualify CORAL investigators, who had to demonstrate that they could follow the renal angiographic methodology and submission protocol to be approved for the randomized phase of the study. Further, the roll-in process was intended to identify operators with potentially higher complication rates and assure that only skilled operators participated in the enrollment of randomized patients. The independent angiographic core lab assessment was essential to assure that the data received was of high quality, that patient selection was appropriate, and that the technical ability of the investigators was consistently high. Prior to participation, the clinical sites were reviewed by a CORAL site selection committee to insure that adequately experienced personnel were available for case performance and study document submission to the multiple core labs and data coordinating center (DCC). Over the course of the roll-in study, a moderate number of issues were encountered that prompted the requirement for performance of additional cases by investigator sites, and some centers never qualified for participation in

the randomized phase of the study. As such, the roll-in phase served the function of standardizing techniques and data submission and identifying weaknesses that could threaten the validity of the randomized phase of the study.

Importantly, some individuals have criticized the prior randomized controlled renal stent studies because of the high rates of adverse events and enrollment of subjects without stenoses severe enough to warrant treatment(3, 6, 7). Furthermore, neither STAR nor ASTRAL used angiographic core laboratories to objectively over-read the degree of stenoses or to evaluate for any angiographic evidence for peri-procedural complications. In the current study, the angiographic core laboratory assessments were done for all submitted angiographic studies and information was formally relayed back to the investigators, the DCC, and the IMC. The current analysis suggests that investigators are likely to over-estimate the diameter stenosis severity by approximately 7%, with a range up to 41%, despite knowing that the studies would be over-read by a core lab. Additionally, investigators were biased to providing a percent stenosis on the high side in that three-quarters of their interpretations exceeded the core lab reading.

This finding of overestimation of the stenosis severity by site investigators has implications for interpreting prior renal stent studies in which there was no angiographic core lab validation of the stenosis severity. For example, in the ASTRAL trial, investigators reported that of 806 participants, 40% had stenosis less than 70%(1). In STAR, renal artery stenoses eligible for enrollment were “ 50%” by investigator interpretation(2). They reported that of 64 participants assigned to receive the stent, 12 did not have stenosis 50% by investigator interpretation, and another 22 had stenosis 50–70% by investigator interpretation(2). Therefore, 34 out of 64 (53%) had stenosis of doubtful clinical significance in the STAR study. The lack of a rigorous patient selection and evaluation process undermines the conclusions from both of these prior studies.

Although nonrandomized and without long-term outcomes, this roll-in population from the CORAL study represents one of the largest renal artery stent series using an independent angiographic core lab over-read of the procedures performed on study patients. Like many other uncontrolled case series, the observation of blood pressure improvement after renal artery stenting in this series should not be interpreted as a successful outcome of the stent procedure, since it could be attributed to regression to the mean or other phenomena associated with clinical trial participation (e.g., Hawthorne effect), since randomized trials have not shown statistically significant differences in blood pressure outcomes between those treated with revascularization and those managed medically(1, 2, 8–10). In addition, we observed that the use of a distal embolic protection device (DPD) during renal artery stenting had no discernible effect on clinical outcomes (Tables 8a and 8b), which is similar to that reported in a randomized trial of DPD use(11).

It is interesting to note that those study patients with baseline chronic kidney disease (CKD) or bilateral renal artery stenosis had a 3.6 to 5.4 hazard ratio for endpoint events through 9 months of follow-up as compared to patients without CKD or bilateral renal artery stenosis. Since all patients underwent renal artery stenting, the findings of this study suggest that stent

placement does not eliminate or significantly reduce the increased risk for cardiovascular events which are associated with CKD or bilateral renal artery stenosis.

We note that there were frequent technical complications noted angiographically (17% of procedures reported a minor complication and 13% had a major complication). There were also 11.5–15% serious adverse events reported at 30 days. However, there is no control group for the roll-in participants, so it should not be assumed that these SAEs would be more or less frequent if the procedures were not done. That is, the frequent observation of SAEs after renal artery stent placement in this series may or may not be attributed to the stent procedures.

Study limitations include the lack of randomization, lack of standardized procedures for use of DPD after protocol changes allowed users to enroll study participants without using DPD's, and lack of observer blinding. Relatively short term follow-up, with limited data points, and no independent adjudication of reported endpoint data by an independent data monitoring committee are also limitations.

In conclusion, the roll-in experience from the CORAL study identified performance issues in approximately 10% of the participating centers that either required additional assessment or disqualified the sites from participation in the randomized phase of the Study. Additionally, investigative sites tend to over-estimate the degree of lesion severity which may lead to the selection of patients with clinically insignificant renal artery stenosis for enrollment in clinical trials of renal artery stent placement, and therefore negatively bias study outcomes. Furthermore, in this patient cohort, a clear benefit of embolic protection on renal function during renal artery stenting was not demonstrated.

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References

1. Wheatley K, Ives N, Gray R, Kalra PA, Moss JG, Baigent C, et al. Revascularization versus medical therapy for renal-artery stenosis. *N Engl J Med*. 2009 Nov 12; 361(20):1953–1962. [PubMed: 19907042]
2. Bax L, Woittiez AJ, Kouwenberg HJ, Mali WP, Buskens E, Beek FJ, et al. Stent placement in patients with atherosclerotic renal artery stenosis and impaired renal function: a randomized trial. *Ann Intern Med*. 2009 Jun 16; 150(12):840–848. W150–W151. [PubMed: 19414832]
3. White CJ. Kiss my astral: one seriously flawed study of renal stenting after another. *Catheter Cardiovasc Interv*. 2010 Feb 1; 75(2):305–307. [PubMed: 20095015]
4. Cooper CJ, Murphy TP, Matsumoto A, Steffes M, Cohen DJ, Jaff M, et al. Stent revascularization for the prevention of cardiovascular and renal events among patients with renal artery stenosis and systolic hypertension: rationale and design of the CORAL trial. *Am Heart J*. 2006 Jul; 152(1):59–66. [PubMed: 16824832]

5. Chobanian AV, Bakris GL, Black HR, Cushman WC, Green LA, Izzo JLJ, et al. Seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. *Hypertension*. 2003 Dec; 42(6):1206–1252. [PubMed: 14656957]
6. George JC, White CJ. Renal artery stenting: lessons from ASTRAL (Angioplasty and Stenting for Renal Artery Lesions). *JACC Cardiovasc Interv*. 2010 Jul; 3(7):786–787. [PubMed: 20650444]
7. Henry M, Benjelloun A, Henry I, Polydorou A, Hugel M. Renal angioplasty and stenting: is it still indicated after ASTRAL and STAR studies? *J Cardiovasc Surg (Torino)*. 2010 Oct; 51(5):701–720.
8. Plouin PF, Chatellier G, Darne B, Raynaud A. Blood pressure outcome of angioplasty in atherosclerotic renal artery stenosis: a randomized trial. *Essai Multicentrique Medicaments vs Angioplastie (EMMA) Study Group. Hypertension*. 1998 Mar; 31(3):823–829. [PubMed: 9495267]
9. Webster J, Marshall F, Abdalla M, Dominiczak A, Edwards R, Isles CG, et al. Randomised comparison of percutaneous angioplasty vs continued medical therapy for hypertensive patients with atheromatous renal artery stenosis. *Scottish and Newcastle Renal Artery Stenosis Collaborative Group. J Hum Hypertens*. 1998 May; 12(5):329–335. [PubMed: 9655655]
10. van Jaarsveld BC, Krijnen P, Pieterman H, Derkx FH, Deinum J, Postma CT, et al. The effect of balloon angioplasty on hypertension in atherosclerotic renal-artery stenosis. *Dutch Renal Artery Stenosis Intervention Cooperative Study Group. N Engl J Med*. 2000 Apr 6; 342(14):1007–1014. [PubMed: 10749962]
11. Cooper CJ, Haller ST, Colyer W, Steffes M, Burket MW, Thomas WJ, et al. Embolic protection and platelet inhibition during renal artery stenting. *Circulation*. 2008 May 27; 117(21):2752–2760. PubMed PMID: 18490527. [PubMed: 18490527]

Figure 1.

Plot of the change in GFR and baseline eGFR. Kidney function MDRD eGFR change score (from the baseline value to the short-term (2–4 week) value) is used as dependent variable. The largest cluster is centered around zero, and those at the lower end of the baseline eGFR range have less change than those with baseline eGFRs over 60 ml/min/1.73 m².

Figure 2. Scatter plot of % stenosis as interpreted by the angiographic core laboratory on the x-axis and corresponding mean pressure gradients on the y-axis ($r=0.21$, $p=0.06$).

Table 1

Population Characteristics (at Baseline)

Characteristics	Distal Protection Device (N=161)	No Distal Protection Device (N=78)	Difference [95% CI]	Total Population (N=239)	P-value
Age					
Mean±SD (N)	70.1±9.1 (161)	70.2±8.8 (74)	-0.1 [-2.5, 2.5]	70.2±9.0 (235)	0.992
Range (Min,Max)	(39,90)	(46,88)		(39,90)	
Male	48.4% (78/161)	50.0% (37/74)	-1.6% [-15.3%, 12.2%]	48.9% (115/235)	0.825
Worst % Stenosis*					
Mean±SD (N)	71.80±12.16 (149)	68.58±11.79 (72)	3.22 [-0.19, 6.62]	70.75±12.11 (221)	0.064
Range (Min,Max)	(31.88,97.18)	(28.66,93.30)		(28.66,97.18)	
Highest Pressure Gradient*					
Mean±SD (N)	55.53±38.35 (68)	52.59±26.97 (17)	2.94 [-16.71, 22.59]	54.94±36.23 (85)	0.767
Range (Min,Max)	(4.00,181.00)	(21.00,95.00)		(4.00,181.00)	
Bilateral	28.6% (46/161)	23.1% (18/78)	5.5% [-6.2%, 17.2%]	26.8% (64/239)	0.368
Hx Diabetes Mellitus	27.3% (44/161)	29.5% (23/78)	-2.2% [-14.4%, 10.1%]	28.0% (67/239)	0.728
Hx CAD	44.1% (71/161)	32.1% (25/78)	12.0% [-0.8%, 24.9%]	40.2% (96/239)	0.075
Hx Stroke/TIA	9.3% (15/161)	6.4% (5/78)	2.9% [-4.1%, 10.0%]	8.4% (20/239)	0.447
Hx CKD	0.0% (0/161)	11.5% (9/78)	-11.5% [-18.6%, -4.4%]	3.8% (9/239)	<.001
Kidney Function-Creatinine					
Mean±SD (N)	1.44±0.52 (160)	1.37±0.50 (73)	0.07 [-0.07, 0.21]	1.41±0.51 (233)	0.340
Range (Min,Max)	(0.59,3.00)	(0.60,2.94)		(0.59,3.00)	

Characteristics	Distal Protection Device (N=161)	No Distal Protection Device (N=78)	Difference [95% CI]	Total Population (N=239)	P-value
Kidney Function-MDRD eGFR					
Mean±SD (N)	49.57±20.77 (160)	52.29±20.35 (73)	-2.71 [-8.46, 3.03]	50.42±20.64 (233)	0.353
Range (Min,Max)	(15.05,137.49)	(16.98,107.70)		(15.05,137.49)	
Kidney Function-MDRD eGFR < 60	73.8% (118/160)	69.9% (51/73)	3.9% [-8.7%, 16.4%]	72.5% (169/233)	0.538
Kidney Function-MDRD eGFR 60	26.3% (42/160)	30.1% (22/73)	-3.9% [-16.4%, 8.7%]	27.5% (64/233)	0.538
Systolic Blood Pressure (SBP)					
Mean±SD (N)	154.65±21.64 (159)	153.32±27.70 (74)	1.33 [-5.24, 7.91]	154.23±23.68 (233)	0.715
Range (Min,Max)	(95.33,209.67)	(96.67,233.00)		(95.33,233.00)	

Table 2

Change Score from Baseline to Short-term Follow-up (2–4 weeks)

Change Score from Baseline to 2 weeks	Distal Protection Device (N=161)	No Distal Protection Device (N=78)	Total Population (N=239)	Difference [95% CI]	P-value
Kidney Function-Creatinine					
Mean±SD (N)	-0.01±0.26 (124)	-0.02±0.26 (56)	-0.01±0.26 (180)	0.02 [-0.07, 0.10]	0.702
Range (Min,Max)	(-1.30,0.60)	(-0.80,0.60)	(-1.30,0.60)		
Kidney Function-MDRD eGFR					
Mean±SD (N)	0.23±12.27 (124)	-0.30±11.43 (56)	0.07±11.98 (180)	0.53 [-3.28, 4.35]	0.783
Range (Min,Max)	(-50.09,58.19)	(-49.17,28.58)	(-50.09,58.19)		
Systolic Blood Pressure (SBP)					
Mean±SD (N)	-14.15±23.34 (129)	-15.51±25.36 (60)	-14.58±23.94 (189)	1.37 [-6.03, 8.76]	0.716
Range (Min,Max)	(-90.00,61.33)	(-74.33,35.00)	(-90.00,61.33)		

Table 3

Variables associated with kidney function MDRD eGFR change score (Results shown are based on univariate analyses -- one covariate at time). Kidney function MDRD eGFR change score (from baseline to 2 weeks) is used as dependent variable.

Variable	Mean change*	Mean change 95% CI	P-value
Age	-0.84222	[-2.61388, 0.92945]	0.3527
Male	-0.18084	[-3.69228, 3.33059]	0.9197
Worst % Stenosis	0.20971	[-1.58890, 2.00832]	0.8195
Highest Pressure Gradient	0.21093	[-2.83253, 3.25440]	0.8924
Bilateral	-1.80450	[-5.71453, 2.10553]	0.3669
Hx Diabetes Mellitus	1.99009	[-1.96853, 5.94871]	0.3258
Hx CAD	-0.51676	[-4.08345, 3.04993]	0.7768
Hx Stroke/TIA	-2.13163	[-8.12570, 3.86245]	0.4867
Hx CKD	-4.15279	[-14.8168, 6.51118]	0.4463
Systolic Blood Pressure (SBP)	-0.63989	[-2.49456, 1.21478]	0.4998
DPD	0.25013	[-1.53105, 2.03131]	0.7835

Table 4

Baseline Variables associated with composite endpoint through 30 days of follow-up. (Results shown are based on univariate analyses -- one covariate at time)

Variable	Hazard Ratio	95% Lower Confidence Limit for Hazard Ratio	95% Upper Confidence Limit for Hazard Ratio	Pr > Chi-Square
Age	1.005	0.901	1.122	0.9270
Male	0.351	0.037	3.374	0.3645
Worst % Stenosis	0.987	0.912	1.068	0.7430
Highest Pressure Gradient	0.971	0.902	1.045	0.4267
Bilateral	2.778	0.391	19.718	0.3070
Hx Diabetes Mellitus	2.520	0.355	17.887	0.3554
Hx CAD	0.477	0.050	4.581	0.5209
Hx Stroke/TIA	3.706	0.385	35.632	0.2566
Hx CKD	0.000	0.000	--	0.9960
Kidney Function-MDRD eGFR at baseline	1.005	0.961	1.052	0.8249
Systolic Blood Pressure (SBP)	1.005	0.958	1.053	0.8482
DPD *	16686916	0.000	--	0.9956

Cox PH Model with Site-Reported Composite Endpoint through 30 days of follow-up as dependent variable.

Hazard ratios of estimates may be unstable due to low 30-day composite endpoint rate.

* Estimate of hazard ratio is unstable due to overall low 30-day composite endpoint rate and the fact that 0 patients in the 'No DPD' group experienced the 30-day composite endpoint.

Table 5

a. Baseline Variables associated with composite endpoint through 9 months of follow-up. (Results shown are based on univariate analyses -- one covariate at time)

Variable	Hazard Ratio	95% Lower Confidence Limit for Hazard Ratio	95% Upper Confidence Limit for Hazard Ratio	Pr > Chi-Square
Age	1.047	0.986	1.112	0.1304
Male	0.825	0.307	2.215	0.7025
Worst % Stenosis	1.028	0.985	1.072	0.2058
Highest Pressure Gradient	0.941	0.873	1.013	0.1075
Bilateral	3.774	1.405	10.136	0.0084
Hx Diabetes Mellitus	1.668	0.606	4.592	0.3220
Hx CAD	0.479	0.154	1.484	0.2020
Hx Stroke/TIA	3.625	1.169	11.242	0.0258
Hx CKD	3.407	0.774	15.000	0.1050
Kidney Function-MDRD eGFR at baseline	0.990	0.965	1.016	0.4658
Systolic Blood Pressure (SBP)	1.003	0.982	1.025	0.7714
DPD	1.513	0.488	4.693	0.4731

b. Baseline Variables associated with composite endpoint through 9 months of follow-up. (Variables selected are based on multivariate analyses – stepwise selection)

Variable	Hazard Ratio	95% Lower Confidence Limit for Hazard Ratio	95% Upper Confidence Limit for Hazard Ratio	Pr > Chi-Square
Bilateral	3.668	1.329	10.128	0.0121
Hx Stroke/TIA	3.248	1.003	10.514	0.0493
Hx CKD	5.421	1.171	25.107	0.0307

Cox PH Model with Site-Reported Composite Endpoint Through 9 Months of Follow-up as dependent variable.

Variables left in the model are significant at the 0.10 level.

Highest pressure gradient is excluded as a candidate for entry due to relatively large number of patients with missing gradient data (see Table 1).

Table 6

Angiographic complications reported by the Angiographic Corelab.

Angiographic Complication	Number (%)
Dissection	11 (4.5%)
Embolus	9 (3.7%)
Occlusion	9 (3.7%)
Incomplete or maldeployment of DPD	1 (0.4%)
Thrombus	3 (1.2%)
Vessel rupture	2 (0.8%)
Wire perforation	2 (0.8%)
Pseudoaneurysm	1 (0.4%)

Table 7

a. Variables associated with Baseline Stenosis Severity
(Results shown are based on univariate analyses -- one covariate at time)

Variable	Mean change*	Mean change 95% CI	P-value
Age	-1.27480	[-2.86844, 0.31883]	0.1184
Male	2.79202	[-0.38690, 5.97094]	0.0866
Highest Pressure Gradient	1.97809	[-0.28717, 4.24335]	0.0907
Bilateral	2.33423	[-1.19649, 5.86495]	0.1964
Hx Diabetes Mellitus	-1.83623	[-5.38937, 1.71690]	0.3122
Hx CAD	-0.37499	[-3.63121, 2.88122]	0.8216
Hx Stroke/TIA	2.29959	[-3.40007, 7.99925]	0.4299
Hx CKD	-6.09644	[-14.1513, 1.95846]	0.1394
Kidney Function-MDRD eGFR	-1.29033	[-2.88119, 0.30052]	0.1133
Systolic Blood Pressure (SBP)	-0.15473	[-1.77604, 1.46659]	0.8518

b. Variable associated with Baseline Stenosis Severity
(Variable selected is based on multivariate analyses – stepwise selection)

Variable	Mean change*	Mean change 95% CI	P-value
Male	2.79202	[-0.38690, 5.9709 4]	0.0866

Worst % stenosis at baseline is used as dependent variable.

Variable left in the model is significant at the 0.10 level.

Highest pressure gradient is excluded as a candidate for entry due to relatively large number of patients with missing gradient data (see Table 1).

Table 8**a. Site-Reported (Unadjudicated) Endpoint through 30 Days of Follow-up. The use of distal embolic protection was not randomized.**

Site-Reported Endpoint (to 30 Days)	Distal Protection Device (N=161)	No Distal Protection Device (N=78)	Total Population (N=239)	Difference [95% CI]	P-value
Composite Endpoint	2.5% (4/157)	0.0% (0/74)	1.7% (4/231)	2.5% [0.1%, 5.0%]	0.166
Death	0.0% (0/157)	0.0% (0/74)	0.0% (0/231)	0.00% [–, –]	--
Stroke	0.0% (0/157)	0.0% (0/74)	0.0% (0/231)	0.00% [–, –]	--
MI	1.3% (2/157)	0.0% (0/74)	0.9% (2/231)	1.3% [–0.5%, 3.0%]	0.329
CHF	1.9% (3/157)	0.0% (0/74)	1.3% (3/231)	1.9% [–0.2%, 4.1%]	0.231
Progressive Renal Insufficiency	0.0% (0/157)	0.0% (0/74)	0.0% (0/231)	0.00% [–, –]	--
Permanent Renal Replacement Therapy	0.0% (0/157)	0.0% (0/74)	0.0% (0/231)	0.00% [–, –]	--

b. Site-Reported (Unadjudicated) Endpoint Through 9 Months of Follow-up. The use of distal embolic protection was not randomized.

Site-Reported Endpoint (to 9M)	Distal Protection Device (N=161)	No Distal Protection Device (N=78)	Total Population (N=239)	Difference [95% CI]	P-value
Composite Endpoint	9.9% (12/121)	6.7% (4/60)	8.8% (16/181)	3.3% [–5.0%, 11.5%]	0.468
Death	0.0% (0/121)	1.7% (1/60)	0.6% (1/181)	–1.7% [–4.9%, 1.6%]	0.154
Stroke	0.0% (0/121)	1.7% (1/60)	0.6% (1/181)	–1.7% [–4.9%, 1.6%]	0.154
MI	5.0% (6/121)	0.0% (0/60)	3.3% (6/181)	5.0% [1.1%, 8.8%]	0.079
CHF	4.1% (5/121)	1.7% (1/60)	3.3% (6/181)	2.5% [–2.3%, 7.3%]	0.383
Progressive Renal Insufficiency	1.7% (2/121)	1.7% (1/60)	1.7% (3/181)	–0.0% [–4.0%, 3.9%]	0.995
Permanent Renal Replacement Therapy	0.0% (0/121)	0.0% (0/60)	0.0% (0/181)	0.00% [–, –]	--

Denominators indicated the total number of patients who had at least 25 days of follow-up or an event through 30 days post procedure.

Denominators indicated the total number of patients who had at least 256 days of follow-up or an event through 270 days post procedure.