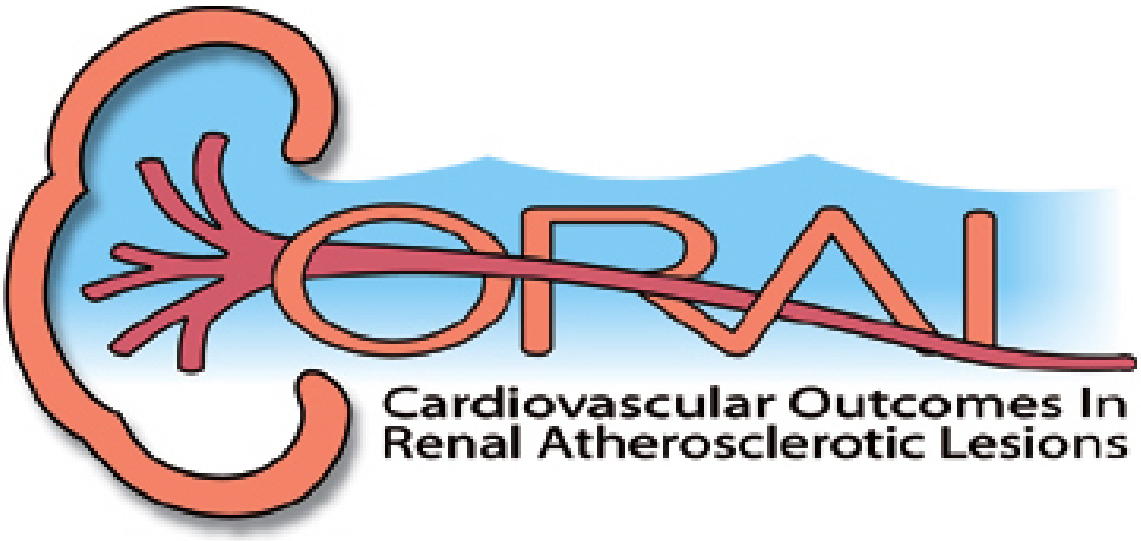
CORAL
Cardiovascular Outcomes In
Renal Atherosclerotic Lesions

PROTOCOL SIGNATURE PAGE

CORAL CLINICAL STUDY PROTOCOL

I have read this protocol and agree to adhere to the requirements. I will provide copies of this protocol and all pertinent information to the study personnel under my supervision. I will discuss this material with them and ensure they are fully informed regarding the investigational device and the conduct of the study according to 21 CFR parts 50, 54, 56 and 812, 45 CFR 46, to GCP as described in ICH guideline E6 and to hospital Institutional Review Boards. (See Appendix A for List of Abbreviations used.)

_____
Clinical Site

_____ _____
Principal Investigator Signature **Date**

_____
Principal Investigator
Printed Name

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PROTOCOL SUMMARY

Title:	CORAL: Cardiovascular Outcomes in Renal Atherosclerotic Lesions
Design:	A prospective, multi-center, unblinded, two-arm, randomized trial
Purpose:	This study is designed to test the hypothesis that medical therapy with stenting of significant renal artery stenoses in patients with systolic hypertension reduces the incidence of adverse cardiovascular and renal events compared with medical therapy alone.
Brief Description:	This study will enroll patients with a history of systolic hypertension, who have documented renal artery stenosis. Patients will be randomized via several pathways to either medical therapy or medical therapy with renal artery stenting and be closely monitored for blood pressure control and management of other risk factors. A subgroup of 400 patients will undergo renal artery Duplex ultrasound at baseline, 1 year and study termination. All patients will have quality of life measures performed, and cost effectiveness data will be collected for analysis.
Enrollment:	1080 patients evaluable Up to 400 roll-in patients (a minimum of 1 patient per investigator)
Clinical Sites:	Up to 100 study sites in the United States and 100 sites outside the United States
Time Course:	Initial enrollment: Q1 2005 Last enrollment: Q1 2010 Last anticipated follow-up contact: Q1 2014
Patient Population:	Patients over 18 years old with documented history of hypertension on ≥ 2 antihypertensive medications and/or renal dysfunction defined as Stage 3 or greater CKD (estimated GFR < 60 mL per minute per 1.73 m^2 calculated by the modified MDRD formula) and ≥ 1 renal artery stenosis ≥ 60% and <100%
Primary Endpoint:	Event-free survival from cardiovascular and renal adverse events defined as a composite of cardiovascular or renal death, stroke, MI, hospitalization for CHF, progressive renal insufficiency, or need for permanent renal replacement therapy.

Secondary Endpoints:

1. Rate of all cause mortality
2. Subgroup interaction in critical subgroups:
   - Men vs. women
   - African Americans vs. non-African Americans
   - Diabetes vs. non-Diabetes mellitus
   - Global vs. Partial renal ischemia
3. Longitudinal renal function
4. Systolic blood pressure response
5. Durability of renal artery patency after stenting
6. Evaluation of renal resistive index: a measure of preservation of microvascular renal artery function
7. Correlation between stenosis severity and kidney function
8. Quality of life
9. Cost effectiveness

Primary Analytical Subset: Intent-to-treat sample

Secondary Analytical Subset: Per protocol (successful procedure) sample

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1.0 INTRODUCTION

1.1 Background

Renal artery stenosis (RAS) is a common problem, present in roughly 1-5% of the 60 million Americans with hypertension[1-3], and in many with peripheral or coronary artery disease without hypertension[4-9]. Recent data suggests an incidence of RAS of 6.8% in patients over the age of 65[10].

Despite the frequency of RAS, there is no consensus on diagnosis, therapy or follow-up. In the absence of evidence-based guidelines, there has emerged a "find it, fix it" approach in some practices where identification of a renal stenosis warrants a stent procedure. Several uncontrolled reports suggest that hypertension and renal function may improve following stent deployment (see below). However, 3 small controlled trials of renal angioplasty, without stenting, have failed to demonstrate a blood pressure benefit[11-13]. Key flaws in all prior studies of the problem are the assumptions that, 1) blood pressure is a suitable surrogate endpoint in this population, and 2) changes in surrogate measures are, by necessity, attributable to the revascularization procedure.

The governmental expense associated with this problem must be considered. Most RAS patients are covered by Medicare due to age (median 72 years, unpublished data). Of patients requiring dialysis, 14-20% have ischemic nephropathy[14-16]. In 2010 expenditures for the Medicare End Stage Renal Disease (ESRD) program are expected to reach $*28 billion* annually [17]. Other clinical events attributable to uncontrolled hypertension and renal failure, including stroke, myocardial infarction, and congestive heart failure, incur considerable expense [18-20]. Thus more aggressive diagnosis and treatment can be warranted, if progressive renal insufficiency and cardiovascular complications are prevented or delayed. Alternatively, if stenting is unnecessary, the cost, estimated at $1.7 billion (Murphy, unpublished data), should be avoided. Thus, money invested in a clinical trial to answer this question will ensure the maximum public health benefit for money spent from the Medicare program.

1.2 Pathophysiology of Renovascular Hypertension

Renal artery stenosis results in neuroendocrine activation with release of renin from renal juxtaglomerular cells, catalyzing the breakdown of angiotensinogen to angiotensin I. Angiotensin I is transformed by ACE into angiotensin II (AT II), with AT II promoting the release of aldosterone from the adrenal cortex[21]. AT II is a potent vasoconstrictor[22] that is implicated in end-organ damage in the heart[23] and kidney[24]. With unilateral renal artery stenosis, and a normally-perfused contralateral kidney, blood pressure elevation is referred to as "renin-dependent" and is characterized by increased peripheral resistance[25, 26]. If the contralateral kidney is absent or stenotic, intravascular volume increases and renin secretion decreases over time[27-32]. This is referred to as "volume-dependent" Goldblatt hypertension. In addition, the sympathetic and central nervous system contribute to hypertension in renal artery stenosis[33-35]. Successful renal artery revascularization may decrease muscle sympathetic nerve activity[34], as does denervation of the affected kidney[36, 37].

1.3 Role of RAS in the Genesis of Renal Insufficiency

The adverse effect of ischemia on the kidney is well established experimentally and clinically. However, the role of atherosclerotic RAS in the genesis of renal dysfunction is controversial. Over 1-4 years atherosclerotic stenoses often progress, some to occlusion[38-41]. RAS is associated with loss of renal size, a reasonable but crude measure of renal function [40]. In patients with significant (60-99%) renal artery stenosis, 20-26% of ipsilateral kidneys demonstrate atrophy of >1 cm in length[42, 43], whereas significant loss of renal size is uncommon without RAS[42]. Occlusion is associated with substantial loss of renal size and function[44].

Several investigators have been unable to demonstrate a relationship between stenosis severity and renal function[45, 46]. While one might conclude from this that stenoses do not cause renal dysfunction, such a conclusion would be unfounded. Fundamentally, the kidney requires blood flow to function. Thus, it is absolutely clear that severe stenoses and occlusions yield a non-functioning kidney. Why then the difficulty relating stenosis severity to function? Clearly, there are factors beyond the degree of stenosis that influence function. Some are intrinsic to RAS, including the duration of the insult, atheroemboli, hypertensive nephrosclerosis of the contralateral kidney, activation of the renin angiotensin system, and finally the effect of the stenosis (including lesion length, minimal lumen diameter, etc) on renal blood flow and intra-renal pressure. Additionally, other factors, such as essential hypertension, diabetes, concomitant medications, generalized atherosclerosis progression, and aging play a role in determining overall renal function. *Whether revascularization of hemodynamically significant stenoses is beneficial, in combination with effective blood pressure lowering, risk factor management, and blockage of the renin-angiotensin system, forms the basis for the current proposal.*

Most research has ascribed a central role of the renin-angiotensin system in ischemic nephropathy. AT II induces efferent arteriolar constriction, which aids in the maintenance of glomerular filtration rate (GFR). In 1983, Hricik et al described renal failure secondary to ACE inhibition with bilateral RAS[47]. It has been proposed that reversal of the AT II-mediated efferent arteriolar vasoconstriction by ACE-inhibition decreases glomerular filtration pressure and thus GFR.

Several observations add to our understanding of ischemic nephropathy. Severe chronic hypoperfusion is usually accompanied by renal atrophy, although normal kidneys remain viable with blood flows and pressures below that required for glomerular filtration[48], since less than 10% of oxygen delivery is required for kidney tissue metabolism. Thus, chronic ischemia does not damage renal tissue simply by lack of oxygen delivery[49]. Gobe et al studied the cellular events related to unilateral RAS where the kidney underwent progressive atrophy[50]. During the initial phase (2-5 days) tubular cell death resulted from both necrosis and apoptosis. During the chronic phase (10-20 days) renal atrophy progressed and cell death resulted from apoptosis alone. After reversal of RAS, evidence of regeneration, consisting of hypertrophy and hyperplasia, was found. These findings imply that chronic ischemia is a dynamic process comprising not only an adaptation to reduced blood flow but also a potential for tubular cell regeneration. Finally, chronic renal failure can be the result of severe global ischemia, but nephrosclerosis also occurs in the non-stenotic kidney, perhaps mediated by hypertension, a

vasculotoxic effect of renin[51, 52], or by AT II through its interaction with endothelin 1, PDGF-β, and TGF-β[24].

Importantly, several investigators have reported that renal artery revascularization is associated with stabilization or improvement in renal function[53-56]. Others have described progressive renal dysfunction during medical therapy[38]. The need for dialysis or renal transplantation, although infrequent (14-20%)[14-16], appears to be related to the proportion of renal mass at risk[57, 58]. Although ESRD is uncommon in the short-term[57], historical data suggests that up to 27% of those with RAS develop chronic renal failure within 6 years[38].

Observational studies demonstrate that parenchymal disease, measured at biopsy, as proteinuria, or with the Duplex renal resistive index (RRI), poses a substantial risk for progression of renal dysfunction[59, 60]. Thus, some have suggested that revascularization should be reserved for those with a normal RRI[61]. In the current proposal we will measure the RRI and the urine albumin/Creatinine (Cr) ratio, and anticipate worsened outcomes in the sub-groups with proteinuria and elevated RRI. However, we will not know whether treatment is superior to medical therapy in these high-risk patients without a randomized trial. It may be the high-risk patients with evidence of proteinuria or other markers of renal injury that receive the greatest benefit from interruption of the renin-angiotensin system, as was seen in the recent AASK study[60].

1.4 Neuroendocrine Activation, and Effect on End-organ Function

Several neuroendocrine systems activated by renal ischemia have deleterious cardiovascular and renal effects. AT II, beyond blood pressure elevation, is implicated in smooth muscle proliferation, plaque rupture, endothelial dysfunction, and inhibiting fibrinolysis[23]. AT II also promotes arterial medial and cardiac myocyte hypertrophy[26, 62-69]. Importantly, myocardial hypertrophy occurs when AT II is present even when blood pressure is controlled[70]. AT II interacts with other peptides like endothelin, TGF-β, and PDGF-β, each of which is implicated in end-organ damage, ventricular hypertrophy, and vascular hypertrophy[24, 69, 71]. Thus, beyond blood pressure effects, neuroendocrine mechanisms activated by RAS may increase the risk of cardiovascular and renal events.

1.5 Renal Artery Stenosis and Renal Dysfunction: Risk of Cardiovascular Events

A critical concept in this study is the linkage between renal artery stenosis, renal dysfunction, and cardiovascular (CV) events. In patients with RAS the risk of CV morbidity and mortality appears to be greater than that expected from the degree of blood pressure elevation. Wollenweber described a 6-year CV-event-free survival of 53%, with risk related to the severity of the renal stenosis[38]. Several others have suggested that the risk of adverse CV events is high and occurs in excess of the hypertension severity[5, 72, 73]. More recently a significant difference in 4-year survival was seen between those with incidental RAS compared to those without, with a graded effect on mortality, according to the severity of RAS[74]. Thus the risk of cardiovascular events appears to be high in RAS and blood pressure control may be a poor surrogate for clinical outcomes.

Renal dysfunction, mild or severe, is associated with increased rates of CV events[75-78] and increased CV mortality[79, 80]. In RAS patients specifically, renal dysfunction is associated with increased CV event rates (see preliminary data) and increased mortality[81, 82]. Ventricular dysfunction and overt congestive heart failure (CHF) are common in patients with RAS[25, 83-85] just as RAS is common in patients with CHF[86]. While several mechanisms activated by RAS may increase CV risk (neuroendocrine activation, renal insufficiency, acceleration of atherosclerosis, and left ventricular hypertrophy [LVH]), others suggest that CV morbidity and mortality in RAS may be attributable to concomitant atherosclerosis found in other vascular beds including the coronary and cerebral circulations[87-92].

1.6 Anti-Hypertensive Therapy to Reduce Risk in RAS

Anti-hypertensive therapy for essential hypertension is highly effective for preventing cardiovascular and renal events[93]. However, there is no outcome data with anti-hypertensive medical therapy for treatment of RAS. Thus, in the absence of outcome data, the rational selection of a first-line agent should be directed at the principal mechanism thought to be responsible for the genesis of the blood pressure response, activation of the renin-angiotensin-aldosterone system (RAAS). Importantly, clinical studies suggest that RAAS inhibition decreases CV events, especially in high-risk patients[94, 95].

While ALLHAT has clearly demonstrated equivalency between classes of anti-hypertensive medications for coronary heart disease events in patients with essential hypertension, important differences in disease-specific outcomes are suggested in this and other studies[95, 96]. Specifically, RAAS inhibiting drugs are the only agents with an indication for retarding the progression to end-stage renal disease, and this is an important component of primary outcome of the current proposal[97, 98] (Jackson JT 2002). The selection of first-line therapy is described in more detail in the Anti-Hypertensive Medical Therapy Care (section 4.8)

Medications can be associated with adverse health effects, such as lack of energy or chronic cough, that may affect quality of life and reduce compliance [99-102]. Fifty to 70% are discontinued or changed within 6 months (Oparil S 1999). Adherence to published guidelines for treatment of hypertension is poor, often with significant adverse impact to patients and the healthcare system [103, 104]. Other factors that may limit the effectiveness of medical therapy include temporal variations in drug levels and variable absorption[105, 106]. Finally, as described above, renal ischemia increases activity in a number of other pathogenic systems that may have deleterious cardiovascular or renal effects.

1.7 Interaction of Renal Revascularization with ARB-ACEI Treatment

Recent clinical trials (HOPE, LIFE) suggest that drugs that block the renin-angiotensin-aldosterone system (ARB-ACEI) have important, non-hemodynamic actions that reduce the incidence of fatal and non-fatal cardiovascular events in high risk patients. On the other hand, glomerular filtration is sustained by angiotensin II induced, efferent arteriolar constriction in patients with severe bilateral renal artery stenosis or unilateral stenosis to a solitary functioning kidney (global renal ischemia), and profound declines in glomerular pressure and GFR may develop when these patients are treated with ARBs or ACEIs. Thus, a possible benefit of

revascularization in patients with global renal ischemia is prevention of hemodynamically mediated acute renal failure following administration of ARB-ACEI allowing treatment with these agents[47]. If so, then a greater proportion of stented patients in the current study may receive ARB-ACEI and this might reduce their likelihood of reaching an endpoint.

In addition, if activation of the RAAS is a critical determinant of cardiovascular outcomes, it is conceivable that there might be an additive effect of revascularization and ARB-ACEI, wherein the combination might result in more complete inhibition of the renin-angiotensin system and better outcomes than drug therapy alone. Consistent with this view are data demonstrating that ACE inhibitors do not completely prevent AT II formation[105, 107, 108] and that ARBs may incompletely block the ATII receptor[106]. Also consistent, in one recent study, combination treatment with ARB and ACEI was more effective in retarding progression of non-diabetic renal disease than either drug alone[109]. To examine the interaction between ARB-ACEI and revascularization in the current study, we will determine whether stenting alters ARB-ACEI utilization and will also perform a secondary analysis of the primary outcome, after adjusting for ARB-ACEI use.

1.8 Renal Revascularization to Prevent Cardiovascular Events

There are no randomized clinical trials comparing renal artery revascularization with medical therapy using clinical endpoints, yet two non-randomized comparisons suggested a benefit of revascularization[73, 110]. However, each group recognized the limitations of uncontrolled comparisons with one group suggesting “despite a trend towards benefit from surgical intervention our data do not prove that intervention is better than medical treatment, largely because the decision on intervention was not randomized. A prospective trial would be required to answer this important question.”

Three randomized clinical trials comparing percutaneous renal artery angioplasty (PTRA) with medical therapy reported a lack of benefit of angioplasty to control blood pressure[11-13]. These studies were small and limited by questionable patient selection (large proportion of mild stenoses), as well as excessive cross-over from medical therapy to PTRA (27-44%)[11, 12]. Nevertheless, in the largest of the 3 studies, patients in the PTRA group were more likely to have improvement in blood pressure control and less likely to develop renal artery occlusion despite a 44% cross over rate[11]. More fundamentally, one must ask whether blood pressure alone, a well-accepted surrogate endpoint for studies of essential hypertension, is an adequate surrogate for clinical events in RAS. Other factors, including renal function, may be better surrogates[74, 81].

1.9 Renal Artery Revascularization Procedures

In 1974, Hunt described lower rates of mortality, stroke, myocardial infarction, and azotemia, and better blood pressure control in surgically revascularized patients than a comparison medical group[110]. Surgery, however, has been associated with significant peri-operative complications and mortality [10]. Most patients with RAS have lesions in other vascular beds making them higher risk operative candidates. Thus, PTRA was an attractive alternative. Notably, the results of PTRA and surgery appear equivalent when compared directly [111]. PTRA was associated

with improved blood pressure control and a decrease in need for anti-hypertensive medications in retrospective studies. However, PTRA has a high restenosis rate for ostial lesions, and 80-85% of all atherosclerotic RAS is ostial. With the advent of stents, the problems associated with angioplasty may be circumvented. Rees et al reported 96% technical success rate with Palmaz stents in ostial lesions[112]. More importantly, stents appears to be superior to PTRA when compared directly [113]. For these reasons, stents have become the favored mode of revascularization for atherosclerotic ostial RAS.

In 2000, approximately 19,800 renal angioplasties were performed for Medicare beneficiaries alone, at an estimated cost of $200 million (Murphy TP, unpublished data). Recent analysis of Medicare data indicates that, from 1996 to 2000, the number of renal stent procedures has increased 364%[114]. Given the frequency and considerable growth of renal artery stenting, it is important to determine whether renal stenting offers benefit in conjunction with optimal medical therapy.

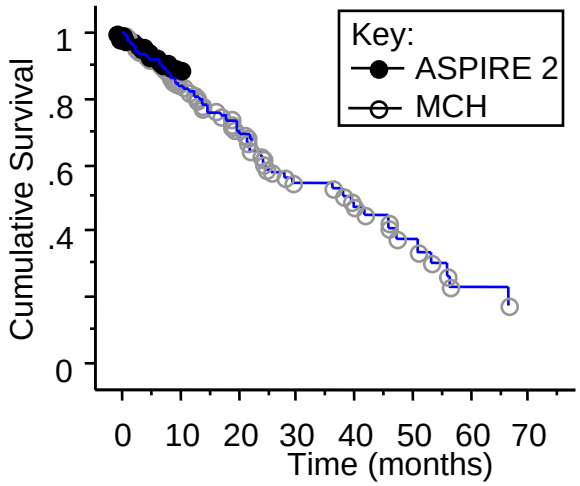
1.10 Preliminary Studies

There is sufficient preliminary data to suggest that the design of this study will lead to a definitive answer. At the outset it should be recognized that, 1) there are no randomized data comparing stent therapy with medical therapy, 2) there are no contemporary data on non-fatal clinical events in medically treated patients with renal artery stenosis, and 3) the data comparing angioplasty (without stenting) with medical therapy are severely limited by study design issues and only assess surrogate endpoints[11-13]. However, we have collected extensive data on clinical event rates after stenting, sufficient to allow us to model the frequency and time to clinical events in the population of interest. To estimate these we have utilized our prospective registry of renal stent patients, selecting for patients that would fulfill the major entry criteria of this proposal (documented history of hypertension while on 2 or more anti-hypertensive medications, and serum Cr $\leq$4.0). To better understand the relationship between renal insufficiency *in this population*, and mortality, we have prospectively followed 271 patients undergoing renal artery stenting since 1993. In 39% the stenosis was bilateral, and or supplied a solitary kidney. Stent therapy reduced stenosis severity from 69$\pm$11% to -1$\pm$11%, $p < 0.001$. Blood pressure, renal function, quality of life and mortality were collected prospectively.

To confirm these rates we have also re-analyzed serious adverse event reports from the ASPIRE 2 renal stent registry, a Food and Drug Administration (FDA) approval trial (Johnson & Johnson) (Rosenfield KR and Cooper CJ, unpublished data). As depicted in Figure 1, event rates in both populations were equivalent.

Figure 1. Event free survival after renal artery stenting.

Results of the Medical College of Ohio Hospital renal stent registry and ASPIRE 2 studies.



1.10.1 Duplex Preliminary Data

ASPIRE 2 was the first trial to demonstrate that Duplex ultrasonography can reliably determine restenosis-free patency of a renal artery stent. ASPIRE 2 led to FDA approval of the balloon-expandable Palmaz stent in renal arteries. Similar studies include the Intratherapeutics renal artery stent trial and the Guidant HERMES renal artery stent trial. These trials have involved over 75 clinical sites, and over 600 patients. The core lab has validated the technique of renal stent Duplex ultrasonography across multiple sites, training many of the clinical sites in the performance of this examination. In the ASPIRE 2 trial, the adequacy of the examinations to allow complete interpretation was 89%.

1.11 Summary

There likely exists a logical progression wherein renal ischemia, due to RAS, leads to clinical events. This pathway can be envisioned in the following manner: Ischemia begets neuroendocrine activation, hypertension, and renal insufficiency. These factors result in pathophysiologic alterations including acceleration of atherosclerosis, enhanced thrombosis, further renal dysfunction and development of left ventricular hypertrophy, amongst others. These in turn lead to clinical events including CHF, myocardial infarction (MI), stroke, progressive renal insufficiency, and ultimately death. At the heart of this study is the fundamental question of whether anti-hypertensive pharmacologic therapy, directed at 1 or several mechanisms, is sufficient to interrupt this process or whether revascularization is required. This study will also look at critical steps in the pathway leading to clinical events including BP control, renal function, and the anatomic stenosis to understand whether these relationships exist. Thus, beyond answering an important clinical question, the study will enhance our understanding of the disease. To address the health policy and quality of care

implications of our findings, this study will carefully examine the impact of these alternative treatments on quality of life and cost-effectiveness of care.

2.0 STUDY OBJECTIVE AND ENDPOINTS

2.1 Primary Endpoint

The primary endpoint is event-free survival from cardiovascular and renal adverse events, defined as a composite of cardiovascular or renal death, stroke, myocardial infarction, hospitalization for congestive heart failure (CHF), progressive renal insufficiency, or need for permanent renal replacement therapy.

A critical decision is whether to utilize a surrogate physiologic measure (BP, GFR, etc), or clinically relevant events as the primary outcome. There have been numerous publications that describe physiologic alterations with renal artery stenosis and intervention; however, none are sufficiently robust surrogates to guide patient treatment. Simply put, an alteration in renal blood flow, GFR, BP, or other measure may imply benefit, but may be insensitive to changes in other important surrogates and may not accurately predict the clinical response. Thus, a "clinical trial" is needed. Importantly, one must consider whether the clinical endpoint should be *total mortality* since this requires no adjudication and the interpretation is unequivocal. However, in this setting, an unrealistically large number of patients would be required to achieve adequate power (>85%). Additionally, short of mortality, other events occur that are very clinically relevant.

Any such trial should incorporate the most contemporary understanding of the disease process under investigation. In RAS that necessitates the consideration of CV endpoints in a composite, since it has become readily apparent that there is a strong link between CV events with renal disease in general and with RAS specifically. As described above, this linkage can be understood in the context of previously identified pathophysiologic mechanisms associated with RAS that include activation of the renin-angiotensin and sympathetic systems, endothelin release, worsened hypertension, the effect of CRI on atherosclerosis progression, etc. Thus, beyond the traditional renal endpoints that should be measured, *progressive renal insufficiency and need for permanent renal replacement therapy*, CV endpoints should be considered. In this context *stroke and myocardial infarction* are well accepted as relevant measures of treatment effectiveness. Finally, *hospitalization for heart failure* must be considered since it is a well-described complication of RAS and is certainly understood within the context of the pathophysiology of RAS (neuroendocrine activation, LVH generation, and hypertension). While CHF hospitalization may seem "softer" than the events listed above, the CEC, founded by Dr. Pfeffer, has demonstrated the ability to critically adjudicate CHF hospitalizations in a number of pivotal clinical trials.

To aggregate these events into a single endpoint, the following criteria should be, and are, met. Firstly, each is clinically important in its own right. Secondly, each non-fatal component has been causally related to mortality. Finally, one must consider whether a weighting scheme is necessary to interpret the results since the endpoint is composed of a diverse construct of clinical events. To an extent, the interpretation of a weighting strategy is perspective-dependent. Thus, a disabling stroke might be worse than death to a patient, less than death to a physician, and more expensive than death to an economist. To that end, the Quality of Life (QOL)-cost effectiveness aims will be critical to the overall interpretation of this work. At completion, the health

economist can appraise the cost-effectiveness, the patient may consider the gain in quality adjusted life years (QALYs), and the physician may look at the aggregate number of events.

In this study, the goal is to provide critical information that will influence physician behavior. Thus, we advocate for the strategy of "no weighting" which is the least cumbersome to interpret[116]. However, we also recognize that there is the possibility of divergence in the direction of some of these measures. As an example, one can conceptualize a result that demonstrates lower rates of progressive renal insufficiency with renal stenting at the expense of slightly higher rates of dialysis, due to the occurrence of athero-embolization. Clearly, pre-specifying the secondary endpoints will be helpful in the interpretation of such divergent results, should they occur. Finally, it should be recognized that divergence, if our understanding of the disease process is correct, is not expected. Frankly, if stenting improves GFR, lowers BP more effectively, and these are linked to adverse outcomes, then the results should be directionally consistent.

These primary endpoint events will be adjudicated by an independent Clinical Events Committee (CEC) blinded to the randomly allocated therapy. The case report forms and documents needed by the CEC for adverse event adjudication are listed in Table 11.

2.1.1 Cardiovascular and Renal Mortality

All-cause mortality is attractive since it is simple to adjudicate and avoids issues of misclassification or ascertainment bias. However, this must be balanced against the loss of power associated with a high rate of non-attributable deaths in an elderly cohort, largely due to cancer. Such events represent noise in the analysis and lead to substantial loss of power. Thus, we propose to use the attributable component, CV and renal mortality, in the primary endpoint. However, as a secondary analysis we will analyze total mortality to demonstrate that directional changes in total mortality are attributable to directional changes in CV-renal deaths.

The CEC will adjudicate all reports of death, to determine the most likely cause of death. The cause of death will be the underlying cause, not the immediate mode of death. The CEC will classify all causes of death as:

1) Cardiovascular
2) Renal-related
3) Non-Cardiovascular (Non-Renal)
4) Unknown

The following is an abbreviated listing of the CORAL endpoint definitions which will be adjudicated by the Clinical Endpoint Committee. This summary does not include all of the nuances associated with each classification. For specific endpoint definitions please refer to the CEC Manual of Operations (MOP).

Cardiovascular death will be sub-classified as:

1) **Fatal Myocardial Infarction Death** (e.g., death occurring within 14 days following MI, abrupt death with suggestive criteria of an infarct such as electrocardiogram (ECG) changes and chest pain, or autopsy-proven recent infarct),

2) **Pump Failure Death** (e.g., death occurring within the context of worsening heart failure symptoms, without evidence of another cause of death)
3) **Sudden Death** (e.g., death occurring unexpectedly in an otherwise stable patient)
4) **Presumed Sudden Death** (e.g., suspected sudden death in a patient last seen > 24 hrs)
5) **Presumed Cardiovascular Death** (e.g., death due to a presumed CV cause, the patient last seen >24 hrs)
6) **Stroke Death** (e.g. death occurring after a documented stroke)
7) **Pulmonary Embolism Death** (e.g., death occurring as a result of a pulmonary embolism)
8) **Procedure-Related Death** (e.g., death occurring during a CV procedure or as a result of a complication of a CV procedure)
9) **Other Cardiovascular Death** (e.g., death due to a documented CV cause not listed above).

Death due to renal causes will be attributed to death due to renal failure and its complications (e.g. uremia, a dialysis procedure, acute renal failure, renal transplant, hyperkalemia in association with renal insufficiency and other complications of renal failure).

If an unequivocal and documented non-cardiovascular and non-renal cause can be established as the primary cause of death, the event will be classified as non-cardiovascular (non-renal). Non-cardiovascular (non-renal) deaths will be further classified into the following categories:

- infection
- malignancy
- pulmonary
- gastrointestinal
- accidental
- suicide
- diabetes (non-cardiovascular)
- unwitnessed death
- other.

For cases of death for which there is insufficient data available to determine if the cause was cardiovascular, renal or non-cardiovascular (non-renal) the event will be classified as unknown.

2.1.2 Permanent Renal Replacement Therapy

ESRD, leading to dialysis or renal transplantation, is associated with considerable morbidity and cost to the Federal government, justifying inclusion as an endpoint of interest (USRDS 2000). Furthermore, RAS can be causally linked to ESRD[44], just as ESRD can be causally linked to mortality. While we did consider dialysis only, as the measure of ESRD, one can conceptualize individuals that undergo renal transplantation, prior to inception of dialysis, should a kidney be available. Clearly, treatment with renal transplantation is a robust event to patients, physicians, and the Federal ESRD program.

Permanent renal replacement therapy is defined when a patient requires hemodialysis, peritoneal dialysis or renal transplantation. Dialysis for the purposes other than treating chronic renal failure will not be considered a study endpoint.

2.1.3 Progressive Renal Insufficiency: 30% Reduction of eGFR from Baseline, Persisting ≥ 60 Days

Several measures of progressive renal dysfunction have been advocated. Previous renal literature has relied heavily upon doubling of Cr as an endpoint of interest and importance[45, 98, 117], however there is now general acceptance of the reduction of eGFR when eGFR is calculated using a reliable formula. For this endpoint, the MDRD formula will be used to calculate eGFR to measure and adjudicate a significant decline in renal function. Importantly, as described above, recent work suggests a causal relationship between renal insufficiency, clinical events, and mortality.

Progressive renal insufficiency will be identified as the irreversible progression of chronic renal disease resulting from pre-renal, intrinsic or post-renal causes. A 30% reduction of eGFR from baseline (or earliest available value) as confirmed by the Core Lab or local lab and separated by greater than or equal to 60 days is required.

2.1.4 Myocardial Infarction

This represents the most widely accepted "hard" measure of cardiac events[95] since it is clearly clinically significant and has a strong causal relationship with early and late mortality[118]. Furthermore, the methods for endpoint ascertainment are well described[119]. While one could consider a more liberal cardiac event measure, such as hospitalization with acute coronary syndrome, such events may be so frequent in this population as to overwhelm the other components of the composite and may not be sufficiently "attributable." Finally, as described above, RAS can be linked to MI through hypertension, neuroendocrine activation and atherosclerosis progression associated with renal insufficiency.

Spontaneous myocardial infarction will be positively adjudicated based on the presence of clinical symptoms or ECG changes AND elevated cardiac markers. Cardiac marker criteria is defined by a rise in Troponin or CKMB greater than the Upper Limit of Normal of the respective marker. A myocardial infarction occurring post procedurally must have marker values three times the Upper Limit of Normal post-percutaneous coronary intervention (PCI) and five times the Upper Limit of Normal post-CABG. A post-CABG MI will also require new pathological Q waves.

2.1.5 Stroke

Stroke is a widely accepted measure of vascular events[95, 120], due to its obvious clinical significance and causal relationship with mortality. In trials of both pharmacologic and non-pharmacologic strategies to control blood pressure, stroke rates are very sensitive to blood pressure control in general[93] and to inhibition of the renin-angiotensin system in specific[95]. Alternatively, we could consider more broad categories for neurovascular events such as

Transient Ischemic Attack (TIA) + stroke, or a more narrow category of disabling stroke. However, TIA can be difficult to adjudicate correctly whereas limiting inclusion to "disabling" strokes leads to a loss of clinically important events that may shed light on treatment efficacy.

Stroke is defined as follows:

1. A focal neurological deficit of central origin lasting **more than** 24 hours, with or without imaging confirmation of cerebral infarction or intracerebral hemorrhage.

OR

2. A focal neurological deficit of central origin lasting **less than** 24 hours with corresponding imaging evidence of cerebral infarction or intracerebral hemorrhage.

OR

3. A focal neurological deficit of central origin lasting **less than** 24 hours that was treated with thrombolytic therapy or directed percutaneous intervention.

OR

4. A non-focal encephalopathy lasting **more than** 24 hours with imaging evidence of cerebral infarction or hemorrhage adequate to account for the clinical state.

Patients with non-focal global encephalopathy will not be considered to have stroke without support from neurological imaging.

Stroke will be further classified as:

a.Ischemic Stroke – stroke with imaging suggesting ischemic changes
b.Ischemic Stroke with Hemorrhagic Conversion - stroke with evidence of hemorrhage on imaging, judged to be hemorrhagic transformation of a primary ischemic stroke
c.Primary Intracranial Hemorrhage – stroke with evidence on imaging of intracerebral hemorrhage not due to transformation of an ischemic stroke
d. Unknown: when imaging is unavailable or inconclusive

2.1.6 Hospitalization for Congestive Heart Failure

As described above, there exists a strong biologic rationale for linking renal artery stenosis to CHF. Importantly, to patients and physicians, this is a very clinically significant event that has a major impact on symptom status and treatment. Finally, CHF is associated with a 6 fold increase in mortality amongst patients with equivalent degrees of left ventricular dysfunction[121].

Hospitalization for CHF will be attributed to documented signs and symptoms of heart failure. Additionally, IV therapy (vasodilators, diuretics or inotropes) must be initiated in a greater than or equal to 12 hour hospital or clinical stay.

2.2 Secondary Endpoints

There will be twelve (12) pre-specified discrete secondary analyses in this randomized trial of 1080 evaluable patients. Two of these, the Quality of Life and the Cost-Effectiveness analyses, are described within the Economic and Quality of Life (EQOL) protocol. The results of these pre-specified secondary analyses will be considered as purely secondary findings of the trial. Moreover, the results of any other (non-pre-specified) analyses will not be considered as secondary findings from this trial. The secondary analyses may be divided into 9 categories:

- All Cause Mortality

- Subgroup Interactions:
  - Men vs. Women
  - African American vs. non-African American
  - Diabetes vs. non-Diabetes Mellitus
  - Global vs. Partial Renal Ischemia
- Longitudinal Kidney Function (1/Cr)
- Systolic Blood Pressure
- Durability of Renal Artery Patency
- Renal Resistive Index: Preservation of Microvascular Renal Function
- Correlation between Stenosis Severity and Kidney Function (1/Cr)
- Quality of Life
- Cost Effectiveness

Additional discussion of secondary endpoints is found in the section on Statistical Analysis.

2.3 Tertiary Endpoints

Tertiary analyses will be regarded as hypothesis-generating findings. These analyses include multivariable models used to estimate the determinants of the primary and secondary endpoints, and pre-specified subset analyses.

3.0 OVERVIEW OF STUDY ORGANIZATION

The CORAL Study is conducted under the direction of the National Heart Lung and Blood Institute of the National Institutes of Health in a cooperative agreement with the CORAL Study team. Overall conduct is the responsibility of the Steering Committee. Operational oversight is provided by an Operations Committee. The Clinical Coordinating Center (CCC) is responsible for oversight of the investigative sites and the Data Coordinating Center (DCC) is responsible for data collection and oversight of the Core Labs. AstraZeneca and Pfizer are responsible for provision of study medications. The CCC and DCC report to the Operations and Steering Committees. Study patient safety and study performance are monitored by the Data and Safety Monitoring Board (DSMB), which reports directly to the National Heart, Lung and Blood Institute (NHLBI). A figure depicting the relationships of the committee structure for this study can be found in the MOP.

3.1 Clinical Coordinating Center

The CCC is located at the University of Toledo, in Toledo, Ohio. The CCC for the CORAL Study has several key functions:

- study development and initiation
- site selection, regulatory oversight, payments, and monitoring
- review of study document development
- oversight of recruitment and retention
- coordination of study meetings
- response to protocol related questions and issues
- maintenance of a 24/7 contact line
- communication (via the website, newsletter, study meetings and other)
- quality assessment of site performance
- key contact for industry sponsors

3.2 Data Coordinating Center

The Data Coordinating Center (DCC) functions will be performed by the Harvard Clinical Research Institute (HCRI), which is located in Boston, Massachusetts. The functions of the DCC include:

- collaborative development of the protocol
- collaborative development of the case report forms (CRFs)
- collaborative development of the Manual of Operations (MOP)
- maintenance of the entire study database, including integration of data from the five core labs, as well as the results of the Clinical Events Committee (CEC)
- maintenance of Adverse Event data and submission of reports to the Study PI- IDE Holder
- production and reconciliation of data queries
- assist the CEC in their role by identifying endpoint events and preparing patient documents for review and adjudication
- generation of study reports for CORAL committees, the Data Safety Monitoring Board (DSMB), the NHLBI Project Officer, and investigational sites

- analyses performed with input and direction from the DCC senior statisticians, the CCC and other key CORAL Study committee members
- generation and maintenance of the trial website

3.2.1 CORAL Study Website

A website will be established for the CORAL Study to assist in the communication of study-related materials and information. This website will:

- eliminate much of the traditional paper report volume
- aid in rapid dissemination of study information
- provide easy access to study information for all parties involved in the trial

The web site will not be used for electronic data capture of the patient data, nor for the dissemination of analyzed data. The CORAL web site will be available to all sites, core labs, the CCC, the DCC, and various committee members. It will be developed by the DCC and CCC and maintained by the DCC. Access to the web site will be secured through the use of passwords and/or equivalent security mechanisms. All personnel connected with the CORAL Study will be identified, and a password will be created for **exclusive** use only. Each person will only have access to documents specific to their individual study unit.

In addition to study personnel, the web site will allow restricted access by enrolled patients and the general public. Through specific web portals, enrolled patients will be able to follow developments in the CORAL Study while the general public will have access to general information and educational materials pertinent to the aims of the study.

3.3 Study Committees

3.3.1 Study Chairs

The overall leadership responsibility of the Study is under the direction of the Study Chairman and Study Co-Chairman.

3.3.2 Steering Committee

The Steering Committee has been established to serve as the main governing body of the trial. The Steering Committee is composed of the Operations Committee members, core lab directors, and subcommittee chairman.

The main roles and responsibilities of the Steering committee are:

- to oversee the overall scientific direction of the trial
- to approve the protocol and any protocol modifications
- to review the case report forms and manual of operations
- to review study progress, including enrollment, adherence, and quality of design
- to review reports from the Operations Committee and provide recommendations
- to resolve issues between core labs or committees

- to approve ancillary study and publication requests submitted by the Publications Committee
- to present the trial results in advance of national presentations

The Steering Committee meets both face-to-face and on teleconference on an ad hoc basis. For the Steering Committee, a quorum will be achieved when at least three fourths of membership is present or represented by proxy. A simple majority vote will be sufficient to ratify the current protocol. However, any significant changes or revisions to the protocol will require a super majority vote of greater than or equal to three fourths of the committee membership.

3.3.3 Operations Committee

The Operations Committee includes the Study Chair, Study Co-chair, Study Leadership from the CCC and DCC, a representative of the Steering Committee, and several representatives from the NHLBI.

The main roles and responsibilities of the Operations Committee are:

- to oversee weekly operational conduct of the study
- to develop and implement the final protocol
- to report monthly to the Steering Committee
- to monitor the Data Coordinating Center operations
- to monitor the Clinical Coordinating Center operations
- to monitor enrollment and site compliance
- to develop and prepare the study agenda and recommendations for the Steering Committee
- to review ancillary study and publication requests submitted by the Publications Committee
- to propose and approve membership of the other committees
- to present the trial results in advance of national presentations
- to approve all manuscripts and study publications prior to submission, as requested by the Publications Committee

The Operations Committee meets via teleconference on a weekly basis. For the Operations Committee, a quorum will be achieved when three fourths of the membership is present. A simple majority vote will be sufficient to ratify decisions of the Operations Committee.

3.3.4 Subcommittees

The following subcommittees report to the Steering Committee. Each committee will determine its own meeting schedule. Meetings are typically held by telephone conference call. A quorum will be achieved when three fourths of a committee's membership is present. A simple majority vote will be sufficient to ratify decisions. Additional subcommittees following these rules will be created by the Steering Committee and their purposes will be detailed in the MOP.

3.3.4.1 Clinical Endpoint Committee (CEC)

The Clinical Endpoint Committee is composed of a Chairman, Co-Chairman and Physician Reviewers with expertise in clinical event adjudication. All members will be selected by the CEC Chairman and will remain blinded to the treatment group for all patients.

The main roles and responsibilities of the CEC include:

- define and adjudicate all investigator-reported endpoints in a consistent and unbiased manner throughout the entire course of the study
- adjudicate the following primary endpoints:
    - All cause mortality
    - Hospitalization for Congestive Heart Failure (CHF)
    - Myocardial Infarction (MI)
    - Stroke
    - Progressive renal insufficiency
    - Need for permanent renal replacement

3.3.4.2 Protocol Committee

The committee is composed of members from the Operations Committee, CCC, DCC and the NHLBI, and chaired by the Principal Investigator of the DCC. The Protocol Committee is responsible for protocol:

- review
- coordination of revisions
- adjudication of conflicting text
- obtain final approval from key study members
- production of the final protocol

3.3.4.3 Statistics Committee

Statistical support for the CORAL project is centralized in the form of a Statistics Committee. This committee is responsible for the appropriate and consistent analysis of all endpoints across the study group. All data analyses presented in any form must be approved or prepared by the statistics committee. The Statistics Committee will work with the Publications Committee by ensuring that all approved projects are assigned a statistician and appropriate data management and analysis support.

3.3.4.4 Interventional Committee

The Interventional Committee consists of investigators with unique experience and expertise in the renal artery stenting procedure, including familiarity with the investigational device used in CORAL. The responsibilities of the Interventional Committee will include:

- determination, selection, and use of devices used in the study
- development of site training guidelines, including presentation of the investigational device and their use at a pre-enrollment investigators meeting, discussion with the site Principal Investigator (PI) after site activation but prior to enrollment of the first patient, and review of angiographic images from site roll-in cases with the Angiographic Core Lab

- monitoring of site investigator and device performance (sites or investigators with more than two (2) stent failures, as identified by the Angiographic Core Lab or DCC/CCC will be subject to additional procedure review by the Interventional Committee)
- periodic regular monitoring of commercial and investigational interventional device availability so that recommendations regarding the use of state-of-the-art devices can be made to the CORAL Steering Committee

3.3.4.5 Site Selection Committee

A Site Selection Committee is responsible for selecting highly motivated participating centers. The selection criteria used to identify sites includes:

1) experience with renal stenting
2) access to the population of interest, with special emphasis on recruitment of women and minorities
3) experience and infrastructure for conducting clinical trials
4) willingness to recruit and follow patients in strict compliance with the study protocol
5) availability of multidisciplinary management of patients with RAS, hypertension, renal insufficiency and CV disease

During the study, this committee will identify and review new sites as needed.

3.3.4.6 Hypertension and Risk Factors Committee

The Hypertension and Risk Factors Committee is responsible for review and approval of study recommendations for the management of specific concomitant medical conditions (including hypertension, atherosclerotic vascular disease, diabetes, hyperlipidemia and renal insufficiency). These recommendations, reviewed annually and on an as-needed basis, will be based upon current guidelines issued by relevant medical societies. Any modifications applicable to CORAL patients will be disseminated throughout the study group.

3.3.4.7 Enrollment and Patient Retention Committee

The Enrollment and Patient Retention Committee is composed of representatives that promote and support the study and provides input to the Steering Committee on issues that arise related to enrollment and patient retention.

3.3.4.8 The Publications and Ancillary Studies Committee

The Publications and Ancillary Studies Committee will evaluate any requests for ancillary studies, substudies, analyses of the data, or any research involving study material, blood samples, examinations, or any data collected as part of the CORAL protocol. The Publications Committee will also assess requests for studies that require new data to be collected on CORAL Study patients. The Publications Committee will meet as needed until data is available to permit analysis of the study endpoints, at which time regular meetings may be scheduled. All such

requests acted on in the Publications Committee will be forwarded to the Steering Committee, for final approval.

The Publications Committee will oversee preparation of manuscripts for publication regarding the CORAL Study, and will be responsible for preparation of the manuscript reporting the primary and secondary endpoints in a timely fashion after data analysis is completed by the DCC. Prior to data collection and analysis, such manuscripts may include those describing the study methods, or the background or reason for the study. No one participating in the study will be permitted to publish or present analyses of data on any CORAL patients or that includes any study data without approval of the Publications Committee.

3.3.4.9 Minority Recruitment Committee

The Minority Recruitment Committee will monitor and address issues related to minority recruitment in CORAL. The Committee is charged with better ascertaining the potential factors affecting site activation in the urban centers where minority recruitment is expected to be higher. Additionally, the Committee will be responsible for palpably identifying barriers and enhancing the study's priority to oversample minority participants. The Committee will work to liase Study Leadership with organizations and societies that can help the study increase minority participation.

3.3.5 Data and Safety Monitoring Board (DSMB)

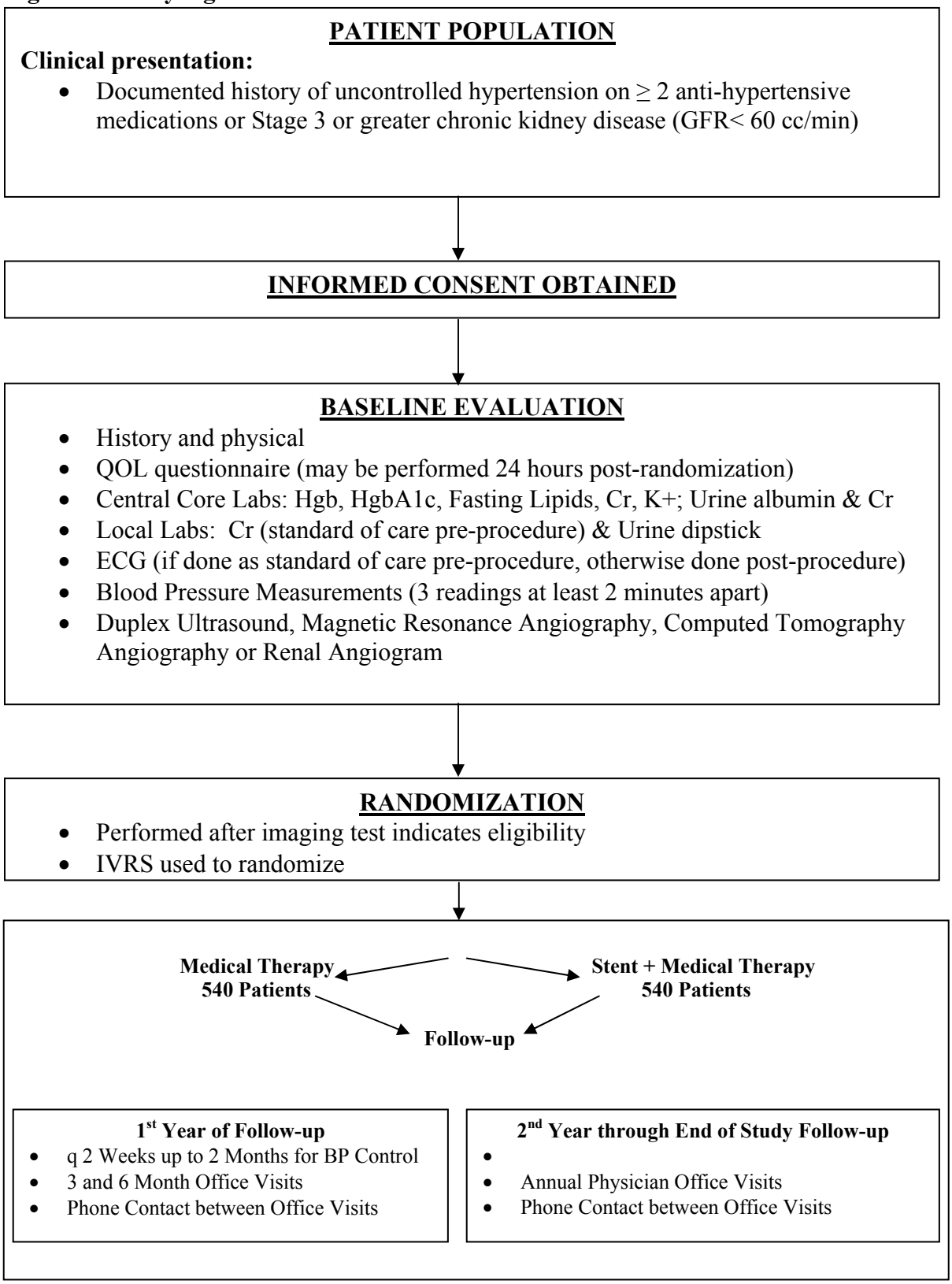
The DSMB will be composed of individuals independent of the study management organization and the investigators. The NHLBI Director approves the membership and the DSMB is advisory to the NHLBI. A nationally recognized member with experience in oversight of clinical trials will chair the DSMB, which is comprised of experts in relevant biomedical fields including radiology, cardiology, nephrology, quality of life and economics, biostatistics, and bioethics.

The main roles and responsibilities of the DSMB are:

- to initially review the protocol and commission a specific regular process for evaluation of trial data
- to review safety data at least annually during the study
- to recommend approval of protocol modifications, if warranted
- to advise the NHLBI directly regarding recommendations for trial modification or early trial cessation

The DSMB will meet at least twice a year. DSMB meetings will be open only to designated NHLBI staff and other individuals who have been approved to attend the meeting of the DSMB. The Chairman of the DSMB will discuss the recommendations of the DSMB with the NHLBI Executive Secretary (an NHLBI staff scientist appointment by the NHLBI), who will inform the NHLBI project officer, who will inform the Study Leadership. Any final decision to discontinue the CORAL Study will be made by the NHLBI.

Figure 2. Study algorithm.



4.0 STUDY DESIGN, TREATMENTS AND PROCEDURES

This is a prospective, multi-center, unblinded, two-arm, randomized study that will randomize 1080 patients at up to 100 sites in the US and 100 sites outside the US (OUS). Patients with evidence for renal artery stenosis will be screened for participation. Informed consent will be obtained and a baseline evaluation (history and physical, QOL, labwork, ECG (if done pre-procedure as standard of care) will be performed. After imaging study and data review indicates that the patient has met all inclusion criteria and none of the exclusion criteria, all such patients who have signed informed consent will be randomized to renal artery stenting with medical therapy versus medical therapy alone.

A subgroup of 400 patients will participate in a renal Duplex ultrasonography substudy, undergoing a Duplex scan at baseline, 1 year and study termination.

It is recommended that patients initially be followed at 2-week intervals up to 2 months, until blood pressure is at target, which is ≤ 140/90, (or, for those patients that have diabetes and/or proteinuria, a blood pressure of ≤ 130/80 will be the target). For the first 6 months of follow-up, patients will be scheduled for an office visit every 3 months. In the subsequent years patients will be seen on an annual basis until the study is ended. Health-related quality of life data and treatment costs will be assessed alongside the core clinical trial to evaluate the relative cost-effectiveness of the 2 treatment strategies. Patients who reach non-fatal primary endpoints will continue to be followed until the end of the overall study is completed.

Prior to the randomization of any patient, the principal interventional investigator must perform one renal stent procedure with study-approved device(s) on a minimum of one roll-in patient who meets a modified set of eligibility criteria (see section 4.5) and successfully submit the study data to the Angiographic Core Lab for evaluation and approval.. All patients in this roll-in registry will be analyzed separately from the main randomized patient cohort. Roll-in patients will sign a separate roll-in informed consent form, undergo the same screening procedures as randomized patients, and receive a Genesis™ stent. The follow-up procedures for the roll-in patients will include an evaluation at 2-4 weeks inclusive of a serum creatinine performed at the local lab. No labwork will be sent to the Biochemistry Core Lab for the roll-in patients nor will they receive study medication. Telephone contacts at 30 days and 9 months will be performed to assess for any adverse events and renal revascularizations.

4.1 Selection of Clinical Sites

The clinical sites selected for this study will have a minimum of one investigator with extensive experience in complex renal intervention, and a second with expertise in hypertension management. After selection, ongoing monitoring of the site will be conducted to facilitate enrollment commitments and to ensure accurate and timely submission of data and compliance with the study policies and procedures. All key staff members at the clinical centers will undergo education on the responsible conduct of research and provide a certificate of completion to the CCC of such education in accordance with Health and Human Services (HHS) policy.

4.2 Patient Population

Patients with a documented history of hypertension and/or chronic kidney disease with a GFR <60 cc/min who are suspected to have renal artery stenosis will be targeted for further screening and evaluation for this study. Personnel at the enrolling centers will be asked to remain in close contact with potential sources for patient referral, including institutional departments of interventional radiology, hypertension, nephrology, internal medicine, cardiology, vascular surgery, and family practice clinics. Special consideration will be given to those patients who may have had a renal angiogram prior to signing the informed consent (see section 4.6.1, 3rd paragraph). No study related activity may occur until informed consent is obtained.

Patients with appropriate clinical presentations who sign informed consent to participate in this study are expected to be randomized if they meet study entry criteria. Randomization will occur after the imaging study is performed.

4.3 Screening Procedures

Each site will complete and maintain an ongoing log for all patients who are screened and who sign informed consent. These logs will be databased and systematically reviewed by the DCC in an effort to identify barriers to recruitment or in missed enrollment of eligible patients. The CCC will consult with sites to maximize the site's enrollment potential.

Patients with evidence for RAS by non-invasive imaging studies may be screened by any of the following research personnel: interventional investigator, hypertension expert investigator, and study coordinator.

Many patients may present with the following clinical problems: suspected secondary hypertension, uncontrolled hypertension, clinical syndromes of heart failure and angina with poorly controlled hypertension, or unexplained renal insufficiency. The modalities for patient identification may include magnetic resonance angiography, captopril renal scintigraphy, computerized tomography angiography, aortography or duplex ultrasound assessment. Patients that are identified with a high probability of renal artery stenosis utilizing these methods will be offered participation. The site screening plan should be approved by the site HIPAA Board or Institutional Review Board (IRB), per local policy.

4.4 Informed Consent

A copy of the site informed consent template must be sent to the CCC for approval prior to submission to the IRB. The consent form must then have approval from the study site's IRB prior to enrolling any subjects into the study. Additionally, the NHLBI will require that all consent forms contain specific language about several essential elements.

A member of the Research Team should approach the patient to obtain written informed consent. The consent process involves an explanation of the purpose of the research study, the expected duration of the patient's participation and a description of the procedures to be followed throughout the study. In the event that study enrollment and all necessary follow-ups take longer

than anticipated, thus delaying the final analysis, the consent form may need to be modified. The patient should be provided a sufficient opportunity to review the consent form and ask questions. The patient must sign and date the consent form prior to performance of any study related procedures. Failure to provide informed consent renders the patient ineligible for the study.

4.5. Enrollment

All patients signing Informed Consent will be recorded onto the Screening & Enrollment Log. This log will indicate study status (randomized or not randomized) and if not randomized, the reason for exclusion. At the time of site monitoring visits, logs and imaging studies of screen failures may be reviewed by CORAL Study personnel.

Patients will be enrolled without regard to gender and will be included or excluded from enrollment based on the inclusion and exclusion criteria listed below.

4.5.1 Inclusion Criteria

1. Either:
    a. Documented history of hypertension on 2 or more anti-hypertensive medications OR
    b. Renal dysfunction defined as Stage 3 or greater CKD based on the new NKF classifications (estimated GFR < 60 mL per minute per 1.73 m^2 calculated by the modified MDRD formula) *
2. One or more severe renal artery stenoses by any of the following pathways:
    a. Angiographic: ≥ 60% and < 100% by renal angiogram OR
    b. Duplex: systolic velocity of ≥300 cm/sec OR
    c. Core lab approved MRA demonstrating
        - Stenosis >80% OR
        - Stenosis >70% with spin dephasing on 3D phase contrast MRA OR
        - Stenosis > 70% and two of the following:
            i. Ischemic kidney is > 1 cm smaller than contralateral kidney.
            ii. Ischemic kidney enhances less on arterial phase.
            iii. Ischemic kidney has delayed Gd excretion.
            iv. Ischemic kidney hyper-concentrates the urine.
            v. 2-D phase contrast flow waveform shows delayed systolic peak
            vi. Post-stenotic dilatation
    d. Clinical index of suspicion combined with a core lab approved CTA demonstrating
        - Stenosis is > 80% by visual assessment on high quality CTA.
        - Stenosis is > 70% on CTA by visual assessment and there are two of the following:
            i. The length of ischemic kidney is > 1 cm smaller than contralateral kidney.
            ii. Reduced cortical thickness of ischemic kidney.
            iii. Less cortical enhancement of ischemic kidney on arterial phase.
            iv. Post-stenotic dilatation

4.5.2 Exclusion Criteria

1. Unable to provide informed consent
2. Unable or unwilling to comply with study protocol or procedures
3. Age <18
4. Fibromuscular dysplasia or other non-atherosclerotic renal artery stenosis known to be present prior to randomization
5. Pregnancy or unknown pregnancy status in female of childbearing potential
6. Participation in any drug or device trial during the study period, unless approved by the Steering Committee
7. Prior enrollment in the CORAL Study
8. History of stroke within 6 months, if associated with a residual neurologic deficit*
9. Any major surgery, major trauma, revascularization procedure, unstable angina, or myocardial infarction 30 days prior to study entry*
10. Any planned major surgery or revascularization procedure, outside of the randomly allocated renal stenting dictated by this protocol, after randomization*
11. Hospitalization for heart failure within 30 days*
12. Comorbid condition causing life expectancy ≤ 3 years*
13. Allergic reaction to intravascular contrast, not amenable to pre-treatment
14. Allergy to stainless steel
15. Allergy to all of the following: aspirin, clopidogrel, ticlopidine
16. Known untreated aneurysm of the abdominal aorta >5.0 cm*
17. Previous kidney transplant
18. a. Stenosis of > 50% of a previously treated revascularized renal artery OR
    b. Treatment of any renal artery stenosis within the past 9 months **(roll-in patients can have prior treatment on the contralateral side)**
19. Kidney size less than 7 cm supplied by target vessel
20. Hydronephrosis, nephritis or other known cause of renal insufficiency, not due to large vessel renal artery stenosis
21. Visualized stenosis of only an accessory renal artery supplying <1/2 of the ipsilateral renal parenchyma, without stenosis in a dominant renal artery
22. Local lab serum Cr >4.0 mg/dl on the day of randomization*
23. Presence of a renal artery stenosis not amenable for treatment with a stent, known to be present prior to randomization
    a. The index lesion cannot be treated with a single stent (i.e >18 mm in length)
    b. The placement of a stent will necessitate covering a renal artery branch renal artery with the stent.
    c. The stenosis is in an artery < 3.5 mm in diameter.
    d. The stenosis involves a segmental renal artery branch.
24. Abrupt vessel closure or dissection after diagnostic angiography [NOTE: Patients with abrupt vessel closure or dissection as a result of diagnostic angiography will not be randomized but will undergo stent revascularization, receive optimal medical therapy and will be followed for the full study period.]

***Roll-in patients do not need to meet these inclusion/exclusion criteria**

For a patient randomized to stenting via a non-invasive pathway or mistakenly by the angio pathway, all stenoses > 60% should be treated, even in vessels less than 3.5 mm diameter (allowed to do PTRA alone or can use a coronary stent off-label) or if incidental, but significant FMD is detected (PTRA alone preferred). Once a patient is randomized to stenting, an effort to eliminate ALL lesions that may cause renovascular hypertension should be treated in order to prevent adversely biasing the stent study group primary CV outcomes.

4.5.3 Vulnerable Patient Populations

Vulnerable populations, specifically prisoners, institutionalized individuals and pregnant women will not be targeted for recruitment. Pregnant patients are excluded for the following reasons: 1) angiographic studies are required that would increase radiation exposure to a fetus, 2) anti-hypertensive medications utilized in this study are contraindicated in pregnancy (angiotensin receptor antagonists).

4.5.4 Inclusion of Women and Minorities

CORAL is a phase III clinical trial that will be conducted in accordance with the newly amended National Institutes of Health (NIH) Policy of Inclusion of Women and Minorities in Clinical Research. Patients will not be excluded from entry based on gender or ethnicity. It will be the goal of the CORAL Study group to achieve ≥ 50% enrollment of women in this study. If recruitment of women falls below 40% of the study cohort, several measures may be taken to insure adequate representation. These include, but are not limited to, decelerating enrollment of men at selected centers and sharing the strategies of centers highly successful at recruiting women with less successful centers.

4.5.5 Recruitment of Minority Patients

It is expected that CORAL investigators will need to screen a greater proportion of African Americans in order to identify those patients with renal artery stenosis, rather than poorly controlled essential hypertension. It is the goal of the CORAL investigators to achieve a cohort of minority patients proportionate to their representation in the population at large. In order to ensure this goal is met, Study Leadership will create a Minority Recruitment Committee to monitor minority recruitment and aid sites in efforts to recruit minority patients.

To achieve robust numbers of African Americans and other minority patients, the CORAL Study Leadership supports local community activities, including advertising in the local communities and use of community health events. Prior to implementation of these recruitment tools, approval of these activities will be sought from the Study Leadership and site IRBs. During the conduct of the study sites will be notified of total and site specific enrollment by fax and on the study website. In both forums we will report enrollment of minority patients. Sites that successfully recruit minority patients will be highlighted on both the newsletter and the website.

Staff training will include cultural competency training to minimize possible barriers. There will be gender and minority recruitment rates established by the Site Selection Committee for each quintile of recruited patients, and if gender and/or minority recruitment falls below these

boundaries, corrective action will be taken to: 1) identify unanticipated barriers to recruitment and remove these; and/or 2) increase the number of sites with diverse patient populations.

Table 1. Targeted/planned enrollment table.

TARGETED/PLANNED ENROLLMENT: Number of Patients 1080			
Ethnic Category	**Sex/Genders**		
	Females	**Males**	**Total**
Hispanic or Latino	40	40	80 (7.4%)
Not Hispanic or Latino	500	500	1000
Ethnic Category Total of All Patients*	540	540	1080
Racial Categories			
American Indian/Alaska Native	6	6	12 (1.1%)
Asian	12	12	24 (2.2%)
Native Hawaiian or Other Pacific Islander	6	6	12 (1.1%)
Black or African American	100	100	200 (18.5%)
White	376	376	752 (69.6%)
Racial Categories: Total of All Patients	500	500	1080*

*Note: We estimate that approximately 80 patients will self-categorize Hispanic/Latino, and will not indicate a race.

Table 2. Schedule of treatments and procedures for randomized patients.

	Index Visit				1st Year Follow-up					
	Baseline	**Randomization**		**Discharge (if applicable)**	**2 Weeks**	**4 Weeks (optional)**	**6 Weeks (optional)**	**8 Weeks (optional)**	**Months 3 and 6**	**1 Year Visit**
Time range for completion	-30 days prior to randomization	Same Day, Prior to	During		± 1 Week	± 1 Week	± 1 Week	± 1 Week	± 1 Month	± 1 Month
Point of contact	Hospital/Office				Office	Office	Office	Office	Office	Physician Office
Informed Consent	X									
History	X			X	X	X		X		X
Physical Exam	X			X						X
QOL Questionnaires [1] **- Physical Symptoms Distress Index - SF-36 - EQ-5D**	X								X (6M only)	X
Local Labwork										
Serum Cr	X									
Urine dipstick	X			X						X
ECG [2]	X'								X(6M only)	X
Blood Pressure	X			X	X	X	X	X	X	X
Duplex Scan [3] **(Only Substudy patients)**	X									X
Biochemistry Core Lab [4]										
Serum Cr		X			X				X	X
Serum K^+		X			X	X	X	X	X	X
Hgb, HgbA1c		X								X
Lipids, fasting		X								X
Cystatin C		X								X
Urine Alb + Cr		X								X
Stored serum, plasma, urine		X								X
Stored DNA		X								
Renal Angiography [5]			X							
ACT Measurements (Only pts randomized to stent)			X							
Medication Compliance Check				X	X	X	X	X	X	X
Adverse Event Assessment [6]		X	X	X	X	X	X	X	X	X

Table 2. Schedule of treatments and procedures for randomized patients (cont).

	Follow-up Beyond 1 Year		Study Termination*
		Annual	
Time range for completion		± 1 Month	± 1 Month
Point of contact		Physician Office	Physician Office
History		X	X
Physical Exam		X	X
QOL Questionnaires [1] **- Physical Symptoms Distress Index** **- SF-36** **- EQ-5D**		X (Years 2 and 3 only)	X
Local Labwork			
ECG [2]		X	X
Blood Pressure		X	X
Duplex Scan [3] **(Only Substudy patients)**			X
Biochemistry Core Lab [4]			
Serum Cr [7]		X	X
Medication Compliance Check		X	X
Adverse Event Assessment [6]		X	X

x': If pre-imaging study ECG has been obtained as standard of care, otherwise the ECG should be obtained immediately after randomization.

**Study termination visit should replace annual visits for subjects whose last annual visit is within 4 months of study termination (anticipated Jan 2014).

1 = QOL questionnaires forwarded to EQOL Core Lab; baseline QOL can be completed up to 24 hours post-randomization.

2 = ECGs forwarded with monitored CRFs to DCC

3 = Duplex scan and technician worksheet forwarded to Vascular Ultrasound Core Lab

4 = Processed blood specimens forwarded to Biochemistry Core Lab

5 = Renal angiograms and technician worksheet forwarded to Angiographic Core Lab

6 = All SAEs will be reported to the DCC and IRBs within 24 hours of knowledge of event; collection of AE information will be continuous between contacts

7 = If the eGFR is reduced 30% from the baseline value based on any of the local lab draws, a serum creatinine sample must be drawn and sent to the Biochemistry Core Lab as soon as possible. If the Biochemistry Core Lab Cr result indicates a reduction of 30% in eGFR, a repeat Cr must be performed in 60 days and sent to the Biochemistry Core Lab to confirm.

Table 2A. Schedule of treatments and procedures for roll-in patients

	Index Hospitalization				1st Year Follow-up		
	Baseline	**Procedure**		**Discharge**	**2 -4 Week**	**4 Week [3]**	**Month 9**
Time range for completion	-30 days prior to angiogram	Same Day, Prior to	During		± 1 Week	± 1 Week	± 1 Month
Point of contact	Hospital				Office Visit	Telephone Call	Telephone Call
Informed Consent	X						
Local Labwork							
Serum Cr	X				X		
Urine dipstick	X			X			
Blood Pressure	X			X	X		
Renal Angiography [1]			X				
Adverse Event Assessment [2]		X	X	X	X	X	X

1 = Renal angiograms and technician worksheet forwarded to Angiographic Core Lab

2 = All SAEs will be reported to the DCC and IRBs within 24 hours of knowledge of event; collection of AE information will be continuous between contacts

3= If the patient returns for the 2 week office visit follow-up, you will need to perform the 4 week Telephone contact. If the patient returns for the 4 week office visit follow-up, the Telephone contact is not required.

4.6 Trial Procedures

4.6.1 Enrollment Procedure

Informed consent must be obtained for all patients who are potential trial candidates prior to the baseline data collection ,testing and protocol-driven procedures. Patients will be entered into the randomized phase of the study after it has been determined that the patient meets all of the inclusion and none of the exclusion criteria. Therefore, enrollment will occur with informed consent and at the time of randomization.

Abrupt Closure/Dissection During Diagnostic Angiogram

For those patients randomized via renal angiogram who experience abrupt closure or dissection during diagnostic angiography and require revascularization with a stent, randomization will not occur. However, these patients will continue to be followed for the full study duration (following the Schedule of Treatments and Procedure in Table 2) and receive optimal medical therapy.

Previous Renal Angiogram Procedures

If a patient has undergone renal angiography as part of clinical care, or if patients undergo a qualifying angiogram but must undergo an additional procedure that precludes entry into the study for a defined period (see exclusion criteria) and the angiographic evaluation meets the study entry criteria, they can be randomized without undergoing an additional angiographic procedure. In this circumstance the enrolling site will be required to submit the films to the Angiographic Core Lab. The Angiographic Core Lab will approve or disapprove within 5 working days the angiogram for meeting patient eligibility criteria.

4.6.2 Baseline Procedures

1. **History & Physical Exam:**
   The history and physical exam will be performed prior to randomization. The history will include a complete review of systems and list of concomitant medication.

2. **Blood Pressure Assessment Procedure:**
   Baseline BP assessment will be monitored during the study when the patient is seated. The BPs will be performed in a quiet room, after five minutes seated, and will be measured in triplicate (each separated by at least 2 minutes), with the study provided Blood Pressure Device.

3. **Lab Evaluation:**
A baseline creatinine should be performed at a local laboratory, prior to randomization as part of standard of care. This will be also used to stratify randomization.

Sites will dipstick the urine and record the results on the corresponding CRF pages.

The following fasting baseline blood work will be also obtained but will only be sent to the Biochemistry Core Lab at the University of Minnesota, if the patient qualifies and is randomized:

- Hgb, HgbA1c
- Creatinine (**)
- potassium
- lipid profile, fasting
- cystatin C
- serum and plasma samples for storage, and a DNA extract for genetic analyses
- baseline urine specimen

** If the serum creatinine increases from the baseline (or earliest recorded) value on any of the local lab draws and suggests that the eGFR has decreased by ≥30%, a serum creatinine sample must be drawn and sent to the Biochemistry Core Lab as soon as possible. If the Biochemistry Core Lab result is indicative of a decline in eGFR>30% from baseline (or earliest recorded), a repeat Cr must be performed in 60 days and sent to the Biochemistry Core Lab to confirm decline.

The samples and data are de-identified before they are released from the research site to the Biochemistry Core Lab. The samples and data will be assigned a unique subject identifier. The link of the subject's identity to the subject identifier will only be kept at the collection site. The samples will be stored for a maximum of ten years after study completion before being destroyed by autoclaving.

(See Manual of Operations for detailed instructions on submission of study specimens.)

4. **QOL Surveys:**
Baseline quality of life data will be obtained from each patient by written, self-administered questionnaire at the time of study intake, prior to randomization or within 24 hours post-randomization. The study coordinator at each site will review the questionnaires for completeness and will attempt to ask any incomplete or poorly understood questions. Overall health-related quality of life (HRQOL) will be assessed using the 36-Item Short-Form Health Survey (SF-36)[122] and the EuroQOL health status instrument (EQ-5D) [123]. Disease-specific quality of life will be assessed using the Side Effects and Symptom Distress Index, a validated measure of the impact of treatment-related side effects on HRQOL, [124, 125]. These instruments are available in several languages and patients who speak one of these languages will be included in the quality of life sub-study. Measurement of baseline QOL for each patient is critical to the study design as this will allow for the use of change scores as the primary study outcome

(i.e., the difference between the measure at follow-up and at baseline), thus adjusting for any minor imbalances in baseline health between the treatment groups and increasing statistical power.

Follow-up quality of life will be assessed in a similar manner by mailed questionnaires at 6 months, and years 1, 2, and 3 after randomization in all study patients. Two weeks prior to each follow-up time point, the EQOL Core Lab will mail each patient a survey that can be self-administered, and returned in a provided stamped envelope. Any patient who fails to return the survey by mail will be given the survey by telephone, administered by a trained research assistant from the EQOL Core Lab. Previous studies conducted by the EQOL Core Lab using these same methods have generally achieved response rates of >95% (of surviving patients).

In addition, quality of life will be assessed at the study closeout contact. For practical reasons, the closeout quality of life survey will be provided to the patient by the local study coordinator (in contrast to the 6 month, 1 year, 2 year, and 3-year surveys).

5. **ECG:**
   The baseline ECG will be obtained immediately following randomization. If an existing ECG was obtained within 30 days prior to randomization as standard of care, the post randomization ECG is not required. Pre-printed ECG labels will be used to cover patient identifiers on the ECG. The labels will contain all patient study identifier information. ECGs will be transmitted with the baseline CRFs to the DCC. Additionally ECGs will be obtained at the 6 month, annual visits and at study completion. All additional ECGs obtained in relation to an adverse event will be labeled appropriately and forwarded to the DCC, as well.

6. **Renal Duplex Ultrasound (Sub-Study):**
   Ultrasonography will be performed in a subgroup of 400 patients at baseline, one year and study termination (3 evaluations per patient during the course of the study). These patients will be consecutively recruited from all patients enrolled, but only at a subset of selected sites experienced at renal Duplex ultrasonography. These sites will have demonstrated the capacity to collect diagnostic quality data in prior clinical trials of renal intervention.

   As described in the Manual of Operations, the renal artery Duplex ultrasound examination will be performed before randomization. Specific guidelines for patient positioning and scanning must be followed. Ultrasound scans will also be performed in the same patients at 1 year and at study termination. Scans will be sent to the Vascular Ultrasound Core Lab for evaluation. The Vascular Ultrasound Core Lab will certify the capabilities of each site to perform renal artery Duplex ultrasonography.

4.6.3 Renal Artery Imaging Evaluation

Renal artery imaging is required to demonstrate severe stenosis of at least one main renal artery for all potentially eligible patients. Imaging tests that can be done include duplex ultrasound, magnetic resonance angiography, ct angiography, or renal angiography. If stenosis qualifies by

duplex ultrasound or renal angiography, the site may randomize the patient. If renal artery stenosis is diagnosed by MRA or CTA, site interpretation requires approval by the MRA/CTA Core Lab (see section 4.6.3.2 below). All images must be submitted to the respective core lab for review and confirmation.

4.6.3.1. Renal Duplex Ultrasound Non-Invasive Pathway to Enrollment

Renal artery duplex examinations done for clinical evaluation of the renal arteries must be submitted to the Duplex Ultrasound Core Lab for review after randomization. Images can be submitted as super VHS video, PAL Video, MOD images, or DICOM images on CD-ROM. From these studies, images should be presented to the core lab that demonstrate: longitudinal view of the abdominal aorta with a peak systolic velocity (PSV) (cm/sec) at the level of the renal arteries; the renal arteries clearly identified with multiple assessments of PSV, EDV at the origin, proximal, mid- and distal segments in two views (i.e. from anterior and lateral decubitus views) All Doppler angles of insonation must be parallel to the long axis of the segment of the renal artery being evaluated, with an angle of insonation $\leq 60^{o}$.

The Duplex Ultrasound Core Laboratory must also see longitudinal pole-to-pole renal length measurements, and ideally would like to receive assessments of the renal resistive index within the medullar branches of the kidney at 0-degree Doppler angle, as described in the manual of operations.

In order to randomize a patient based upon duplex ultrasonography, a systolic velocity elevation to ≥300 cm/sec is required. Note that many patients may have ≥60% stenosis by contrast arteriography that won't meet this criterion. They potentially can still be entered into the CORAL Study, but will require information indicating severe stenosis by another accepted imaging method (either MRA, CTA, or renal angiography).

The duplex core lab will carefully review all submitted images in order to minimize false positive interpretation and enrollment of ineligible patients. If a site enrolls any patients who do not meet entry criteria on subsequent angiographic evaluation, or in the opinion of the duplex ultrasound core lab the images are felt to be of insufficient quality to support the interpretation or the findings consistent with the diagnosis are not present, the site may be instructed to have all non-invasive tests submitted to the core lab and pre-approved prior to randomization or may be asked to terminate enrollment with this pathway. The frequency of false positive enrollment relative to renal angiography performed in the patients randomized to stenting will be monitored as described in section 4.6.3.4.

4.6.3.2 Magnetic Resonance Angiography Non-Invasive Pathway to Enrollment

MRA images must be submitted to the MRA/CTA Core Lab for their review and may be required in DICOM format. The MRA examination should be done using a combination of 3-D Gadolinium MRA and 3-D phase contrast technique performed post gadolinium enhancement. The examination should show convincing evidence of severe stenosis according to the following criteria:

Core Lab approved MRA demonstrating:

- Stenosis > 80%, OR
- Stenosis > 70% with spin dephasing on 3D phase contrast MRA OR
- Stenosis > 70% and two of the following:
  i. Ischemic kidney is > 1 cm smaller than contralateral kidney.
  ii. Ischemic kidney enhances less on arterial phase.
  iii. Ischemic kidney has delayed Gd excretion.
  iv. Ischemic kidney hyper-concentrates the urine.
  v. 2-D phase contrast flow waveform shows delayed systolic peak.
  vi. Post-stenotic dilatation

The MRA/CTA Core Lab will review all submitted images *prior to randomization* in order to minimize false positive interpretation and enrollment of ineligible patients. After severity of stenosis is confirmed by the MRA/CTA Core Lab the patient may be enrolled and randomized without additional lesion evaluation. After a period of observations the MRA/CTA Core Lab may approve an individual clinical site to randomize patients based on preliminary local interpretation of the MRA study. In such cases the MRA studies should still be forwarded to the MRA/CTA Core Lab for confirmation. The frequency of false positive enrollment relative to renal angiography performed in the patients randomized to stenting will be monitored as described in section 4.6.3.5.

Note that patients who do not meet these criteria for any reason may still be enrolled in CORAL, but they will require other diagnostic information supporting a diagnosis of severe renal artery stenosis. That could be done using duplex ultrasound, CTA, or renal angiography.

4.6.3.3 CT Angiography Non-Invasive Pathway to Enrollment

CTA images must be submitted to the MRA/CTA Core Lab for their review and may be required in DICOM format. The CTA should be done by the sites using their routine protocols for best results. There should be clinical index of suspicion combined with a Core Lab approved CTA demonstrating the following:

- Stenosis is > 80% by visual assessment on high quality CTA.
- Stenosis is > 70% on CTA by visual assessment and there are two of the following:
  i. The length of ischemic kidney is > 1 cm smaller than contralateral kidney.
  ii. Reduced cortical thickness of ischemic kidney.
  iii. Less cortical enhancement of ischemic kidney on arterial phase.
  iv. Post-stenotic dilatation

The MRA/CTA Core Lab will review all submitted images prior to randomization in order to minimize false positive interpretation and enrollment of ineligible patients. The frequency of

false positive enrollment relative to renal angiography performed in the patients randomized to stenting will be monitored as described in section 4.6.3.5.

Note that patients who do not meet these criteria for any reason may still be enrolled in CORAL, but they will require other diagnostic information supporting a diagnosis of severe renal artery stenosis. That could be done using duplex ultrasound, MRA, or renal angiography.

4.6.3.4 Renal Angiography

The purpose of the renal angiographic methods is to provide guidelines for acquiring images that will allow the Angiographic Core Lab to capture the necessary primary data for analysis. The simplest way to acquire and submit all necessary angiographic data is outlined in the Angiographic Core Lab Manual of Operating Procedures.

4.6.3.5 Monitoring of Enrollment using Non-invasive Methods and Correlation with Renal Angiography

Although strict and specific criteria have been proposed for randomization using the non-invasive modalities of duplex ultrasound, MRA, or CTA, there is the potential for randomizing patients who prove not to meet angiographic criteria of ≥60% diameter stenosis. It is important to monitor these occurrences, as such enrollment could bias results toward the null hypothesis. Since all patients randomized by non-invasive testing to stenting will still undergo renal angiography, we will use this group for monitoring the correlation of non-invasive measurements and renal angiography. Therefore, it is critical to follow the Renal Angiographic Methods during the intervention for all patients entering the study via the non-invasive testing pathway. In addition, the duplex ultrasound and MRA/CTA core labs will carefully review all submitted images in order to minimize false positive interpretation and enrollment of ineligible patients. If MRA or CTA is planned as the method for enrollment, core lab review and approval is required prior to randomization. Thus, monitoring will occur at several levels.

1. 1. A subcommittee of the Operations committee will review each case where a patient is enrolled based on non-invasive criteria that proves to be false positive according to later angiographic interpretation by the clinical site or angiographic core laboratory. This may result in modification of non-invasive criteria approved for randomization or suspension of the non-invasive pathway at a particular site.

   2. The Duplex Ultrasound and MRA/CTA Core Labs will review all images submitted as meeting criteria for enrollment. If the images are felt to be of insufficient quality to support the interpretation, or if in the opinion of the core lab the findings consistent with the diagnosis are not present, the site may be suspended from the non-invasive pathway for enrollment.

   3. All patients who are randomized by either duplex ultrasound, MRA, or CTA to the stent arm will undergo analysis for correlation with angiographic determination of stenosis. A randomization failure will be defined if any of the following are noted:

1. The site determines that the lesion diameter stenosis is not ≥60%.
2. The Angiographic Core Lab determines that the lesion diameter stenosis is less than the mean minus 2 standard deviations of lesions enrolled using the angiographic method and <60% diameter stenosis However, obtaining a translesion systolic pressure gradient will over-ride a QVA measurement of ≤ 60% as two dimensional angiography has its known pitfalls.
3. The Angiographic Core Lab determines that the angiographic pattern is consistent with fibromuscular dysplasia and not atherosclerosis.

If any randomization failure occurs at any site, the non-invasive pathway resulting in failure may be closed for that site. If there are 11 or more randomization failures across the study, then either or both non-invasive pathways may be closed depending on performance of each non-invasive modality.

4.6.4 Randomization Procedure

An Interactive Voice Randomization System (IVRS) will be used to administer the randomization scheme. This procedure will be performed once the final inclusion criteria have been met and no exclusion criteria are present. Patients will be randomized to one of the two treatment arms, labeled respectively 'Medical Therapy' and 'Stent Intervention + Medical Therapy'. Randomization will be stratified by site and by the patient's serum creatinine (<1.6 or ≥ 1.6 to ≤ 4.0) performed locally as standard of care. The site number, patient number, gender, ethnicity and race, whether use of an embolic protection device is planned, and the creatinine value will all be required to obtain the randomization allocation. After the allocation is determined, a randomization number will be given, which will be used in the patient identifier. The patient identifier will be attached to all data (CRFs, ECGs, angiograms, etc.) submitted to the DCC and the core labs.

4.7. Renal Stent Intervention with Medical Therapy Care

All patients randomized to receive a renal stent will also be receiving the anti-hypertensive medical therapy as described below. In addition, prior to the renal stent intervention procedure, those patients randomized to receive a stent will be given 325 mg of aspirin, and clopidogrel or ticlopidine in doses determined by the physician's discretion and per hospital standard of care. During the intervention, prior to stent deployment an ACT of ≥ 225 seconds should be achieved. Post-procedure, the patient will be maintained on aspirin 81-325 mg per day indefinitely. Clopidogrel is to be used at 75 mg per day for 4 weeks (or ticlopidine if the patient is unable to take clopidogrel).

Table 3. Summary of renal stent intervention medical therapy.

Medication	Pre-Procedure	During Catheterization	Post-Procedure	Follow-up Long-term
Aspirin	81-325 mg QD	No	81-325 mg QD	81-325 mg QD for duration of trial
Clopidogrel [1]	300-600 mg po (day of procedure)[2]		75 mg po QD	75 mg po QD for 4 weeks
or Ticlopidine	or 500 mg loading dose (within 24 hours of procedure)		or 250 mg bid	or 250 mg bid for 4 weeks

1 Ticlopidine may be used if patient is unable to tolerate clopidogrel.
2 If patient on at least 5 days of daily clopidogrel, then loading dose not necessary, and continue daily dose.

4.7.1 Device Training Procedure/Roll-ins

Prior to entry into the randomized phase of the CORAL project, all investigators will be required to perform a minimum of one case with the Genesis™ stent for the treatment of atherosclerotic renal artery stenosis. The angiogram and relevant data must be submitted to the Angiographic Core Lab for approval. Patients enrolled in the roll-in phase will all receive the Genesis stent. They will be followed in "standard-of-care" fashion, and will not undergo the other protocol-required assessments, interventions, or follow-up, nor will they receive study medication. Roll-in patients will sign a separate roll-in informed consent form, undergo the same screening procedures as randomized patients, and receive a Genesis™ stent. The follow-up procedures for the roll-in patient will include an evaluation at 2-4 weeks inclusive of a serum creatinine performed at the local lab. No labwork will be sent to the Biochemistry Core lab for the roll-in patient. Telephone contacts at 30 days and 9 months will be performed to assess for any adverse events and renal revascularizations.

Entry of sites into the randomized phase is contingent upon Angiographic Core Lab review of the Primary Interventionalist's compliance with the study protocol, and the clinical site's ability to comply with, the Core Lab's Renal Angiography Methods.

Training of Additional Interventional Sub-Investigators

Certification of additional investigators requires a completed "Application for Additional Interventional Sub-Investigator" submitted to the CCC confirming that the investigator has completed all regulatory requirements for the CORAL trial. Once the application is faxed into the CCC,the Sub-Investigator is eligible to perform cases.

4.7.2 Stent Procedure

All patients in the stent therapy arm shall undergo implantation of a Genesis stent if the lesion is of suitable size for treatment with this device (reference artery estimated between 3.5 and 8 mm diameter and lesion length <2 cm long). **For patients that are randomized via the invasive pathway, planned use of angioplasty without stenting, or use of non-study stents is not permitted.** For patients randomized via the non-invasive pathway, all renal artery stenoses ≥ 60% should be treated (including arteries < 3.5 mm in diameter), even if treatment requires use of angioplasty without stenting or stenting with non-study systems.

For patients randomized to stent therapy who have multiple renal artery stenoses, all renal arteries must be treated if they are ≥ 60%. Stenting of multiple vessels may be done during the same procedure, or staged at 2-4 week intervals, if in the best interest of the patient. If a stenosis meeting eligibility criteria on the contralateral side is noted during the follow-up period for a patient in the stent group, that lesion should be treated with a stent within 4 weeks of identification.

Only patients with stenoses involving at least one dominant renal artery (supplying at least half of the renal parenchyma or the largest of any renal artery to that kidney) should be considered for inclusion in the trial, if inclusion is based upon the angiographic evaluation. In contrast, stenting of vessels supplying <1/2 of the renal parenchyma is permitted when a dominant renal artery stenosis is also present. An FDA-approved embolic protection device may be used at operator discretion. However, these devices are not approved by the FDA for the indication of embolic protection during renal artery stenting and their utility in renal stent procedures is not established. Embolic protection device use or attempted use must be documented on the appropriate case report form(s). The devices available in the US are listed in the table below.

Table 4. FDA-approved embolic protection devices.

Manufacturer	Device Name
PercuSurge	PercuSurge Guardwire Temporary Occlusion and Aspiration System
Medtronic	Export Aspiration Catheter
Boston Scientific	Boston Scientific FilterWire EX
Boston Scientific	Filter Wire EZ and EZ Bent Tip Retrieval Sheath
Kensey Nash	Triactiv System
Kensey Nash	Triactiv FX Embolic Protection System
Guidant	RX AccuNet 2 Embolic Protection System
Abbott Vascular	Emboshield Embolic Protection System
Velocimed	Proxis System
ev3	SpideRx Embolic Protection Device
St. Jude	Proxis System
Cordis	AngioGuard XP

Copies of the Instructions for Use for the study stent are located on the CORAL website.

Table 5. Selection of Genesis™ stent size.

Vessel Size (mm)	Genesis™ Stent size (mm)
<3.5	Exclusion
3.5 to 4.5	4
4.5 to 5.5	5
5.5 to 6.5	6
6.5 to 7.5	7
7.5 to 8.0	7
>8.0	Exclusion

Pre-dilation should be considered prior to treatment with the stent, although it is not required. Use of a monorail balloon is recommended for pre-dilation, although not required. After performing pre-dilation, stenting will be performed with a Genesis™ stent according to accepted technique. Stenotic lesions should be located in the renal artery such that a stent would terminate proximal to the bifurcation of a renal artery branch. The Genesis stent is supplied in 12, 15 and 18 mm lengths and can be used in vessels from 3.5 to 8.0 mm in diameter (see Table 4 for appropriate sizing). The goal of stent treatment will be to achieve 1:1 sizing of the treated lesion with a normal appearing segment of vessel distally. However, if, in the investigator's opinion, there is a reasonable risk of renal perforation or rupture, with symptoms of back pain or other symptoms, less than 1:1 stenosis expansion is acceptable. The residual stenosis should be <50% with a >30% reduction in stenosis severity associated with normal renal arterial blood flow (TIMI grade 3).

Following successful stenting, a "post-stent" pressure gradient between the main renal artery distal to the stent and the abdominal aorta may be obtained in a manner identical to the baseline determination. A systolic pressure gradient of less than 10 mmHg between the main renal artery distal to the renal stent and the abdominal aorta should be obtained before treatment is considered complete. If a post-stent pressure is obtained, it will be recorded on the CRFs and a copy of the pressure tracings should be submitted to the Angiographic Core Lab along with the other required materials.

The CORAL Interventional Committee will annually review stent and other device availability to ensure that as technology changes, state-of-the-art devices will be available for the CORAL Study.

4.7.3 End of Procedure

The end of the procedure is defined as the time the last angiography is completed. If the patient is returned to the angiography laboratory and a guiding catheter is reinserted and an interventional procedure is performed, this will be considered a repeat intervention.

4.7.4 Use of Additional Stents; Stents for Bailout

Occasionally, procedural variations occur during renal artery stenting that increase procedure time or complexity but have no adverse clinical consequence. Examples include proximal stent malpositioning, distal device malpositioning requiring additional stent implantation, post-treatment dissection requiring additional stent placement or initial stent non-deployment requiring retrieval with subsequent successful stent placement during the same procedure. Since it is possible that these procedural variations may affect vessel patency or have delayed clinical sequelae, the details of any procedural complexities should be recorded.

In addition, anatomic success for stent placement requires positioning of the implanted stent within the target lesion. If the target lesion is adequately covered, excessive stent deployment in the aorta or into the renal artery should be considered a procedural complexity and not a device or anatomic failure.

4.8 Anti-hypertensive Medical Therapy Care

4.8.1 Study Medication

All patients should be treated with an angiotensin receptor blocker or angiotensin converting enzyme inhibitor, unless otherwise contraindicated. The preferred drug will be an angiotensin II type 1 receptor blocker (ARB), Atacand (candesartan cilexetil) and Atacand/ HCT (candesartan cilexetil/ hydrochlorothiazide).

After initiation or an increase in dose of Atacand or Atacand/HCT, a serum potassium and Cr determination, performed at a local lab, are recommended 2 weeks after such change (see prescribing information for drug monitoring).

Patients should also be prescribed Caduet (amlodipine/atorvastatin) at randomization, unless otherwise contraindicated. The recommended starting dose of Caduet is 5/40, but may be adjusted based on blood pressure, concurrent medical therapies, and lipid status. For patients taking calcium channel antagonists or HMG-CoA reductase inhibitors (statins), these agents should be discontinued and replaced with Caduet unless otherwise indicated (see prescribing information for drug monitoring).

If other drugs are needed to control blood pressure, the patient's insurance company or the participant will need to cover this cost. There will be no limit on the number or class of additional antihypertensive drugs that patients can receive in either treatment arm.

Target Blood Pressure

Forced titration of medication will occur until goal blood pressure is reached. Consistent with JNC VII recommendations, the target blood pressure in patients without co-morbidities will be ≤140/90 mmHg, in patients with diabetes and/or chronic kidney disease, a lower target of ≤ 130/80 will be used. Sites that fall below acceptable boundaries will be contacted by the Hypertension and Risk Factors Committee.

Please refer to the Concomitant Medical Therapy Section in the Manual of Operations for more information. Tables 5 and 6 provide additional information about the use of second and third line drug therapy.

Table 6. Recommended titration protocol for anti-hypertensive agents.

Anti-hypertensive Drug Management Algorithm					
	Starting dose	**First stepped dose**	**2nd step**	**3rd step**	**4th step**
First line drug:					
ARB					
Candesartan or	16 mg QD	32 mg QD			
Candesartan hydrochlorothiazide	16/12.5	32/12.5	32/25		
Calcium Antagonist / Statin					
Amlodipine/Atorvastatin	5/40	10/- or -/80			
First line replacement for Candesartan or Candesartan HCT if patient cannot tolerate ARB:					
ACEI					
Lisinopril	10 mg QD	20 mg QD	40 mg QD		
Second line therapies:					
Calcium antagonist					
Amlodipine (for statin intolerant patients)	5 mg QD	10mg QD			
Beta-blocker					
Metoprolol	50 mg BID	100 mg BID			
Carvedilol	6.25 mg BID	12.5 mg BID	25 mg BID		
Alpha-blocker					
Doxazosin	1 mg QD	2 mg QD	4 mg QD	8 mg QD	16 mg QD
Vasodilator:					
Hydralazine	10 mg QID	25 mg QID	50 mg QID	75 mg QID	
Minoxidil	2.5 mg QD	10 mg QD			

Table 7. Guidelines for use of third-line drugs in patients with co-morbid medical conditions.

Third-line Drugs Used with Co-morbid Medical Conditions	
Co-morbid condition	***Drug***
Angina	beta blockers, calcium antagonists
Atrial tachycardia and fibrillation	beta blockers, calcium antagonists
Diabetes mellitus with proteinuria	RAAS inhibitor
Diabetes mellitus type 2	diuretic (per ALLHAT)
Dyslipidemia	alpha-blocker
Essential tremor	beta blocker (non-cardioselective)
Heart failure	Carvedilol, metoprolol ACEI, diuretic
Hyperthyroidism	beta blocker
Migraine headache	beta blocker (non-cardioselective)
Myocardial infarction	beta blocker ACEI
Osteoporosis	thiazide diuretic
Benign prostatic hypertrophy	alpha-blocker

4.9. Post-Randomization Procedures

The following items will be performed and/or reviewed with each patient after randomization or prior to discharge if applicable:

1. history & physical exam will be performed post-procedure or prior to discharge if applicable with a review of all systems, and concomitant medication use
2. blood pressure assessment procedure will be performed post-procedure or prior to discharge if applicable
3. urine sample for dipstick analyses will be performed at the site post-procedure or prior to discharge if applicable
4. confirmation of appropriate study medications (see 4.8.1)
5. adverse event assessment and study endpoint ascertainment will be performed
6. patient's contact information will be obtained and additional phone numbers including work numbers, primary care physician (PCP) numbers and a nearest friend or relative's number will be included

4.10 Follow-up Procedures

Patients will be scheduled for 4-6 visits during the first year of follow-up and for 1 visit/year for the duration of the study. During these visits the patient will be seen by the study coordinator and a physician (physician visit required at annual visits) for performance of a physical

examination, if applicable, and ascertainment of any adverse events since the previous visit. The current hypertensive medications will also be reviewed for adherence to the CORAL study treatment algorithm. If the blood pressure is not well controlled, recommendations will be made to the treating physician based on this algorithm. Study coordinators should also contact patients between office visits and will assess study compliance, adverse events and study endpoints. These contacts will be used to promote study patient retention.

1. **2 Week Office Visit (+/- 1 week)**
   - Review of concomitant medication use.
   - Blood Pressure Assessment (will continue every 2 weeks up to 2 months until target B/P is achieved*)
   - Creatinine (Cr) (**) and Potassium (K+) blood draw for Biochemistry Core Lab
   - Adverse event assessment
   - Confirm Study Medications
   - Medication compliance check

*Additional visits at 2 week intervals, for the first 2 months of the study are recommended if the patient is not at blood pressure target (≤140/90 mmHg and in patients with diabetes and/or chronic kidney disease, a lower target of ≤ 130/80 will be used).

** If the serum creatinine doubles from the baseline value on any of the local lab draws, a serum creatinine sample must be drawn and sent to the Biochemistry Core Lab as soon as possible. If the Biochemistry Core Lab result is doubled from baseline, a repeat Cr must be performed in 60 days and sent to the Biochemistry Core Lab to confirm doubling.

2. **3 Month Office Visit (+/- 1 month)**
   - Review of concomitant medications
   - Blood Pressure Assessment
   - Cr and K^+ blood draw for Biochemistry Core Lab**
   - Adverse event assessment
   - Confirm Study Medications
   - Medication compliance check

3. **6 Month Office Visit (+/- 1 month)**
   - Review of Concomitant Medications
   - Blood Pressure Assessment
   - QOL Surveys (administered by the EQOL Core Laboratory)
   - ECG
   - Cr and K^+ blood draw for Biochemistry Core Lab **
   - Adverse event assessment
   - Confirm Study Medications
   - Medication compliance check

4. **Annual Physician Office Visits (+/- 1 month)**
   - History & Physical Exam + Concomitant Medications
   - Blood Pressure Assessment
   - QOL Surveys: (years 1, 2 and 3 only administered by the EQOL Core Laboratory)
   - ECG
   - Biochemistry Core Lab Specimens:
     - Yearly: Cr**
   - Adverse event assessment
   - Confirm Study Medications
   - Medication compliance check
   - Renal Duplex ultrasound (for sub-study patients only): 1 year and closeout

6. **Study Closeout**
   - History & Physical Exam + Concomitant Medications
   - Blood Pressure Assessment
   - QOL Surveys (administered by site personnel)
   - ECG
   - Biochemistry Core Lab Specimens: Cr**
   - Urine dipstick obtained at site
   - Study endpoint ascertainment
   - Medication compliance check
   - Renal Duplex ultrasound (for sub-study patients only)

If a patient chooses to prematurely terminate their participation in the Study, the patient should be encouraged to undergo all Study closeout procedures.

4.10.1 Study Subject Retention

Enrolled subjects are asked to remain within their center and study (randomization) assignments until study completion. Several scenarios may occur that result in the loss of follow-up of CORAL participants. Below are suggested strategies, in order of preference, to retain the subjects for as long as is feasible if one of these scenarios arises:

- Subject moves to a new location:
  1. Stay with their enrolling site, or
  2. Transfer subject to CORAL center located at or near their new location, or
  3. Obtain remote follow-up from CORAL remote follow-up site*

- Study site closes during the trial:
  1. Transfer active subjects to another center locally.
  2. Obtain remote follow-up from CORAL remote follow-up site*

- Subject wishes to withdraw from participation:

1. Obtain patient consent for phone follow-up from local site
2. Obtain patient consent to track vital status by local site
3. Obtain patient consent for phone follow-up and or tracking of vital status from CORAL remote follow-up site*

***CORAL remote follow-up sites:**

A selected CORAL center with active patients will be offered the opportunity to remotely follow additional patients who no longer have an active local site or who wish to be followed by a different site. When notice is obtained that a site intends to withdraw from the study, or when a patient no longer wishes to be seen at their local center, study leadership, monitors, and other personnel will encourage transfer to this remote follow-up site. The remote follow-up site will discuss follow-up procedures with the patient and answer questions over the phone. If the patient is willing and agrees, the remote follow-up site will send the subject an informed consent document for review and signature. Once the consent is mailed back to the remote follow-up site, the signed copy will be provided to the subject and the enrolling center for their records.

These subjects will then have a follow-up schedule consistent with the current protocol, although phone follow-up will be the primary resource for collection of study data. To facilitate collection of blood samples, the remote follow-up site will ship the lab kits to the subjects with instructions to take to a local lab for processing and submission to the CORAL Biochemistry Core Lab. The remote follow-up site will assess and report all adverse events, including those meeting serious criteria, following the outlined study procedures for all subjects.

4.11 Timing of Randomization and Assigned Treatment

All efforts should be made to minimize the time between random treatment assignment and application of the assigned treatment. In practice, randomization should occur whenever possible just after qualification, in which stent treatment or medical treatment alone is immediately carried out.

4.12 Concomitant Surgical and Medical Therapies

All surgical and medical therapies will be directed by the patient's health care providers.

4.12.1 Surgical Therapies

Patients will be randomized only if there is no planned coronary or cerebrovascular revascularization procedure, or renal procedure outside of randomly allocated renal stenting dictated by the CORAL protocol. After randomization, all additional renal angiograms and revascularization procedures performed should be done following the recommendations listed below:

- the Genesis™ stent should be the stent of choice, if available; use of an EPD is at the discretion of the investigator
- Repeat Renal Angiography and Repeat Renal Revascularization CRFs should be completed for each procedure

- any resulting adverse events should be listed on the adverse event log
- 2-4 weeks after a revascularization procedure, the patient should return to their physician for evaluation of their blood pressure and adjustment, if necessary, of their antihypertensive medication

All other procedures or surgical therapies will be directed by the health care provider.

4.12.2 Medical Therapies

1. The clinical site Principal Investigator will be asked to commit to closely following prevailing guidelines.

2. The DCC will monitor study-wide and site-specific rates of use of indicated therapies and blood pressure control (measured annually).

3. Critical values for blood pressure (systolic ≥ 160, diastolic ≥ 100) will be reviewed by the DCC and the Hypertension and Risk Factors Committee with follow-up to the sites when issues or concerns arise.

4. Sites that fall below acceptable boundaries (www.nhlbi.nih.gov/guidelines) will be contacted by the Hypertension and Risk Factors Committee to determine reasons for non-compliance with evidence-based therapies.

5. Sites with continued non-compliance with indicated, evidence-based therapy will be discussed by the Operations Committee. Possible actions range from enhanced educational efforts to suspension from future patient accrual. In all cases, suspended sites will be obligated to continue following all enrolled patients.

4.12.3 Concomitant Therapies/Routine Medical Care

The prevailing guidelines, as discussed below, regarding treatment of patients with hypertension, atherosclerotic vascular disease, diabetes and or renal insufficiency should be followed in both treatment arms. These guidelines will be reviewed on a yearly basis by the Risk Factors and Hypertension Management Committee. Any modifications applicable to CORAL patients will be adopted throughout the study. Compliance with evidence-based therapy of CORAL patients will be encouraged and enforced in the following ways:

Secondary Prevention

CORAL patients all have hypertension and atherosclerotic vascular disease. As such, guidelines for such patients apply.

1. *Smoking Cessation*
   Smoking cessation is essential in patients with atherosclerotic vascular disease. Smoking triggers vascular spasm, reduces the anti-ischemic effects of β-adrenoceptor blockers, and doubles mortality after acute MI. Smoking cessation reduces progression of vascular disease and reduces rates of re-infarction and death within

one year of quitting. However, one third to one half of MI patients return to smoking within 6 to 12 months. Thus, aggressive measures to assist patients in smoking cessation should be pursued at each clinical site.

Houston-Miller and Taylor[126] advocate a stepped approach to smoking cessation:

- Provide a firm, unequivocal message to quit smoking
- Determine if the patient is willing to quit
- Determine the best quitting method
- Plan for problems associated with withdrawal
- Set a quit date
- Help the patient cope with urges to smoke
- Provide additional help as needed
- Follow up by telephone call or visit

Nicotine gum and patches have been shown to mitigate symptoms of nicotine withdrawal in recovering patients. Clonidine has been shown to be effective in women but not men, the reason for this finding is unclear. Lobeline has not been shown to have any advantage over placebo but is again under investigation.

Local behavioral medicine smoking cessation programs may be available to accept referrals of patients. Information on smoking cessation, including availability of local smoking programs, is available on the American Lung Association's Freedom From Smoking web page (http://www.lungusa.org/ffs/index.html). Patients can call 1-800-TRY TO STOP for information, or see the web site at www.trytostop.org.

2. *Long-Term Use of Aspirin*

The long-term use of aspirin in hypertensive patients with vascular disease and patients after myocardial infarction results in a significant reduction in subsequent cardiovascular events and mortality [127, 128]. In six randomized, placebo-controlled trials in which patients were randomly selected between 1 week and 7 years after a myocardial infarct, meta-analysis reveals a reduction in vascular mortality of 13% among those randomly assigned to aspirin with a reduction in nonfatal reinfarction of 31% and nonfatal stroke of 42%. Although all of these trials involved the use of aspirin in doses ranging from 300 to 1500 mg/d, a recent trial of patients with hypertension in which aspirin 75 mg/d was used demonstrated a significant reduction of 15% in cardiovascular events [129]. This suggests long-term use of aspirin in a dose as low as 75 mg/d is effective. Clopidogrel may be used as an alternative in aspirin allergic patients. Ticlopidine is also an antiplatelet agent that has been effectively used in unstable angina and cerebrovascular disease.

3. *Management of Lipids*
   We will follow guidelines established by the NHLBI, including those in the ATP III update (www.nhlbi.nih.gov/guidelines). Recent clinical trials suggest that low-density lipoprotein (LDL)-lowering therapy reduces total mortality, coronary mortality, major coronary events, and strokes in patients with established CHD [130]. Importantly, ATP III emphasizes the importance of "CHD risk equivalence," stating that "clinical forms of non-coronary atherosclerosis carry a risk for clinical CHD approximately equal to that of established CHD and hence constitute a CHD risk equivalent." CORAL has adopted the therapeutic option of an LDL cholesterol of <70 mg/dl as the goal of therapy in secondary prevention. This goal is supported by clinical trials with both clinical and angiographic endpoints as well as by prospective epidemiologic studies. All CORAL patients should have a goal of LDL < 70mg/dl. This can be reached, first, through therapeutic lifestyle changes including diet and exercise. In addition, these patients will be encouraged to take atorvastatin / amlodipine as an adjunct to achieve LDL goal.

Use of lipid lowering treatment will be captured on the CRFs.

4. *Management of Diabetes*
   Patients will be considered to have diabetes if they are currently prescribed to take any oral agent or insulin therapy for a diagnosis of diabetes or have a history of a fasting blood glucose >126 mg/dl or a two-hour post-prandial (or oral glucose tolerance test) value > 200 mg/dl. While patients with diabetes will be included in the current study, we recognize the potential confounding effect of diabetes on all event rates, including renal dysfunction if diabetic nephropathy occurs. New diagnoses of diabetes will be determined by current guidelines, including HgbA1c > 6.5% and random glucose > 200 mg/dl, confirmed on a separate occasion by the same test. If different tests are used and results are discordant, then a third test should be performed with diagnosis determined by the 2 results in concordance. We will follow evidence-based guidelines outlined within Diabetes Care, Supplement 1, Jan 2002, "American Diabetes Association Clinical Practice Recommendations 2002." Control of HgbA1c <7%, without significant hypoglycemia as recommended in the ADA Standards of Care is considered the goal, with better control associated with reductions in microvascular complications [131, 132]. Additionally, medical nutrition therapy, multi-disciplinary foot care (for patients with high risk feet), retinopathy screening, and physical activity are recommended.

5. *Management of Chronic Kidney Disease (CKD)*
   We will follow guidelines established by the National Kidney Foundation Kidney Disease Quality Initiatives (www.kidney.org/professionals/doqi/guidelineindex.cfm). The management of CKD represents the management of the common conditions that complicate CKD. Hypertension, diabetes and lipid disorders are specifically addressed above. To address the general issue of medical therapy to prevent the progression of CKD, patients will be treated with an ARB *per protocol* (see discussion above). Dietary modifications will be recommended as outlined in the clinical guidelines and as dictated by clinical practice. For example, restrictions of

dietary phosphate and/or the addition of phosphate binders may be necessary in some cases. Dietary modification of protein intake is difficult to implement, and it is not anticipated that such an action will be required in many patients in this trial.

6. *Management of Restenosis in Stent Group*

The CORAL Study is designed to test the question of whether renal artery patency, established with stent placement, prevents clinical events. Failure to maintain patency of the renal artery, through the process of restenosis, may limit the effectiveness of stent treatment. However, not all restenoses are functionally significant and re-treatment with balloon angioplasty or stenting carries risk.

When restenosis is suspected, it is recommended that the initial evaluation can be done with Renal Artery Duplex Ultrasonography as described in the study protocol. However, depending upon patient status and other factors, either computed tomographic angiography, captopril renography, or contrast angiography are acceptable alternatives, with the technique determined by the local accuracy of these methods and also according to the preferences of local investigators. Restenosis confirmed angiographically to be ≥60% must be treated by balloon angioplasty and/or additional stenting. Endpoints for the re-intervention are a reduction of stenosis to <30% by diameter. When restenosis is found and treated, the Duplex scan should be repeated one year after treatment to determine whether the restenosis has recurred, as described in the Figure 3 diagram, and continue to be evaluated and / or treated within this algorithm.

The following strategies are suggested when restenosis is detected or may be suggested by the patients clinical status:

1. **Restenosis detected by Duplex ultrasonography at one year evaluation (for Renal Duplex Sub-Study patients or clinically driven exams).**
   There may be stent patients who have restenosis detected during their scheduled renal Duplex ultrasound examinations required by this protocol. Unless indications for revascularization accompany the Duplex findings (restenosis confirmed angiographically to be ≥60%) they should not undergo reintervention. When restenosis meets angiographic inclusion criteria, retreatment with balloon angioplasty or stenting is recommended.

2. **Worsened hypertension after initial improvement.**
   Patients in the renal stent group who experience worsening in their blood pressure control and an increasing need for medication (need for one or more additional medications), after an initial improvement, should undergo evaluation for restenosis and be retreated if a hemodynamically significant restenosis is present.

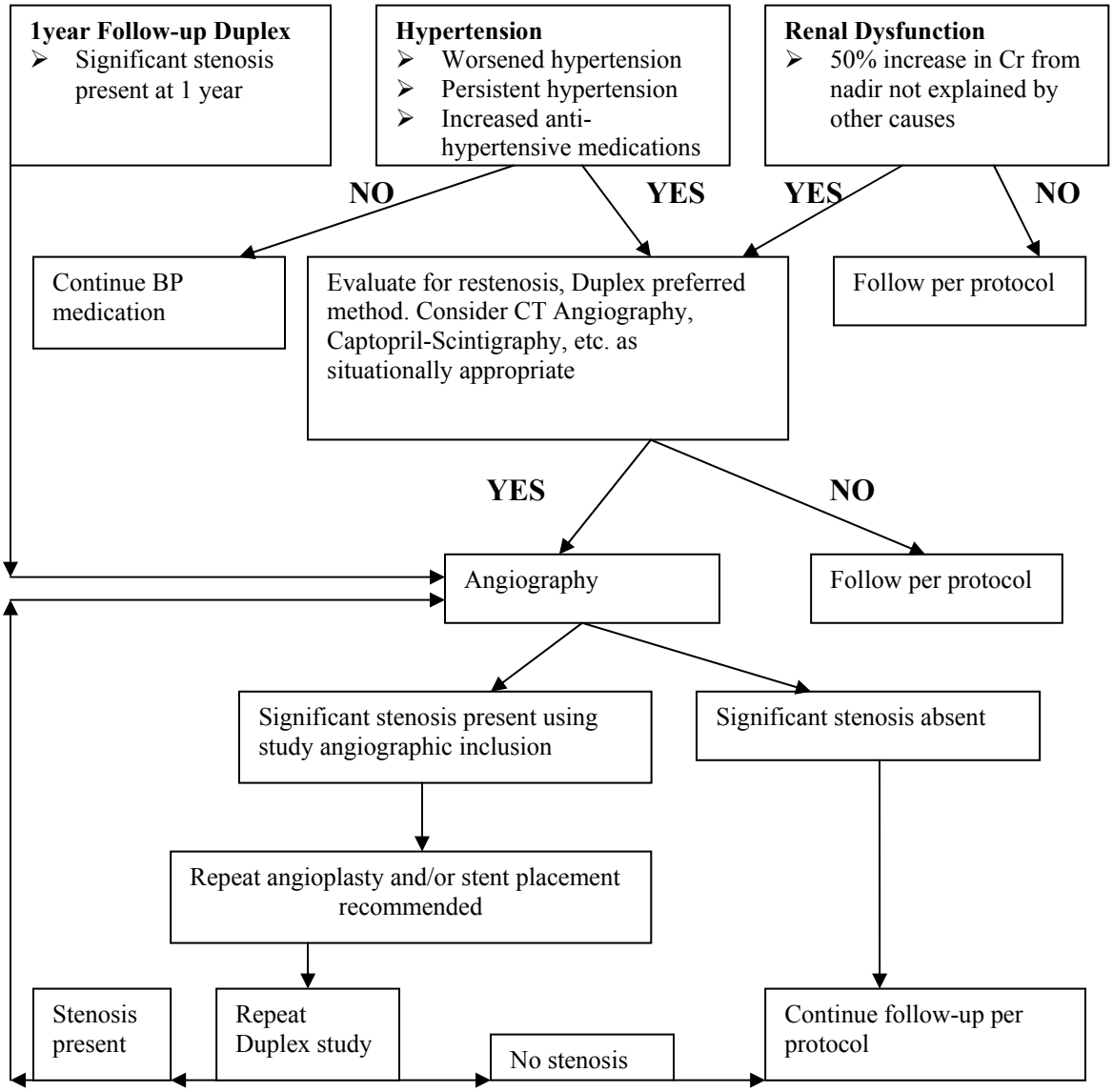
3. **Sustained hypertension**
   Failure of blood pressure improvement (inability to reach systolic blood pressure target described in Section 4.8.1) within 3-6 months after the index stent procedure may indicate restenosis or early recoil of an incompletely stented lesion. In this

circumstance evaluation for restenosis is recommended, with treatment of hemodynamically significant stenoses.

4. **Increased need for anti-hypertensive medications**
   Escalating need for additional anti-hypertensive medications (need for one or more additional medications) to maintain target blood pressure in patients allocated to stenting may indicate restenosis. In this circumstance evaluation for restenosis is recommended, with treatment of hemodynamically significant stenoses if present.

5. **Decline in renal function**
   Patients with baseline chronic renal failure who experience improved renal function after stent placement that deteriorates, as measured by an increase in serum creatinine by 50% must undergo an evaluation for restenosis and reintervention if hemodynamically significant restenosis is present.

Figure 3. Algorithm for restenosis evaluation



4.12.4 Cross-over Management

A major threat to the scientific integrity of the CORAL Study is if medically assigned patients subsequently receive a stent due to the belief that stenting will offer a benefit to the patient who is perceived to have done poorly with assigned medical treatment alone. Enrolling sites must accept the fundamental fact that motivates this study; at present, there is no direct evidence that renal artery stenting improves outcomes for any subset of patients with renal vascular disease. Nevertheless, the investigators are aware of reports of recovery of renal function following revascularization in patients with sudden, total renal ischemia and accept that individual patients may benefit from revascularization in this setting. Under the following set of circumstances, stenting is permitted in patients randomized to medical therapy and will not constitute a protocol violation. **However, all the following circumstances MUST be present:**

1. The patient presents with anuric acute renal failure,
2. Complete occlusion of **all** arteries to the one kidney if there is a solitary kidney or complete occlusion of **all** arteries to both kidneys if there are two kidneys documented angiographically, and
3. There is at least one kidney distal to a complete occlusion that is greater than 8 cm in length.

Renal stenting of a patient randomized to medical therapy may also be considered once a patient has reached a primary endpoint of the study that has been formally adjudicated and accepted by the Clinical Endpoints Committee. The study leadership maintains that there is no clear evidence demonstrating that it is necessary or beneficial for such a patient to cross-over, even though a component of the primary endpoint has occurred. Nevertheless, we recognize that that there will be occasions when the investigators, or the patients themselves, may wish to cross from the medical arm to the stent treatment. For this reason the following procedures have been established:

1. Investigator will call the CCC whenever they are considering cross-over and will complete the Crossover CRF Form found in the MOP.
2. In such special cases where stenting is strongly desired, a Crossover Committee, Chaired by an independent expert in nephrology/hypertension and made up of members from the Study Leadership, will review the application for formal approval, in which cross-over allowances may be made;
3. The investigator will be notified of the Crossover Committee's decision.

Renal stenting that is performed in a patient randomized to medical therapy under any other set of circumstances will be considered a major protocol violation and a cross-over. Any unapproved cross-over will constitute grounds for study sanction, up to and including dismissal of the investigation site or investigator. It is not the intent of the protocol to interfere with the doctor-patient relationship recognizing that this relationship supersedes the investigator's scientific role in the CORAL Study. It is therefore imperative the investigators select only those patients that are appropriate for participation in this protocol as reassignment after randomization cannot be tolerated.

We emphasize the importance of understanding the unproven benefit of renal stenting and the position of equipoise each investigator must possess regarding these two treatments under randomization. Moreover, we will re-emphasize the importance of maintaining pure alignment of the two samples with their assigned treatments in order to preserve statistical power. Cross-over can be devastating by potentially reducing power, adding bias, and nullifying the chance to properly test the study hypotheses.

When cross-over is inevitable, the patient will be strongly encouraged to continue all study follow-up contacts, testing and use of Study Medication per protocol after the stent procedure. If the patient chooses to terminate from the study after crossover, then the patient will be encouraged to undergo all final exit procedures.

4.12.5 Economic and Quality of Life Assessments

HRQOL and treatment costs will be assessed alongside the core clinical trial to evaluate the relative cost-effectiveness of the 2 treatment strategies. HRQOL and functional status will be assessed using a combination of generic and disease-specific measures selected to cover a broad range of health domains that may be affected by renovascular hypertension, its treatment, and its complications. Overall HRQOL will be assessed using the 36-Item Short-Form Health Survey (SF-36)[122] and the EuroQOL health status instrument (EQ-5D) [123]. Disease-specific quality of life will be assessed using the Side Effects and Symptom Distress Index, a validated measure of the impact of treatment-related side effects on HRQOL, [124, 125]. Further details regarding the rationale for selection of these instruments and specific analytic approaches are detailed in the Manual of Operations. These measures will be assessed using a standardized, written questionnaire at baseline, 6 months, years 1, 2, and 3 and closeout.

Medical care resource utilization and cost data will be collected prospectively for the index hospitalization and the full follow-up period. Baseline quality of life data will be obtained from each patient by written, self-administered questionnaire at the time of study enrollment and prior to randomization (up to 24 hours post-randomization). A trained research assistant at each site will review the questionnaires for completeness and will attempt to ask any incomplete or poorly understood questions. The baseline QOL assessment will include each of the generic and disease-specific instruments as described above. Two weeks prior to each follow-up time point, the EQOL Core Lab will mail each patient a survey that can be self-administered and returned in a provided stamped envelope. Any patient who fails to return the survey by mail will be given the survey by telephone, administered by a trained research assistant from the EQOL Core Laboratory. In our experience, central coordination of the follow-up quality of life assessments is important in order to maximize compliance and ensure uniform assessment. Previous studies by the EQOL Core Laboratory using these same methods have generally achieved response rates *of* >95% *(of surviving patients)* at all time points. The final questionnaire performed at closeout will be administered by the enrolling centers' staff.

For each index renal stent procedure, detailed resource utilization will be collected using standardized case report forms. Follow-up medical resource utilization will be assessed by detailed questionnaires completed during each scheduled patient contact. In addition, hospital bills will be collected throughout the study period. Hospital charges will be converted to costs by multiplying by each hospital's cost-center specific direct cost-to-charge ratio [133]. All other resources will be converted to costs on the basis of standardized unit costs for each item or service. The unit cost for each medical service will be based on the cost that would be paid by Medicare, rather than on charges.

Finally, the cost and quality of life data will be integrated into a computer-simulation model to perform a formal cost-effectiveness analysis. Full details of the analytic and model-development approach are summarized in the Manual of Operations. Primary data from the clinical trial as to the costs and quality of life impact of renal artery stenting and medical therapy will be used to extrapolate lifetime medical costs and quality-adjusted life expectancy for a hypothetical cohort of patients eligible for treatment with either technique [134]. We will use these data to calculate an incremental cost-effectiveness ratio for the more expensive technique compared with the less

expensive technique, and by comparing this ratio with those for other medical interventions, determine whether one treatment strategy is preferred on economic grounds [135].

5.0 STATISTICAL PLAN

The primary endpoint is event-free survival from cardiovascular and renal adverse events, defined as a composite of cardiovascular or renal death, stroke, myocardial infarction, hospitalization for congestive heart failure (CHF), progressive renal insufficiency, or need for permanent renal replacement therapy. The adverse events reported in the ASPIRE 2 renal stent approval trial and the University of Toledo renal stent registry were used to estimate the frequency and distribution of discrete events that compose the primary endpoint. Admittedly, both utilize event rates in patients receiving "active treatment", or stenting. This frequency will also be used to estimate the event rate in the control group. This conservative stance is appropriate since the underestimation of event rates leads to additional power and randomized trials often have lower event rates than registry studies.

To estimate the effect size, the best available data from a non-randomized registry[110] will be utilized. Importantly this threshold of effect size (25%) is a clinically reasonable goal for an expensive and invasive treatment. A smaller effect on a composite outcome, with an expensive and invasive therapy, is unlikely to be sufficiently compelling to justify such treatment. Finally a definitive answer to this question is needed, thus at least 85% power will be used. Using these parameters we have defined a sample of 1080 randomized patients that will be enrolled in a 66 month clinical trial. Additionally, all roll-in patients will be analyzed separately. Descriptive statistics will be provided.

5.1 Sample Size Determination for Primary Endpoint

In this section we present the power properties of the primary endpoint statistical analysis. The assumptions specified below are what we anticipate as feasible and realistic. The power calculations are robust to changes of the order of magnitude of up to 10%. First, the anticipated event rates and distributional assumptions for the treatments are as follows:

- Primary endpoint rate for the control (medical) arm is 30% at 24 months.
- Accrual will occur on an escalating basis with average of 30 patients/month (see section 5.4)
- There will be an expected 7.5% lost-to-follow-up at 24 months (lost-to-follow-up hazard rate is 0.0032 dropouts/month).
- Minimum desired treatment effect reduces the 24-month event relative rate by 25%, from 30% to 22.5%.
- Alpha error = 5% (2-sided)
- Patients will be followed for incidence of the event from time of treatment until end of study (minimum follow-up time of 18.5 months, maximum follow-up time of 66 months).
- 50% of the subjects will be enrolled approximately 70% through the 48-month enrollment period.
- Treatments will be compared using the log rank test.

Notation:

$\lambda_{Control}$	= 0.01486 events/month
$t_{median/Control}$	= 46.64 months
λ_{Stent}	= 0.0106 events/month
$t_{median/Stent}$	= 65.26 months
λ ratio	= 0.715

Where $\lambda_{Control}$ is the expected monthly hazard rate for the control arm, and $t_{median/Control}$ is the expected time to the median (50th percentile) event for the control arm, λ_{Stent} is the expected monthly hazard rate for the renal stent arm, and $t_{median/Stent}$ is the expected time to the median event for the renal stent arm, and λratio is the hazard ratio between renal stent and control.

The 28% relative hazard reduction λ (ratio = 0.715) we seek may be viewed as a moderate benefit. However, contemporary trials often seek moderate treatment effects, which are often associated with profound patient benefit, as pointed out by Peto and coworkers (Peto 1998). Therefore, we feel that the 25% treatment effect (28% relative hazard reduction) sought in this trial represents the minimum moderate effect that will provide substantial patient benefit.

The null hypothesis will be equality of treatment and the alternative will be a two-sided alternative tested by the log-rank test (two sided alpha = 0.05).

Hypotheses:

H_0: $\lambda_{stent}(t) = \lambda_{control}(t)$

H_A: $\lambda_{stent}(t) \neq \lambda_{control}(t)$

Where $\lambda_{stent}(t)$ is the primary endpoint hazard for the renal stent arm at time t (i.e., the interim analysis time points), and $\lambda_{control}(t)$ is the primary endpoint hazard for the medical control arm at time t.

Two sided log-rank test (alpha = 0.05)
Sample size (87.5% power) = 1080 patients, including those lost-to-follow-up based on the expected follow-up hazard rate above.

While the sample size computations have been done to insure 87% power to detect the superiority of the stent over the medical care, we are also interested in having a quantification of the magnitude of the difference between the stent arm and the medical care arm. Thus we will have our primary test be a two sided test (alpha = 0.05 by logrank test) and will examine the confidence interval quantifying the difference in hazard rates between the stent and medical care. We will also perform a secondary analysis of all primary endpoint events utilizing CEC definitions that were in effect prior to the Steering Committee revision in August 2011.

5.1.1 Interim Analysis

A Data Safety Monitoring Board (DSMB) will be used to periodically monitor data to ensure subject safety. In addition, the DSMB will inspect the log-rank test comparing treatments with respect to the time to primary endpoint, after approximately 50% of the planned follow-up is completed. This interim analysis should serve mainly to test our assumptions of event rates and

treatment effect and provide reasonable assurances that the study will be adequately powered in the final analysis.

At this time, the DSMB may recommend stopping the study for overwhelming efficacy or futility, or increasing the sample size beyond 1080 in order to achieve 80% conditional power for detecting a significant treatment difference at the final analysis. The algorithm for recalculating sample size is based on the sample size recalculation for survival analysis algorithm discussed in Li et al. (2002) and Li et al. (2005). Specifically,

a. the log-rank ChiSquare statistic will be calculated based on the interim data. The positive square root of this statistic will be taken to form a log-rank Z-statistic.

b. If the log-rank Z-statistic is less than or equal to 0.675 (or if its two-sided value is greater than or equal to 0.50) then the null hypothesis may be accepted at the interim stage and the trial may be stopped for futility. If the log-rank Z-statistic is greater than 2.831 (or if its two-sided p-value is less than 0.00928) the study may be stopped for overwhelming efficacy of one treatment over the other. These critical values of 0.675 and 2.831 are obtained from Li et al. (2002).

c. If the study is not halted for futility or for overwhelming efficacy, then the number of additional primary endpoints required to yield 80% conditional power to detect a significant treatment effect by the end of study will be calculated. The z-critical value to be used in the final analysis to declare treatments significantly different (via logistic regression), regardless of the number of additional events (if any), is 1.99 (or i.e., the two-sided significance level to be used to declare treatments significantly different at the end of the study will be 0.046591). This critical value controls the two-sided significance level at 0.05 when using the above-mentioned critical values at the interim stage and when assessing additional number of events required for 80% conditional power (Table 1 of Li et. al. [2002]).

5.2 Statistical Analysis Plan

5.2.1 Analysis Population

The primary endpoint of time to development of one of the components of the primary composite endpoint will be evaluated on an intent-to-treat basis. Patients will therefore be analyzed according to the investigational treatment regardless of the subsequent sequence of events. Those patients who meet eligibility requirements for primary endpoint ascertainment include all patients enrolled who do not withdraw consent. Various other samples will also be analyzed. Such analyses will include those with complete follow up, those who actually receive the assigned treatment (e.g., per protocol patients), and inclusion of patients into the stent arm with abrupt vessel closure that receive stent therapy prior to randomization and are followed in accordance with the study protocol. These analyses will be secondary and it is anticipated that they will be consistent with the primary intent-to-treat analysis.

5.3 Secondary Analyses: Endpoints and Subsets

Some secondary analyses have already been discussed above, such as analysis of the individual component variables of the primary endpoint, and covariate adjusted analysis of the primary endpoint. The expectation of these analyses will be to investigate consistency of the primary analysis across the components and in the presence of covariate adjustments. In addition to these secondary analyses on the primary endpoint, we will undertake a formal pre-specified analysis of a parsimonious set of secondary endpoints. Below we discuss in detail secondary analyses of selected secondary endpoints and subsets.

5.3.1 Type I Error Control

The overall trial sample size was determined to provide adequate power to test the hypothesis of no difference in the primary endpoint between the two randomized arms with a two-sided type I error of 0.05. Although formal calculations for type I error control have been made for the primary endpoint, the secondary endpoints will also be evaluated with some consideration of type I error control. Such consideration varies from spreading the allowable type I error among all pre-specified secondary endpoints, to a more practical approach of limiting the number of pre-specified secondary endpoints without formal type I error correction. In the former approach, Davis has recommended the primary endpoint be compared using a significance level of alpha (5% in our case), and that the secondary endpoints be evaluated using a significance of (α/(k+1) where k is the number of secondary outcomes to be evaluated [136]. In the latter approach, Pocock cautions that such formal Bonferroni-like corrections may be too severe (especially for correlated endpoints). He suggests that a limited number of secondary endpoint comparisons may be made using a significance level of alpha (5% in our case) for each comparison, but that the results should be clearly labeled as secondary findings [137].

Thus, in each category, (blood pressure, renal function, arterial patency and intrarenal resistance), a "principal analysis" has been identified and pre-specified (systolic blood pressure, slope of reciprocal creatinine, Duplex-determined stenosis severity, and renal resistive index) to minimize the problem of multiplicity, and help to differentiate outcomes that may be viewed as important findings of the study versus outcomes that may be merely hypothesis generating. For purposes of relative comparison, these principal analyses will be defined in terms of statistical power to show a pre-specified difference in the outcome assuming a 5% type I error. Since these analyses are still considered secondary to the primary analysis, there will be no formal correction of the type I error.

5.3.2 Secondary Endpoints

There will be twelve (12) pre-specified discrete secondary analyses in this randomized trial. Two of these, the Quality of Life and the Cost-Effectiveness analyses, are described within the EQOL protocol. The results of these few pre-specified secondary analyses will be considered as purely secondary findings of the trial. Moreover, the results of any other (non-pre-specified) analyses will not be considered as a secondary finding from this trial. The secondary analyses may be divided into 9 categories.

- All Cause Mortality
- Subgroup Interactions:
  - Men vs Women
  - African Americans vs non-African Americans
  - Diabetes vs non-Diabetes Mellitus
  - Global vs partial renal ischemia
- Longitudinal Kidney Function (1/Cr)
- Systolic Blood Pressure
- Durability of Renal Artery Patency
- Renal Resistive Index: Preservation of Microvascular Renal Function
- Correlation between Stenosis Severity and Kidney Function (1/Cr)
- Quality of Life
- Cost Effectiveness

5.3.2.1 All-cause mortality

The expected all-cause mortality rate for the reference population of patients with renal artery stenosis is not well established. Those patients on hemodialysis due to ESRD from RAS have poor survival estimates of 18% for 5 years and 5% for 10 years[14]. The proposed randomized trial aims to treat patients with pre-dialysis renal insufficiency due to renal artery stenosis. The "all-cause" mortality rate for patients referred for renal artery stenting at the University of Toledo Hospital (was 22.9% at 2 years and 37.6% at 3 years). A less severe estimate of all-cause mortality may be derived from Dorros and Burket [81, 138, 139]. At 3 years, the cumulative probability of survival was 74% (corresponding to a 3-year mortality rate of 26%). Although the current trial aims to test the potential benefit of renal artery stenting, we may conservatively estimate the medical control arm 3-year survival rate using Dorros's observations.

All Cause Mortality Endpoint. The mortality endpoint is death due to any cause. Given reasonable assumptions based on the literature reviewed above, the proposed study will have good power to detect treatment differences on mortality. Below we list the assumptions and sample size calculations needed to attain 80% power.

Clinical Assumptions:

- Survival rate for the control (medical) arm is 74% at 36 months.
- Accrual will occur on an escalating basis with average of 30 patients/month (see section 5.4)
- - There will be an expected 7.5% lost-to-follow-up at 24 months (lost-to-follow-up hazard rate is 0.0032 dropouts/month).
- Desired treatment effect decreases the 36-month mortality rate from 26% to 19% (corresponding to event-free survival rate from 74% to 81%).
- Study duration and follow-up ≥66 months (under assumption of full enrollment)
- Alpha error = 5% (2-sided)
- Patients will be followed for incidence of death from time of treatment until end of study (minimum follow-up time of 18.5 months, maximum follow-up time of 66 months).
- 50% of the subjects will be enrolled approximately 70% through the 48-month enrollment period.
- Treatments will be compared using Cox proportional hazards regression.

Sample Size Justification for Survival:

$\lambda_{Control}$	= 0.0084 events/month
$t_{median/Control}$	= 82.9 months
λ_{Stent}	= 0.0059 events/month
$t_{median/Stent}$	= 118.4 months
expected λratio	= 0.70

Where $\lambda_{Control}$ is the expected monthly hazard rate for the control arm, and $t_{median/Control}$ is the expected time to the median (50th percentile) event for the control arm, λ_{Stent} is the expected monthly hazard rate for the renal stent arm, and $t_{median/Stent}$ is the expected time to the median event for the renal stent arm, and λ ratio is the hazard ratio between renal stent and control.

Alpha error	= 5% (2-sided)
Power	= 80%
Expected patient accrual	= average 30 patients per month

Formulas:

Hypotheses:

H_0: $\lambda_{Stent}(t) = \lambda_{Control}(t)$

H_A: $\lambda_{Stent}(t) \neq \lambda_{Control}(t)$

Where $\lambda_{Stent}(t)$ is the mortality hazard for the renal stent arm at time t (i.e., the end of the trial), and $\lambda_{Control}(t)$ is the mortality hazard for the medical control arm at time t.

The current study sample (under the assumption of 1080 patients with 7.5% lost to follow-up) has 85% power to detect an approximate 30% relative difference in mortality hazard between the two arms.

Cardiovascular-renal mortality. An adjudication of all deaths will be performed by the CEC, who are blinded to treatment assignment. A separate analysis of cardiovascular-renal death will be performed in a similar method as all-cause mortality (see above). From the University of Toledo database (the 2 and 3-year mortality rates are shown below.

Table 8. One to five-year mortality of patients referred for renal artery stenting at Medical College of Ohio.

	All cause mortality	Cardiovascular-renal mortality
1 year	13.3	9.3
2 year	22.9	15.7
3 year	37.6	25.4
4 year	47.7	29.3
5 year	58.1	38.1

The expected cardiovascular mortality rate is approximately two-thirds of the all-cause mortality rate, corresponding to an expected cardiovascular-renal death free survival rate of 83% for the control arm. Using the same statistical method as for all-cause mortality (shown above), the current study sample (under the assumption of 1080 patients with 7.5% lost to follow-up) has 80% power to detect a 34% reduction in the 3-year cardiovascular death-free survival rate (from 83% to 88.7%). This corresponds to having 80% power to detect a 36% difference in mortality hazard between the two arms (expected treatment-to-control hazard ratio of 0.64), if the trial terminates with a total study duration of ≥55 months.

5.3.2.2 Subset Interaction Analysis

The overall primary endpoint result will be tested in pre-specified categorical subsets via four binary group interaction tests: 1) men vs. women, 2) African American vs. non-African American, 3) diabetes mellitus vs. non-diabetes mellitus, 4) global renal ischemia (bilateral stenosis or unilateral stenosis in solitary kidney) versus partial renal ischemia (unilateral stenosis with contra-lateral non-stenosed and functioning kidney).

Although limited information exists on gender-dependent outcomes of renal revascularization, most suggest equivalence[140, 141]. However, no large series has carefully assessed the influence of gender on outcomes with revascularization. The large number of women participants in the CORAL Study, expected to exceed 40%, will allow us to address possible gender differences in outcomes. However, since prior studies do not support a significant gender difference, the CORAL Study is not required to provide statistical power for an analysis by gender. The incidence of renovascular disease in African Americans has been the subject of several studies including the Cooperative Study of Renovascular Hypertension[142]. Just as with gender, there is no evidence to suggest outcome differences that make it necessary to power the CORAL Study to assess study end points separately in minority patients. While prior studies do not suggest significant differences in the importance of the intervention based on ethnicity/race, CORAL investigators will over-sample African Americans. In summary, while we are not required to power the study to detect gender or race-based differences in outcomes, the study group considers these to be issues of high social importance to merit subset interaction analysis.

In distinction, both diabetes and the presence of global ischemia may have an impact on the outcomes of renal revascularization. Clearly, diabetes is an independent factor for progressive renal dysfunction and cardiovascular events[97]. Additionally, global renal ischemia is thought to be pathophysiologically distinct from regional ischemia[26], and may alter the ability of the patient to be treated with angiotensin specific anti-hypertensive medications[47]. For these reasons we will perform subset interaction analysis comparing diabetics vs non-diabetics and comparing patients with global vs. regional renal ischemia.

5.3.2.3 Evaluation of Longitudinal Renal Function

A longitudinal analysis of reciprocal creatinine will be performed and contrasted between the two arms. The reciprocal of the serum creatinine level is an established measure of renal health and correlate of glomerular filtration rate.

Creatinine will be collected every 12 months. We will analyze these data employing longitudinal analysis methods. First, we will examine the distribution of creatinine reciprocal at each time period. We anticipate that the reciprocal of creatinine will bring the distribution to near symmetry for all time periods. We will, however, also examine logs of creatinine. Next, we will examine the time series of the transformed creatinine. We anticipate that the time series of 1/creatinine will, in general, be linear. Quadratic and cubic models may also be appropriate. Given the best time series model we will estimate the parameters of the model (e.g., slopes for the linear model). Treatment differences (stents versus medical care) will be examined by comparing these coefficients.

The above analysis may face two difficulties: (1) censoring due to death, renal replacement therapy, drop out, missing visits and other missing data problems and (2) plateauing of 1/creatinine over time for some patients. The curve fitting method described above can deal with some of the missing data issues. We will, however, use random effects models if necessary to attain the necessary model coefficients. Further, this model can be used directly to fit the data and test for treatment differences over time. For plateauing we will redo the analysis fitting the data up to the plateau. We will examine the sensitivity of the analysis results to this strategy.

The anticipated results of these analyses will be that the stent group will have smaller slopes (slower progression) that the medical treated group. We will also have quantification of the progression.

5.3.2.4 Systolic Blood Pressure Response

Systolic blood pressure (Syst BP) will be utilized as the primary measure of blood pressure control since it is a well established measure of treatment efficacy (whereas pulse pressure is not) and has better correlation to clinical events in an elderly population than diastolic pressure [143]. Analysis of the blood pressure response may provide insight into the mechanism of action of stent therapy. Patients will have periodic office-seated blood pressure determinations at baseline, and follow-up (2 weeks, then annually until study termination). Systolic blood pressure will be considered as a response variable to the randomized intervention (renal stenting), and the interaction between treatment and time on blood pressure response will be estimated (Proc Mixed for repeated measures, SAS v8, Cary N.C.). The statistical procedure will first test for the interaction, and if no significant interaction is detected, then the main effect of treatment will be estimated. Unfortunately, estimates of power to detect interaction or main effects require information on the unknown within-patient variance estimates. Therefore, we have simplified the calculation to a simple comparison of mean blood pressure estimates at a single point in time. Full use of the longitudinal data will increase the power and reduce the detectable effect difference calculated below. The current study sample (under the assumption of full recruitment (1080 patients) using baseline systolic blood pressure estimates derived from two well-

established renal stent databases, (see Oriel and Cooper C unpublished data) has 90% power to detect a 6 mmHg difference between the two arms at a single point in time. This upper bound of detectable difference should be clinically relevant, as Stamler has found that a reduction in systolic blood pressure of 5 mmHg or more was associated with a 10.5% reduction in coronary and 15.5% reduction in cerebrovascular death rates[144].

Formula assumptions:

$\mu_{Syst\ BP}$ =170 mmHg
$\sigma_{Syst\ BP}$ = 28 mmHg

Hypotheses:

H_0: $\mu_{Syst\ BP/Stent} = \mu_{Syst\ BP/Control}$
H_A: $\mu_{Syst\ BP/Stent} \neq \mu_{Syst\ BP/Control}$

Where $\mu_{Syst\ BP}$ is the mean systolic blood pressure estimate in patients eligible for this trial, $\sigma_{Syst\ BP}$ is the standard deviation estimate for systolic blood pressure, $\mu_{Syst\ BP/Stent}$ is the mean systolic blood pressure for the renal stent arm, and $\mu_{Syst\ BP/Control}$ is the mean systolic blood pressure for the medical control arm.

Under the assumption of full recruitment (1080 patients) the

Alpha error	= 5% (2-sided)
Power	= 90%
Expected patient accrual	= 1080
Expected lost-to-follow-up rate	= 7.5%
Evaluable patients	= 1000
Detectable difference	= 6 mmHg

5.3.2.5 Evaluation of Renal Artery Disease Within the Duplex Ultrasound Subset

A substudy of patients undergoing renal Duplex ultrasonography at baseline, 1 year, and study termination, will be nested within the larger randomized trial. The selection of the patients included from the medical therapy arm will be solely based on a consecutive series of patients enrolled at clinical sites with proven Duplex ultrasonography expertise, and thus should represent a random sampling of the reference population. The determination by Duplex ultrasonography includes peak velocity of the main index renal artery (a measure of main arterial narrowing or renarrowing after stenting, or "R1" resistance) at one year and termination, and measure of renal resistive index (a measure of arteriolar or "R2" resistance) at baseline, one year and termination[61]. Thus, a subset of 400 consecutive patients will undergo renal Duplex ultrasound at baseline, 1 year follow-up, and at termination from the study (with expected 90% follow-up, or 360 evaluable patients).

In addition to a descriptive analysis of the Duplex measurements in this randomized subset, we intend to test two (2) secondary hypotheses: 1) that combined durability of patency and freedom from complete occlusion rate is higher in the stent arm compared with the medical arm, and 2) that the renal resistive index (RRI) is lower for the stent arm than for the medical arm.

5.3.2.5.1 Durability of Renal Artery Patency After Stenting

The hypothesized beneficial mechanism of renal artery stenting for RAS is the relief of an obstructed renal artery. Some reliable measure of renal patency is thus required to interpret the difference or lack of difference that might be observed in the primary endpoint of this randomized study. Moreover, some measure of renal arteriolar resistance for both arms would shed further light onto the final results of the trial.

Candidate techniques to measure these parameters include contrast angiography, magnetic resonance (MR) angiography, and Duplex ultrasonography. Contrast angiography is invasive, adds risk for follow-up studies, and cannot determine arteriolar resistance. MR angiography is relatively new, but cannot be performed within available metal stents. Duplex ultrasonography offers both a reliable measure of renal artery patency and a measure of arteriolar resistance.

Renal artery stenosis will be defined as an ordinal outcome using a Duplex correlate for the conventional definition of <60%, ≥60%, and 100% diameter stenosis. With an expected rate of renal occlusion in the medical group of 11% [41], and 1% in the stent group (unpublished data, ASPIRE 2 study, Duplex core lab), we should have sufficient power to detect a difference in the rate of renal occlusion, if the frequency of renal occlusion is consistent with prior reports. A definition of restenosis has been derived, and the incidence following renal stenting is expected to be 17% based on the ASPIRE 2 renal stent registry (Cordis Corporation, unpublished data). Thus, assuming 1% total occlusion and 16% restenosis without occlusion after stenting, and 11% total occlusion and the remainder (89%) restenosis (by definition they must have ≥60% stenosis to enter the trial), the expected outcomes are tabulated below by the three mutually exclusive stenosis categories,

Table 9. Distribution of expected stenoses at terminal Duplex evaluation in the CORAL Study.

Arm	Stenosis <60%	≥60% Stenosis <100%	100% stenosis
Medical	0%	89%	11%
Stent	83%	16%	1%

A table of the Duplex percent diameter stenosis results at termination Duplex study will be constructed. A Chi-square trend test with linear weights will be performed. A supportive ordinal logistic regression model will also be performed to adjust for important covariates. If the above estimates are realized, the 400 patient sample (with up to 10% lost-to-follow-up) will have over 99% power to show a statistically (with 5% false positive rate) significant difference. Given the above estimated medical arm rates, the Duplex subset would provide 90% statistical power to detect an 8% difference in stenosis rate ≥ 60%.

5.3.2.5.2 Renal Resistive Index: A measure of preservation of microvascular renal artery function

Using data of patients with renal artery stenosis from the Duplex ultrasonography core laboratory (Jaff), we expect the mean resistive index of 0.73 and a standard deviation of 0.07. A comparison of mean resistive indices between the two groups at termination will be the principal

comparative test. The current study sample (under the assumption of 400 patients (with 10% lost to follow-up) has 90% power to detect a 0.024 difference between the two arms.

Resistive Indexes formula assumptions:

μ_{RI} = 0.73
σ_{RI} = 0.07

Hypotheses:

H_0: $\mu_{RI/Stent} = \mu_{RI/Control}$
H_A: $\mu_{RI/Stent} \neq \mu_{RI/Control}$

Where μ_{RI} is the follow-up mean resistive index (RI) estimate of in patients eligible for this trial, σ_{RI} is the standard deviation estimate for peak velocity, $\mu_{RI/Stent}$ is the follow-up mean resistive index estimate of the renal stent arm, and $\mu_{RI/Control}$ is the follow-up mean resistive index estimate for the medical control arm.

Under the assumption of full recruitment (400 patients) the

Alpha error	= 5% (2-sided)
Power	= 90%
Expected patient accrual	= 400
Expected lost-to-follow-up rate	= 10%
Evaluable patients	= 360
Detectable difference	= 0.024

5.3.2.6 Analysis of Angiographic Endpoints

Qualitative and quantitative assessment
The abdominal aortogram is evaluated for the presence of a left and right kidney, to identify the main renal artery to each kidney, to identify accessory renal arteries, to grossly assess renal artery patency and to subjectively evaluate the extent of atherosclerotic disease in the abdominal aorta in the region of and below the renal arteries. The aortogram is then assessed to evaluate for the presence or absence of stenosis of the main renal artery and its branches. The area of stenosis will be identified, evaluated qualitatively for the presence or absence of calcification on the "native" non-subtracted image, concentricity versus eccentricity of the stenosis, the presence of ulceration, or evidence of fibromuscular hyperplasia. The affected kidney will be measured from the delayed radiograph obtained after the diagnostic aortogram using the ruler placed under the patient.

Quantitative analysis of the RAS under investigation will be performed using the Medis Quantitative Vascular Analysis (QVA-CMS®) program. Quantitative analysis of the renal artery diameter at the location of maximal stenosis (minimum luminal diameter, MLD) is performed.

The selective renal angiogram is analyzed to confirm characteristics of the stenotic lesion identified on the diagnostic abdominal aortogram and to evaluate the intra-renal branches prior to any intervention. The main renal artery and segmental branches are inspected for evidence of fibromuscular dysplasia, and segmental branch stenoses.

The final post stent angiogram is analyzed to determine vessel patency , the percent residual stenosis, segmental and intrarenal branch patency, and stent positioning relative to the abdominal aorta and for any procedural related complications, including dissection (flow and non-flow limiting), vessel occlusion (main renal artery vs. segmental branch), embolus vs. thrombus, guidewire-induced perforation, vessel rupture and spasm. Quantitative analysis of the renal artery diameter at the site of treatment (stent placement) compared with the "normal" renal artery diameter is performed in the exact manner to the method utilized for measuring the degree of stenosis from the diagnostic abdominal angiogram. The contrast filled vessel lumen at its narrowest point between the parallel walls of the stent (minimum lumen diameter, MLD) is compared to the segment of "normal" renal artery used to calculate the pre-treatment stenosis. The "residual" stenosis measurement is recorded as is the post-stent minimum lumen diameter (MLD). Reference calibration is performed in the exact manner similar to that of the diagnostic abdominal angiogram utilizing the reference catheter.

The "final" post stent angiogram is analyzed to identify procedural complications, including dissection (flow and non-flow limiting), vessel occlusion (main renal artery vs. segmental branch), embolus vs. thrombus, guidewire-induced perforation, vessel rupture and spasm.

Aim 1: Longitudinal kidney function (1/creatinine) vs. lesion severity.

To test the hypothesis that angiographic severity of RAS correlates with improved clinical response and that the correlation is greater after renal stenting, pre-treatment degree of stenosis and minimal lumen diameter (MLD) will be related to kidney function (1/creatinine) over time. Summaries of degree of stenosis and MLD will be constructed by using the involved renal artery for patients with unilateral disease or a solitary functioning kidney and the average across organs for patients with bilateral disease. If a significant relationship is found with respect to the primary endpoint, we will further assess if maximum degree of stenosis yields different conclusions when used as a metric in patients with bilateral disease. Further, if maximum degree of stenosis or is also predictive, we will investigate the minimum degree of stenosis among the involved arteries. Similarly when evaluating MLD, if the average is promising, we will investigate first the minimum of the involved renal arteries, and then if significant differences are seen further assess the maximum.

Long term benefit will be assessed by relating changes in kidney function (1/creatinine) (KF) over time for the stent and medical therapy groups to degree of stenosis at baseline. Similarly, kidney function (1/creatinine) will be related to baseline MLD. KF will be investigated using the reciprocal of measured creatinine as an endpoint. The profiles of KF will be generated using random coefficient regression (RCR) models using all available data for each patient (Rutter, CM, 1994). The structure of the RCR model allows for a random intercept (initial KF level) and slope (rate of change of KF per unit time) to be associated with a level of a variable of interest. The RCR model, in essence, averages slopes and intercepts calculated for each patient and accounts for the correlation among repeated measurements over time. Tests for equality of intercept and slope will be generated using the appropriate partial F-tests. Models will also include a term for treatment group, as well as terms allowing all two and three way interactions

involving time and the variable of interest. This will facilitate the construction of partial F-tests to further evaluate if the aforementioned variables have differential effects on the slope and intercept depending on which treatment was received. Linearity of KF over time will be assumed and verified in the models. A random effect for center will also be present in the model to control for differences in variability. As both variables of interest will be allowed to affect the intercept and slope in a continuous manner, estimates and 95% simultaneous confidence intervals will be generated and compared for the 25th, 50th, and 75th percentile values of the parameter of interest. Estimates will be generated at the highest levels of complexity deemed necessary by statistical testing. Estimated profiles over time and 95% confidence intervals will be generated using model coefficients and variance estimates for visual comparison. All models will be fit using the MIXED procedure in SAS version 8.2.

In a cohort of 96 patients treated with renal angioplasty +/- renal stenting kidney function (1/creatinine) over 30 months post-treatment was related to pre-treatment degree of stenosis in a manner similar to that outlined above. A statistically significant relationship between degree o f stenosis and the slope of reciprocal creatinine was noted ($p<0.01$). We found a ten percent change in percent stenosis to be associated with a 0.0016 unit change in reciprocal Cr per month. Using sample size techniques based on slope of regression line analyses (DuPont and Plummer, 1998), we found that a detectable difference in slope of 0.0005 units is possible with 90% power given the proposed sample size. This is consistent with a 31% decrease in slope in the medical therapy group compared to the stent therapy group.

Aim 2: Definition of baseline and post-stent angiographic and hemodynamic lesion characteristics of the study population

Descriptive statistics and exploratory data analyses will be used to summarize and tabulate baseline and post-stent lesion characteristics. Pearson Chi-Square statistics and Spearman rank correlation coefficients, as appropriate, will be used to explore relationships between measurements. Lesion characteristics will be summarized overall and distributions will be examined. Hierarchical cluster analysis will be carried out using squared Spearman rank correlations as similarity measures. (Harrell, FE, 2002) This will allow for better understanding of which variables explain the same pathological and physiological phenomenon. The various correlation analyses may be examined to quantify relationships between angiographic and hemodynamic lesion characteristics, both pre and post treatment.

Change in anatomic and hemodynamic parameters may be assessed and summarized in the stent therapy group. A generalized linear model will be used to estimate the differences between pre and post treatment measurements (Crowder MJ, 1990). The model will account for the paired nature of the data by adjusting the variance-covariance matrix for the correlation among measurements taken on the same patient. The model will include a term for pre vs. post-treatment, as well as a random effect for center. The difference between pre and post treatment means will be estimated and 95% confidence intervals will be generated.
In an evaluation of 96 patients undergoing stent therapy +/- PTRA, pre and post-treatment stenosis were evaluated independently by 5 readers. Degree of stenosis was measured on an 11 point scale (0-100%). Averages were calculated across all 5 readers and differences between pre and post-treatment degree of stenosis were generated. We found an average decrease in degree of

stenosis of 58.7% (standard deviation, 19.2) after treatment. Using this for guidance, we will have the ability to estimate the change in degree of stenosis in the stented group (500 patients) with a 95% confidence interval half-width (margin of error) of 1.68%.

To test the hypothesis that altering degree of stenosis yields improvement in anatomic and hemodynamic parameters, a generalized linear model will be constructed. Change in angiographic degree of stenosis will be related to peak systolic, mean and diastolic pressure gradients across renal artery lesions when data are available. Non-linear relationships will be investigated using restricted cubic spline functions and a random effect for center will be included. Statistical significance for the relationship with each hemodynamic parameter will be assessed with the corresponding partial F-test. The above models will be fit using the MIXED procedure in SAS version 8.2.

Aim 3: Quality assurance and control

Analysis at Angiographic Core Lab of inter-reader agreement in the interpretation of renal angiograms by the personnel who will participate in the CORAL Study will be performed quarterly. This will be accomplished by first inserting 6 previously agreed upon angiographic test images for the first quarter and having the images re-read by both participants in the Angiographic Core Lab. This data will be used for planning the number of test images needed for detecting the desired margin of error in subsequent quarters. Kendall's Coefficient of Concordance, a number similar to a rank correlation calculated across all pairs of readings, will be used to summarize reader consistency. Likewise, discrepancies will be calculated between each reader and the original agreed upon reading for each measure of interest and summarized. 95% confidence intervals will be generated for both measures of agreement using bootstrap re-sampling procedures. This will be carried out on readings for each reader separately to continually assess the need for any action to be taken. This will allow us to know the magnitude and range of differences that are being seen on an ongoing basis, as well as get a sense of the consistency in relative rankings of measures across patients by different reviewers. Allowances will be made for the variety of methods of image submission by clinical sites, as it has become evident that a minority of clinical sites are able to actually provide the Angiographic Core Lab with original DICOM data from the angiographic studies.

Aim 4: Determinants of restenosis after renal intervention

Peak systolic velocity (PSV) at one year will be used as a marker for degree of restenosis using Duplex ultrasound. In the subset of patients deemed to have restenosis, angiograms will be carried out and PSV will be related to lesion characteristics determined from the angiogram. It is estimated that 15 to 20% will have restenosis. A generalized linear model will be used to relate PSV to MLD, lesion reference diameter, lesion length and presence or absence of diabetes. The model will also include an adjustment term(s) for pre-treatment PSV. Degrees of freedom (amount of complexity or number of knots in spline functions) will be allocated in the model according to the strength of the quadratic rank generalization of Spearman's rank-correlation (allowing non-monotonicity) between predictors and response. (Harrell, FE, 2002) Restricted cubic spline functions of the predictors will be used to model non-linearity. Penalized maximum likelihood methods will be used to shrink regression coefficients to the level of complexity

supported by the data. (Harrell, FE, 2002) It is generally accepted that between 10 and 15 data points allow for adequate estimation of one parameter. Therefore, given the projected sample size, approximately 7 effective degrees of freedom are available, which should be sufficient given minor non-linear relationships. As a summary, Wald chi-square statistics, minus total degrees of freedom, will be ranked and compared to determine the strength of and relative contribution to prediction of PSV.

5.3.2.7 Effect of Stenting on Quality of Life

Health-related quality of life (HRQOL) and treatment costs will be assessed alongside the core clinical trial to evaluate the relative cost-effectiveness of the 2 treatment strategies. HRQOL and functional status will be assessed using a combination of generic and disease-specific measures selected to cover a broad range of health domains that may be affected by renovascular hypertension, its treatment, and its complications. Overall HRQOL will be assessed using the 36-Item Short-Form Health Survey (SF-36)[122] and the EuroQOL health status instrument (EQ-5D) [123]. Disease-specific quality of life will be assessed using the Side Effects and Symptom Distress Index, a validated measure of the impact of treatment-related side effects on HRQOL, [124, 125]. Further details regarding the rationale for selection of these instruments and specific analytic approaches are detailed in the Manual of Operations. These instruments are available in several languages. Those patients who speak one of these languages fluently will be included in the quality of life sub-study. These measures will be assessed using a standardized, written questionnaire at baseline, 6 months, and 12 months after randomization, and annually thereafter (up to 3 years). In addition, a final survey will be administered to all surviving patients at the time of study closeout.

5.3.2.8 Cost-Effectiveness of Renal Artery Stenting

Medical care resource utilization and cost data will be collected prospectively for the index hospitalization and the full follow-up period. For each index renal stent procedure, detailed resource utilization will be collected using standardized case report forms by the local research coordinator at the study site. Follow-up medical resource utilization will be assessed by detailed questionnaires completed during each scheduled patient contact. In addition, hospital bills will be collected throughout the study period. These billing data will be collected by a trained research assistant at the EQOL core laboratory. Hospital charges will be converted to costs by multiplying by each hospital's cost-center specific direct cost-to-charge ratio [133]. All other resources will be converted to costs on the basis of standardized unit costs for each item or service. The unit cost for each medical service will be based on the cost that would be paid by Medicare, rather than on charges.

Finally, the cost and quality of life data will be integrated into a computer-simulation model to perform a formal cost-effectiveness analysis. Full details of the analaytic and model-development approach are summarized in the Manual of Operations. Primary data from the clinical trial as to the costs and quality of life impact of renal artery stenting and medical therapy will be used to extrapolate lifetime medical costs and quality-adjusted life expectancy for a hypothetical cohort of patients eligible for treatment with either technique [134]. We will use these data to calculate an incremental cost-effectiveness ratio for the more expensive technique

compared with the less expensive technique, and by comparing this ratio with those for other medical interventions, determine whether 1 treatment strategy is preferred on economic grounds [135].

5.3.3 Tertiary and Exploratory Analyses: Secondary Endpoint Correlations and Pathophysiological Models, Risk Factor Determination and Multivariable Modeling

Tertiary analyses will be regarded as hypothesis generating findings. These analyses include multivariable models used to estimate the determinants of the primary and secondary endpoints, and pre-specified subset analyses.

5.3.4 Subset Analysis

The overall primary endpoint result will be tested in pre-specified categorical subsets. The categories include:

- Presence or absence of renal dysfunction (this is a stratified randomized parameter)
- Global Renal Ischemia Patients
- Non-global Renal Ischemia Patients.
- Renal resistive index (within the Duplex subset)
- Presence or absence of proteinuria
- Kidney size
- Diabetes: Diabetic Patients alone
- Diabetes: Non-diabetic Patients
- Dyslipidemia: Patients with LDL levels ≥ median
- Dyslipidemia: Patients with LDL level < median
- Gender: Men alone
- Gender: Females alone
- Race: African Americans
- Race: Non-African-Americans

The analyses for these subgroups will include examining the difference between procedures (stent versus medical therapy alone) for each subgroup and then a comparison of appropriate different subgroups (e.g., males versus females).

The analyses within subgroups (e.g., male alone) will proceed in the same fashion as the analyses of the combined data. That is, for example, for the composite primary endpoint log rank tests will be performed comparing treatments. In a fashion similar to the analyses for the components of the primary composite endpoints, graphical displays will be produced to examine the consistency across subgroups. The analyses will then be extended to compare subgroups (such as males versus females). Below we discuss one important analysis that considers gender and race.

5.3.4.1 Analysis Plan of the Intervention Effect by Gender and Racial Subgroups

The importance of examining the effect of hypertension interventions on women and ethnic minority populations has been highlighted by the Joint National Committee on prevention,

detection, evaluation and treatment of high blood pressure (JNC-VII). However, since prior studies do not support significant gender or racial differences in the effect of renal stenting on event rates or outcomes, the CORAL Study is not required to provide statistical power for a separate end point analysis by gender or race. Although this trial has been designed to detect the effectiveness of renal stenting across all eligible patients, we recognize the need to check whether the magnitude of the impact is similar in these important subgroups, to generate hypotheses for future investigation.

To accomplish this goal, Cox regression models will be expanded to include interaction terms between treatment arm and various chosen subgroups, specifically women and African Americans. If an interaction term is significant, then treatment effects will be calculated and presented by subgroup. If the interaction term is not significant, then the term will be dropped from the model and a single treatment effect will be summarized for the entire cohort. The Table below has been constructed to illustrate the kinds of differences in treatment effect between men and women, and also between black and white patients, that could be detected with our current design.

The calculations were based on enrollment estimates that suggest 40% of the 1000 analyzable patients will be female, and that 18.5% will be African American. As before, we assume that the 2-year event rate with medical therapy only will be 30%. For the cohort overall, we had previously assumed that stents would reduce this event rate by 25% (from a 30% to 22.5% event rate, for a relative risk [RR] of 0.75). In looking for effect modification between gender and stent therapy, we now assume that the effect of stents will be strongest in the male patients, for example, reducing the event rate by a relative risk of 0.75, of 0.70, and so on, down to a relative risk of 0.50. We then calculated how much higher the relative risk in women would have to be in order to be able to be distinguished from the relative risk in men, with 80% power and 5% 1-sided type I error. The type I error was chosen to be 1-sided because our concern was to be able to determine whether stenting in females has no efficacy or is harmful, rather than to determine whether stenting is more efficacious in females. Identical calculations were carried out looking for effect modification in African Americans.

Table 10. The differences in relative risk that are detectable in patient subgroups.

	Detectable relative risk, stent vs. medical therapy alone	
	In Female Patients:	In Black Patients:
Assumed relative risk (RR) in the reference group (i.e., male or white patients):		
RR=0.75 (30% v 22.5%)	RR>1.30	RR>1.51
RR=0.70 (30% v 21%)	RR>1.23	RR>1.43
RR=0.65 (30% v 19.5%)	RR>1.16	RR>1.35
RR=0.60 (30% v 18%)	RR>1.09	RR>1.29
RR=0.55 (30% v 16.5%)	RR>1.02	RR>1.21
RR=0.50 (30% v 15%)	RR>0.95	RR>1.15

The table above shows that if the overall efficacy of stent therapy is primarily due to the male patients, for example if we assume that RR=0.60 in the male patients, then we will be able

statistically to determine if females in contrast receive no benefit or are actually harmed by stent therapy (i.e., RR>1.09). In racial comparisons, because the number of minority patients is more limited, we will only be able to detect whether stenting is beneficial in white patients (i.e., RR=0.60) in contrast to being mildly harmful (i.e., RR>1.29) in African American patients.

The above analyses will be performed to examine other groups such as diabetics versus non-diabetics.

5.3.5 Relationship Between Kidney Function (measured as 1/Cr) and Macro and Micro-Vascular Renal Disease

One novel aspect of this randomized trial is the ability to measure kidney function (in terms of the reciprocal of creatinine) as well as serial renal Duplex ultrasound to track the progress of both main renal artery lesions, stented or not, as well as the extent of microvascular disease as assessed by resistive indices. This provides the unique opportunity to determine the mechanism by which kidney function declines in patients with RAS. There is no doubt that atheromatous renal artery stenosis can progress to complete occlusion and that this can result in loss of kidney function [40]. Revascularization in this setting is sometimes associated with improvement in renal function [145]. Even in the absence of complete occlusion, observational studies demonstrate that renal function worsens with time in many patients with RAS. This fact has led some to suggest that progressive RAS is a common cause of ESRD accounting for as many as 20% of all patients over the age of 50 reaching dialysis[14, 15, 146]. According to this hypothesis, the kidney distal to a significant stenosis gradually loses nephrons due to ischemia.

Presently, a large number of renal artery interventions are performed with the primary goal of preserving kidney function, based on this assumption. However, whether loss of kidney function in patients with RAS actually results from progression of the main renal artery disease is uncertain. Against this hypothesis, split renal function studies demonstrate that the non-stenotic kidney is as likely to have impaired function as the post-stenotic kidney in patients with unilateral RAS [147]. In fact, advanced renal failure has often been observed in patients with unilateral renal vascular disease and this cannot be explained on the basis of main renal artery disease[46, 147, 148].

Technically successful interventions do not always improve kidney function [149] and the correlation between the degree of stenosis and GFR (estimated in this study by reciprocal of creatinine) is low, except in patients with complete occlusion[46]. These data suggest that other processes are at work that account for loss of function in this setting. In fact, progressive renal atrophy is better correlated with systolic blood pressure than arterial stenosis in patients with atherosclerotic RAS[43]. Also consistent with this view, patients with hypertension and vascular disease are at risk for hypertensive nephrosclerosis and atheroembolic disease and both of these processes can progress to end stage renal disease. The exact percentage of RAS patients that lose kidney function from each of these processes is completely unknown.

Importantly, the proposed randomized trial will correlate serial anatomic assessments of macro and micro vascular disease with measures of kidney function in patients with renal artery stenosis. These data will allow a relationship between progression of main renal artery disease,

renal microvascular disease, and declining kidney function in this population to be precisely determined.

5.3.6 Evaluation of Renal Artery Restenosis

As described above, we propose using a RAR >2.5 as our Duplex criterion for restenosis (≥60% angiographic stenosis) except in the circumstances of low <50 and high >120 cm/sec aortic velocities. Whenever feasible, the Duplex determination will be confirmed angiographically. The expected incidence of restenosis following renal stenting is 17%, based on the ASPIRE renal stent registry (see preliminary data above).

The categories for restenosis described above, assessed at one year after implantation in all 540 patients in the stent group, will be used to describe restenosis-free performance of the Genesis stent. This will be compared to the restenosis rates derived from the ASPIRE renal stent registry (17%).

The incidence of restenosis within the treatment group will be analyzed and reported after the last study patient has reached their one year anniversary and all one year Duplex data has been collected and analyzed. No Duplex data from the medical therapy group will be reported until the main findings of the study are reported after study completion.

Descriptive statistics of renal artery peak systolic velocity and ratio of renal artery: aortic PSV will be reported. The incidence of restenosis, will be presented in 2 forms: 1) all patients meeting the Duplex criteria, and 2) a corrected value incorporating the results of subsequent angiographic confirmation.

In addition to observing and reporting the categorical rate, the continuous measure of transformed percent diameter stenosis will be displayed using conventional continuous frequency distribution curves commonly used in the coronary artery restenosis literature[150] The curves will be displayed for both arms, and individual curves will be superimposed for baseline and at 1-year follow-up. These graphs will be very helpful in describing the change in lumen dimension.

The occurrence of binary restenosis will also be used as a covariate in a multivariable model of the primary endpoint. Specifically, first we will evaluate the treatment assignment term as a covariate using the primary endpoint as the dependent variable. The model will be adjusted for other relevant terms. We anticipate that the model will be underpowered, but should correlate with the larger multivariable treatment effect model. Second, we will insert the binary restenosis term, evaluated for both the medical and stent arms, to determine whether there is a significant contribution to the model by the restenosis term as well as an improved goodness of fit. If such an improvement model is observed, this will provide secondary evidence that patency and maintenance of patency has an important influence on the primary endpoint, over and above treatment assignment. This result would support the overall hypothesis that reversing renal artery stenosis has clinical benefit.

5.3.7 Adjusted Analysis of Endpoints, Controlled for Risk Factors

Use of ACE-ARB treatment, anti-platelet therapy, dyslipidemia, hypertension and cigarette smoking have established effects on cardiovascular outcomes [151]. Such risk modifiers will be employed in this trial for both randomized arms according to the published guidelines (see above). The importance of controlling for known cardiovascular and cerebrovascular risk factors for the determination of the primary endpoint and selected principal secondary endpoints will be performed, adjusted with and without the randomized treatment effect. Moreover, risk factor adjustment for these selected endpoints will also be performed to give an adjusted main treatment (randomized stent intervention) effect estimate. However, we also recognize that hypertension control may be mechanistically linked to the intervention effect and differences in blood pressure control between treatment groups may be observed as a consequence. Therefore, we will be prepared to perform the adjusted analyses with and without blood pressure as a covariate.

5.3.8 Multivariable Modeling of Event-free Survival

An important feature of this trial will be to generate hypotheses related to subgroups at differential risk if a significant treatment effect is observed, whether beneficial or hazardous. As such, a predictive model that identifies those baseline characteristics, including treatment assignment, associated with risk will be created. Utilizing appropriate uni- and multi-variate methods, we will also incorporate HgbA1c levels (as a measure of diabetes) and albuminuria (as a measure of renal injury), lesion characteristics, presence of LVH, severity of hypertension, etc. The interpretation and inference of such multivariable modeling will be regarded as limited due to the problem of multiple comparisons. Multivariable testing will use linear regression for continuous response variables and logistic regression for dichotomous response variables. The time-sensitive nature of any response variable may be displayed by using a Kaplan-Meier plot, while differences between groups for such variables tested by logrank tests. Multivariable testing of alternative hypotheses or determinants of time-sensitive outcomes, such as event-free survival for any secondary response variable, may also be required. If needed, we will rely upon the Cox proportional hazards regression model.

5.3.9 Other Pre-planned Tertiary Analyses

The rates of Target Lesion Revascularization (TLR) and number of anti-hypertensive medications will be examined.

5.4 Overall Clinical Trial Timeline

Figure 4 shows the original and modified clinical trial timeline. The original timeline was based on a 6-month start-up after funding to develop the clinical sites and early achievement of the target enrollment goal of 54 patients per month. Based on these projections, it was estimated that the overall clinical trial should last approximately 6 years. The modified timeline incorporates the impact of early experience in time to site activation and enrollment challenges in the current environment that include biases from potential referring physicians towards both an extreme conservative approach of avoiding stenting and a very aggressive approach of always

recommending stenting. While these challenges represent true clinical equipoise and point increasingly to the importance of the results from this study, they have required additional time and effort on the part of study leadership at the individual site level and in various national education forums to focus attention on the importance of a definitive answer to this scientific question. Thus, the modified timeline reflects additional time to more slowly develop educated and interested clinical centers as well as expansion of the study to sites outside of the United States. The overall clinical trial should last approximately 6 years from time of first randomization. This prediction is based on the following assumptions:

- The "start-up" period will be a continual process with development and monitoring of active sites until a steady state enrollment is realized in Q2 2007.
- At an average enrollment of 30 patients/month and a peak or steady-state of 42 patients/month, the expected enrollment phase of 1080 patients should take 47 months or until end of Q1 2009. While the timeline is still aggressive based on evident early enrollment trends, we believe the feasibility of this modified project timeline is reasonable and is supported by expansion of active clinical sites. The sample size is at the minimum to support the testing of our hypotheses, and the follow-up and proposed budgets are also optimized for actual successful execution. We have redoubled our efforts to manage and educate clinical sites and obtain reasonable assurances of enrolling approximately 0.3-0.5 subjects per site per month. Furthermore, the new enrollment trend accounts for a significant proportion of sites performing at only intermediate (0.3 patients per month) and poor status (0 patients per month).
- The formal clinical trial duration timed from first randomization will be approximately 66 months, until end of Q3 2010, based on progressive achievement to the steady state of active sites and enrollment rates and allowing 18 months for minimum follow-up of last patient enrolled.
- A 6-month "close-out" period will be required to perform final primary and secondary endpoint analyses, and preparation of a final report.
- Given the above goals, a timeline of 72 months from time of first enrollment is projected or end of Q1 2011.

Statistical Implications of Modified Timeline

The original clinical trial timeline allowed for maximum follow-up time of 5.5 years for first patient enrolled and a minimum of 3 years for last patients enrolled. To insure that the study meets its scientific objectives, modifications of enrollment rates and follow-up duration will need to be analyzed carefully in terms of any impact on statistical power.

The following time commitments and assumptions for individual patients can be expected from the modified study timeline:

- Maximum follow-up is expected to be 5.5 years for the first patient enrolled.
- Minimum follow-up is expected to be 1.5 years for the last patient enrolled.
- Based on enrollment slope all but approximately 250 patients will have >2 years follow-up.
- 50% of subjects will be enrolled 70% through the enrollment period.
- Assume 7.5 % drop-out rate

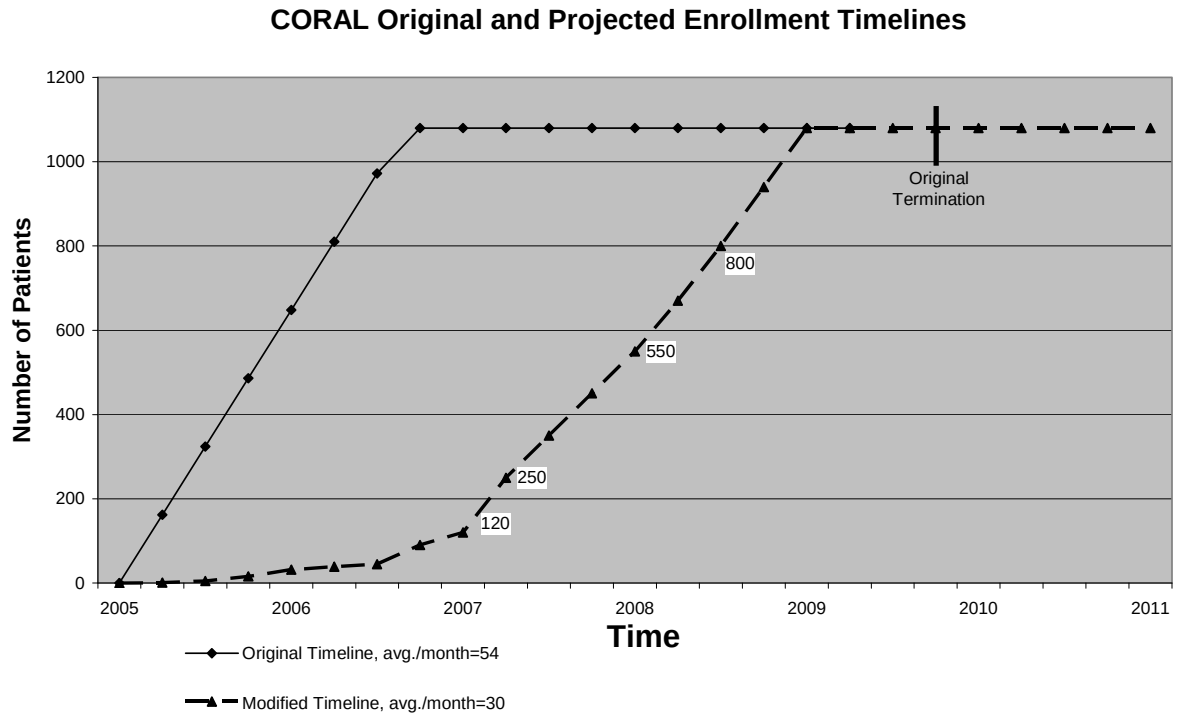
- Assume 77.5% event-free rate for treatment and 70.0% event-free rate for control

This yields 85% power to detect a significant difference at the 0.05 alpha level.

Even though this modified timeline has the advantage of basis on early experience in managing enrollment and clinical sites in the trial, it remains aggressive based on current experience. Study leadership will continue to monitor according to these projections and make appropriate modifications, including recommendation to terminate the study if enrollment can not be maintained that approximates these projections.

The study leadership will remain masked to the effectiveness data and will not evaluate the effectiveness data for early termination of the study, as described in section 5.1.1 *Group Sequential Testing Considerations*."

Figure 4. Project timelines



6.0 ADVERSE EVENTS /SERIOUS ADVERSE EVENTS

6.1 Adverse and Serious Adverse Event Definitions

a) **Adverse Events (AE):** An AE is any untoward medical occurrence observed in a patient that occurs in association with the use of an administered investigational intervention, whether considered intervention related or not. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the investigational intervention, whether or not considered related to the investigational intervention. Pre-existing conditions, which worsen during a study, are to be considered adverse events.

b) **Serious Adverse Events (SAE):** A SAE is any adverse drug (or investigational device) experience occurring at any dose that results in any of the following outcomes: death, a life-threatening adverse drug experience, in-patient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse Study Medication or investigational device experience when, based upon appropriate medical judgment, they jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. (CFR & ICH Guidelines, 2000)

In this study, patients should be encouraged to report AEs spontaneously or in response to general, non-directed questioning (e.g., "How has your health been since the last visit?"). Any time during the study, the patient may volunteer information that resembles an AE. If it is determined that an AE has occurred, the investigator should obtain all the information required to complete the AE Form of the CRF.

6.2 Documentation

Adverse events must be listed on the appropriate CRF. All AEs will be characterized by the following criteria:

- Intensity or Severity
- Expectedness
- Relatedness
- Outcome
- Treatment or Action Taken.

6.3 Intensity or Severity

The following categories of the intensity of an adverse event are to be used:

- **Mild**: Awareness of a sign or symptom that does not interfere with the patient's usual activity or is transient, resolved without treatment and with no sequelae;

- **Moderate**: Interferes with the patient's usual activity, but the patient is still able to function;
- **Severe**: Events that interrupt a patient's usual daily activity and generally require a systemic drug therapy or other treatment.

6.4 Expectedness

All AEs will be evaluated as to its expected occurrence (as described in the protocol) or whether it was unexpected to occur.

- **Expected**: An adverse event is expected when the specificity and severity of the event is consistent with the applicable product information (i.e., Investigator's Brochure or risk information described in the investigational plan and informed consent);
- **Unexpected**: An adverse event is unexpected when the specificity or severity of an adverse event is not consistent with the applicable product information (i.e., Investigator's Brochure or risk information described in the investigational plan and informed consent). Unexpected as defined above refers to an adverse event that has not been observed before.

6.5 Relatedness

The Principal Investigator (PI) will evaluate if the AE or SAE is related to the Study Medication or Study Devices. Relatedness is defined in the following manner:

- **Unlikely**: The PI has determined that the event has no relationship to the use of Study Medication or Devices;
- **Possibly or Probably:** The PI has determined that the event has a reasonable relationship to the use of the Study Medication or Devices;
- **Not Known:** The PI is unable to determine the relationship of the event to the Study Medication or Devices.

6.6 Outcome

The clinical outcome of the AE or SAE will be characterized as follows:

- **Death:** The SAE form must be completed for this outcome;
- **Recovered:** The patient returned to baseline status;
- **Symptoms Continue:** Patient did not recover and symptoms continue.

6.7 Treatment or Action Taken

AEs and SAEs will resulted in:

- **Intervention:** Surgery or procedure;
- **Other Treatment:** Medication dose reduction/interruption or discontinuation;
- **None:** No action is taken.

6.8 Expedited Reporting of Serious Adverse Events

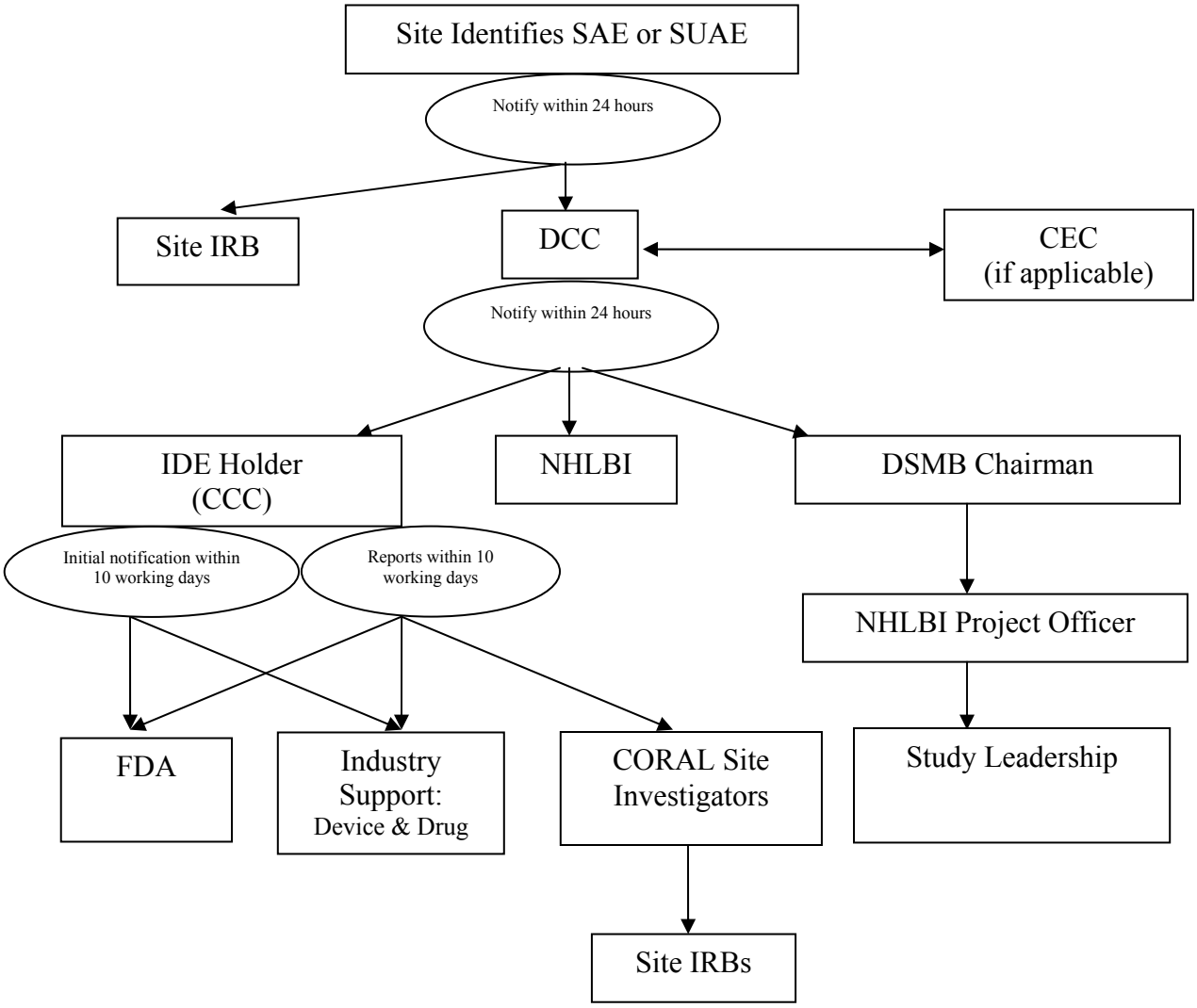
The procedure for reporting any Serious Adverse Event is as follows:

- Report any serious adverse events to the DCC within 24 hours of knowledge of event by fax (617-307-5656).
- Report any serious adverse event to the IRB according to the investigational site's IRB procedures.
- Complete appropriate Event Form for any complication and/or serious adverse events.
- Attach physician/nurse notes or summaries regarding the event to the Event Form.
- Report of a patient death must be accompanied by a completed Study Exit Form, a brief statement of the pertinent details, the death records, death certificate, and autopsy report (if performed).
- Provide completed, signed copies of the Study Exit Form and attachments to the DCC.

Clear pathways have been developed for the reporting and analysis of serious adverse events (see diagrams below). In this regard, the sites are responsible for SAE identification. SAEs are reported by the site to the local IRB and to the DCC within 24 hours of becoming aware of the event. The DCC will forward SAE reports within 24 hours of receipt during a working day to the IDE Holder, the NHLBI and to the DSMB Chairman. The DSMB Chairman will utilize his/her discretion to monitor these events, and, on an ad hoc basis, call a DSMB meeting to review events. The SAE report will also be forwarded to the CEC, if appropriate.

The IDE Holder will forward the site reported SAE to the FDA, device and drug providers, and to the site within 10 working days of its receipt. The site will be responsible to forward the report to its IRB. Utilizing this strategy allows identification of serious or systematic hazards in a timely fashion, facilitating corrective action and appropriate reporting to regulatory agencies.

Figure 5. Serious adverse event or unanticipated serious adverse event reporting.



6.9 Reporting of Study Endpoint Adverse Events

The primary aim of the CORAL Study is to test the effect of the study treatment on the following serious adverse events: cardiovascular or renal death, myocardial infarction, stroke, hospitalization for congestive heart failure, permanent renal replacement therapy, and progressive renal insufficiency. Whenever such an event is suspected or identified, an Endpoint Data Collection Form should be completed for each suspected event and sent to the DCC as soon as possible along with the required supporting source documentation. The source documentation required for each reported event is found at the bottom of each Endpoint Data Collection Form.

Table 11. Required CRF and source documents for CORAL events.

Suspected Event	CRF Pages	Site Source Documentation
ALL EVENTS	- Specific event CRFs, as appropriate for the event - SAE Notification Form - Concomitant Medication Log, as appropriate	NOTE: Prior to sending source documentation to DCC: *1. All patient identifiers will be thoroughly blinded.* *2. Each page of source documentation needs to be labeled with the patient's study ID.* *3. Each document should be properly labeled with provided labels.* Discharge Summary or Physician Narrative**. **Physician Narrative should be provided in any of the following instances: 1) discharge summary is available but does not contain adequate details of event being reported, 2) discharge summary is not able to be obtained or was not done, or 3) event occurred outside of a hospital. A Physician Narrative should consist of a clear, concise, and accurate description of the event or events being reported and should support the data recorded on the endpoint data collection form. Sites should use their own judgment if there are source documents that may have other document title, such as Discharge Abstract, Death Summary, etc.
MI	- SAE Form - Endpoint Data Collection Forms	- Cardiac marker lab reports drawn in association with the event, if abnormal. All reports should be labeled with date and time and include upper limit of normal (ULN) for each marker drawn. Cardiac markers consist of CK, CKMB and Troponin.
Stroke	- SAE Form - Endpoint Data Collection Forms	- Imaging Reports, if applicable - Neurology Consult Notes, if applicable - Note: Discharge Summary and/or Physician Narrative should contain details related to focal neurological deficit and how diagnosis was obtained.
CHF	- Subsequent Hospitalization Form - Concomitant Medication Log - Endpoint Data Collection Forms	- CEC requires documentation of specific medication given and route of therapy. Medication Logs should be provided if either Discharge Summary or Physician Narrative do not detail the treatment received and route of therapy.
Progressive Renal Insufficiency	- SAE Form - Endpoint Data Collection Forms	- Renal consult note - Dated Lab Reports from the Biochemistry Core Lab and or site documenting creatinine values drawn in association with this event
Permanent Renal Replacement Therapy	- SAE Form - Endpoint Data Collection Forms	-Renal consultation notes -Operative Report, only if Discharge Summary is not available -Dialysis records
Death	- SAE Form - Study Exit Form - Endpoint Data Collection Forms	- Autopsy Report, if performed. If site is not able to obtain autopsy report, please report principle autopsy findings in Physician Narrative. - In the setting of a Fatal MI, cardiac marker reports (peak including ULN labeled with date and time) and ECGs performed in the setting of the event.

7.0 ADMINISTRATIVE RESPONSIBILITIES

7.1 Institutional Review Board (IRB) Information

This protocol and the informed consent document must be reviewed and approved by the appropriate IRB before enrollment of patients can begin. Changes or additions to the study protocol or informed consent document at the enrolling center must be approved in writing by the Clinical Coordinating Center and the enrolling center's local IRB.

7.2 Patient Informed Consent

Informed consent is mandatory and must be obtained from all patients prior to their participation in this trial. Informed consent must be obtained in accordance with the FDA regulation 21CFR, Part 50 or other relevant national or international regulations and/or normative standards, such as ISO 14155.

The sample Patient Informed Consent Form is found on the CORAL website. A copy of the approved Patient Informed Consent Form along with a copy of each patient's signed and dated consent form must be maintained by each investigator in a designated clinical trial administrative file. A signed copy of the consent form must be given to each patient.

7.3 Confidentiality

All information and data sent to the DCC, Angiographic Core Lab, Vascular Ultrasound Core Lab, MRA/CTA Core Lab, ECG Core Lab, Biochemistry Core Lab, and Economics-Quality of Life Core lab concerning patients or their participation in this trial will be considered confidential. Only authorized DCC or other core lab personnel, FDA, NIH and study personnel will have access to these confidential files. Authorized regulatory personnel have the right to inspect and copy all records pertinent to this trial. All data used in the analysis and reporting of this evaluation will have no identifiable reference to the patient.

7.4 Records and Reports

7.4.1 Records

Records to be maintained by the investigator include:

- Signed Confidentiality Agreement
- Study Protocol
- Protocol Amendments
- Signed clinical trial agreement and/or Investigator's Agreement
- FDA Form 1572
- IRB approval letter
- IRB approved Informed Consent document

- IRB Re-approval Letters
- IRB Membership List
- IRB Correspondence
- Sponsor Correspondence
- CVs/licenses for all investigators and research coordinators
- Site Personnel Signature List
- Delegation of Responsibility Form
- Financial Disclosure/Conflict of Interest Forms
- Patient Screening & Enrollment Log
- Telephone Logs
- Site Visit/Monitor Log
- Lab certification and lab test normal ranges
- Device Accountability Logs
- NIH Training Certifications for Responsible Conduct of Research
- Cultural Competency Training Certificates
- Angiographic Core Lab Certificate

The following records must be maintained for each patient enrolled in the trial:

- Signed Patient Informed Consent Form
- All completed CRFs
- Supporting source documentation for values or responses in CRFs
- Supporting documentation of any complications and/or adverse events

The investigator must retain copies of procedure reports, procedure nursing notes and the results of any interventional procedures that occur. The DCC reserves the right to secure data clarification and additional medical documentation on patients enrolled in this trial.

7.4.2 Reports

Investigators are required to prepare and submit to the local IRB, DCC, CCC, and Core Labs complete, accurate and timely forms and reports, when necessary, according to Table 12.

Table 12. Responsibilities for preparing and submitting forms and reports.

Type of Report	Prepared by Investigator For	Time of Notification
Case Report Forms	DCC	Within 14 days
Case Report Forms and Diagnostic Tests/Samples	Angiographic Core Lab Vascular Ultrasound Core Lab MRA/CTA Core Lab Biochemistry Core Lab EQOL Core Lab ECG Core Lab at the DCC	Within 14 days
Patient death during the trial	DCC, IRB	Within 24 hours of knowledge of event
Unanticipated complications, Serious AEs	DCC, IRB	If serious or life threatening within 24 hours of knowledge of event
Patient withdrawal	DCC, IRB	Within 5 working days
Withdrawal of IRB approval	CCC	Within 5 working days
Deviations from the investigational plan	IRB, DCC	Within 5 working days
Informed consent not obtained from randomized patient	IRB, DCC	Within 5 working days
Other information upon the request of the IRB, or DCC	As appropriate	As requested

Records and reports will remain on file for a minimum of two (2) years after the completion/termination of the investigational trial. They may only be discarded upon notification by the CCC. To avoid error, the principal investigator should contact CCC before the destruction of any records and reports pertaining to the trial to ensure they no longer need to be retained. In addition, the CCC should be contacted if the principal investigator plans to leave the investigational site.

8.0 STUDY DATA REPORTING AND PROCESSING

8.1 Data Monitoring and Quality Control

8.1.1 Case Report Forms (CRFs)

CRFs will be used to collect all patient data during the trial. Sample forms are provided on the website. Data will be collected on 3-part (white, yellow, pink) no carbon required (NCR) paper CRFs. Study coordinators at each clinical site will perform primary data collection based upon source-documented hospital chart reviews. CRFs will be completed and forwarded to the DCC in an expedited fashion. Patient data from the clinical sites should be completed within pre-specified time limits, usually on or within 2 weeks of each patient's study visit.

The white and yellow NCR pages of each CRF will be forwarded via FedEx to the DCC for data entry. The pink NCR page will remain at the clinical site. To track data flow to the DCC and all core laboratories, the DCC will provide study sites with CRF and laboratory transmission forms. These forms will be completed each time data or media (CDs, videos, etc.) are submitted to the DCC or core laboratories. A tracking report will be provided for each clinical site to verify receipt of data.

Clintrial, a fully relational database, ensures proper tracking of CRFs between the individual clinical sites and the DCC. Deficiencies identified by the master tracking system will be communicated by fax or regularly scheduled teleconferences between the study site coordinators, the DCC, and the CCC.

To avoid personal identification of patients, all patient forms will be coded with a patient identifier. Each patient identifier includes a three-digit number pre-designated for the site, a site patient number up to four-digits, and a unique randomization number. This entire patient identifier will be transcribed onto all patient-related study materials, including information shared with the core labs. The DCC has no means of identifying patients by their initials.

8.1.2 Data Reporting

The investigator, or an individual designated by him/her, is responsible for recording all data from the trial on the CRFs supplied by the DCC. The data on each CRF must be legibly handwritten with a black ball-point pen.

The investigator is required to sign the CRF on the appropriate pages to verify that he/she has reviewed the recorded data.

Completed CRFs will be reviewed at the investigational site by authorized study personnel at regular intervals throughout the trial. To this end, the investigator must permit inspection of the trial files and patient CRFs by such representatives and/or responsible government agencies.

8.1.3 Data Review

All CRFs will be tracked at the DCC and missing or unclear data will be requested as necessary throughout the trial. The DCC will request further documentation such as physician and/or cardiac cath lab procedure notes when complications, major adverse events, or malfunctions are observed and reported.

Data entry and development of the primary database for the trial will be performed by the DCC. The DCC will also be responsible for auditing the database and confirming the overall integrity of the data.

8.2 Study Data Collection

8.2.1 Data Quality Control

To ensure proper tracking of case report forms obtained from the individual clinical sites, a master tracking system for forms will be utilized. Deficiencies identified by the master tracking system and any other specific clinical site needs will be communicated by fax or regularly scheduled teleconference between the study site coordinators, DCC, CCC and the Device and Drug providers as indicated.

8.3 Site Monitoring

The CCC will be responsible for study monitoring. Study site monitoring will be performed by, the CORAL Study Leadership and the CCC. Representatives of the Study Leadership, DCC, CCC, NHLBI, Drug and Device providers may participate in these site visits. An investigator's meeting will occur in order to orient the prospective investigators and staff to the stent device, the study protocol, applicable regulations and requirements, and expectations of the study, including the numbers and time frame for patient selection, consenting and enrollment, and required clinical data and record keeping, etc. The prospective study site will be evaluated prior to the initiation of the clinical investigation to ensure that it has an adequate patient base and facilities and can provide sufficient staff and documentation support to conduct the study properly.

No study site may receive shipment of the study materials until the following documents are received by the CCC:

- Written IRB approval for conduct of the study
- IRB-approved informed consent document
- Signed Investigator's Letter of Agreement
- Signed Clinical Trial Agreement
- Investigator's and Co-investigators' current curriculum vitae

The study monitor will maintain personal contact with the investigator and staff throughout the study by phone, fax, mail, e-mail and on-site visits. The site will be visited to ensure that the following items are in compliance with regulations and as stated per protocol:

- screening activities
- adequate patient enrollment with properly obtained and documented informed consent (in accordance with 21 CFR Parts 50 and 56)
- accurate data reporting and current records are being maintained
- adequate accounting of shipments/dispensing of Study Materials and Voucher Cards
- the facilities being used by the investigator continue to be acceptable for the purposes of the study
- the study protocol and investigational plan is being followed
- changes to the protocol have been approved by the IRB and/or reported to the sponsor and the IRB

Additionally, the review of subject records will be completed by comparing a representative number of those subject records to determine:

- there are no omissions in the reports of specific data elements
- missing visits or examinations are noted
- subjects failing to complete the study and the reason for each failure are noted in the reports.

The monitor will compile and file an observation report at each visit that will be provided to the Coral Study Leadership and other appropriate study personnel.

At the close of the study at an investigational site, the clinical monitor will make a final on-site visit. The purpose of this visit is to collect all outstanding study data documents, ensure that the investigator's files are accurate and complete, review record retention requirements with the investigator, make a final accounting of all study supplies shipped to the investigator, provide for appropriate disposition of any remaining supplies, and ensure that all applicable requirements are met for the study. The observations and actions made at this visit will be documented as a final report for investigator and sponsor acceptance.

8.3.1 Communication

In the initial phases of the protocol, weekly or biweekly group teleconference calls including the DCC, CCC, and clinical sites may be conducted to resolve any problems concerning the protocol and data collection.

8.3.2 Recruitment Tracking

A recruitment status report generated by the DCC will identify variations in recruitment frequency among sites. The frequency of these reports varies based on speed of enrollment and/or study timeline. For a well-balanced study, a normal distribution in recruitment is expected; however, outliers will be routinely investigated for study compliance.

Table 13. Schedule for case report form completion and submission.

	CRFs	Submission Schedule
Enrollment	**Randomization Form** **Baseline Form**	FedEx to the DCC within two weeks
Treatment	**Baseline Lesion Diagnostic Form** **Intervention Procedure Form** **Lesion Treatment Form**	FedEx to the DCC within two weeks
Hospital Discharge	**Index Visit Completion Form**	FedEx to the DCC within two weeks
Follow-ups	**Contact Form** **Study Exit Form** **Adverse Event Log** **Concomitant Medication Log** **Study Drug Discontinuation Form** **Any applicable Event Forms**	FedEx to the DCC within two weeks
Study Endpoints/ SAEs	**Endpoint Data Collection Forms**	FedEx to the DCC within two weeks DCC may request forms to be faxed to DCC if necessary for adjudication
	Serious Adverse Event Reporting Form	Fax to the DCC within 24 hours of the event

8.4. Confidentiality and Protection of Study Files

Passwords will be issued to appropriate HCRI personnel to ensure confidentiality and protection of the data by allowing variable levels of access to the computer system. For example, only the data entry person or Data Manager enters and/or verifies data. All other personnel may view the data in a read-only format. The hard copies of the CRFs are kept in a locked file room when not in use for data entry or data cleaning.

9.0 ETHICAL AND REGULATORY CONSIDERATIONS

9.1 Roles of Study Leadership, Device and Drug Providers and NHLBI

The National Heart, Lung and Blood Institute of the National Institutes of Health will oversee and assist the CORAL Study Leadership for the overall conduct of the study. The Study Leadership will work with both the Device and Drug providers to ensure applicable guidelines and regulations for conducting clinical trials are met. This study will be conducted in compliance with the protocol, Good Clinical Practice (GCP), the applicable regulatory requirements of the US Food and Drug Administration (FDA), ICH Guidelines and state and local legal and ethical requirements. The following documents contain the policies and procedures designed to ensure adherence to Good Clinical Practice:

1. ICH Harmonized Tripartite Guidelines for Good Clinical Practice 1996

2. US 21 Code of Federal Regulations dealing with clinical studies (including parts 50 and 56 concerning informed consent and IRB regulations)

3. Declaration of Helsinki, concerning medical research in humans (Recommendations Guiding Physicians in Biomedical Research Involving Human Subject, Helsinki 1964, amended Tokyo 1975, Venice 1983, Hong Kong 1989, Somerset West 1996).

The investigator agrees, when signing the Protocol Signature Page, to adhere to the instructions and procedures described in the protocol and thereby adheres to the principles of Good Clinical Practice.

9.2 General Duties (21 CFR 812. 40 and 312.32))

General duties of the CCC consist of providing the protocol and study documents to the principal investigator for submission to the IRB, obtaining documentation of IRB approval prior to shipping study materials, selecting investigators, ensuring proper clinical site monitoring and ensuring patient informed consent is properly obtained.

The DCC is responsible for providing the IDE Sponsor with quality data that satisfies federal regulations and informing them of unanticipated adverse events, serious adverse events, and deviations from the protocol. The DCC will prepare written progress reports and a final report.

9.3 Supplemental Applications (21 CFR 812. 35 and 312.30))

As appropriate, the CCC will submit changes in the Investigational Plan to the investigators to obtain Institutional Review Board approval of any such changes.

9.4 Maintaining Records (21 CFR 812. 140)

The DCC will maintain copies of correspondence, data, serious adverse events and other records related to the clinical trial. The CCC will maintain records related to the signed Investigator Agreements and all regulatory documents.

9.5 Submitting Reports (21 CFR 812. 150 (B) and EN 540, 5.4.12 and 5.6.15)

The IDE Holder will submit the required regulatory reports identified in this section of the regulation. This includes reporting of unanticipated adverse device effects, serious adverse events, withdrawal of IRB approval, current investigators list, annual progress reports, recall information, final reports and protocol violations, and any other reporting requirements imposed by the reviewing IRB.

The DCC will notify the IDE Holder within 24 hours of any unanticipated adverse device effects, serious adverse events, withdrawal of IRB approval or protocol violations. The DCC will also prepare an annual progress report and a final report for the IDE Holder.

9.6 Site Record Retention Policy

All core laboratories and clinical sites will maintain study records for two years after the FDA is notified that research under the Investigational Device Exemption (IDE) has been terminated by the IDE Holder.

9.7 Risks and Benefits

Potential risks
Risk of participation in this study can be identified in relation to 6 separate phases: the risk of the initial baseline evaluation, the risk of the invasive assessment or non-invasive renal imaging study, the risk of the renal stent procedure (if required), risk of medical therapy, the risk of adverse events during the follow-up phase and other risks in this patient population. Each of these phases is described below.

Risk of Baseline Evaluation and Non-Invasive Imaging Studies
During the initial baseline evaluation the risks include those of phlebotomy (very low risk). The risk of the non-invasive imaging tests including the Duplex scan, MRA, and CTA are expected to be minimal.

Risk of the invasive assessment including angiography
Risks include those of vascular access (bleeding, blood vessel injury, pseudoaneurysm formation, emergency surgery), contrast reaction, athero-embolization, or injury to the renal artery. Further risks include contrast-associated acute tubular necrosis. The likelihood and seriousness of these risks are described in Table format below for the invasive assessment and for the stent procedure. To minimize risks all sites will utilize “best methods” as dictated by the protocol for the invasive evaluation. This will include pre-hydration and utilization of agents, such as n-acetyl cysteine, that may reduce the risk of contrast nephropathy in those with baseline renal dysfunction[152]. Appropriate angiographic technique will be utilized to expose patients to the least amount of contrast dye and radiation while providing high resolution angiograms.

Risk of Stent Procedure

The risks associated with the renal stent procedure include failure to deliver a stent to the treatment site, embolization of the stent, thrombosis of the vessel during the procedure, atheroembolization during the procedure, dissection of the renal artery or aorta, renal artery rupture, renal artery pseudoaneurysm formation, allergic reaction to the stent, or spasm of the renal artery. These are listed in Table format below with seriousness and likelihood. To minimize these risks we will exclude those who would be placed at unnecessary risk (allergic to stainless steel or have untreated abdominal aortic aneurysms >5.0 cm During study conduct, the CCC will maintain a 24/7 hotline with interventionalists, and be available for questions.

Risk of Medical Therapy

In addition, there may be risks associated with medical therapy. Specifically, as discussed above, use of RAAS blocking agents, including ARBs, can cause acute renal failure. Importantly, this is thought to be hemodynamically-mediated and is generally reversible with cessation of the medication. We will require the sites to measure all adverse events related to the use of these agents (acute renal failure, hyperkalemia, syncope, allergic reaction, cough, symptomatic hypotension, angioedema, sexual dysfunction other adverse reaction). Specific populations of patients, including those with bilateral renal artery stenosis or renal stenosis in a solitary functioning kidney, will be monitored centrally for excessive rates of medication related side effects. If the rates of medication side effects exceed acceptable boundaries (as described in the various medications' package inserts), the study protocol will be modified to protect study patient safety.

In addition the associated risks with Caduet (Amlodopine/Atorvastatin) are as follows:

Amlodopine is a long-acting calcium channel blocker with clinical data suggesting that treatment with amlodopine was well tolerated in more than 11,000 patients at doses up to 10mg daily. Most adverse events reported were of mild to moderate severity. The most common side effects are headache and edema with complaints of dizziness, flushing, palpitations, fatigue, nausea, abdominal pain and somnolence also reported.

Atorvastatin is a synthetic lipid-lowering agent and in controlled clinical trials of 2502 patients, <2% discontinued use of medication due to adverse events. The most frequently reported events thought to be related were constipation, flatulence, dyspepsia and abdominal pain. Other side effects include headache, infection, back pain, diarrhea, asthenia, flu syndrome, sinusitis, pharyngitis, rash, arthralgia and myalgia.

Rare cases of rhabdomyolysis with acute renal failure secondary to myoglobinuria have been reported with the atorvastatin component of Caduet and with other drugs in the HMG-CoA reductase inhibitor class.

The risks of adverse events during the follow-up phase include those directly related to an untreated renal artery stenosis (stenosis progression, renal occlusion, loss of renal function, or aggravated hypertension) or to a treated renal artery stenosis (atheroembolization, stent thrombosis, restenosis, renal occlusion, or loss of renal function). Additional risks include those

of adverse cardiovascular events attributable to hypertension or renal dysfunction, including stroke, myocardial infarction, heart failure, and death. Fundamentally, the rationale for the current study is to identify the treatment strategy (medical therapy or stenting with medical therapy) that results in the fewest serious adverse events.

Risks of Renal Intervention

The listing below categorizes the potential adverse events associated with the study procedures, and classifies the events into degrees of seriousness depending on whether the event is associated with the invasive procedure alone or with the addition of the implanted stent.

Table 14. Risks of renal intervention.

Potential Adverse Effects	Seriousness	Invasive assessment	Stent
Bleeding	Low-High	< 5%	< 5%
Bleeding from access site	Low-High	< 5%	< 5%
Blood vessel injury	Moderate	< 1%	< 1%
Pseudoaneurysm	Moderate	< 1%	< 5%
Permanent renal failure	High	< 1%	< 5%
Permanent renal insufficiency	High	< 2%	< 10%
Transient Renal Failure	Low	< 5%	< 5%
Renal infarction	High	<0.1%	<0.1%
Need for Surgery	Moderate-High	<0.1%	< 1%
Death	High	<0.1%	<0.1%
Loss of arm or leg	High	<0.1%	<0.1%
Stroke	High	<0.1%	<0.1%
Vessel thrombosis/occlusion	Moderate	<0.1%	< 1%
Allergic reaction	Low-Serious	< 1%	< 1%
Failure to deliver the stent	Moderate	NA	< 1%
Renal artery aneurysm	Moderate	<0.1%	< 1%
Restenosis	Moderate	NA	< 30%
Renal artery perforation or rupture	High	<0.1%	≤ 1%
Renal artery spasm	Low	<0.1%	< 10%
Vessel dissection	Moderate	<0.1%	< 10%
Embolization of stent	Moderate	NA	< 5%
Fever	Low	<0.1%	< 1%
Hypotension	Low	<1%	< 1%
Hypertension	Moderate	< 5%	< 5%
Infection	Moderate	<1%	< 1%
Atheroembolization	High	<1%	< 1%
X-ray exposure	Very low	100%	100%

Other risks, not associated with the investigational stent, in patients with renal artery stenosis and hypertension

In this population the other adverse clinical events seen include angina, unstable angina, myocardial infarction, arrhythmias, congestive heart failure, dizziness, syncope, rupture or

occurrence of aortic aneurysms. As a consequence, the following procedures are often performed in this population: coronary artery bypass surgery, percutaneous coronary intervention, carotid endarterectomy, repair of aortic aneurysms.

Recruitment plans and consent procedures

Patients referred for the management of renal artery stenosis will be screened. Generally, they will have been identified from a population of patients with 1 or more of the following clinical problems: suspected secondary hypertension, uncontrolled hypertension, clinical syndromes of heart failure and or angina with poorly controlled hypertension, or unexplained renal insufficiency. Personnel at the enrolling centers will be asked to remain in close contact with potential sources of patient referral including institutional departments of interventional radiology, hypertension, nephrology, internal medicine, cardiology, vascular surgery, and family practice clinics. Additionally, the coordinators will be asked to review logs of the CT, angiography, magnetic resonance, nuclear medicine, and non-invasive vascular labs for potential study patients. Patients undergoing angiographic evaluation for other indications, found to have renal artery stenosis, will be eligible if they have systolic hypertension or CKD and meet the other entry criteria. The modalities for patient identification may include magnetic resonance angiography, captopril renal scintigraphy, computerized tomography angiography, aortography or ultrasonographic Duplex assessment. Patients that are identified by these methods to have a high probability of renal artery stenosis will be offered participation. Concurrently, the patients' primary, referring and treating physicians will be notified of their intention to participate. Patients signing informed consent will undergo a baseline evaluation. When potential participants with renal artery stenosis are identified that are excluded for a remediable cause, the study personnel will be asked to remain in appropriate contact with the patient to determine whether eligible status can be achieved.

Patients meeting inclusion criteria and having no exclusion criteria for the study will be invited to participate. Complete details of the study will be discussed with these patients. In addition, the patients will be required to read and understand the IRB-approved consent form provided to them. If they are illiterate, the consent form will be read to them by the principal investigator or their designee. This process will occur in a non-coercive environment in fully awake patients. If the patients have recently undergone diagnostic angiography and have received sedatives, appropriate time will be given for the sedation to wear off before consent is obtained. Both verbal and written consent will be obtained. The original consent form will be kept with the study records. Patients will receive a copy of the consent form and a copy will be placed in the patients' medical record. Importantly, no patient will undergo a research-related procedure until informed consent has been obtained.

Protection Against Risks

Protection of study personnel

Enrolling investigators and their coordinators will be exposed to the risks of blood exposure. Additionally the enrolling investigators will be exposed to x-rays. In both circumstances the investigators and their personnel will be required to follow their institutional guidelines for minimizing risk associated with blood and x-ray exposure.

Protection of study patients

To minimize the risk of the invasive assessment and the stent procedure, at study initiation, all investigators will be instructed on appropriate methods and the use of the stent revascularization system. Certification on this system will be utilized to document satisfactory performance within acceptable safety standards. Additionally, all enrolling investigators will be instructed on appropriate patient selection, in an effort to minimize the risk associated with the use of these devices. Appropriate angiographic technique and ALARA principles will be utilized to expose patients to the least amount of contrast dye and radiation while providing high resolution angiograms. Should adverse events occur, either from the interventional procedure or from other causes, the reporting and analysis of these events described in this protocol along with oversight from the DSMB, provide added protection to study patients.

At all study sites (the enrolling centers, core labs, DCC and CCC) the patient material will be maintained in strict confidence. To that end specific guidelines will be followed as they relate to use of patient identifiers, storage of patient information, transmission of data or patient information, disclosure of data, data access and contact with study patients. Sites, core labs and the DCC will be monitored for compliance with these standards by a pre-specified group within the Study Leadership.

Potential benefits to the patients and to mankind.

Benefits to patients

In this trial all patients with renovascular hypertension will receive appropriate pharmacologic therapy for hypertension and other cardiovascular risks. During the course of therapy, they will be cared for by experts in the management of hypertension and renal artery stenosis. In addition, 1/2 will receive renal artery stents. Since this is a study with mandated prospective follow-up conducted by experts in both the medical management and interventional management of renal artery disorders, it is possible that the care they receive will be superior to the care they might receive outside the setting of this trial.

Benefits to mankind

Currently, the most frequently utilized strategies for the renal artery stenosis with hypertension include the placement of endovascular stents or anti-hypertensive medical therapy. Renal artery stenting has demonstrated promise for improving blood pressure control and renal function. However, it also has the potential for serious complications, including death and renal failure. A randomized study comparing stenting with medical therapy will provide us with the necessary information to make important decisions about treatment allocation.

Importance of the knowledge to be gained

As described above, considerable controversy surrounds the appropriate treatment of renal artery stenosis. A clear resolution to this controversy, with the conduct of an appropriately designed and powered clinical trial, is likely to resolve the current controversy as well as generate new hypotheses that may lead to further refinement in treatment. For the participating patients CORAL investigators believe the risks incurred are reasonable since the appropriate allocation of therapy is currently unclear and the study provides the patients with defined treatments and clear-cut standards for follow-up.

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APPENDIX A: List of Abbreviations

ABBREVIATION	DESCRIPTION
2-D	Two-dimensional
3-D	Three-dimensional
AE	Adverse Event
CCC	Clinical Coordinating Center
CEA	Cost Effectiveness Analysis
CEC	Clinical Endpoint Committee
CFR	Code of Federal Regulations
CHF	Congestive Heart Failure
Cr	Creatinine
CR	Clinical Reviewer
CORAL	Cardiovascular Outcomes in Renal Atherosclerotic Lesions
CRF	Case Report Form
CRO	Contract Research Organization
CTA	Computed Tomography Angiography
DCC	Data Coordinating Center
DM	Data Manager
DSA	Digital Subtraction Angiography
DSMB	Data Safety Monitoring Board
ECG	Electrocardiogram
EN	European Nations
EQOL	Economics and Quality of Life
EPD	Embolic Protection Device
ESRD	End Stage Renal Disease
FDA	Food and Drug Administration
FOV	Field of View
GCP	Good Clinical Practice
GFR	Glomerular Filtration Rate
HCRI	Harvard Clinical Research Institute
HHS	Health and Human Services
HRQOL	Health-related quality of life
ICH	International Conference on Harmonization
IDE	Investigational Device Exemption
IRB	Institutional Review Board
IVRS	Interactive Voice Randomization System
JNC-VII	Joint National Committee on prevention, detection, evaluation and treatment of high blood pressure
LDL	Low-Density Lipoprotein
LVH	Left Ventricular Hypertrophy
MedDRA	Medical Dictionary for Regulatory Authorities
MI	Myocardial Infarction
MR	Magnetic Resonance

MRA	Magnetic Resonance Angiography
NCR	No Carbon Required
NDA	New Drug Application
NHLBI	National Heart, Lung and Blood Institute
NIH	National Institutes of Health
PC	Phase Contrast
PCP	Primary Care Physician
PI	Principal Investigator
PM	Project Manager
PMA	Pre-Market Approval
PVC	Premature Ventricular Contraction
QA	Quality Assurance
QALY	Quality Adjusted Life Year
QC	Quality Control
QOL	Quality of Life
RAS	Renal Artery Stenosis
RR	Relative Risk
SAE	Serious Adverse Event
SC	Steering Committee
SO	Safety Officer
SOP	Standard Operating Procedure
SUAE	Serious Unanticipated Adverse Event
TD&D	Trial Design and Development
TIA	Transient Ischemic Attack
ULN	Upper Limit of Normal

APPENDIX B: Definitions

ABRUPT CLOSURE
Occlusion of a vessel during a procedure, either diagnostic or therapeutic.

ACUTE GAIN
Acute gain is defined as the immediate dimensional change in minimal luminal diameter (in mm) that occurs after the final post-dilation as compared to the minimal luminal diameter at baseline and measured by quantitative coronary angiography from the average from 2 orthogonal views.

ACUTE PROCEDURAL FAILURE
Acute procedural failure is defined as any of the following events: 1) failure to achieve <50% diameter stenosis (assessed by the Angiographic Core Lab) using the treatment device, or 2) in-hospital Major Adverse Events (MAE).

ACUTE RENAL FAILURE
Acute renal failure is defined as a transient (less than four weeks), reversible increase in serum creatinine of greater than or equal to 0.5 mg/dl documented by at least 2 separate blood samples.

BLEEDING COMPLICATION
Bleeding complications are defined as blood loss resulting from the percutaneous revascularization procedure requiring transfusion of blood products.

CEREBROVASCULAR ACCIDENT (CVA)
Cerebrovascular accident is defined as sudden onset of vertigo, numbness, weakness, aphasia, or dysarthria due to vascular lesions of the brain such as hemorrhage, embolism, thrombosis, or rupturing aneurysm, that persisted >24 hours.

DE NOVO LESION
A lesion not previously treated.

DEATH
Cardiovascular death is defined as occurring due to any of the following related conditions:

a. Fatal Myocardial Infarction
b. Pump Failure
c. Sudden Death
d. Presumed Sudden Death
e. Presumed Cardiovascular Death
f. Stroke
g. Pulmonary Embolism
h. Procedure-Related
i. Other Cardiovascular
j. Renal Related

DEVICE SUCCESS
Device success, defined as attainment of <50% (by Angiographic Core Lab assessment) residual diameter stenosis of the target lesion in the parent vessel with the study stent, and Angiographic Core Lab confirmation of marker separation into the side-branch or passage of balloon into the side branch post deployment and no impairment of renal flow.

DIABETIC PATIENT
Patients will be considered to have diabetes if they are currently prescribed to take any oral agent or insulin therapy for a diagnosis of diabetes or have a history of a fasting blood glucose >126 mg/dl or a two-hour post-prandial (or oral glucose tolerance test) value > 200 mg/dl.

DISSECTION, NHLBI (National Heart, Lung, and Blood Institute) CLASSIFICATION

Type A	Small radiolucent area within the lumen of the vessel disappearing with the passage of the contrast material.
Type B	Appearance of contrast medium parallel to the lumen of the vessel disappearing within a few cardiac cycles.
Type C	Dissection protruding outside the lumen of the vessel persisting after passage of the contrast material.
Type D	Spiral shaped filling defect with or without delayed run-off of the contrast material in the antegrade flow.
Type E	Persistent luminal filling defect with delayed run-off of the contrast material in the distal lumen.
Type F	Filling defect accompanied by total occlusion.

EMERGENT BYPASS SURGERY
Emergency bypass surgery is defined as renal surgery performed on an urgent or emergent basis for severe vessel dissection or closure, or treatment failure.

IN-LESION MEASUREMENT
In-lesion measurement is defined as the measurements either within the stented segment or within 5 mm proximal or distal to the stent edges.

IN-STENT MEASUREMENT
In-stent measurement is defined as the measurements within the stented segment.

LATE LOSS
Late loss is defined as the difference between the in-stent MLD at follow-up angiography and the post-procedure in-stent MLD.

LESION SUCCESS
Lesion success is defined as attainment of <50 % final residual diameter stenosis of the target lesion using any percutaneous method, i.e., the stent followed by another device (such as an additional non-protocol stent).

MAJOR ADVERSE EVENTS (MAE)
MAE endpoints were defined as the occurrence of any of the following: cardiovascular or renal death, stroke, MI, hospitalization for CHF, progressive renal insufficiency, and permanent renal replacement therapy.

MINIMAL LUMINAL DIAMETER (MLD)
MLD is defined as the mean minimum lumen diameter derived from two orthogonal views (by the quantitative angiography laboratory).

MYOCARDIAL INFARCTION
Myocardial infarction is defined as positive cardiac markers and either ECG changes or suggestive clinical presentation.

PRIOR RESTENOSIS LESIONS
Defined as a lesion in a vessel segment that had undergone a prior percutaneous treatment.

PROCEDURE SUCCESS
Procedure success is defined as attainment of <50% (by Angiographic Core Lab assessment) final residual diameter stenosis of the target lesion in the parent vessel using the study stent and no occurrence of in-hospital MAE.

PROTECTION, COMPLETE
Sufficient distance is available beyond the treatment site to accommodate the embolic protection device prior to any branch vessels.

PROTECTION, PARTIAL
There is a side branch that is proximal to the intended position of a deployed embolic protection device. However, a portion of the kidney can be "protected" safely.

PROTECTION, NO
No intended or actual use of an embolic protection device.

RESTENOSIS
Restenosis is defined as ≥50% in-stent diameter stenosis at the follow-up angiogram. If an in-stent measurement is not available, the in-lesion diameter is used.

RVD (Reference Vessel Diameter)
Defined as the average of normal segments within 10 mm proximal and distal to the target lesion from 2 orthogonal views (when available) using the Angiographic Core Lab assessment.

SERIOUS ADVERSE EVENT
Defined as any undesirable clinical event that resulted in death, injury or invasive interventions, including MAE (defined above), stent thrombosis, bleeding complications, or vascular complications.

STENT THROMBOSIS
Defined as angiographic thrombus or subacute closure within the treated vessel involving the previously stented segment at the time of the clinically driven angiographic restudy.

TARGET LESION REVASCULARIZATION (TLR)
TLR is defined as any repeat percutaneous intervention of the target lesion or surgery of the target vessel.

TARGET VESSEL FAILURE (TVF)
TVF is defined as the need for repeat revascularization of the target vessel.

TARGET VESSEL REVASCULARIZATION (TVR)
TVR is defined as any repeat percutaneous intervention of the target vessel or surgery of the target vessel.

VASCULAR COMPLICATION
Vascular complication is defined as the occurrence of any of the following resulting from the index procedure:
Hematoma at access site >6 cm
False aneurysm of femoral artery
AV fistula
Retroperitoneal bleed
Peripheral ischemia/nerve injury
Need for vascular surgical repair