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Although the treatment of atherosclerotic renal artery stenosis with percutaneous angioplasty, stenting, and surgical revascularization has gained widespread use, few prospective randomized controlled trials (RCTs) exist that compare these techniques with each other or against the standard of medical management alone. To facilitate this process and help answer many important questions about the appropriate application of renal revascularization, well-designed and rigorously conducted trials are needed. These trials must have clearly defined goals and must be sufficiently sized and performed so as to withstand intensive outcomes assessment. Toward this end, the present statement provides guidelines and definitions for the design, conduct, evaluation, and reporting of renal artery revascularization RCTs. In addition, areas of critically needed renal artery revascularization investigation are identified. It is hoped that this information will be valuable to the investigator who wishes to conduct research in this important area.

I. Overview

The use of revascularization techniques for the management of renal artery stenosis in patients with hypertension, renal insufficiency, pulmonary edema, and unstable angina has become increasingly prevalent. Renal artery stent placement, in particular, has gained increasing acceptance on the basis of historical results of renal angioplasty and the attractiveness of percutaneous compared with surgical revascularization. Despite extensive clinical experience over the past 10 years and the publication of multiple articles describing renal revascularization with renal artery stents, renal angioplasty, and surgical renal revascularization, few prospective RCTs have been reported. These few existing reports have used differing reporting criteria and study methodology, and they have failed to clarify the clinical appropriateness of different methods of renal artery revascularization.

The objective of the present statement is to outline the necessary elements and definitions essential for the uniform reporting of multicenter clinical trials that evaluate renal artery revascularization techniques.

II. General Considerations

A. Study Design

As with any procedure that has potential widespread use in human patients, methods of renal artery revascularization must undergo rigorous health technology assessment based on outcome analysis. The American Heart Association (AHA) recognizes that such assessments must be conducted in a reasonable period of time and yet obtain sufficient data to support clinical decision-making and regulatory approval. Renal artery stenting, in particular, represents a new revascularization technique that has undergone tremendous procedural growth, which justifies a critical reanalysis of indications and outcomes. Because it is likely that funding and clinical research opportunities for the evaluation of renal revascularization will be limited, it is important that any study protocol be well designed and rigorously conducted. These conditions are best achieved in prospective RCTs that directly compare outcomes between different treatment cohorts. Finally, it is imperative that trials be conducted by investigators who have demonstrated experience in the performance of renal revascularization and the conduct of RCTs; the level of...
experience necessary for participation in a RCT may be determined by the trial sponsor and should be clearly stated.

Before designing and implementing any renal artery revascularization trial, a clear study hypothesis and objective are required. Study objectives can be broadly categorized into three groups: (1) specific criteria defined to evaluate clinical outcomes after revascularization; (2) specific criteria defined to evaluate anatomic outcomes (eg, restenosis, target vessel occlusion); and (3) specific criteria defined to evaluate the mechanical performance of a particular stent, bypass material, or other revascularization device. To assure the most reliable collection and interpretation of data, outcome determinations should be prospective and integrated into the design of the RCT.

B. The Issue of Renal Artery Stenting

Of all existing revascularization techniques, renal artery stent placement is perhaps the most widely applied and poorly tested. For example, it is still unknown if percutaneous renal artery angioplasty or stent placement is superior to medical therapy or surgical revascularization in reducing cardiovascular mortality, providing prolonged improvements in blood pressure control, or preserving renal size and function. The AHA has identified the following clinical questions relevant to renal artery stenting as those warranting further investigation: (1) prospective comparison of clinical disease progression and anatomic progression of renal artery stenosis in symptomatic patients treated with percutaneous renal revascularization (percutaneous transluminal renal angioplasty [PTRA]/stents), medical therapy (control of medical risk factors), and/or surgical revascularization; (2) prospective comparison of prophylactic stenting (or surgical revascularization) versus observation or medical therapy alone in asymptomatic patients to evaluate the progression to clinically evident disease; and (3) prospective comparison of outcomes in patients who receive renal artery stents and different postprocedural anticoagulation regimens or other therapies to prevent restenosis.

Each of these study questions may serve as a template for investigators or industry to develop a study protocol and initiate further clinical evaluation via a product development protocol or other regulatory pathway. As described above, the type (causes) of RAS that will be included in a renal revascularization RCT must be described. Furthermore, treated lesions must be categorized angiographically as ostial, nonostial, or branch stenoses. For this purpose, ostial lesions are defined as those in which the leading edge of the stenosis is within 5 mm of the opacified aortic lumen. Nonostial stenoses are contained entirely within the main renal artery with the leading edge of the lesion beginning >5 mm from the aorta. Branch stenoses are lesions in which any component of the stenosis extends into the divisional or segmental arterial branches.

No established consensus exists about the degree of renal arterial narrowing that justifies an attempt at revascularization. However, lesions causing <50% angiographic diameter stenosis are generally not considered to be hemodynamically important, and it is therefore recommended that a ≥50% diameter stenosis be considered the minimum threshold for patient inclusion in a renal revascularization RCT. Because the criteria for duplex ultrasound evaluation of the renal arteries categorizes vessels as ≥60% diameter stenosis, this threshold may be used rather than 50% diameter stenosis if confirmed by angiography. In patients with renal artery stenosis ≥50% but ≤80%, the RCT should establish clear criteria for the presence of a hemodynamically significant stenosis. Although not validated with regard to clinical outcome after revascularization, a translesional pressure gradient of ≥20 mm Hg peak systolic or 10 mm Hg mean has been used in prior reports.

In specific situations, most notably in cases in which downstream (intrarenal) resistance is altered, lesser degrees of stenosis in the main renal artery may produce clinically evident disease. For such studies, the rationale for including patients with lesser degrees of stenosis must be explained with regard to the study hypothesis, and the absolute values of RAS for study eligibility must be defined.

B. Study Population

The study design and population must be established before patient accrual. In general, patient enrollment criteria should be chosen that accurately reflect the population affected by renovascular disease so that results of the study can be translated to clinical practice. Inclusion and exclusion criteria must be clearly stated. This prevents the inappropriate enrollment and treatment of patients who do not fulfill study criteria, and it allows for an accurate analysis of well-defined and discrete end points. Both the anatomic and clinical parameters necessary for study inclusion should be clearly defined. To avoid selection bias, the size of the total population referred for study enrollment, as well as the percentage of patients evaluated but not enrolled, should be reported.

III. Reporting Standards

To allow accurate evaluation of outcomes and comparisons across study groups and between different trials, uniform reporting standards are necessary. Reporting standards should be consistent with prior published documents and should include definitions for describing all quantifiable outcomes of the study procedure. The following study definitions are recommended.

A. Renal Artery Stenosis

Renal artery stenosis (RAS) is defined as narrowing of the lumen of the renal artery. The most common causes of RAS are atherosclerosis and fibromuscular dysplasia. Rarer causes include vasculitis, neurofibromatosis, congenital bands, pheochromocytoma, extrinsic compression, emboli, aortic dissection, and radiation. As described above, the type (causes) of RAS that will be included in a renal revascularization RCT must be described. Furthermore, treated lesions must be categorized angiographically as ostial, nonostial, or branch stenoses. For this purpose, ostial lesions are defined as those in which the leading edge of the stenosis is within 5 mm of the opacified aortic lumen. Nonostial stenoses are contained entirely within the main renal artery with the leading edge of the lesion beginning >5 mm from the aorta. Branch stenoses are lesions in which any component of the stenosis extends into the divisional or segmental arterial branches.

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(1) Clinical Criteria for Revascularization

Although treatment criteria are determined by the study hypothesis and are therefore protocol specific, several clinical criteria for revascularization in the presence of a significant RAS are well established. These include:

• Hypertension: accelerated hypertension (sudden worsening of previously controlled hypertension); refractory hypertension (hypertension resistant to treatment with at
least 3 medications of different classes, including a diuretic; malignant hypertension (hypertension with coexistent evidence of end-organ damage, including left ventricular hypertrophy, congestive heart failure, visual or neurological disturbance, and/or advanced [grade IV] retinopathy); hypertension with a unilateral small kidney; or hypertension with intolerance to medication.

- **Renal salvage:** sudden unexplained worsening of renal function; impairment of renal function secondary to antihypertensive treatment, particularly with an angiotensin-converting enzyme inhibitor or angiotensin II receptor blocker; or renal dysfunction not attributable to another cause.

- **Cardiac disturbance syndromes:** recurrent “flash” pulmonary edema out of proportion to any impairment of left ventricular function, or unstable angina in the setting of significant RAS.

The value of prophylactic renal revascularization in patients without clinical manifestations of disease (ie, hypertension, renal insufficiency, cardiac disturbance) is unproved. However, a study comparing revascularization to observation with the purpose of evaluating progression to clinically evident disease in asymptomatic patients would warrant the use of prophylactic revascularization as part of a RCT. For such a trial, the study hypothesis, inclusion criteria, outcomes, study duration, and potential risks must be clearly defined.

(2) Exclusion Criteria

For a particular RCT, patient exclusion criteria are similarly determined by the investigational design and study hypothesis. However, RCTs that incorporate the use of catheter angiography with iodinated contrast should exclude patients who have a history of severe idiosyncratic contrast reaction, including laryngeal edema, convulsions, profound hypotension, unresponsiveness, cardiopulmonary arrest, and clinically manifest arrhythmias. If not designated within the study design, patients with severe renal dysfunction (ie, glomerular filtration rate [GFR] < 30 ml/min) should also be evaluated cautiously for trial participation, particularly if concomitant evidence of severe renal atrophy (ie, renal length of < 7 cm) or extensive nephrosclerosis of the target kidney is present.

(3) Patient Characteristics

Other patient factors such as age and comorbid medical conditions may affect the clinical outcome after revascularization, and risk stratification may be determined by the demographics of the treated population. The minimum information that should be recorded includes patient age and sex; cardiovascular risk factors, including diabetes mellitus, significant comorbid cardiovascular conditions, or relevant history of cardiovascular events; current medications, medication changes, and medication compliance during the course of the study; and any history of prior renal dysfunction.

C. Methodology

Standardized techniques and procedures for obtaining study data must be used to allow reliable and reproducible data collection and valid comparisons between RCTs. These techniques will need to be reevaluated as new methods are described and validated.

(1) Imaging-Procedural Methods

Images should be recorded with the use of static or digital (filmless) media. For sonographic evaluation, real-time data should also be recorded on videotape. Core laboratory review and image analysis strengthens the objectivity of reporting and is recommended whenever feasible.

(a) Noninvasive Evaluation of RAS

- **Renal duplex criteria.** Such criteria need to be established by the investigator as part of the study design. The use of validated techniques and reporting standards is recommended whenever possible. Renal duplex sonography (RDS) methods and reporting standards that deviate from these validated techniques should be described in detail. Resistive indices may be predictive of outcomes and should be obtained. Examples of established RDS velocimetric criteria for a > 60% RAS, using a Doppler angle of 60 degrees, include direct criteria (peak systolic renal artery velocity, > 3.5; renal artery to aortic peak systolic velocity ratio) and indirect criteria (tardus parvus pulse, rise time > 0.07 seconds, difference in resistive index > 0.15 between kidneys or evaluated segmental arteries, loss of early systolic peak reflective wave complex).

- **Magnetic resonance angiography (MRA).** Myriad techniques for performing MRA exist. Preliminary data suggest that gadolinium-enhanced three-dimensional volume-acquisition techniques provide better diagnostic accuracy when correlated with arteriography. Details of the pulse sequences, slice thickness, reconstruction algorithm, and other critical parameters used need to be included. Stenosis determination is made by measuring the ratio between the diameter of the narrowest segment of the imaged renal artery and the diameter of a normal (reference) segment of the artery proximal to the stenosis or distal to poststenotic dilation. In cases of poststenotic signal loss due to turbulent dephasing of spins, binary grading of RAS as present or absent may be appropriate.

- **Computed tomographic angiography (CTA).** Similar to MRA, numerous acquisition sequences have been described for CTA. Reporting must include but should not be limited to the following: equipment used, slice thickness, table-step, pitch, amount and type of radiation contrast, contrast injection rates, and imaging delay. Source as well as reconstructed images should be recorded. RAS is measured with the same technique described for MRA.

- **Radionuclide renal scanning.** Scanning may be performed with the use of different radiopharmaceuticals to define total global function, effective renal plasma flow, glomerular filtration, or tubular secretion. Thus, the type, dose, and rationale for each radiopharmaceutical used must be explained in the study protocol. Additional minimum information that should be reported includes the timing and technique of scanning, a description of patient preparation and adjunctive medications, and the method of analysis.
used. New techniques need appropriate validation by a previously described reference standard. Images should be recorded on emulsion film or other fixed static or digital media for core laboratory review.

(b) Angiographic Evaluation of RAS
Catheter angiography remains the “gold standard” for the evaluation of RAS. Adequate lesion assessment requires selection of the appropriate imaging obliquity to avoid inadvertent false-negative interpretations in patients with focal orificial lesions and to prevent arterial foreshortening resulting in an underestimation of stenosis length.110–111 Craniocaudal angulation is occasionally necessary, particularly for the evaluation of branch renal artery lesions or stenosis occurring in transplant renal arteries.112 An initial flush aortogram is usually sufficient to demonstrate both main renal arteries and may avoid the risk of unnecessary selective catheterization in patients with widely patent arteries. In addition, the presence of an abdominal aortic aneurysm or marked aortic atherosclerosis may be delineated and should be documented. Nonionic low-osmolar contrast material is recommended and may be associated with a lower incidence of radiocontrast-induced nephropathy. In RCTs that include patients with prior contrast reactions or renal insufficiency, alternative contrast agents including CO₂ gas and gadolinium-containing contrast agents (ie, MRA contrast material) may be considered.113,114 The technique used and contrast doses should be reported. In addition, for all patients, appropriate measures to reduce the risk of contrast-induced nephrotoxicity should be considered, including the use of adequate preprocedural hydration. Any specific measures or medications used to prevent nephrotoxicity should be recorded.115,116 This is especially important in patients with elevated baseline serum creatinine levels. Patients with moderate renal insufficiency should be cautiously evaluated, and appropriate measures should be taken to avoid exacerbating renal dysfunction. Patients with severe renal insufficiency (eg, GFR <10 to 20 mL/min) should not receive iodine-containing radiocontrast unless absolutely necessary for evaluation or revascularization in the context of the study being conducted—eg, the use of iodinated contrast to evaluate revascularization in patients with advancing renal insufficiency. In patients at risk for contrast nephropathy, the serum creatinine should be measured immediately after intervention so that any necessary clinical care can be instituted.

To allow calibration and measurements, at least one image should be obtained with the use of an appropriate reference standard, such as a catheter containing radio-opaque markers, and it is strongly recommended that the source-image distance, source-object distance, and imaging obliquity used for this image be recorded on the procedure record for reference during subsequent angiograms. Should it be necessary to change these parameters, additional calibration images should be obtained. Multicenter studies should use a core laboratory to verify these measurements.

• Measurement of RAS. Stenosis determination is made by measuring the ratio between the diameter of the narrowest segment of the imaged renal artery and the diameter of a normal (reference) segment of the artery proximal to the stenosis or distal to poststenotic dilation. Reported results should include percent stenosis, the minimal luminal diameter (MLD) of the target segment before and after treatment, and the MLD of the reference segment. Descriptive evaluations such as percent luminal change, early lumen gain, and late lumen loss should be used only if corresponding absolute luminal measurements are also provided.

• Hemodynamic (manometric) measurements. A calibrated electronic measuring device should be used, and zeroing should be performed before pressure measurements by opening the pressure tubing to room air. The height of the pressure transducer in relation to the patient must remain constant at the level of the kidney throughout the procedure. When multiple transducers are used for simultaneous pressure measurements, these should all be maintained at the same height. Pressure measurements should be internally consistent and reproducible. The technique for obtaining hemodynamic pressures must be described. Acceptable techniques include simultaneous or sequential measurements from a coaxially placed catheter or pressure-sensing wire positioned in the renal artery (distal to the stenosis or treated site) and a guiding catheter or sheath positioned in the aorta; simultaneous or sequential measurements from a selective renal artery catheter or pressure-sensing wire and a separate aortic pigtail catheter (inserted from a different access site); and simultaneous measurements with a double-sensor catheter.117

Pullback pressures with a single transducer are less reliable because of the significant beat-to-beat variability of intravascular pressures and therefore should be avoided. Measurements of augmented pressure gradients after the intra-arterial administration of a vasodilator may be used (with the technique, vasodilator agent, and dose described), although this has not proved beneficial in the evaluation of RAS and may in fact represent a potential area of study. The hemodynamic parameters for intervention should be clearly defined.

To avoid damping the guide/sheath pressure when the coaxial technique is used, the guide/sheath should be ≥1 French size (inner diameter) larger than the catheter.118,119 Selective renal artery catheters should be as small as possible (ideally <5 French) and have ≥1 sidehole to prevent pressure damping against the vessel wall. Absolute values for the systolic, diastolic, and mean pressures in the aorta and renal artery should be documented.

(2) Reporting of Revascularization Technique

(a) Percutaneous Transluminal Renal Angioplasty and Stenting
Numerous technical approaches for performing transluminal renal angioplasty and stent placement have been reported.9,15,16,18,120 Procedural details need to be described, particularly with regard to techniques that may deviate from previously published methodology. Complications that are directly related to specific procedural aspects need to be noted (eg, guiding catheter injury) to allow accurate comparisons between techniques. To permit optimal patient treat-
ment, trials that have a study arm in which balloon angioplasty alone is used (without a primary intent to stent) should include a crossover arm that allows stent placement after failed angioplasty ("provisional stenting"), with the criteria for angioplasty failure strictly defined. The following minimum technical information should be provided:

- **Overview of PTRA and stenting technique used.** Procedural details unique to the study design should be elaborated on in depth.
- **Case-specific alterations in the described technique that may affect outcome (ie, protocol deviations).**
- **Balloon sizing.** If intentional overdilation or underdilation is performed, this should be noted.
- **Stenting technique:** primary (without prior PTRA), provisional, after predilation, etc.
- **Size and type(s) of stent(s) used.** If used, stent postdilation should be noted.
- **Total procedure time and fluoroscopy time.** If possible, contrast type and volume.
- **Dosimetry should be obtained and the patient skin-entry dose recorded.**
- **Contrast type and volume.**

**Technical Definitions for Renal Artery Stenting.** The indications for renal artery stent placement are an extension of established principles for PTRA.121 For a particular RCT, the indications for stent placement should be clearly defined. Examples of currently used definitions and indications for renal artery stenting include122:

- **Angioplasty failure:** stent placement for technically failed angioplasty due to elastic recoil or flow-limiting dissection resulting in >30% residual luminal narrowing, complete or nearly complete absence of antegrade renal artery flow, or significant residual translesional gradient (as defined in the study protocol). In the presence of an angiographically visible dissection at the treatment site, the residual lumen is measured from the widest opacified lumen regardless of cracks or other irregularity, recognizing that the true lumen is difficult to measure accurately in this situation.74
- **Restenosis:** stent placement for recurrent stenosis (>50% diameter luminal narrowing) or recurrent translesional gradient after initially successful PTRA, with recurrent clinical symptomatology.
- **Provisional stenting:** stent placement performed for one of the above-described criteria. This has also been called "selective stenting."
- **Primary stenting:** stent placement without an initial attempt at balloon dilation (also referred to as "direct stenting"123) or after intentionally undersized predilation solely for the purpose of facilitating stent positioning.11,14,19

It is recognized that specific investigations may use other indications for stent placement that are not included in these definitions. In such instances, the exact indications used in the RCT must be fully defined, explained, and supported in the study design.

**(b) Surgical Revascularization**

Renovascular hypertension can be treated surgically via a variety of techniques. Reconstructive techniques include renal artery bypass, endarterectomy, and renal reimplantation. In patients who have severe hypertension and nonreconstructable renal arteries or small dysfunctional kidneys, nephrectomy is an alternative. When bypass is used, the donor artery (eg, infrarenal aorta/ hepatic artery), type and diameter of conduit (eg, vein, polytetrafluoroethylene), and the type of distal anastomosis (eg, end to side, end to end) should be clearly identified. Endarterectomy can be performed through a transverse incision with a patch or a longitudinal aortotomy or can be performed as part of a larger endarterectomy of the renal and visceral vessels. Standard techniques for each of these procedures have been described in the literature.51,69,124–131 Precise description of the technique is essential because risk and outcome can vary tremendously with each approach. For example, extra-anatomic (hepato-, spleno-, or ilio-renal) bypass is a less invasive approach to renal reconstruction that avoids the need for aortic cross-clamp. The performance of an additional procedure in association with renal artery revascularization should be noted. For example, the addition of aortic reconstruction (aneurysm repair or aortobifemoral bypass) to renal artery bypass increases morbidity and mortality rates. It should be noted whether the procedure is primary or reoperative, following a prior failed bypass and/or stent. Outcomes of the various techniques and combinations should be differentiated. Any operative technique that varies greatly from these methods should be described in detail. Additional technical information that should be provided for operative renal revascularization includes type of incision (eg, midline, subcostal, flank), surgical approach (eg, retro or transperitoneal), renal ischemic times, the use of complete or incomplete aortic occlusion, the use of and type of renal perfusate, total operative time, and blood loss. All perioperative complications (within 30 days) should be recorded.

**(c) Reporting of Complex Procedures**

Occasionally, during percutaneous or surgical revascularization, procedural variations occur that increase procedure time or complexity but have no adverse clinical consequence. Examples include proximal stent malpositioning, distal device malpositioning requiring additional stent implantation, posttreatment dissection requiring additional stent placement or extension of a surgical bypass, initial stent nondeployment requiring retrieval with subsequent successful stent placement during the same procedure, intraoperative revision of a surgical anastomosis, or a need for unanticipated additional surgical procedures. Because it is possible that these procedural variations may affect vessel patency or have delayed clinical sequelae, the details of any procedural complexities should be captured and recorded.

**(3) Clinical Determinations**

 Determination of clinical variables with discrete quantifiable values must be performed with standardized techniques to assure that reported results are not biased by procedural methods and to allow comparison between different studies. For renal revascularization, the most common quantifiable clinical measurements will be blood pressure and renal
function. The following methods of determination are recommended for RCTs.

(a) Measurement of Blood Pressure
Hypertension is defined and evaluated according to the guidelines outlined in the most recently published report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC). It is recognized that JNC is a global report for the evaluation of hypertension in a generalized population, and the applicability of these standards to patients with renovascular disease remains undefined. By these standards, hypertension is defined as systolic blood pressure ≥140, diastolic blood pressure ≥90, or the use of antihypertensive medication. Blood pressure should be measured with certified, calibrated, and validated equipment. The size of the bladder within the blood pressure cuff must encircle at least 80% of the arm. The methodology used must be defined in detail in the study protocol. Although alternative methodology may be appropriate for different RCTs, the following techniques for blood pressure determination have been proposed by the AHA and represent the current “gold standard”:

- Patients should be seated in a chair with their backs supported and their arms bared and supported at heart level. Patients should refrain from smoking or caffeine ingestion for 30 minutes before blood pressure measurement, and measurement should begin after at least 5 minutes of rest.
- If necessary, blood pressure may be measured in the supine position. However, the patient should then be in the same position for subsequent measurements.
- Both systolic and diastolic blood pressure should be recorded, with the first appearance of sound used to define systolic blood pressure and the disappearance of sound used to define diastolic blood pressure.
- Two or more readings separated by 2 minutes should be averaged. If the first 2 readings differ by >5 mm Hg, additional readings should be obtained and averaged.
- Blood pressure should be measured in both arms, and the higher value obtained should be used. For consistency, the site of blood pressure measurement should be recorded, and follow-up pressures should be maintained from the same arm. In patients with bilateral upper-extremity arterial stenoses that result in spuriously low arm pressures, a thigh cuff should be used. The appropriately sized blood pressure cuff must again be used, and the site used must be well documented for future examinations.

(b) Evaluation of Antihypertensive Medications
At the time of each blood pressure determination, the exact antihypertensive medications and doses being taken must be recorded. However, differences in the numbers and/or types of medications used to manage hypertension between two treatment groups or two points in time may be subjective. Furthermore, the clinical importance of such a difference is not intuitive and might not impact patient outcomes or clinical practice. To avoid confounding subsequent analyses of hypertension benefit, methodology must be incorporated into the design of the RCT to control for the differing effects of the multiple currently available classes and formulations of antihypertensive medications. One method for this is the use of daily defined doses of antihypertensive medications, as described by the World Health Organization International Society of Hypertension guidelines. An alternative method is the development of a standardized or recommended drug regimen for study subjects, with contingencies for patients who have either improvements or deterioration in blood pressure control during the course of the RCT. Such methodology has been previously described. More than one medication algorithm can be established to accommodate comorbid conditions, although it is then necessary that patients be randomized in roughly equal numbers between the two treatment groups (ie, using block randomization). The exact antihypertensive protocol must be systematically described, and any subject deviations from the protocol must be documented.

(c) Evaluation of Renal Function
For purposes of RCTs, the GFR is the most reliable measure of functional renal impairment. Although serum levels of creatinine alone and cystatin C are inadequately crude surrogates for GFR, these should be obtained on a defined periodic schedule and may serve as a trigger for formal GFR measurements. Formal GFR testing should be performed on all test subjects with validated and reproducible methodology. One reliable technique for GFR testing in patients with renovascular hypertension is the calculation of the plasma disappearance of a marker substance such as iohexol or iothalamate with the use of chromatography or electrophoresis. Alternatively, although less accurately, GFR can be estimated by including serum creatinine with other demographic measurements in a prediction equation. Although the use of a prediction equation for calculating GFR avoids the cost, inconvenience, variability, and risks inherent in other, more complex measurement techniques, these equations are valid only if renal function is in a steady state, which can be defined by a constant serum creatinine in a given time interval, eg, 24 hours. The following two equations represent formulae that have sufficiently proven reproducibility in generalized populations to be used for RCTs but have not been validated in patients with renovascular hypertension. The exact technique or equation used for GFR testing should be reported in the study design:

(1) Cockcroft-Gault
\[
\text{GFR (mL/min) = } \frac{[140 – \text{age in years}] \\
\times [\text{weight in kilograms}] \times [0.85 \text{ in females}]}{[\text{serum creatinine, mg/dL (72)}]} \times [0.762 \text{ if female}] \times (71.80 \text{ if black}) \\
\times \frac{[\text{serum urea nitrogen, mg/dL (0.7017}]^{0.170}}{[\text{albumin, g/dL}]}^{0.318}
\]

(2) Modification of Diet in Renal Disease (MDRD) Study Prediction Equation
\[
\text{GFR (mL/min/m²) = } 170 \times [\text{plasma creatinine, mg/dL}]^{0.999} \times [\text{age in years}]^{0.167} \times [0.762 \text{ if female}] \\
\times [1.180 \text{ if black}] \times [\text{serum urea nitrogen, mg/dL}]^{0.170} \times [\text{albumin, g/dL}]^{0.318}
\]
D. Outcomes Reporting

(1) Anatomic Success

(a) Percutaneous Revascularization

Anatomic success refers to successful revascularization of the target renal artery with resolution of target vessel obstruction and without residual flow limitation or compromise of distal perfusion. For percutaneous techniques, completion angiography (after PTRA or stenting) provides the best means for determining anatomic success. For stent placement, this is often evaluated after postdeployment intrastent balloon dilatation is performed to maximize stent expansion.

For purposes of RCTs, anatomic success is defined as a <30% residual stenosis after PTRA or stenting. Residual stenosis after treatment is calculated as the ratio of the residual target vessel lumen diameter to the diameter of the reference segment of artery. After angioplasty alone, this residual target vessel lumen is measured from the narrowest opacified lumen but including the outer margin of opacified intimal cracks or other irregularity. After stenting, there is scaffolding of the multiple tissue planes often seen after PTRA alone, with a resulting smoother angiographic lumen. Consequently, the residual target vessel lumen should be measured at the site of minimal remaining luminal diameter, whether within or adjacent to the stent.

In addition, anatomic success for stent placement requires positioning of the nonconstrained (expanded, implanted) stent within the target lesion. The lesion must be entirely covered by the stent. Usually, this requires coverage of at least 1 to 2 mm of the artery adjacent to the target lesion. Thus, for ostial lesions, the final stent position should be flush with or projecting <2 mm into the aorta. However, if the target lesion is adequately covered, excessive stent deployment in the aorta should be considered a procedural complexity and not anatomic failure.

(b) Surgical Revascularization

Some form of intraoperative assessment of the completeness of surgical revascularization should be performed. The adequacy of distal perfusion after surgical bypass or endarterectomy is usually determined by visual inspection or manual palpation of the renal artery distal to the target lesion. The use of intraoperative duplex sonography is strongly encouraged. The probe can be placed directly on the artery in question, allowing B-mode imaging in conjunction with assessment of velocities. These techniques allow defects as small as 1 mm in size to be identified.

(2) Hemodynamic Success

Hemodynamic success should be assessed after PTRA or stent placement. In particular, the degree of remaining stenosis after PTRA may be difficult to assess because of residual luminal irregularity caused by small angioplasty-induced dissections. Translesional pressure measurements should be obtained with the methods previously described. Both peak systolic and mean pressures may be used, although the value used needs to be specified in the trial design. Hemodynamic success is defined as a lowering of the translesional gradient to below the threshold established for intervention. Gradients both before and after treatment should be recorded. Hemodynamic success after surgical bypass is determined by assessing the target renal artery pulse. Intraoperative Doppler ultrasound or direct pressure measurements may also be used and should be described.

(3) Clinical Success

In order for a renal vascular intervention to be clinically successful, there must be a beneficial impact on a patient’s quality or duration of life or objective improvement or resolution of the clinical indicator for which treatment was initiated. For patients who had more than one clinical indicator, the effect of treatment on each condition should be reported individually.

(a) Clinical Events

The cardiovascular mortality rate of patients with renovascular hypertension is worse than that of patients with essential hypertension. The contribution of hypertension to this increased risk is unknown; it is possible that the risk is attributable to the presence of systemic atherosclerotic disease, and concomitant coronary artery and cerebrovascular disease, rather than to the presence of hypertension. Patients with renal artery hypertension also have elevated levels of vasoactive hormones including angiotensin, F2-isoprostaneoids, prostaglandin I2, natriuretic peptides, transforming growth factor-β, and endothelin, all of which are implicated in hypertension, renal injury, and possible cardiac injury, as well. Elevated cardiovascular mortality rates may be further attributable to the higher incidence of end-stage renal disease in patients with renovascular disease.

Determinations of the hypertension or renal functional benefit after renal revascularization represent, at best, a surrogate marker of cardiovascular events. Thus, clinical events should be considered the “gold standard” for examining the effect of renal artery interventions. Examples of clinical events that may be evaluated include overall patient mortality rate, cardiovascular mortality rate, and nonfatal cardiovascular events. These latter events include acute myocardial infarction, unstable angina, congestive heart failure, flash pulmonary edema, and stroke. Clinical events may also be combined with renal function evaluation or hypertension assessment as a composite clinical outcome, eg, dialysis-free survival.

Investigators should clearly describe all reference events that will be used as study end points, and the event-free survival at predefined interval(s) should be reported. For composite clinical end points, the rates of both the composite end point and the individual component events should be described and stratified.

(b) Hypertension

The impact of revascularization on hypertension should be described according to a modification of the 1987 Renal Working Group guidelines. As discussed earlier, methodology must be incorporated into the trial to account for variations in antihypertensive regimens over time or between study groups. Cure, improvement, failure, and benefit can only be defined when measured at least 120 days after treatment randomization.
- **Cure**: diastolic blood pressure < 90 mm Hg and systolic blood pressure < 140 mm Hg off antihypertensive medications.
- **Improvement**: diastolic blood pressure < 90 mm Hg and/or systolic blood pressure < 140 mm Hg on the same or reduced number of medications (or reduced number of defined daily doses as described by the World Health Organization\(^{134}\)) or a reduction in diastolic blood pressure by at least 15 mm Hg on the same or reduced number of medications.
- **Failure**: no change or inability to meet above criteria for cure or improvement.
- **Benefit**: cure or improvement.

(c) Renal Function

There have been varied definitions in the literature of renal functional benefit after renal artery stent placement, with most reports relying on an absolute value of the change in serum creatinine ("binary or dichotomous outcome") as the parameter for success. In this model, the absolute value of GFR after treatment is used to construct thresholds, which define discrete reporting of outcomes, ie, "failure" or "benefit." However, although such absolute binary determinations may be used in assessing renal function, it is important to recognize that the impact of intervention may be manifested not only by a change in the absolute value of GFR but also as stabilization or slowed decline in previously diminishing GFR.\(^{153–157}\) In other words, the trend in renal function over time may provide an equally valid and valuable assessment of treatment effect as the absolute measure of renal function at discrete time points after intervention. Hence, renal function benefit may be evaluated by both absolute binary methods and breakpoint analysis\(^{154,156,157}\) to evaluate the slope of renal functional decline before and after intervention. Because measurements of serum creatinine obtained immediately after revascularization may be transiently affected by the effects of radiocontrast or periprocedural hydration, early assessments of functional outcome should be performed with creatinine values obtained ≥ 1 week after intervention.

When the breakpoint analysis method is used in a RCT, sufficient sequential determinations of GFR both before and after intervention are necessary to avoid statistical bias. Patients should have available data for > 5 GFR determinations over a > 3-month period before treatment randomization. Follow-up data with sequential GFR determinations should be obtained at defined periodic intervals beginning ≥ 1 week after treatment (randomization), with a sufficient number of values recorded over an observation period of at least 3 months to obtain a valid quantification of treatment effect.\(^{154,157}\) Additional determinations of GFR (or serum creatinine) may be performed at more frequent intervals in patients with deteriorating renal function evident on scheduled evaluations. Long-term follow-up and reporting of late-term data are recommended whenever possible.

For studies that evaluate only the absolute value in the change in serum creatinine or GFR, it is recommended that ≥ 2 measurements be obtained both before and after intervention to reduce the variation inherent in a single measurement. If these values are similar to within 10%, their average value should be used; in contrast, any greater discrepancy in these GFR values should be rectified by additional GFR measurements until ≥ 2 consistent values are obtained.

For breakpoint analysis, the model shown in the Figure is recommended. The following definitions of functional benefit are recommended and are based on a threshold effect size (E\(_{th}\)) determined by the investigator:

- **Improvement**: increase in the absolute value of the estimated GFR after treatment by ≥ (E\(_{th}\))% compared with pretreatment values, or a ≥ (E\(_{th}\))% positive change in the slope of the GFR after treatment.
- **Stabilization**: absolute value of the estimated GFR within ± (E\(_{th}\))% of pretreatment values, or a positive change (improved renal function) in the slope of GFR < (E\(_{th}\))% after treatment. This is applicable only if α\(_1\) < 0.
- **Failure**: deterioration in estimated GFR after treatment by ≥ (E\(_{th}\))%, or a zero value or negative change in the slope of the GFR after treatment (α\(_1\) ≥ α\(_2\)).
- **Benefit**: improvement or stabilization.

(4) Patency and Restenosis

**Patency** is defined broadly as continued flow through the treated vessel or surgical bypass and may be determined by invasive or noninvasive imaging, direct intraoperative observation, or postmortem examination. Although evaluation with conventional contrast angiography is optimal, both duplex ultrasound and MRA have been used for the assessment of patency. Previously described definitions for patency should be used\(^{24}\):

- **Primary patency**: uninterrupted patency with no procedures performed on or at the margins of the treated segment or bypass.
- **Assisted primary patency**: any procedure performed in the treated segment or bypass before thrombosis that might prevent eventual failure. This includes patency after procedures performed for restenosis (> 50% luminal narrowing).
- **Secondary patency**: any procedure that restores patency after occlusion.
The number and types of reinterventions performed to achieve assisted primary patency and secondary patency should be documented. Furthermore, the durability of repeat interventions should be assessed by recording the time interval between treatments. Any significant trends observed during the assisted or secondary patency interval should also be noted (eg, reduced durability with each subsequent intervention).

Restenosis is defined as progressive narrowing of the treated vessel lumen or surgical bypass after intervention. After revascularization, mild degrees of restenosis are usual and do not require reintervention.\(^5\)\(^,\)\(^18\) As noted above, a \(\geq 50\%\) angiographic diameter recurrent narrowing should be considered the threshold for maintained anatomic success. However, as noted earlier, renal duplex ultrasound categorizes patients as having stenoses \(>60\%\) or \(<60\%\) rather than \(50\%\). This \(60\%\) threshold may therefore be used as the standard for restenosis in patients followed by noninvasive ultrasound criteria. Furthermore, because recurrent arterial stenosis after revascularization may occur without accompanying clinical sequelae, investigators may elect to define restenosis with clinical parameters. The rationale and details of this approach must then be explained in depth within the protocol.

Consistent angiographic methods for determining restenosis are necessary to the proper interpretation of anatomic results. For RCTs, it is recommended that restenosis be measured as the ratio of the MLD at the time of the assessment to the reference vessel diameter or the diameter of the implanted stent or bypass graft (REF): \(\%\) restenosis = \(\text{MLD} \div \text{REF} \times 100\).

A binary description of anatomic success is included in the definition of assisted primary patency. In addition, continuous measures of restenosis should also be reported, including the average and range of restenosis at follow-up.

E. Complications

To allow comparison between study groups within a trial and between RCTs, complications need to be listed individually (number and description) as well as within a general classification schema (Appendixes 1 and 2). All complications occurring within 30 days or during the same hospitalization as the revascularization procedure should be reported.\(^74\) Specific individual complications and their class should be recorded according to previously published definitions.\(^74\)\(^,\)\(^158\) In addition, complications should be classified according to their severity and clinical impact. In particular, the incidence of transient renal insufficiency, such as may occur as a result of contrast-induced nephrotoxicity, should be reported. The following severity classification is recommended (modified from reference 143).

(1) Major Clinical Adverse Events

Major clinical adverse events (MaCE) are events resulting in an additional procedure, unplanned treatment, prolonged hospitalization, transfusion, or death (eg, arterial thrombosis treated with thrombolytic therapy, renal failure, femoral pseudoaneurysm or hematoma requiring surgical exploration or other directed therapy, retroperitoneal bleeding). Death occurring within 30 days of the renal stent procedure or during the same hospitalization as the procedure should be recorded as a procedure-related mortality.

(2) Minor Clinical Adverse Events

Minor clinical adverse events (MiCE) are events that cause some morbidity or patient discomfort but do not fulfill criteria for a MaCE (eg, nonsurgical femoral hematoma or ecchymoses, neuroplegia of the superficial femoral cutaneous nerve, small drop in hematocrit not requiring transfusion or prolonged hospitalization, transient rise in serum creatinine \(<20\%\) from baseline).

F. Statistics and Data Analysis

Statistical methodology must be clearly reported. Sample size is based on expected differences in outcomes between treatment groups. The statistical power of the RCT needs to be defined, and the study should be sufficiently powered to allow clinical applicability of the results. Because crossovers between treatment arms confound statistical evaluation of results, the study design should be carefully planned so that crossovers are avoided as much as possible. One method of preventing treatment crossovers is by careful selection of study end points (ie, clinical events) such that crossovers occur only after an end point has been reached. To allow an accurate evaluation of this delayed revascularization strategy, patients who change treatment because of achievement of an end point should be serially followed up for comparison with the primary treatment cohort.

In rare instances, the exact number of patients enrolled may be based on a sequential method in which the final number of subjects is determined by periodic interim analysis of the data throughout the entire clinical trial, until either (1) statistical analysis shows no difference in the study arms, or (2) differences between the treatment groups unequivocally exceed statistical significance.

Appropriate statistical methods for assessing outcome are exceedingly important. Many statistical tests can be applied to reporting these data provided that they represent accepted analytic methods. Two specific means of assessing data, however, deserve note. Long-term results of revascularization or natural history data are best presented by use of life-table analysis.\(^74\) A life-table defines the cumulative outcome or success of an intervention versus time of follow-up. The actuarial method or the Kaplan-Meier (product-limit method) is usually used. The latter is preferable under most circumstances because it provides results independent of the choice of the time of intervals studied. The standard error of each estimate should be calculated, and standard errors \(>10\%\) should be clearly indicated. To test for a statistically significant difference between two outcome curves, the generalized Wilcoxon (Breslow) test or the log-rank (Mantel-Cox) test should be used.

IV. Conclusions

As the indications and materials for renal revascularization continue to evolve, adherence to rigorous, well-defined study
objectives and methodology must be maintained. Uniform reporting definitions remain the best method for allowing accurate comparisons of studies that use differing revascularization technologies or techniques. The AHA recommends the methods and definitions included within this document as important general elements that should be included in describing the results of a RCT. The development of new and validated revascularization strategies may in the future mandate revision of the present reporting standards.

Appendix 1
Percutaneous Procedure Complications Master List

<table>
<thead>
<tr>
<th>Complication</th>
<th>Class</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abscess</td>
<td>General nonvascular</td>
</tr>
<tr>
<td>Infectious/inflammatory</td>
<td>General nonvascular</td>
</tr>
<tr>
<td>Angina/coronary ischemia</td>
<td>Cardiac</td>
</tr>
<tr>
<td>Idiosyncratic reaction</td>
<td>Medication related</td>
</tr>
<tr>
<td>Allergic/anaphylactic reaction</td>
<td>Contrast related</td>
</tr>
<tr>
<td>Arterial occlusion/thrombosis, puncture site</td>
<td>Vascular</td>
</tr>
<tr>
<td>Arterial occlusion/thrombosis, remote from puncture site</td>
<td>Vascular</td>
</tr>
<tr>
<td>Arteriovenous fistula</td>
<td>Vascular</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>Cardiac</td>
</tr>
<tr>
<td>Contamination of pleural cavity (urine, bile, malignancy, empyema, other)</td>
<td>Respiratory/pulmonary</td>
</tr>
<tr>
<td>Device malfunction with adverse effect</td>
<td>Device related</td>
</tr>
<tr>
<td>Death related to procedure</td>
<td>Death</td>
</tr>
<tr>
<td>Death unrelated to procedure (30-day mortality)</td>
<td>Death</td>
</tr>
<tr>
<td>Embolization, arterial</td>
<td>Vascular</td>
</tr>
<tr>
<td>Fluid/electrolyte imbalance</td>
<td>General nonvascular</td>
</tr>
<tr>
<td>Hematoma bleed, remote site</td>
<td>Vascular</td>
</tr>
<tr>
<td>Hematoma bleed at needle, device path: nonvascular procedure</td>
<td>Vascular</td>
</tr>
<tr>
<td>Hematoma bleed, puncture site: vascular procedure</td>
<td>Vascular</td>
</tr>
<tr>
<td>Incorrect drug</td>
<td>Medication related</td>
</tr>
<tr>
<td>Incorrect dosage</td>
<td>Medication related</td>
</tr>
<tr>
<td>Intimal injury/dissection</td>
<td>Vascular</td>
</tr>
<tr>
<td>Ischemia/infarction of tissue/organ</td>
<td>Vascular</td>
</tr>
<tr>
<td>Incorrect site of administration</td>
<td>Medication related</td>
</tr>
<tr>
<td>Local infection</td>
<td>Infectious/inflammatory</td>
</tr>
<tr>
<td>Liver failure</td>
<td>General nonvascular</td>
</tr>
<tr>
<td>Migration</td>
<td>Device related</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>Cardiac</td>
</tr>
<tr>
<td>Malposition</td>
<td>Device related</td>
</tr>
<tr>
<td>Nausea/vomiting</td>
<td>General nonvascular</td>
</tr>
<tr>
<td>Other (cardiac)</td>
<td>Cardiac</td>
</tr>
<tr>
<td>Other (contrast related)</td>
<td>Contrast related</td>
</tr>
<tr>
<td>Other (CNS complication)</td>
<td>Neurological</td>
</tr>
<tr>
<td>Other dose-dependent complication</td>
<td>Contrast related</td>
</tr>
<tr>
<td>Other (device related)</td>
<td>Device related</td>
</tr>
<tr>
<td>Other (gastrointestinal)</td>
<td>General nonvascular</td>
</tr>
<tr>
<td>Other (general nonvascular)</td>
<td>General nonvascular</td>
</tr>
</tbody>
</table>

Appendix 2
Surgical Complications Master List

Systemic/Remote
- Cardiac
- Stroke
- Venous
- Pulmonary
- Renal
- Metabolic

Local/Vascular
- Healing complications
- Graft complications
- Hemorrhage
- Thrombotic
- Embolic
- Renal
- Gastrointestinal

Adapted from reference 74.
Local/Nonvascular

- Wound
- Lymphatic
- Venous
- Ureteral
- Spinal cord

Appendix 3

Members of the Society of Interventional Radiology FDA Device Forum Committee

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References


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Guidelines for the Reporting of Renal Artery Revascularization in Clinical Trials
John H. Rundback, David Sacks, K. Craig Kent, Christopher Cooper, Daniel Jones, Timothy Murphy, Kenneth Rosenfield, Christopher White, Michael Bettmann, Stanley Cortell, Jules Puschett, Dan Clair and Patricia Cole
for the AHA Councils on Cardiovascular Radiology, High Blood Pressure Research, Kidney in Cardiovascular Disease, Cardio-Thoracic and Vascular Surgery, and Clinical Cardiology, and the Society of Interventional Radiology FDA Device Forum Committee

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