

Guidelines for the Reporting of Renal Artery Revascularization in Clinical Trials

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Although the treatment of atherosclerotic renal artery stenosis with use of percutaneous angioplasty, stent placement, and surgical revascularization has gained widespread use, there exist few prospective randomized controlled trials (RCTs) comparing these techniques to each other or against the standard of medical management alone. To facilitate this process as well as help answer many important questions regarding 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, this document provides guidelines and definitions for the design, conduct, evaluation, and reporting of renal artery revascularization RCTs. In addition, areas of critically necessary renal artery revascularization investigation are identified. It is hoped that this information will be valuable to the investigator wishing to conduct research in this important area.

J Vasc Interv Radiol 2003; 14:S477-S492

Abbreviations: GFR = glomerular filtration rate, PTR = percutaneous transluminal renal angioplasty, RAS = renal artery stenosis, RCT = randomized controlled trial

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 based on historic results of renal angioplasty (1-3) and the attractiveness of percutaneous compared to surgical revascularization (4). Despite extensive clinical experience during the past 10 years and the publication of multiple papers describing renal revascularization with use of renal artery stents (5-23), renal angioplasty (24-51), and surgical renal revascularization (52-70), few prospective randomized controlled trials (RCTs) have been reported (4,71-75). These few existing reports have used differing reporting criteria and study methodology and have failed to clarify the clinical appropriateness of different methods of renal artery revascularization (72-75).

The objective of this article 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

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 (76). The American Heart Association (AHA) recognizes that such assessments must be conducted in a reasonable period of time, and yet sufficient data to support clinical decision-making and regulatory approval must be obtained. Renal artery stent placement in particular represents a new revascularization technique that has undergone tremendous procedural growth, justifying 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 directly

This article first appeared in J Vasc Interv Radiol 2002; 13:959-974.

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This article also appears in the September 17, 2002 issue of *Circulation*.

None of the authors has identified a conflict of interest.

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DOI: 10.1097/01.RVI.0000094621.61428.d5

comparing outcomes between different treatment cohorts. Finally, it is imperative that trials be conducted with 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 is required. Study objectives can be broadly categorized into three groups: (i) specific criteria defined to evaluate clinical outcomes after revascularization; (ii) specific criteria defined to evaluate anatomic outcomes (eg, restenosis, target vessel occlusion); (iii) 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.

The Issue of Renal Artery Placement

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 issues relevant to renal artery stent placement 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 stent placement (or surgical revascularization) versus observation or medical

therapy alone in asymptomatic patients to evaluate the progression to clinically evident disease.

3. Prospective comparison of outcomes in patients receiving renal artery stents and different postprocedure 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 (77).

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 earlier published documents (78,79) 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 (80). Rarer etiologies include vasculitis, neurofibromatosis, congenital bands, pheochromocytoma, extrinsic compression, emboli, aortic dissection, and radiation (81).

Lesion description.—As stated earlier, 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 (23). Nonostial stenoses are contained entirely within the main renal artery with the leading edge of the lesion beginning more than 5 mm from the aorta. Branch stenoses are lesions in which any component of the stenosis extends into the divisional or segmental arterial branches.

There is no established consensus regarding the degree of renal arterial narrowing that justifies an attempt at revascularization. However, lesions causing stenosis of less than 50% angiographic diameter are generally not considered to be hemodynamically important (82), and it is therefore recommended that a $\geq 50\%$ -diameter stenosis be considered the minimum threshold for patient inclusion in a renal revascularization RCT (83,84). Because the criteria for duplex ultrasound (US) evaluation of the renal arteries uses a vessel categorization of $>60\%$ diameter stenosis (85,86), this threshold may be used rather than 50% diameter stenosis if confirmed by angiography. In patients with renal artery stenosis $\geq 50\%$ but $\leq 80\%$, 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 earlier reports (8,18,20).

In specific situations, most notably in cases in which downstream (intra-renal) resistance is altered, lesser degrees of stenosis in the main renal artery may possibly produce clinically evident disease (87). For such studies, the rationale for including patients with lesser degrees of stenosis must be explained with respect 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 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 not fulfilling study criteria as well as allowing for an accurate analysis of well-defined and discrete endpoints. 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 and the percentage of patients evaluated but not enrolled should be reported.

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:

1. Hypertension (88–91): 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 neurologic disturbance, and/or advanced [grade IV] retinopathy), hypertension with a unilateral small kidney, and hypertension with intolerance to medication.
2. Renal salvage: sudden unexplained worsening of renal function (92); impairment of renal function secondary to antihypertensive treatment, particularly with an angiotensin-converting enzyme inhibitor or angiotensin II receptor blocker (93,94); renal dysfunction not attributable to another cause.
3. Cardiac disturbance syndromes: recurrent “flash” pulmonary edema out of proportion to any impairment of left ventricular function (95–97); 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 unproven. However, a study comparing revascularization to observation or medical therapy with the purpose of evaluating progression to clinically evident disease in asymptomatic patients would warrant the use of prophylactic revascularization as part of an RCT. For such a trial, the study hypothesis, inclusion criteria, outcomes, study duration, and potential risks must be clearly defined.

Exclusion criteria.—For a particular RCT, patient exclusion criteria are similarly determined by the investigational design and study hypothesis. However, for RCTs that incorporate the use of catheter angiography with use of iodinated contrast material, patients should be excluded in whom there is a history of severe idiosyncratic contrast material reaction, including laryngeal edema, convulsions, profound hypotension, unresponsiveness, cardiopulmonary arrest, and clinically manifest arrhythmias (98). 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 there is concomitant evidence of severe renal atrophy (ie, renal length <7 cm) or extensive nephrosclerosis of the target kidney.

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. Minimal 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 compliance during the course of the study, and any history of 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 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.

• Noninvasive evaluation of RAS

- 1) Renal duplex 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 (85,86,99–101). RDS methods and reporting standards deviating from these validated techniques should be described in detail. Resistive indexes may be predictive of outcomes and should be obtained (99,102). Examples of established RDS velocimetric criteria for a >60% RAS with use of a Doppler angle of $\leq 60^\circ$ include:
 - 2) Direct criteria: >180 cm/sec peak systolic renal artery velocity, >3.5:1 renal artery-to-aortic peak systolic velocity ratio; indirect criteria: tardus et parvus pulse, rise time >.07 seconds, difference in resistive index >.15 between kidneys or evaluated segmental arteries, loss of early systolic peak reflective wave complex.
 - 3) Magnetic resonance (MR) angiography: there exist myriad techniques for performing MR angiography (103–106). 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 caused by turbulent dephasing of spins, binary grading of RAS as present or absent may be appropriate.
 - 4) Computed tomographic (CT) angiography: similar to MR angiography, numerous acquisition sequences have been described for CT angiography

(107–110). Reporting must include, but not be limited to, the following: equipment used, slice thickness, table-step, pitch, amount and type of radiocontrast material, contrast injection rates, and imaging delay.

Source and reconstructed images should be recorded. RAS is measured with use of the same technique described for MR angiography.

- 5) Radionuclide renal scanning: scanning may be performed with use of different radiopharmaceuticals to define total global function, effective renal plasma flow, glomerular filtration, or tubular secretion (111–113). 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 with use of a previously described reference standard. Images should be recorded on emulsion film or other fixed static or digital media for core laboratory review.

• 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 (114–115). Craniocaudal angulation is occasionally necessary, particularly for the evaluation of branch renal artery lesions or stenoses occurring in transplant renal arteries (116). 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 including patients with previous contrast reactions or renal insufficiency, alternative contrast agents including CO₂ gas and gadolinium-containing contrast agents (ie, MR angiographic contrast material) may be considered (117,118). The technique used and contrast material 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 (119,120). This is especially important in patients with elevated baseline serum creatinine levels. Levels in 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 <10–20 mL/min) should not receive iodine-containing radiocontrast material unless absolutely necessary for evaluation or revascularization in the context of the study being conducted; ie, use of iodinated contrast material to evaluate revascularization in patients with advancing renal insufficiency. In patients at risk for contrast nephropathy, the serum creatinine level 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 acquired with use of an appropriate reference standard such as a catheter containing radiopaque markers, and it is strongly recommended that the source-image and source-object distances and imaging obliquity used for this image be recorded on the procedure record for reference during subsequent angiographic procedures. 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.

- 1) 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.

- 2) 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).
- Simultaneous measurements with use of a double-sensor catheter (121).

Pullback pressures obtained with a single transducer are less reliable because of the significant beat-to-beat

variability of intravascular pressures and should be avoided. Measurements of augmented pressure gradients after the intraarterial administration of a vasodilator may be used (with the technique and vasodilator agent and dose described), although this has not proven 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 using the coaxial technique, the guide/sheath should be at least 1 F (inner diameter) larger than the catheter (122,123). Selective renal artery catheters should be as small as possible (ideally <5 F) and have at least one side hole 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.

• Reporting of revascularization technique

Percutaneous transluminal renal angioplasty and stent placement: numerous technical approaches for performing transluminal renal angioplasty and stent placement have been reported (9,15,16,18,124). 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 treatment, trials containing a study arm of balloon angioplasty alone (without a primary intent to place a stent) should include a crossover arm allowing stent placement after failed angioplasty ("provisional stent placement") according to strictly defined criteria for angioplasty failure. The following minimum technical information should be provided:

- Overview of PTRAs and stent placement 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 over- or underdilation is performed, this should be noted.
- Stent placement technique: primary (without previous PTRAs), 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, dosimetry should be performed and the patient skin-entry dose should be recorded.
- Contrast material type and volume.

Technical definitions for renal artery stent placement: the indications for renal artery stent placement are an extension of established principles for PTRAs (125). For a particular RCT, the indications for stent placement should be clearly defined. Examples of currently used definitions and indications for renal artery stent placement include (126):

1. Angioplasty failure: stent placement for technically failed angioplasty as a result of 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 (78).
2. Restenosis: stent placement for recurrent stenosis (>50% diameter luminal narrowing) or recurrent translesional gradient after initially successful PTRAs, with recurrent clinical symptomatology.
3. Provisional stent placement: stent placement performed for one of the criteria described. This has also been called "selective stent placement."
4. Primary stent placement: stent placement without an initial

attempt at balloon dilation (also referred to as "direct stent placement" [127]), or after intentionally undersized predilation 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 by the RCT must be fully defined, explained, and supported in the study design.

Surgical revascularization: renovascular hypertension can be treated surgically via a variety of techniques. Reconstructive techniques include renal artery bypass, endarterectomy, or 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 (infrarenal aorta, hepatic artery, etc), type and diameter of conduit (vein, polytetrafluoroethylene, etc.), and type of distal anastomosis (end-to-side, end-to-end) should be clearly identified. Endarterectomy can be performed through a transverse incision with use of 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 (55,73,128–135). Precise description of the technique is essential because risk and outcome can vary tremendously with each approach. For example, extraanatomic (hepato-, spleno-, or iliorenal) 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. It should be noted whether the procedure is primary or reoperative after previous failed bypass and/or stent placement. 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 (midline/subcostal/flank), surgical approach (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 d) should be recorded.

Reporting of complex procedures: occasionally, procedural variations occur during percutaneous or surgical revascularization 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.

2. *Clinical determinations.*—Determination of clinical variables with discrete quantifiable values must be performed with use of 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:

• Measurement of blood pressure

Hypertension is defined and evaluated with use of 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) (136). 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 mm Hg, diastolic blood pressure ≥ 90 mm Hg, 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 (137):

- 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 pressures 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 more than 5 mm Hg, additional readings should be obtained and averaged.
- Blood pressure should be measured in both arms, with the higher value obtained being used. For consistency, the site of blood pressure measurement should be recorded and follow-up pressures should be measured from the same arm. In patients with bilateral upper extremity arterial stenoses resulting in spuriously low arm pressures, a thigh pressure measurement may be used if there is no lower extremity arterial stenosis above the cuff. The appropriately sized blood pressure cuff

must again be used, and the site used must be well documented for future examinations.

• 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 (138). An alternative method is the development of a standardized or recommended drug regimen for study subjects, with contingencies for patients who have improvements or deterioration in blood pressure control during the course of the RCT. Such methodology has been previously described (73). 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, with use of block randomization). The exact antihypertensive protocol must be systematically described, and any subject deviations from the protocol must be documented.

• 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 (139), 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 use of 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 iothexol or iohalamate (140–143) with use of chromatography or electrophoresis. Alternatively, although less accurate, GFR can be estimated by including serum creatinine levels with other demographic measurements in a prediction equation (144–146). 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 level in a given time interval, eg, 24 hours. The following two equations represent formulas 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:

Cockcroft-Gault Equation (144):

$$\text{GFR (mL/min)} = [(140 - \text{age [y]}) / (\text{weight [kg]})] \times (0.85 \text{ in females}) / (\text{serum creatinine [mg/dL]}) \times 72$$

MDRD Study Prediction Equation (146):

$$(\text{GFR [mL/min]} / 1.73 \text{ m}^2) = 170 \times (\text{PCR [mg/dL]}^{-0.999}) \times (\text{age [y]}^{-1.76}) \times (0.762 \text{ if female}) \times (1.18 \text{ if black}) \times \text{SUN [mg/dL]}^{-1.70} \times (\text{albumin [g/dL]}^{3.18})$$

D. Outcomes Reporting

1. *Anatomic success.*—**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 PTRAs or stent placement) provides the best means for determining anatomic success. For stent placement, this is often evaluated after postdeployment intrastent balloon dilation is performed

to maximize stent expansion. For purposes of RCTs, anatomic success is defined as a <30% residual stenosis after PTRAs or stent placement. 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 (78). After stent placement, there is scaffolding of the multiple tissue planes often seen after PTRAs 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 1–2 mm of the artery adjacent to the target lesion. Therefore, for ostial lesions, the final stent position should be flush with or projecting <2 mm into the aorta (18,147). However, if the target lesion is adequately covered, excessive stent deployment in the aorta should be considered a procedural complexity and not anatomic failure.

Surgical revascularization: There should be some form of intraoperative assessment of the completeness of surgical revascularization. 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 (133–135). 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 PTRAs or stent placement. In particular, the degree of remaining stenosis after PTRAs may be difficult to assess as a result of residual luminal

irregularity caused by small angioplasty-induced dissections (148–150). Translesional pressure measurements should be obtained with use of 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 before and after treatment should be recorded. Hemodynamic success after surgical bypass is established by assessing the target renal artery pulse. Intraoperative Doppler US 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 initiating treatment. For patients in whom there was more than one clinical indicator, the effect of treatment on each condition should be reported individually.

• Clinical events

The cardiovascular mortality rate in patients with RVH is worse than that in those with essential hypertension (151,152). 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-isoprostanoids, 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 further be caused by the higher incidence of end-stage renal disease occurring in patients with renovascular disease.

Determinations of the hypertension or renal functional benefit after renal revascularization represent, at best, a surrogate marker of cardiovascular

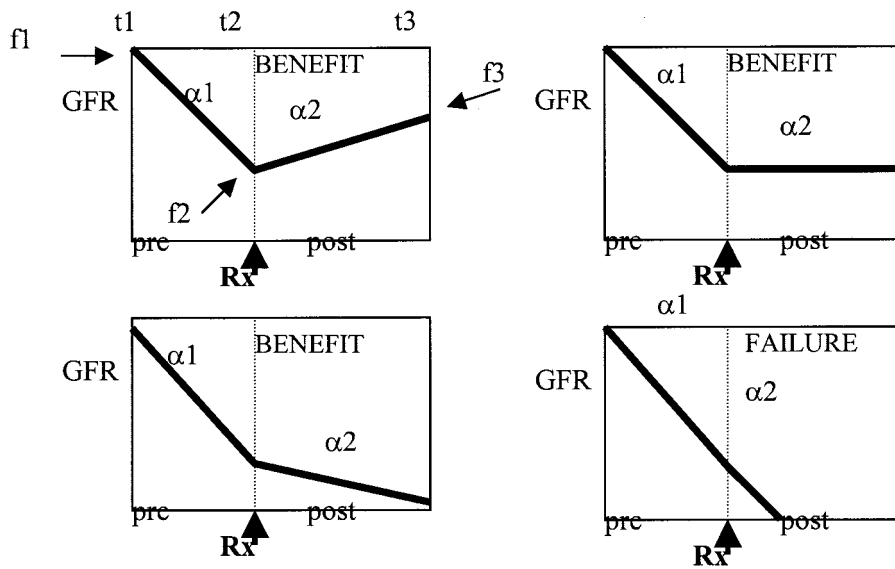


Figure. Breakpoint analysis of renal function after therapy. For breakpoint analysis, the following model is recommended: α_1 = slope of GFR before treatment = $(f_2 - f_1) / (t_2 - t_1)$; α_2 = slope of GFR after intervention = $(f_3 - f_2) / (t_3 - t_2)$; $\Delta\alpha$ = change in slope of GFR after treatment = $\alpha_2 - \alpha_1$; f_1 = value of GFR at a definable time (t_1) before intervention; f_2 = value of GFR at the time of intervention (t_2); f_3 = value of GFR at a definable follow-up time (t_3).

events. Thus, clinical events should be considered the gold standard for examining the effect of renal artery interventions (153). Examples of clinical events that may be evaluated include overall patient mortality, cardiovascular mortality, and nonfatal cardiovascular events. These latter events include acute myocardial infarction, unstable angina, congestive heart failure, flash pulmonary edema, and stroke (154). Clinical events may also be combined with renal function evaluation or hypertension assessment as a composite clinical outcome, ie, dialysis-free survival (155).

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

• Hypertension

The impact of revascularization on hypertension should be described with use of a modification of the 1987 Renal Working Group guidelines (156). As discussed earlier, methodol-

ogy 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 be defined only when measured at least 120 days after treatment randomization.

- Cure—diastolic blood pressure <90 mm Hg and systolic blood pressure <140 mm Hg, off anti-hypertensive 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 [138]) or a reduction in diastolic blood pressure by at least 15 mm Hg with the same or a reduced number of medications.
- Failure—no change or inability to meet these criteria for cure or improvement.
- Benefit—cure or improvement.

• 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 that 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 (157–161). 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 using both absolute “binary” methods and breakpoint analysis (158,160,161) to evaluate the slope of renal functional decline before and after intervention (**Figure**). 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 use of creatinine values obtained at least 1 week after intervention.

When using the breakpoint analysis method in a RCT, sufficient sequential determinations of GFR before and after intervention are necessary to avoid statistical bias. Patients should have available data for more than five GFR determinations over a period of more than 3 months before treatment randomization. Follow-up data with sequential GFR determinations should be obtained at defined periodic intervals beginning at least 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 (158,161). 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 level or GFR, it is recommended that two or more measurements be obtained before and after intervention to reduce the variation inherent in a single measurement. If these values are similar 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 two or more consistent values are obtained.

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 $\geq(E_{TH})\%$ compared to pretreatment values, or a $\geq(E_{TH})\%$ positive change in the slope of the GFR after treatment.
- Stabilization—absolute value of the estimated GFR within $\pm(E_{TH})\%$ of pretreatment values, or a positive change (improved renal function) in the slope of GFR $<(E_{TH})\%$ after treatment. This is applicable only if $\alpha_1 < 0$.
- Failure—deterioration in estimated GFR after treatment by $\geq(E_{TH})\%$, or a zero value or negative change in the slope of the GFR after treatment ($\alpha_1 \geq \alpha_2$).
- 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, and postmortem examination. Although evaluation with conventional contrast angiography is optimal, duplex US and MR angiography have been used for the assessment of patency. Previously described definitions for patency should be used (78):

- 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 (ie, 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 herein, a recurrent narrowing of $\geq 50\%$ angiographic diameter should be considered the threshold for maintained anatomic success. However, as noted earlier, renal duplex US categorizes patients as having stenosis greater than or less than 60% rather than 50%. This 60% threshold may therefore be used as the standard for restenosis in patients, followed by noninvasive US criteria. In addition, because recurrent arterial stenosis after revascularization may occur without accompanying clinical sequelae, investigators may elect to define restenosis with use of 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 minimal luminal diameter (MLD) at the time of the assessment to the reference vessel diameter or the diameter of the implanted stent or bypass graft (REF):

$$\% \text{ restenosis} = (\text{MLD} / \text{REF}) \times 100$$

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) and a general classification schema (Appendixes 1 and 2) should be used in addition. All complications occurring within 30 days or during the same hospitalization as the revascularization procedure should be reported (78). Specific individual complications and their class should be recorded with use of previously published definitions (78,162). 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. An acute persistent deterioration of renal function exceeding the previously described 20% threshold should be considered a complication. The following severity classification is recommended (modified from reference 147):

1. *Major clinical adverse events* ("MaCE").—Major clinical adverse events are those resulting in an additional procedure, unplanned treatment, prolonged hospitalization, transfusion, or death (eg, arterial thrombosis treated with thrombolytic therapy, renal failure, acute persistent postprocedural deterioration of renal function $>20\%$ from baseline, 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* ("MiCE").—Minor clinical adverse events are those that cause some morbidity or patient discomfort but do not fulfill criteria for a major clinical adverse event (eg, nonsurgical femoral hematoma or ecchymoses, neuroplegia of the superficial femoral cutaneous nerve, slight decrease in hematocrit not requiring transfusion or prolonged hospitalization,

transient increase in serum creatinine level <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 endpoints (ie, clinical events) such that crossovers occur only after an endpoint has been reached. To allow an accurate evaluation of this delayed revascularization strategy, patients who change treatment because of achievement of an endpoint should be followed serially for comparison to the primary treatment cohort.

Rarely, the exact number of patients enrolled may be based on a sequential method whereby the final number of subjects is determined by periodic interim analysis of the data throughout the entire clinical trial until either (i) statistical analysis shows there is no difference in the study arms or (ii) differences between the treatment groups unequivocally exceeds 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 (78). 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 independently of the choice of the time of intervals studied.

The SE of each estimate should be calculated, and standard errors >10% should be clearly indicated. To test if there is a statistically significant difference between two outcome curves, the generalized Wilcoxon (Breslow) test or the log-rank (Mantel-Cox) test should be used.

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 involving 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 an RCT. The development of new and validated revascularization strategies may in the future mandate revision of this current reporting standard.

APPENDIX 1

Percutaneous Procedure Complications Master List (from Reference 96)

Complication	Class
Abscess	
Infectious/inflammatory	
Angina/coronary ischemia	Cardiac
Idiosyncratic reaction	Medication-related
Allergic/anaphylactoid reaction	Contrast-related
Arterial occlusion/thrombosis, puncture site	Vascular
Arterial occlusion/thrombosis, remote from puncture site	Vascular
Arteriovenous fistula	Vascular
Congestive heart failure	Cardiac
Contamination of pleural cavity (urine, bile, malignancy, empyema, other)	Respiratory/pulmonary
Device malfunction with adverse effect	Device-related
Death related to procedure	Death
Death unrelated to procedure (30-day mortality)	Death
Embolization, arterial	Vascular
Fluid/electrolyte imbalance	General nonvascular
Hematoma bleed, remote site	Vascular
Hematoma bleed at needle, device path: nonvascular procedure	Vascular
Hematoma bleed, puncture site: vascular procedure	Vascular
Incorrect drug	Medication-related
Incorrect dosage	Medication-related
Intimal injury/dissection	Vascular
Ischemia/infarction of tissue/organ	Vascular
Incorrect site of administration	Medication-related
Local infection	Infectious/inflammatory
Liver failure	General nonvascular
Migration	Device-related
Myocardial infarction	Cardiac
Malposition	Device-related
Nausea/vomiting	General nonvascular
Other (cardiac)	Cardiac
Other (contrast-related)	Contrast-related
Other (central nervous system complication)	Neurologic
Other (dose-dependent complication)	Contrast-related
Other (device related)	Device-related
Other (gastrointestinal)	General nonvascular
Other (general nonvascular)	General nonvascular
Other (hematologic)	General nonvascular
Other (infectious/inflammatory)	Infectious/inflammatory
Other (medication-related)	Medication-related
Other (neurologic)	Neurologic
Other pleural complication	Respiratory/pulmonary
Other (respiratory/pulmonary)	Respiratory/pulmonary
Other (vascular)	Vascular
Pancreatitis	Infectious/inflammatory
Pulmonary embolism	Respiratory/pulmonary
Pulmonary embolism	Vascular
Peritonitis	Infectious/inflammatory
Hypotension	Cardiac
Hypoxia	Respiratory/pulmonary
Pulmonary edema	Respiratory/pulmonary
Peripheral nervous system complication	Neurologic
Pneumothorax	Respiratory/pulmonary
Pseudoaneurysm	Vascular
Respiratory arrest	Respiratory/pulmonary
Renal failure	Contrast-related
Arrhythmia	Cardiac
Septicemia/bacteremia	Infectious/inflammatory
Seizure	Neurologic
Septic shock	Infectious/inflammatory
Stroke	Neurologic
Tissue extravasation	Contrast-related
Transient ischemic attack	Neurologic
Unintended perforation of hollow viscus	General nonvascular
Vascular perforation or rupture	Vascular
Vagal reaction	Cardiac
Vasospasm	Vascular
Venous occlusion/thrombosis, puncture site	Vascular
Venous occlusion/thrombosis, remote from puncture site	Vascular

APPENDIX 2: SURGICAL COMPLICATIONS MASTER LIST

A. Systemic/remote

Cardiac
Stroke
Venous
Pulmonary
Renal
Metabolic

B. Local/vascular

Healing complications
Graft complications
Hemorrhage
Thrombotic
Embolitic
Renal
Gastrointestinal

C. Local/nonvascular

Wound
Lymphatic
Venous
Ureteral
Spinal cord

Acknowledgment: The AHA writing group acknowledges the contributions of the following individuals:

SIR FDA Committee members: Patricia E. Cole, MD, PhD, John F. Cardella, MD, Curtis W. Bakal, MD, Gary J. Becker, MD, FACC, FACR, Antoinette S. Gomes, MD, Louis G. Martin, MD, Donald L. Miller, MD, Anne C. Roberts, MD, David Sacks, MD, John H. Rundback, MD, and Anthony C. Venbrux, MD.

AHA Kidney Council members: Stanley Cortell, MD, MPH, and Jules Puschett, MD.

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AHA Council on Cardiovascular Surgery: K. Craig Kent, MD, and Daniel G. Clair, MD.

AHA Council on Hypertension: Daniel Jones, MD.

AHA Council on Clinical Cardiology: Kenneth Rosenfield, MD, and Christopher White, MD.

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