RENAL ARTERY STENTING – CURRENT STATUS

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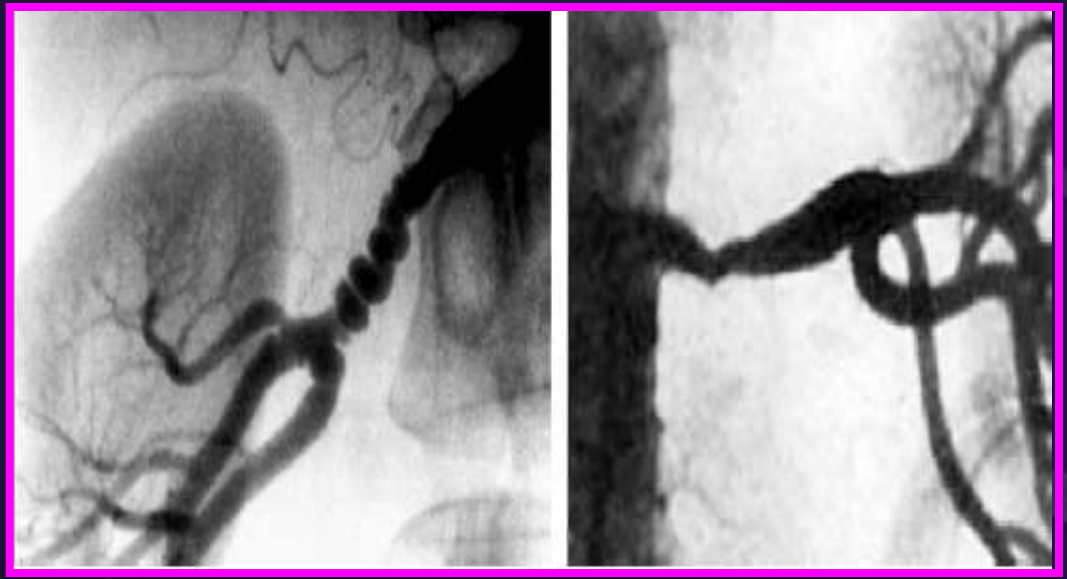

Introduction

- Renal artery stenosis (RAS) is caused by a heterogenous group of diseases with different pathophysiology, clinical manifestations, treatment approaches, and outcomes.
- The 2 most common forms of RAS-
  - Fibromuscular dysplasia (FMD)
  - Atherosclerosis (ARAS)
- Renovascular syndromes are broadly classified into-
  - Renovascular hypertension
  - Ischemic nephropathy

Caveats

- These terms are misleading, because they imply a causal relationship between RAS, hypertension, and renal dysfunction, which is difficult to prove in humans.
- Data supporting renal revascularization are limited by-
  - Heterogeneous causes of hypertension and renal dysfunction
  - Insufficient understanding of the relationship between RAS and nephropathy
  - Inconsistent techniques for ambiguous terminology and end points to assess benefit,
  - Lack of large-scale randomized trials

Epidemiology

Fibromuscular dysplasia

- An uncommon disease
- Of unknown etiology
- Typically occurs in women
- < 30 years of age
- Often affects the renal, carotid & femoral arteries
- Unilateral or bilateral renal FMD might cause renovascular hypertension, but renal failure is unusual

Should be considered in young patients if severe hypertension is not associated with obesity, oral contraceptives, or known renal parenchymal disease.

Atherosclerotic renal artery stenosis

- A common clinical entity
- Affecting 7% of patients older than age 65years
- 60% of patients with hypertension, coronary or peripheral artery disease, and renal insufficiency
- Unlike FMD, ARAS rarely causes renovascular hypertension but is commonly associated with renal dysfunction

Clinical Manifestations

Hypertension and cardiovascular manifestations

- Onset of severe hypertension at age 30 years (FMD) or at age 55 years (ARAS)
- Resistant, accelerated, or malignant hypertension
- The classic manifestation is “flash” pulmonary edema not explained by coronary artery or valvular disease, especially if left ventricular function is normal

- Other cardiovascular manifestations include
  - Severe hypertension associated with ACS
  - Acute aortic syndromes
  - Stroke
  - TIA
  - Intracranial hemorrhage
  - Encephalopathy
  - Papilledema

Renal manifestations

- Presentation can be as acute renal failure, with a rise in serum creatinine within 14 days of initiation of ACE I or ARB
- Although considered a marker for bilateral RAS, this observation is neither sensitive nor specific for RAS
- Other manifestations are-
  - Subtle or insidious, including unexplained chronic renal failure
  - Small kidney, and asymmetry in renal dimensions
- Ischemic nephropathy is an important cause of chronic kidney disease and end-stage renal disease-5% to 15% of patients initiating dialysis each year

Table 1. ACC/AHA Guidelines for Renal Arterial Disease (2)

	Level of Evidence	Class
1. Clinical indications for evaluation for RAS		
Hypertension manifestations		
Hypertension onset age <30 yrs (FMD)	B	I
Hypertension onset age >55 yrs (ARAS)	B	I
Resistant hypertension	C	I
Accelerated hypertension	C	I
Malignant hypertension	C	I
Renal manifestations		
Acute renal failure after ACEI/ARB	B	I
Unexplained small kidney	B	I
Asymmetry in renal dimensions >1.5 cm	B	I
Unexplained chronic renal failure	B	II A
New dialysis	B	II A
Cardiovascular manifestations		
Unexplained pulmonary edema	B	I
Multivessel CAD alone	B	II B
PAD alone	B	II B
Unexplained CHF	C	II B
Refractory angina	C	II B

Assessment of RAS and Its Clinical Significance

Screening for RAS

- There are no guidelines for routine screening for RAS
- In some patients, the diagnosis of RAS is made incidentally during angiographic evaluation of lower extremity arterial diseases, whereas in others a high index of suspicion is required, on the basis of existing guidelines as described

2. Screening tests for RAS		
RDU, MRA, CTA	B	I
Contrast angiography for ambiguous noninvasive tests	B	I
Captopril renal scintigraphy	C	III
Selective renal vein sampling	B	III
Plasma renin activity	B	III
Captopril-stimulated renin secretion	B	III

- The mere presence of angina, congestive heart failure, coronary artery disease, and peripheral artery disease are not strong indications for evaluation of RAS in the absence of other considerations mentioned previously
- Impromptu “drive-by” renal arteriography during unrelated angiographic procedures is not recommended

Establish the diagnosis of RAS

- Invasive angiography is sometimes recommended to confirm the diagnosis of RAS; determine the etiology; identify dual, accessory, or aberrant renal arteries; identify diseases of the abdominal aorta; and evaluate the nephrogram.
- In most cases, abdominal aortography with digital subtraction provides superb images of the abdominal aorta and renal circulation, with a power injector and 10 to 15 cc of contrast

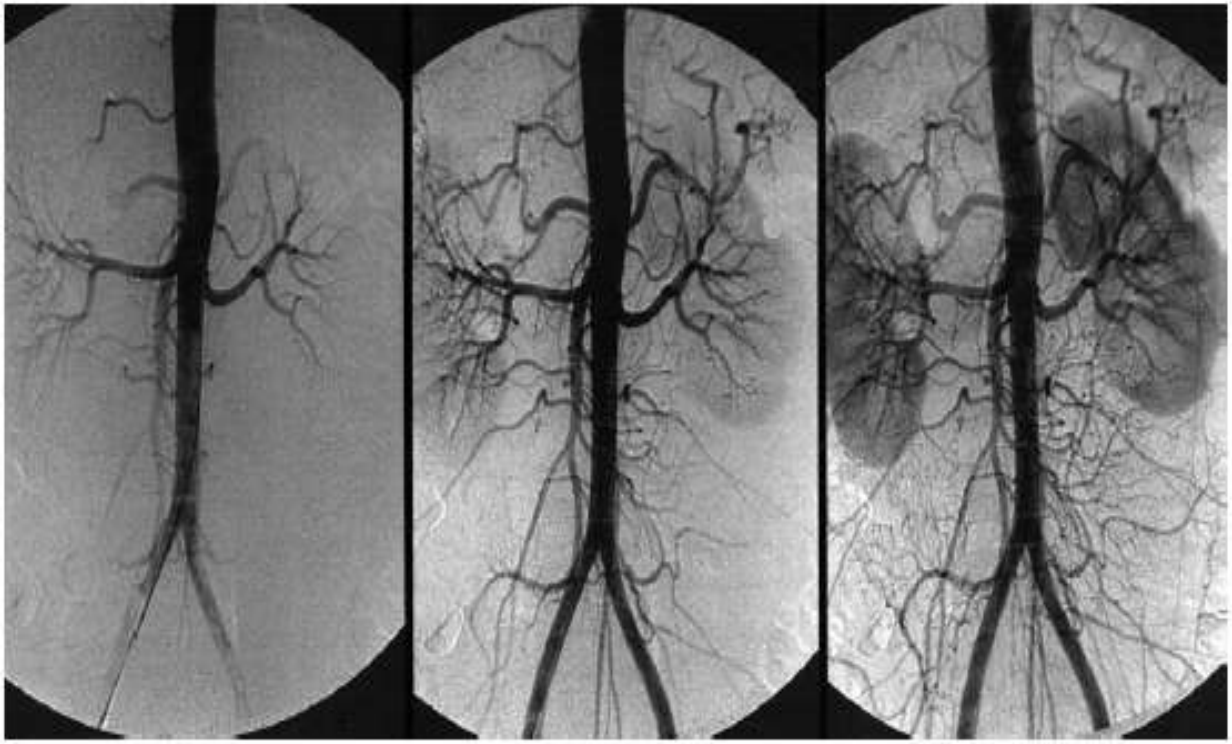

Figure 2. Conventional Abdominal Aortogram With Digital Subtraction Angiography (Anteroposterior Projection)

The early **(left)**, mid **(middle)**, and late **(right)** phases of contrast injection are shown. Aortography is used to identify the configuration of the renal arterial origin (see Fig. 3) as well as associated disease of the abdominal aorta and visceral circulation.

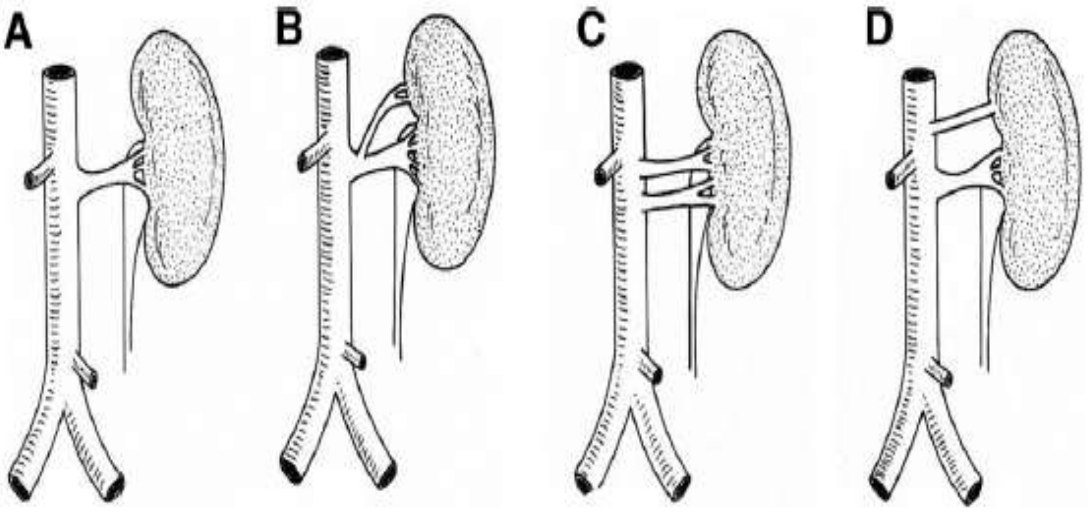

Figure 3. Schematic Representation of Common Configurations of Renal Arterial Origins From the Abdominal Aorta

(A) Single renal artery occurs in 55% of population. **(B)** Single renal artery with early bifurcation occurs in 14% of population. **(C)** Dual arterial circulation in which 2 major renal arteries supply a single kidney occurs in 8% of population. **(D)** Single major renal artery and 1 or more smaller accessory renal arteries occur in 7% of population. Other configurations (not shown) occur in 16%, including aberrant origins of the renal arteries from other visceral vessels, iliac arteries, and aortic bifurcation (modified from Uflacker R. *Atlas of Vascular Anatomy, 2nd edition.* Philadelphia, Pennsylvania: Lippincott, Williams, and Wilkins, 2007:609).

- Because 30% of patients have dual, accessory, or aberrant renal arteries , selective angiography alone might preclude complete assessment of the renal arteries

- Once “anatomic” RAS is recognized, it is important to establish a relationship between RAS and vital organ injury.

Relationship Between RAS and Renal Dysfunction

- When RAS and nonvascular etiologies of renal dysfunction co-exist, it might be difficult to establish RAS as the culprit.
- Patients with nephropathy might not improve after renal artery revascularization, depending on the extent of baseline nephropathy before revascularization and the degree of renal injury after revascularization
- The relationship between renal ischemia and nephropathy is central to understanding published studies and ongoing trials of RAS, and failure to do so is the most important source of ambiguity about the benefits of renal revascularization.

Clinical evaluation of nephropathy

Serum creatinine	Easy to measure and inexpensive. Relatively insensitive to degree of renal dysfunction (see Fig. 6) and not reliable for differentiating nephropathy from renal ischemia.
Proteinuria	Easy to measure and inexpensive. Proteinuria ≥1 g/24 h is t lesser degrees of
Renal dimensions	rable. Renal length ury (atrophic
RRI	ity. Although RRI t should not be ble renal
Renal arteriogram	absence of intra-renal arteriolar disease are indicators of reversible renal dysfunction. Poor cortical blood flow and severe diffuse intrarenal arteriolar disease are markers of advanced nephropathy (see Fig. 5).
Renal biopsy	Reliable for histologic confirmation of nephropathy but not practical for most patients

RRI = renal resistive index.

Advanced nephropathy is characterized by

- Proteinuria >1 g/day
- Renal length < 10 cm
- Resistive index > 0.8

None of these parameters is an absolute predictor of outcome, and over-reliance on any single test might exclude patients who might benefit from revascularization

Problems of serum creatinine

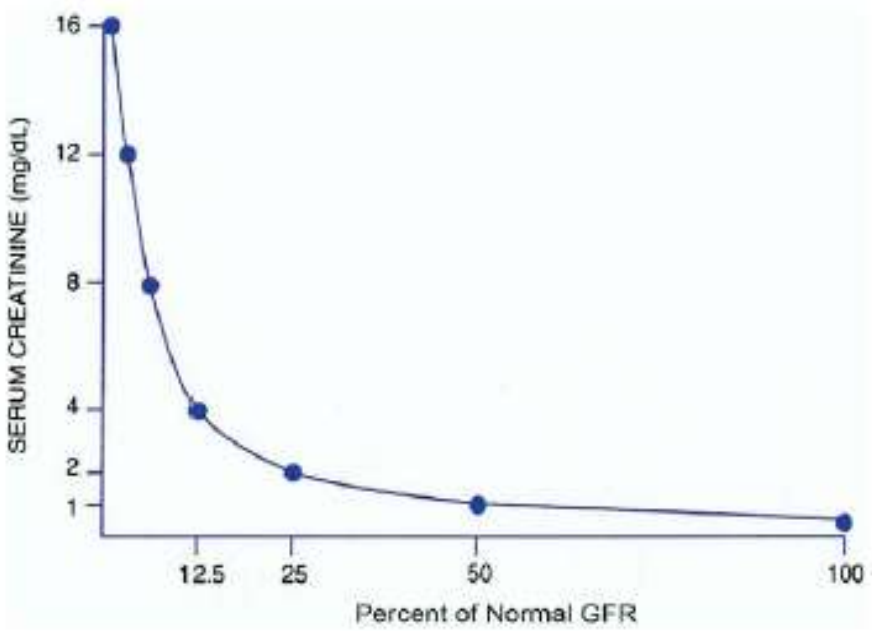

Figure 6. Relationship Between GFR and Serum Creatinine Concentration

Loss of 50% of glomerular filtration rate (GFR) is not associated with measurable elevation of serum creatinine. When >75% of GFR is lost, there is a strong relationship between GFR and serum creatinine (modified from reference [9]).

- Serum creatinine is insensitive to glomerular filtration rate (GFR) until 50% to 75% of renal mass has been lost
- Stated in another way, a patient who loses 50% of renal mass (as might occur after nephrectomy or with unilateral renal artery occlusion) should have a normal creatinine
- Serum creatinine 2 mg/dl in a patient with unilateral ARAS is generally indicative of significant nephropathy

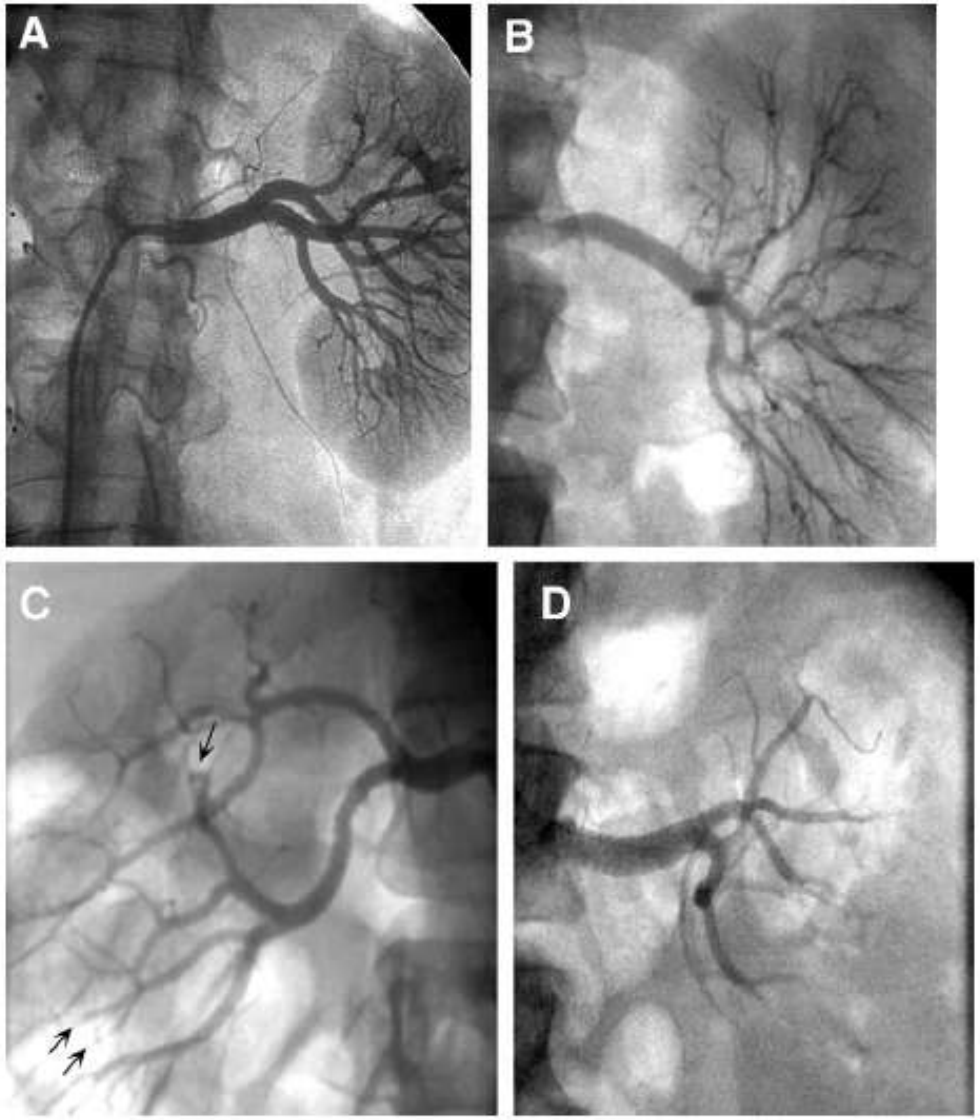

Figure 5. Arteriographic Patterns of Progressive Nephropathy

(A) Normal kidney (renal resistive index [RRI] 0.6) with normal cortical blood flow and intrarenal arteriolar circulation. **(B)** Mild hypertensive nephropathy (RRI 0.7) with mild diffuse intrarenal arteriolar narrowing and preserved cortical flood flow. **(C)** Advanced hypertensive nephropathy (RRI 0.8), with diminished cortical blood flow, vascular pruning **(arrows)**, and diffuse intrarenal arteriolar narrowing. **(D)** End-stage kidney due to hypertensive nephropathy (RRI 0.9). with no cortical blood flow and extensive intrarenal arteriolar disease.

Clinical evaluation of renal ischemia

Noninvasive assessment of renal blood flow
^{125}I-Iothalamate GFR (Total GFR)
^{99M}Tc-DTPA (split renal function and single-kidney GFR)
Invasive assessment of significance of RAS
Percent diameter stenosis by visual estimates or quantitative angiography
Translesional pressure gradient
Fractional flow reserve
Intravascular ultrasound
Renal frame counts
Renal blush score

Non Invasive assessment

- Nuclear scintigraphy with technetium-labeled pentetic acid (99MTc-DTPA) is reliable for measuring fractional renal blood flow and, when used in conjunction with ^{125}I Iothalamate, allows accurate measurement of total- and single kidney-GFR
- In patients with unilateral RAS, hypoperfusion of the stenotic kidney is reasonable evidence for renal ischemia; patients with normal renal blood flow might have RAS but not ischemia.

Invasive evaluation of renal ischemia

- Stenosis severity determined by visual estimates or quantitative angiography has a poor correlation with hemodynamic significance
- Translesional pressure gradients (TLG) > 20 mm Hg, with small catheters or special pressure wires, are considered hemodynamically significant
- FFR can determine the hemodynamic significance of RAS, and FFR < 0.80 might predict a favorable blood pressure response to revascularization
- Intravascular ultrasound is extremely useful for assessing vessel dimensions and stenosis severity in FMD patients and, when used with TLG, provides useful assessment of ischemia

New classification for RAS, renal ischemia, and nephropathy

Table 4. Classification of RAS, Renal Perfusion, and Renal Parenchymal Disease

Type	I A	I B	II A	II B
Perfusion	NL*	Renal ischemia	NL*	Renal ischemia
Parenchymal disease	No	No	Yes	Yes
Scr	NL	URAS–NL BRAS–NL or ↑	NL or ↑	NL or ↑
Proteinuria	No	No	Might be present	Might be present
RRI	<0.7	<0.7	>0.8	>0.8
Arteriolar narrowing	None	None or mild	Yes	Yes
Arteriolar pruning	None	None	Yes	Yes
Cortical blood flow	NL	NL	↓	↓
Biopsy	NL	NL	Abnormal	Abnormal
Nuclear GFR	NL	URAS: NL	↓	URAS: ↓
DTPA split function		BRAS: NL or ↓		BRAS: ↓
	URAS: SYM	URAS: ASYM	URAS: SYM	URAS: ASYM
	BRAS: SYM	BRAS: SYM or ASYM	BRAS: SYM	BRAS: SYM or ASYM
TLG	None	≥20 mm Hg	None	≥20 mm Hg
FFR	NL	<0.8	NL	<0.8

*These patients have "anatomic" renal artery stenosis (RAS) but no renal ischemia (normal perfusion).

↑ = increased; ↓ = decreased; ASYM = asymmetric; BRAS = bilateral renal artery stenosis; DTPA = ^{99M}-Tc-labeled pentetic acid; FFR = fractional flow reserve; GFR = glomerular filtration rate; NL = normal; RRI = renal resistive index; Scr = serum creatinine; SYM = symmetric; TLG = translesional pressure gradient; URAS = unilateral renal artery stenosis.

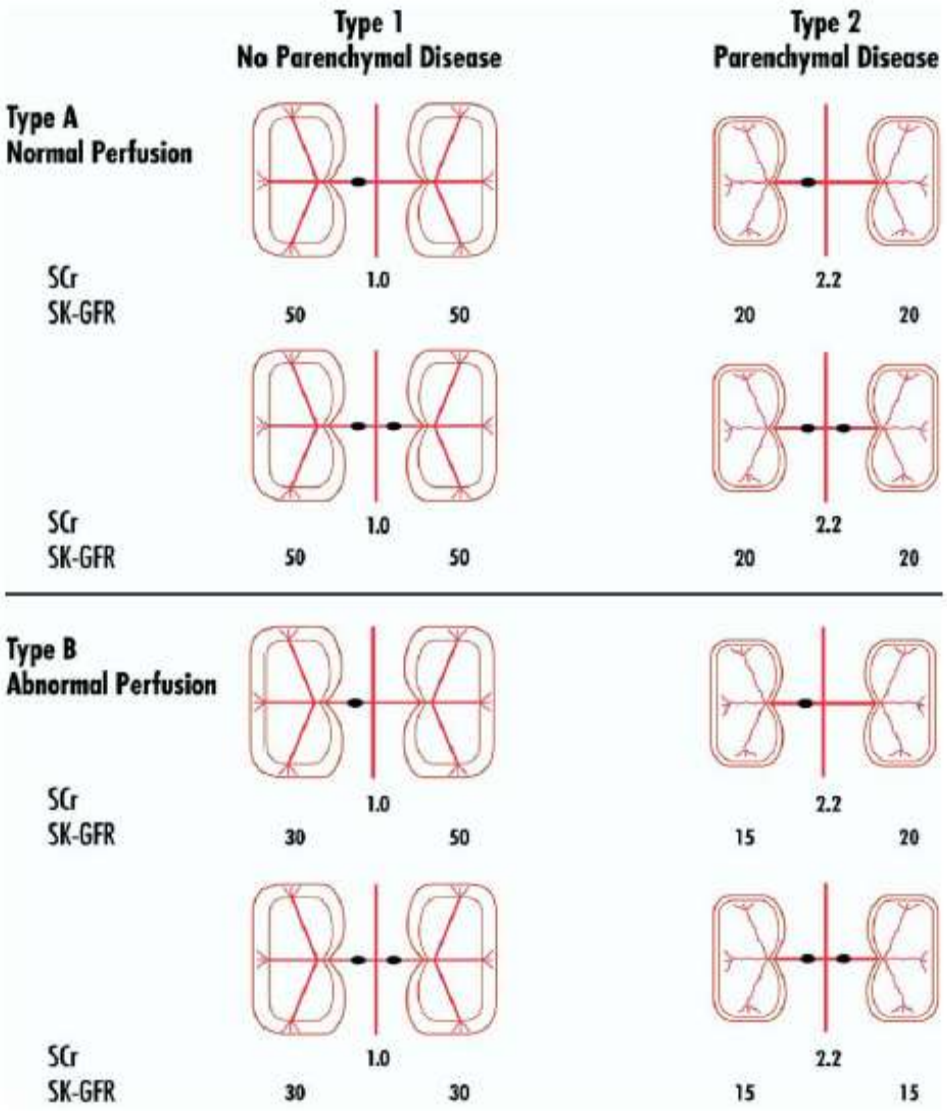

Figure 7. Schematic Illustration of Disorders of Nephropathy (Type 1 or 2) and Renal Ischemia (Type A or B)

- The best candidates for revascularization are those with vital organ injury, renal ischemia ,and no nephropathy.

Indications for Revasularization

Table 1. ACC/AHA Guidelines for Renal Arterial Disease (2)

	Level of Evidence	Class
3. Indications for revascularization*		
Asymptomatic bilateral ARAS	C	II B
Asymptomatic solitary ARAS	C	II B
Asymptomatic unilateral ARAS	C	II B
RAS and Class I indications for RAS evaluation	B	II A
RAS and intolerance to medication	B	II A
Bilateral ARAS and progressive renal dysfunction	B	II A
Solitary ARAS and progressive renal dysfunction	B	II A
Unilateral ARAS and chronic renal dysfunction	C	II B
ARAS and unexplained pulmonary edema	B	I
ARAS and unexplained recurrent CHF	B	I
ARAS and unstable angina	B	II A

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Atherosclerotic Peripheral Vascular Disease Symposium II: Intervention for Renal Artery Disease

Krishna J. Rocha-Singh, Andrew C. Eisenhauer, Stephen C. Textor, Christopher J. Cooper, Walter A. Tan, Alan H. Matsumoto, Kenneth Rosenfield and for Writing Group 8

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Grade I: Renal artery stenosis is present, but there are no clinical manifestations (normotensive with normal renal function).

Grade II: Renal artery stenosis is present, but patients have medically controlled hypertension and normal renal function.

Grade III: Renal artery stenosis is present, and patients have evidence of abnormal renal function, medically refractory hypertension, or evidence of volume overload.

Table. Clinical Factors Favoring Medical Therapy and Revascularization or Surveillance for Renal Artery Stenosis

Factors favoring medical therapy and revascularization for renal artery stenosis
Progressive decline in GFR during treatment of systemic hypertension
Failure to achieve adequate blood pressure control with optimal medical therapy (medical failure)
Rapid or recurrent decline in the GFR in association with a reduction in systemic pressure
Decline in the GFR during therapy with ACE inhibitors or ARBs
Recurrent congestive heart failure in a patient in whom the adequacy of left ventricular function does not explain a cause
Factors favoring medical therapy and surveillance of renal artery disease
Controlled blood pressure with stable renal function (eg, stable renal insufficiency)
Stable renal artery stenosis without progression on surveillance studies (eg, serial duplex ultrasound)
Very advanced age and/or limited life expectancy
Extensive comorbidities that make revascularization too risky
High risk for or previous experience with atheroembolic disease
Other concomitant renal parenchymal diseases that cause progressive renal dysfunction (eg, interstitial nephritis, diabetic nephropathy)

Renal Artery Revascularization: Technical Considerations

Table 1. ACC/AHA Guidelines for Renal Arterial Disease (2)

	Level of Evidence	Class
5. Type of renal artery revascularization		
Renal stent for ARAS patients who meet criteria	B	I
Angioplasty for FMD, with bailout stenting	B	I

Fibromuscular Dysplasia

- Balloon angioplasty is the intervention of choice, and stenting is used for bail-out indications.
- Procedural success approaches 100%, and restenosis occurs in 10% within 10years
- Renal angioplasty is better in discrete lesions in major renal arteries and worse in diffuse FMD in smallsegmental, arcuate, and interlobar vessels.
- Pressure wire and IVUS to assess TLG, vessel dimensions, and stenosis severity are recommended
- Patients with nonobstructive FMD should be treated conservatively

Atherosclerotic RAS

- Stenting is recommended to eliminate elastic recoil, minimize dissection, and maximize lumen enlargement
- Most studies report procedural success rates of 95% to 100%, residual diameter stenosis 10 %, restenosis rates of 10% to 15% within 1 year, and major complications in < 2%

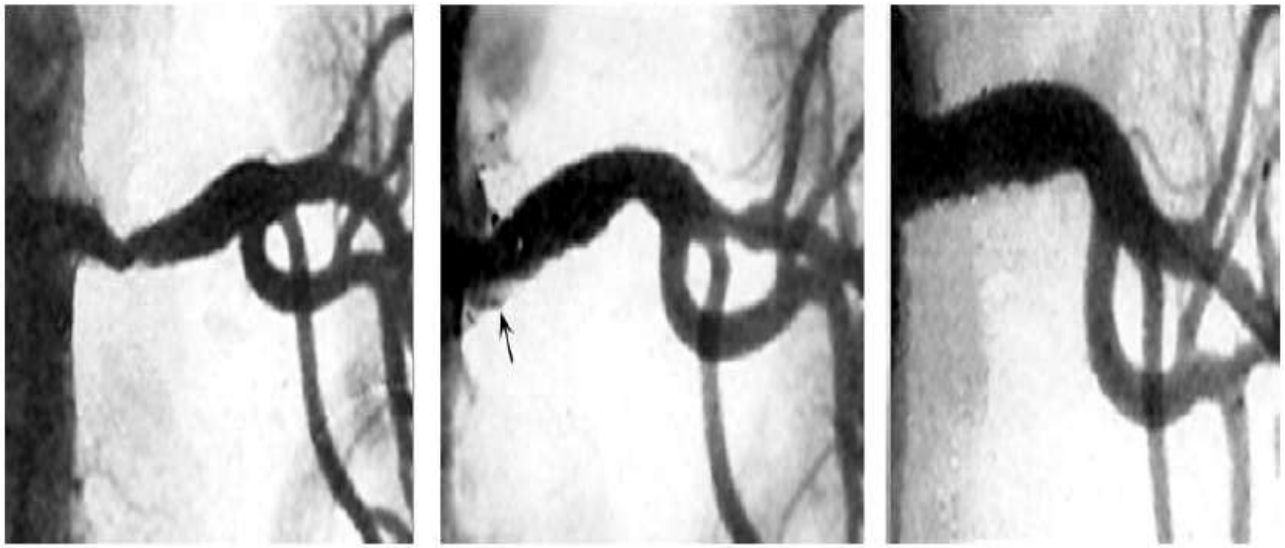

Figure 8. Endovascular Revascularization of Atherosclerotic Renal Artery Stenosis

(**Left**) Baseline image before intervention (same as Fig. 1, right panel). (**Middle**) Suboptimal angiographic result after balloon angioplasty, characterized by significant residual stenosis, elastic recoil, and dissection (**arrow**). (**Right**) Final result after stent placement demonstrates optimal lumen enlargement.

Avoiding Renal Injury

- Selective renal arteriography should be guided by abdominal aortography; the catheter-in-catheter or no-touch techniques should be used to minimize contact with the aortic wall and injury to the renal ostium during guiding catheter engagement
- The nephrotoxic effects of radiographic contrast are minimized by maintaining adequate hydration, limiting contrast volume, and using digital subtraction angiography.
- Renal embolization during revascularization seems to be fairly common , and 1 small randomized study suggested potential benefit of a combination of distal embolic protection and intravenous abciximab .
- All patients should be evaluated for post-procedural nephropathy and have regular follow-up

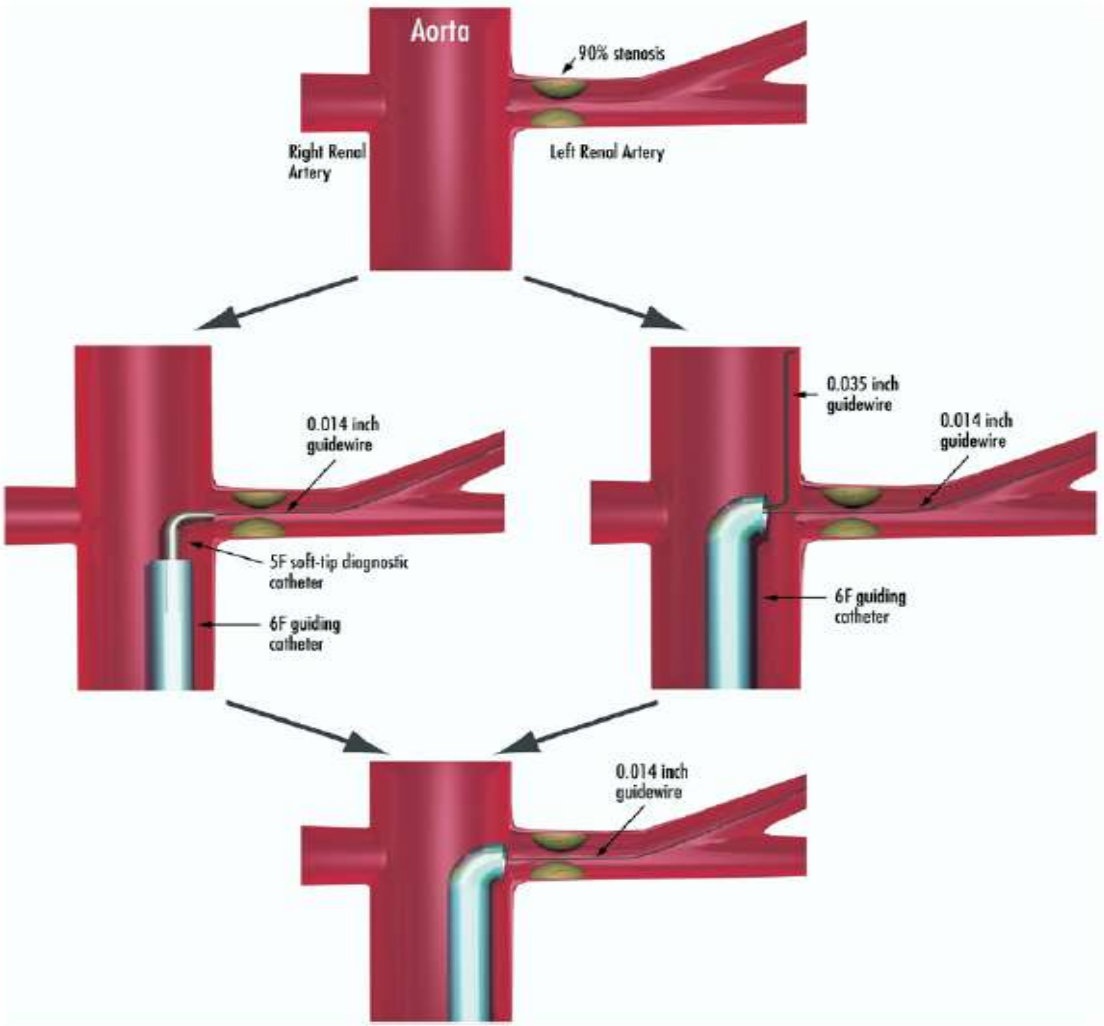

Figure 9. Schematic Illustrations of Invasive Techniques to Avoid Renal Artery Injury and Atheroembolization During Renal Artery Stenting

(Left) Catheter-in-catheter technique employs a tapered 4- or 5-F soft-tip diagnostic catheter loaded inside a 6- or 7-F guiding catheter. After the renal artery is engaged with the diagnostic catheter, the 0.014-inch angioplasty wire is advanced across the stenosis and positioned distally. The guiding catheter is advanced over the diagnostic catheter, and once positioned the diagnostic catheter is removed. **(Right)** The no-touch technique uses a 0.035-inch J wire inside the guiding catheter, to lift the tip off the aortic wall. With the 0.035-inch wire in place, the guiding catheter is aligned with the renal artery, and a 0.014-inch guidewire is used to cross the stenosis. The 0.035-inch guidewire is removed, and the guiding catheter is advanced over the 0.014-inch wire to engage the renal artery.

Outcomes After Renal Artery Revascularization

Outcome of renal revascularization to cure hypertension

- *After ARAS revascularization, hypertension cure (normal blood pressure, no medication) is observed in 10% of patients, regardless of the revascularization technique*
- Patients with ARAS do not have renovascular hypertension, as evidenced by similarities in the extent of renin activation compared with hypertensive patients without RAS and the low cure rate of hypertension after successful revascularization
- The most likely explanations are that patients with ARAS have essential hypertension, many do not have renal ischemia, and unrecognized hypertensive nephropathy leads to self-perpetuating hypertension.

Outcome of renal revascularization to improve renal function

- Several studies documented improvement in creatinine and in the slope of reciprocal creatinine after stenting, compatible with beneficial effects of revascularization on renal function
- Nevertheless, 25% to 30% have deterioration in renal function despite revascularization
- The explanations for failure to improve or stabilize renal function after revascularization are multifactorial-
  - Revascularization of patients without renal ischemia
  - Insensitivity of the creatinine to changes in GFR when 50% of renal mass is revascularized (e.g., unilateral ARAS)
  - Failure to identify baseline nephropathy
  - Procedure-induced nephropathy

ARAS & Cardiovascular outcomes

- Four-year survival rates are 57% and 89% for patients with and without ARAS, respectively, and mortality rates are higher with more severe ARAS and with bilateral ARAS
- Although ARAS adds incremental risk to cardiovascular morbidity and mortality, there are no data that renal revascularization improves cardiovascular outcomes

CORAL (Cardiovascular Outcomes in Renal Atherosclerotic Lesions) trial

- Ongoing trial of 1,080 patients with ARAS randomized to optimal medical therapy or to optimal medical therapy plus renal artery stenting
- Patients must have unilateral or bilateral ARAS, resistant hypertension, and/or chronic kidney disease stage 3
- The primary end point is a composite of cardiovascular or renal death, stroke, myocardial infarction, hospital stay for heart failure, progressive renal insufficiency, or the need for renal replacement therapy

» THANKS