PVD III: RENOVASCULAR DISEASE: DIAGNOSIS, TREATMENT AND MANAGEMENT

Coordinator: Thomas Sos, MD, FSIR

FACULTY

Michael Bettmann, MD, FSIR
Rob Lookstein, MD
Timothy Murphy, MD, FSIR
John Rundback, MD, FSIR

Clinical Tips:

1. Primum non nocere or (Thou shalt not screw around)
Intervene only when indicated, work fast but carefully

2. Limit iodinated contrast
The degree of contrast induced renal failure correlates with the amount (volume and concentration) of iodinated contrast used

3. Image in the proper oblique
Use cross sectional imaging to optimize lesion visualization and decrease number of injections

4. Balloon and Stent sizing
Measurements can be calibrated from marker or catheters with known dimensions

5. Catheterization
Soft tip wires and catheters are least traumatic to vessels
Firm catheters are very useful in very severe stenosis and total occlusions
Limit manipulation
Keep away from aortic wall (“No touch”, Sos “flick”)

6. Beware of the glide
Hydrophilic wires are more likely to contribute to dissections, perforations, or loss of access

7. Preserve access
Never remove guidewire until certain of success

8. Lost stents
Try snaring out first
May be deployed in an innocuous location- iliac, aorta

9. The enemy of good…is better…
Perfect placement the first time is always the goal however,
Stent deployment is imprecise if you must error always error on the possibility of extending the stent too far into the aorta
Extend the stent past the lesion by a couple of mm on each end.

The following questions are frequently asked in these workshop sessions. Usually, there is more than one approach to challenges encountered while performing renal vascular interventions. The answers to each of these questions reflect the view of one or more renovascular workshop faculty member answering the question but not necessarily the views of all of the renovascular workshop faculty. Some of the questions were answered by faculty members from prior years.

Question 1: When treating Renal Artery Stenosis percutaneously, when should I use brachial versus femoral access?

Answer: Femoral access is the preferred route for most renal artery interventions. The brachial approach is reserved for difficult cases. More recently, there has been interest in radial artery access.
The femoral approach provides the shortest distance to the renal arteries. This provides excellent catheter control and guidewire steering. The complication rate is lower with the femoral route as well.[1] The brachial approach is associated with more hematomas, nerve injuries, and vessel occlusions. It also introduces a small risk of stroke. The complication rate with the brachial approach compared to that of the femoral approach is even greater in patients with a small or diseased brachial artery or when a 7 French or larger sheath is required. The large size and easy compressibility of the femoral artery means that the 6-8 French sheath required for renal intervention is usually well tolerated.

Problems with the femoral approach usually arise with increasing caudal angulation of the renal arteries. Crossing a renal artery stenosis and maintaining wire access during intervention in a renal artery that has a relatively acute caudal angulation can be problematic even with the use of reverse curve catheters. These problems are compounded by rigid (in-elastic) arteries, tight calcified stenoses, and a dilated abdominal aorta. A combination of all these problems can sometimes make angioplasty from a femoral approach nearly impossible.

In these difficult cases, a brachial approach can be an invaluable alternative.[2] The renal arteries come off the aorta at a gentle angle when approached from above—they can usually be selected with a multipurpose catheter. The relatively straight line from aorta to renal artery makes it possible to push a catheter, sheath, or balloon across a tight, calcified, lesion without the guidewire looping in the aorta as it does when pushing from a femoral approach.

Because of the higher complication rate seen with brachial access, it is rarely used for percutaneous intervention without first attempting intervention from a femoral approach. Exceptions to this rule include: prior studies (angiography, CTA, or MRA) that demonstrate an extreme caudal angle to the renal artery, aortic or bilateral ilio-femoral occlusions, and large friable appearing plaques limited to the infra-renal aorta. An infrarenal abdominal aneurysm might also be an indication for a brachial approach, but in most cases we find it better to have the patient undergo open repair of the aneurysm first, or to fix the renal artery as part of an endovascular aneurysm repair. Some would also list a graft in the femoral region as a reason to use a brachial approach. Potential additional complications associated with graft material in the groin include graft thrombosis, graft infection, and catheter kinking or fracture. In practice these are not common, but can have serious sequela [3,4].

More recently, some authors have advocated a radial artery approach over a high brachial approach because of the lower complication rate and higher patient satisfaction [5]. Patients can be ambulated more quickly and develop few hematomas with a radial approach. The nerve palsy associated with brachial hematomas does not occur with a radial artery access. The main limitations of the radial approach are that very long sheaths and guidewires are required which leads to problems with catheter pushability and guidewire torque control and that sheath size is usually limited to 6 French. Further investigation of this method is required.

1. Hessel SJ, Admas DF, Abrams HL. Complications of Angiography. Radiology 1981; 138:273-281.
2. De Sanctis JT. Renal artery angioplasty and stenting. Sem Intervent Radiol 2001; 18: 23-36.
3. Wade GL, Smith DC, Mohr LL. Follow-up of 50 consecutive angiograms obtained utilizing puncture of prosthetic vascular grafts. Radiology 1983; 146: 663-664.
4. Mani RL, Costin BS. Catheter angiography through aortofemoral grafts: prevention of catheter separation during withdrawl. AJR 1977; 128: 328-329.
5. Scheinert D, Braunlich S, Nonnast-Daniel B, Schroeder M, Schmidt A, Biamino G, Daniel WG, Ludwig J. Transradial approach for renal artery stenting. Catheter Cardiovasc Interv 2001; 54:442-447.

Question 2: What is the current role for renal angioplasty/stenting in the treatment of a hypertensive patient with renal artery stenosis?

Answer: Renovascular hypertension (RVHTN) is characterized by well-known clinical, physiologic and anatomic criteria. Renal artery stenosis (RAS) is not equivalent to RVHTN and can be found incidentally in a significant number of older patients without clinical sequelae. Therefore, before proceeding to treat any stenosis, it has to be severe enough (anatomic criteria) to cause significant reduction in flow or pressure across it (See the next Q&A for further discussion). Even when RAS is judged to be severe, renal angioplasty (PTRA) may not always lead to a tangible clinical benefit.

The only positive data supporting surgical revascularization over medical is dated (Hunt, Strong), not randomized, and did not use currently available antihypertensive medications, like ACE inhibitors and angiotensin receptor blockers. There are numerous uncontrolled reports of reduced blood pressure after renal artery angioplasty or stenting, but these are limited due to the lack of control groups, "regression to the mean" phenomenon seen with extreme blood pressure measurements, and lack of proof of improved clinical outcomes compared with medical therapy. In an era of "Evidence-based Medicine", more science on the benefits of renal artery revascularization is needed before general recommendations can be made. Until that time, treatment must be tailored based on best estimates from available clinical information for each patient.

The technical success rate of over 95% in experienced hands has improved significantly over the years and complications decreased to the degree it could be argued that PTRA/S could be used in certain clinical setting as a diagnostic and therapeutic tool. In many ambiguous situations fixing the lesion to see what happens may not be an unacceptable approach. The alternative surgical treatment is quite invasive, and without clear evidence of superiority of surgery in results and outcome it is hard to justify in most circumstances not to try PTRA/S first.

The following is a summary of the common presentations of RAS:

1. Fibromuscular dysplasia: PTRA is the treatment of choice. The most common beaded Medial Fibroplasia (with aneurysms) type responds readily to balloon inflation and rarely if ever recurs when properly dilated. Stenting may have a higher percentage of intrastent intimal hyperplasia restenosis rate than that of pure ballooning. Therefore stenting should be reserved to recurrent lesions or to repair unintended complications. If new medically treated stents show no intimal hyperplasia on follow-up then stenting might play a bigger role.

2. Other non-atherosclerotic lesions: Fibromuscular, Hypoplastic, Vasculitis and neurofibroma lesions. Response is not always predictable. Given the potential to cure, high safety and relative low risk, PTRA should be the treatment of choice. Just as with atherosclerotic lesions, ostial lesions are less likely to respond with balloons alone. If the balloon expands but the lesion recoils then add stenting. Stenting is contraindicated if the balloon has persistent waist in tough fibrotic lesions. This simply indicates that the stent will have the same narrowing, Many renal artery lesions treated with PTA initially demonstrate less than pleasing results, however, with time frequently there is remodeling and improvement on follow-up.

3. Atherosclerotic:
   a. Unilateral-non ostial: PTRA is the treatment of choice. Stenting is frequently required to improve residual stenoses or gradients.
   b. Unilateral-ostial/periostial: Stents essentially equalized treatment of these lesions with non-ostial lesions. Ballooning alone is rarely successful. Surgery for failed PTRA/S.
   c. Bilateral: The majority are ostial or periostial. Technical difficulty and uncertainty of outcome increase with increased complexity of lesions. PTRA/S (Stent almost always) is first choice provided operator has good experience.
   d. Unilateral with impaired renal function: No stenosis in opposite renal artery is evidence that there is parenchymal damage. PTRA/S could be tried on the hope that the involved side was protected.
   e. Bilateral with Azotemia: PTRA/S is indicated. Complexity is greatly increased but PTRA/S is still indicated. Improvement in BP control and renal function are common. Most series indicate at least 70% improvement or stabilized renal function in azotemic patients. Use of CO2 is encouraged. Gadolinium must be avoided in patients with an eGFR <= 60 cc/min due to the theoretical risk of nephrogenic systemic fibrosis. LOCM and hydration (with or without bicarbonate) may be useful in preventing CIN, although the key goal is to limit total iodinated contrast volume.
   f. Associated with AAA: PTRA/S for infrarenal aneurysms. This indication is widening with the popularity of endovascular AAA repair. Open repair is indicated if aneurysm involves origin of renal arteries.
   PTRA/S offers most durable results among all arteries treated percutaneously and least invasive best choice of available treatments for RAS.

Question 3: When evaluating renal artery stenosis angiographically, when should I measure pressure gradients? How should I do it? What is a significant pressure gradient?

Answer: The most important factor in deciding whether angioplasty/stenting is indicated is the degree of stenosis. Flow and pressure across a stenosis do not begin to be affected before at least a diameter reduction of 60% or luminal area of 80% (1). Theoretically, stenoses below 50% are hemodynamically insignificant and above 70% are significant and we would not need to have pressure measurement done in these clear cut situations. Unfortunately, measuring the degree of stenoses angiographically is not always easy, or reliable and wide inter-observer variations exist. Despite these observations, I still think that many lesions at both ends of the spectrum could be called, based on imaging alone, without the need for pressure gradient measurement. Measuring pressure gradients has its own technical problems. For example, a four French (1.35mm) catheter across a small 4 mm main renal or division artery with 50% non significant stenosis becomes severely stenotic when this catheter reduces the residual lumen by more than half. The problem with the size of the catheter across a lesion could be practically eliminated if the use of pressure guide wire system, (2). Another problem is if the lesion requires a 018 or 014 wire system to safely cross it, advancing a 3.2-3.7 French tapered balloon catheter to dilate it through a guiding catheter or sheath is easier and safer than trying to advance a 4 French catheter to measure a gradient. The coaxial technique, I believe, is the technique of choice for PTRA/S and should be the only choice in distal main and FMD lesions. Pressure sensing wires have utility and may also serve as buddy wires to facilitate subsequent stent wire insertion.

Another common pitfall is the constant change in systolic blood pressure on the angiographic table which could be a source of uncertainty when the gradient is small. Therefore, simultaneous recording in the renal artery and aorta is preferable when possible. A pressure drop across a stenosis does not occur until a critical stenosis is reached (1). The decrease in flow and pressure increases precipitously when the stenosis reaches a critical degree. Not finding a gradient is helpful in ruling out a significant stenosis. A 20 mm or greater systolic gradient results from a significant stenosis. In a moderate stenosis with less than 20mm systolic gradient the decision to treat has to be made on clinical indications and available physiologic tests. There are some who have proposed the criterion of 10**%** peak systolic gradient; this is more accurate than an absolute gradient of 10-20mm Hg; this was recently validated in careful human experiments with use of pressure wires and sampling of rennin from the renal veins – rennin secretion began at a 10% MEAN ARTERIAL PRESSURE GRADIENT.

Some advocate relying on the angiographic appearance in the clearly mild or severe cases, though there is evidence that angiographic assessment of stenosis severity can be very inaccurate and both over and underestimate lesion severity. Angiography with pressure gradient measurements should be performed whenever the degree of stenosis is questionable and when angiographic findings are in contradiction with clinical and/or physiologic tests or when the degree of stenosis angiographically is in the "gray zone" (50-70%).

Recent developments include a catheter that uses a thermodilution technique to measure flow (Angioflow) before and after an intervention. Currently these are 6 FR and may be too big for some tight stenoses but would be useful in a mild stenosis to determine if an angioplasty were necessary or not. Another development is the Radi pressure wire which is a tip enable pressure transducer on a guide wire. This is currently used in coronary angiography to assess the severity of lesions prior to angioplasty and to assess improvement afterwards.

It is fair to say that these devices are not generally used in renal angioplasty especially because of their great cost.

REFERENCES:

1. May AG, DeWeese JA, Rob CG: Hemodynamic effects of arterial stenosis, Surgery 1963; 54: 250.
2. Gross MC, Kramer J, Uhlich F et al. Determination of renal arterial stenosis severity: Comparison of pressure gradient and vessel diameter. Radiology 2001; 220:751-756
3. B. De Bruyne, G. Manoharan, N. Pijls, K. Verhamme, J. Madaric, J. Bartunek, M. Vanderheyden, G. Heyndrickx: **Assessment of Renal Artery Stenosis Severity by Pressure Gradient Measurements.**
   Journal of the American College of Cardiology, Volume 48, Issue 9, Pages 1851-1855

Question 4: If an asymptomatic stenosis of a renal artery is detected, should I fix it?

Answer: Essential Hypertension and renal artery atenosis (RAS) are both highly prevalent. Ischemic Renal Failure (IRF) is also increasingly encountered in the aging population. However, the relationship between RAS and hypertension as well as IRF is imperfect. Most patients with RAS and hypertension in fact have Essential Hypertension. Autopsy studies as well as serial angiographic studies indicate that RAS may be encountered in up to 77% of hypertensive patients but is also present in approximately 50% of patients who were normotensive in life. In one study, 81% of RAS found at autopsy was in patients who were normotensive in life. RAS is clearly a progressive disease also. This again has been proven by serial angiographic studies. Risk of progression is highest when RAS exceeds 60%, and the risk of occlusion becomes significant if RAS exceeds 80%. In addition, contra-lateral RAS develops in approximately 20% of patients within two years following discovery of a unilateral RAS. What should temper the indiscriminate use of renal revascularization is the realization that revascularization has an imperfect outcome for both blood pressure control and renal function improvement. In addition, predictability of benefit in a given patient is extremely difficult except in a few special circumstances. In general, cure of atherosclerotic RVH is rare, but control of hypertension may be made easier. In-patients with IRF, renal function may improve in approximately 40% of patients following revascularization, but continued decline may be expected in up to 30% of patients. Regarding benefits relating to IRF, studies have indicated that both long term survival as well as clinical benefit is maximal when baseline creatinine is normal or at least under 1.5. Survival and clinical benefit markedly decline with rising baseline creatinine.

Two unambiguous circumstances can easily be dispensed with when dealing with incidentally discovered RAS. Firstly, if RAS is under 50% diameter reduction, patients should almost never be offered revascularization. At the other extreme, in the absence of significant contraindications, patients with critical or pre-occlusive renal artery stenosis should be offered renal revascularization by angioplasty and stent placement. In our practice, we have established a threshold of 80% diameter reduction for this category of patient. This is all the more important for patients that may have bilateral lesions which are incidentally discovered.

Controversy surrounds those patients who present with unsuspected moderate renal artery stenosis ranging from 50 to 75%. In these patients, revascularization should be considered if control of hypertension remains sub-optimal following ideal medical therapy, or if incipient renal failure is present and parenchymal causes of renal insufficiency can be excluded. The majority of these patients should be followed medically and Captopril nuclear renography should be performed to establish a physiologic basis for renal vascular insufficiency. In addition, the resistive index should be measured using color Doppler ultrasonography. If the resistive index is 80 or higher, minimal benefit may be expected from revascularization, and this should influence the clinical decision to intervene or defer treatment.

If there are no clinical indications and the stenosis is not physiologically significant (>5-10% mean arterial gradient), then these stenoses should not be stented. Such lesions should be followed clinically and vigorously treated by statins, glucose and BP control cessation of smoking, exercise and other lifestyle alterations to prevent progression.

REFERENCES:

1. Holley KE, Hunt JC, Brownal JR, Kincaid OW, Sheps SG. Renal artery stenosis: a clinical pathologic study in normotensive and hypertensive patients. AM J Med 1964; 37:14-22.
2. Tollefson DF, Ernst CB. Natural history of atherosclerotic renal artery stenosis associate with aortic disease. J Vasc Surg 1991; 14:327-331.
3. Radermacher J, Chavan A, Bleck J, et al. Use of doppler ultrasonography to predict the outcome of therapy for renal-artery stenosis. New England Journal of Medicine 2001; 344: 410-412.
4. Sheng Kang, Yangfeng Wu, Xian Li. Effects of statin therapy on the progression of carotid atherosclerosis: a systematic review and meta-analysis. Atherosclerosis 177 (2004) 433–442.
5. Cannon C, Braunwald E, McCabe C, Rader D, Rouleau J, Belder R, Joya S, Hill K, Pfeffer M, Skene A, and the Pravastatin or Atorvastatin Evaluation and Infection Therapy-Thrombolysis in Myocardial Infarction 22 Investigators. N Engl J Med 350;15:1495-1504
6. Nissen S, Tuzcu M, Schoenhagen P, Crowe T, Sasiela W, Tsai J, Orazem J, Magorien R, O'Shaughnessy C, Ganz P, and the Reversal of Atherosclerosis with Aggressive Lipid Lowering (REVERSAL) Investigators. Statin therapy, Ldl cholesterol, c-reactive protein, and coronary artery disease. N Engl J Med 352;1:29-38

Question 5: What should I do if I can pass a guidewire across the stenotic lesion, but cannot get an angiographic catheter to follow?

Answer: Everyone has been in the situation of getting a wire across a lesion and not being able to get a catheter across it. The first question however, should not be; ”I have a wire across the lesion, now how can I get a catheter across it?” The first question should be: **“What catheter and guidewire combination is optimal for the specific lesion to be treated?”**

The choice of the initial catheter and guidewire combination greatly influences the chance of success. Catheter choice is difficult to advise because most operators already have their favorite catheters. **However…**

Cobra catheters are rarely useful. They will usually engage the renal orifice and a floppy guide wire can be advanced across the stenosis, however, it can be difficult to push the cobra catheter across the lesion especially if it is ostial. In these cases the catheter and floppy guide wire will typically tend to buckle up into the aorta.

Since the renal vessels usually have a caudally directed origin, “recurve” type catheters are desirable and most frequently used. “Recurve” catheters also allow the operator to exert more axial force to cross tight lesions. We generally use the Sos Omni Selective™ series of catheters as our primary catheter. Sos Omni Selective™ catheters (AngioDynamics Glens Falls, NY, USA) are “recurve” style catheters which have a short enough side arm to reform in the descending thoracic aorta just distal to the left subclavian artery thus eliminating the risks associated with reforming the catheter in the aortic arch or visceral vessels.

Very often, an 0.014” diameter guidewire can be passed across the lesion through a 6 F LIMI or renal guide, and a stent placed directly on a sub-4 French balloon. Occasionally, predilation with a 2.5 or 3 mm diameter sub-4 balloon will be required to “soften up” the lesion first. Coronary balloons as well as dedicated through-lumen low-profile balloons are available from several manufacturers.

An extremely floppy soft tip guide wire such as a "Bentson" (available from many manufacturers) with the guide wire extending several centimeters out the end of the catheter tip is the least traumatic way to cross stenoses. Most lesions can be crossed by leaving ~ 1 cm of wire out of the catheter while pushing it cephalad. (Figure 1) The wire will flip into proximal stenoses, or the funnel shaped nubbins of proximal occlusions. Once the guide wire is in the proximal vessel, it can be further advanced through the stenosis and the catheter pulled down or pushed across the lesion. The soft wire is removed and the arterial pressure distal to the stenosis is recorded and nitroglycerine is administered. If there is any question whether the catheter tip is intraluminal then a careful test injection can be performed. Most stenoses and some short occlusions, especially proximal lesions, can be traversed using this method. If initial attempts at crossing the lesion are unsuccessful, reevaluate the angle of the axis of the stenotic vessel, eccentricity and irregularity of the plaque and reposition, and try an appropriate differently shaped catheter. The catheter position can be adjusted to alter the course of the guide wire and respiratory motion can also be used. If the angle is appropriate, but a soft wire will not cross the lesion, careful use of a hydrophilic straight or angled wire such as a Glidewire™ (Terumo) may be successful.
NOTE: The hydrophyllic wire should be exchanged for a non hydrophyllic wire as soon as possible after crossing the lesion.

If the abdominal aorta is very diseased, a long sheath which extends to the level of the renal arteries can be used to protect the aorta to decrease the risk of thrombo, athero, and cholesterol embolization. The use of a sheath will also facilitate the transmission of torque and push to the catheter tip allowing better catheter control and safety.
To exchange the diagnostic catheter for the balloon catheter, a guide wire, which has a very soft, atraumatic, tip and a rapid transition to a stiff shaft is useful. This type of wire can be safely advanced into the segmental branches and provide the needed shaft stiffness to facilitate advancing a balloon across the stenosis. The TAD II (Peripheral Systems Group) wire has a very stiff 0.035" shaft tapering to a very floppy highly radiopaque 0.018" tip. The rigid shaft of the TAD II wire can be shaped to closely match the natural curve of the renal artery and its origin from the aorta, facilitating passage of the balloon catheter.

In really difficult cases a microcatheter (Terumo Progreat or similar, I like the Total Cross catheters for renal work) can be used to cross the lesion and the catheter exchanged out for an 014 wire. These wires are quite stiff and provide excellent support. A rapid exchange (monorail) small diameter balloon can be used to predilate the stenosis. As they have a very low profile they cross tight or tortuous stenoses easily. This (almost) always works.

Occasionally despite using these techniques a catheter will not follow the wire. Some suggestions are:

- Torque the catheter slightly anteriorly or posteriorly in an attempt to get the catheter tip to better align with the lumen of the stenosis and allow passage of the catheter.
- If the tip of the catheter is stable within the stenosis the soft guidewire can be removed and a stiffer guidewire inserted. This technique can easily lead to a dissection especially if hydrophilic wires are used.
- Exchanging for a hydrophilic catheter can sometimes work.
- If the lesion is severe or a frank occlusion is present, we use a stiffer catheter such as the AngiOptic Omni Selective (AngioDynamics, Queensbury , NY). This allows more axial force to be exerted against the lesion. Care must be taken to avoid promoting embolization or a dissection secondary to the stiffness of the catheter.
- A lower profile system can be used such as changing from a 0.035” to a 0.018” system.
- A guiding catheter can be used to support the system and allow for more axial push.
- ***If the artery is very caudally directed then a left high brachial approach might allow for a higher chance of success.***

REFERENCES:

1. Trost DW, Sos TA. Percutaneous transluminal angioplasty and stenting in renal artery stenosis. Renal artery thrombolysis. In Clinical Urography 2nd edition Pollack & McClennan (Eds). W.B Saunders Company, Philadelphia, PA. 2000

2.

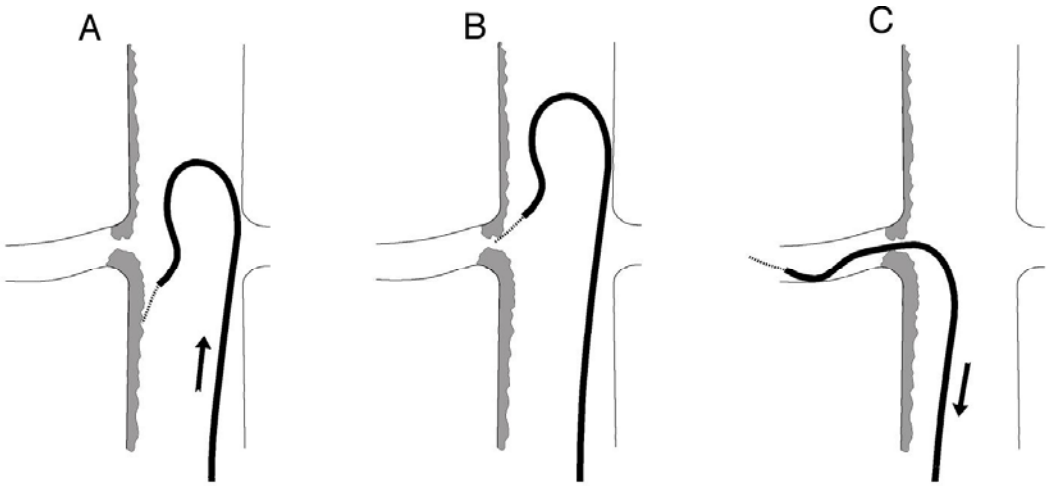


Figure (1)
Push Up Method of crossing a renal artery stenosis
A) Starting below the renal ostium
B) The catheter with leading guidewire are advanced crainally until the wire pops into the ostium,
C. The catheter shaft is withdrawn pulling the tip out into the renal artery

Question 6: When treating renal artery stenosis, when should I place an intravascular stent? What stent should I use?

Answer: Renal artery stents have revolutionized the ability to percutaneously treat nearly all renal artery stenoses, and there is often "peer pressure" by referring physicians as well as patients to perform stenting as the primary intervention for RAS. Despite this, some prudence is necessary. Most case of fibromuscular dysplasia (FMD) respond adequately to angioplasty alone (PTRA), with excellent initial and long-term patency and clinical results (1). Similarly, non-ostial or truncal atheromatous lesions also are well treated with PTRA alone, with comparable results to stenting (2).

In patients with ostial RAS caused by encroaching aortic atheroma, most operators would agree that stenting should be more liberally applied both to improve technical success and maintain target vessel caliber. Van de ven and colleagues demonstrated restenosis rates of 48% and 14% after PTRA and stenting respectively, although the higher patency with stenting did not correlate with improved hypertension control (3). Similarly, for lesions located near the aortic lumen, Baumgarter et al also found stents to provide superior primary patency than PTRA (2). Although operator and case dependent, stenting is usually performed after an attempt at PTRA to assure that the stenosis can be crossed with the balloon and stent and to confirm that the lesion is not inelastic (a contraindication to stenting).

The SCVIR Standards of Practice Committee in 2002 adopted the following indications and contraindications for renal artery stent deployment (4):

I. Indications
   a. Failure to attain a satisfactory result by renal artery angioplasty as determined by:
      i. More than 30% stenosis of the luminal diameter, measured from the outer margins of intimal fissures, after balloon angioplasty.
      ii. Failure to eliminate a hemodynamically significant pressure gradient

iii. Presence of a flow limiting dissection of the renal artery

b. Stenosis of the ostium of a renal artery that has a normal diameter of 5 mm or greater.
c. Restenosis of a lesion that was successfully treated with balloon angioplasty in the past

II. Relative Contraindications
a. An inelastic stenosis that cannot be reduced to less than 50% with balloon angioplasty.
b. The presence of sepsis.
c. If the stent would preclude surgical slavage should restenosis occur, i.e., isolation of branch arteries.
d. For stenosis of an artery normally measuring 4 mm or less in diameter.

The decision as to which stent to use is more difficult and is often determined by operator and institutional training, experience and preference. The only stents currently approved by the U.S. FDA is the Palmaz stent (Cordis, Warren, NJ) and the Renal Bridge stent (Medtronic AVE, Santa Rosa, CA), although other stent platforms are currently undergoing rigorous regulatory evaluation. No single device been shown definitively to outperform another, although balloon-expandable stents are predominantly used in the U.S. Stents are usually provided as premounted on a delivery balloon, with “nesting” of the stent into the balloon material to reduce the introduction profile. Systems are available on 0.035’, 0.018’, or monorail (rapid-exchange) 0.014” wire compatible platforms. Just about every major company now has a stent; some of the systems that we have used in our practice include the Palmaz Genesis and Express stents (Cordis; 0.035”), Racer stent (EV3, Minneapolis, MN; 0.018”), Renal Double-Strut Intrastent (Sulzer Intratherapeutics, St. Paul, MN), Angiodynamics platinum stent (0.035”), NIR stent (Boston Scientific Inc., Watertown, MA, 0.018”), and Herculink stent (Guidant Corporation, St. Paul MN; 0.014”). Advantages of 0.035 inch wire based systems include proven reliability, secure and accurate stent tracking, and easy positioning. Advantages of low profile 0.014”-0.018” compatible systems include the potential for reduced plaque and vessel irritation with possibly less cholesterol embolization, and the ability to cross and dilate the lesion with a single wire. Future stent decisions will be based on the availability of adjunctive anti-embolization devices and the success of stent based drug or radiation delivery platforms.

REFERENCES:

1. Tegtmeyer CJ, Selby JB, Hartwell GD, et. al. Results and complications of angioplasty in fibromuscular disease. Circulation suppl. I 1991; 83: I155-159.
2. Baumgartner I, von Aesch K, Do DD, Triller J, Birrer M, Mahler F. Stent placement in ostial and nonostial atherosclerotic renal arterial stenoses: a prospective follow-up study. Radiology. 2000; 216: 498-505.
3. Van de ven PJG, Beutler JJ, Kaatee R, et al. Transluminal vascular stent for ostial atherosclerotic renal artery stenosis. Lancet 1995; 346: 672-674.
4. Martin LG, Cardella J, Rundback JH, et al. Quality Improvement Guidelines For Angiography, Angioplasty And Stenting For The Diagnosis And Treatment Of Renal Artery Stenosis In Adults. JVIR 2002; 13: 1069-1083.

Question 7: Is the New England Journal of Medicine article questioning the utility of renal angioplasty for treatment of renovascular hypertension valid?

Answer: The article by van Jaarsveld et al. (NEJM 2000; 342:1007-14) was a study that involved 26 institutions in Europe that randomly assigned patients with presumed renovascular hypertension to either PTRA or medical therapy. Crossover of patients from the medical therapy group to the PTRA group was allowed after 3 months. However, data was based on an"intention to treat" analysis. The conclusion of the Abstract of the manuscript stated that "in the treatment of hypertension and renal artery stenosis, PTRA has little advantage over medical therapy".

There were several major problems related to the study:

1. Of the 106 patients enrolled in the study, 10 (9.4%) did not have significant renal artery stenosis (< 50% stenosis at angiography). Therefore, about 10% of the patients enrolled in the study did not have criteria that would justify the diagnosis of renovascular hypertension.

2. During the 5 year enrollment period, the 26 institutions involved with the study were able to enroll only 106 patients. Therefore, the average enrollment per institution was 1 patient per year, raising concern about the technical capabilities of the operators performing the PTRA.

3. There is no definition of a technical success of PTRA. It is unclear whether a technically successful PTRA was achieved in the majority of patients treated. However, 3 patients had renal artery occlusions and no attempt was made to treat them with percutaneous techniques; however, they were still included in the analysis for response to PTRA. At least 4 other PTRA procedures were noted to be technical failures, yet placing a stent to salvage the "failure" was not performed. Therefore, at least 7 (12.5%) of the 56 PTRA patients were inadequately treated. An additional, 5 (8.9%) patients in the PTRA group were treated despite having stenosis of less than 50%. In short, 12 (21.4%) of the 56 patients enrolled in the PTRA group were biased towards having a suboptimal clinical response to PTRA.

4. Lastly, 44% (22/50) of the patients randomly assigned to medical therapy subsequently underwent PTRA for worsening and/or refractory hypertension before the 12 month data analysis. Yet, because of the "intention to treat" analysis, these patients were still included in the medically treated patient group at the 12 month data point. In short, 33% (34/106) of the patients in the study were inadequately treated with PTRA (12) or underwent PTRA (22) despite being inappropriately analyzed as being a medically treated patient at the 12 month data analysis. Yet, despite the major flaws in the study design and data analysis, the 3 month data (before crossover from the medical therapy group to PTRA was allowed) actually supports that PTRA is clinically beneficial when compared to medical therapy. At 3 months of follow-up, the number of blood pressure medicines (2.1 vs. 3.2, $P < 0.001$), creatinine clearance (70cc/min vs. 59cc/min, $P = 0.03$), and abnormal renal scintigrams (36% vs. 70%, $P = 0.002$) were better for the patients in the PTRA group versus the medical therapy group, respectively. At 12 months of follow-up, despite using an "intention to treat" analysis, the number of blood pressure medications required by the PTRA group was 1.5 versus 2.2 ($P = 0.002$) for the medical therapy group, with comparable blood pressure control. In addition, the number of patients in whom the renal artery stenosis progressed to total renal artery occlusion at 12 months was 0 for the PTRA group and 16% for the medical therapy group. Lastly, an increase in creatinine of greater than 50% above the baseline level was seen in only 3.6% of the PTRA group versus 12% in the medical therapy group. With regards to blood pressure control at 12 months, 68% of the PTRA group had improved blood pressure control versus 38% of the medical therapy group. Blood pressure control worsened in only 9% of the PTRA group, while 33% of the medical therapy group had worsened blood pressure control. Again, the difference between the PTRA and medical therapy group would most likely have been amplified if 44% of the medical therapy group had not undergone PTRA prior to the 12 month follow up analysis. Lastly, the blood pressure of the patients receiving medical therapy at 3 months follow-up was 176+/-31 over 101+/-14. After crossover of 44% of these patients to PTRA between 3 and 12 months, the 12 months follow-up blood pressure in the medically treated group was actually improved (163+/-25 over 96+/-10), presumably due to the crossover of patients to PTRA; therefore, obscuring the difference between the PTRA and Medical therapy groups at 12 months follow-up.

   It is also interesting to note that while the abstract conclusion suggested that PTRA had little advantage over medical therapy for treatment of hypertension and renal artery stenosis, the conclusion of the discussion in the manuscript actually states that "use of PTRA and/or stenting should be restricted to refractory hypertension despite use of 3 blood pressure medications, renal artery stenosis in the presence of a rising creatinine, and renal artery stenosis in the presence of a worsening renal scintigram". It is amazing that the message of the abstract is so different from the conclusion of the Discussion.

In summary, the manuscript by van Jaarsveld et al. was a valiant attempt to perform a randomized controlled trial, the study was very flawed with an incorrect Abstract conclusion. Indeed, for physicians who only read abstracts, this study has been very detrimental and misleading for physicians caring for patients with renovascular hypertension. However, despite the problems with this investigation, the study actually supports the belief that there is benefit of PTRA over medical therapy in the treatment of renovascular hypertension. The study also provides some useful data on the natural history of renal artery stenosis (by demonstrating that 16% of patients treated with medical therapy actually have the renal artery stenosis progress to total renal artery occlusion at 12 months of follow-up).

Question 8: Should a stenosis involving a branch vessel in a kidney of a patient with hypertension be treated? In a patient with renal insufficiency? If so, how?

Answer: Stenosis of renal artery branches are mostly observed in patients with atherosclerotic disease or fibro-muscular dysplasia (FMD). In atherosclerotic disease, branch vessel stenoses are often multiple and commonly affect diabetic and chronically hypertensive patients. Localized branch vessel stenoses are more commonly seen in patients with FMD.

Because CTA and MRA are sub-optimal for evaluating segmental renal arteries, catheter angiography is still recommended for investigating branch lesions. Compared to main renal arteries, angioplasty of branch vessels is technically more challenging because it involves smaller vessels commonly located at bifurcations. As such, stenting should be avoided in most cases. These lesions are more prone to spasm, and accurate balloon sizing is more difficult. Because of these technical considerations and the lack of supporting literature, the indication to perform renal branch vessel angioplasty should be carefully weighed against the possible benefits according to each specific anatomic and clinical situation.

Atherosclerotic branch vessel lesions

Atherosclerotic involvement of renal artery branches is usually multifocal and is commonly seen in patients with risk factors such as diabetes or chronic hypertension. Because atherosclerosis is a systemic disease, the contralateral kidney should also be evaluated. The investigation should include functional and anatomic imaging studies. Importantly, patients with an averaged bilateral Doppler resistive index of 0.80 or greater should not be treated with angioplasty regardless of the clinical indication (hypertension or renal failure). Anatomic evaluation of branch stenosis should be performed with selective catheter angiography to properly evaluate the extension of these lesions. Angioplasty should be considered only in patients with isolated or localized branch lesions in the following situations:

Patients with hypertension: PTA of atherosclerotic branch lesions should be considered only when medical therapy has failed. The lesion must be significant on selective angiography and should involve a large branch (at least 3mm). Distal lesions or stenoses that involve small branches (2mm or less) should not be considered for angioplasty.

Patients with renal failure: In general, isolated branch stenosis does not explain renal failure. Most of these patients have coexisting distal angiosclerosis that will not improve after angioplasty. PTA can only be justified in lesions located at the main renal artery bifurcation (if there is significant stenosis of the distal main renal artery) in patients with atrophic or absent contralateral kidney.

I. Fibro-muscular dysplasia

FMD usually involves the distal part of the main renal artery, and extension into the renal branches is common. Isolated involvement of branch vessels is also possible, although less common. Medial involvement is the most common form of FMD. Typically, these lesions respond well to angioplasty, and a good clinical outcome can be expected in hypertensive patients (70% cure and 25 % improvement). A low restenosis rate (9%) is observed after PTA of branch stenoses caused by FMD, and recurring lesions can be treated with repeat angioplasty. Less common adventital and intimal forms of FMD are clinically more resistant to angioplasty (less than 50% improvement) due to technical failures and recurrences, especially

if multiple lesions are present. Angioplasty should be considered in lesions that involve large branches in the following situations:

Patients with hypertension:
1. Medial FMD.
2. If intimal or adventitial FMD is suspected (long and smooth lesions), angioplasty should be considered after failure of medical therapy.
3. Multiple branch stenoses should also be considered after failure of medical treatment.

Patients with renal failure: Renal failure is seldom observed in patients with FMD. When present, renal failure is seen with aggressive forms of FMD with bilateral involvement of intrarenal arteries. In this aggressive form, multiple dissections and occlusions of intrarenal branches are observed. Angioplasty or stenting of large segmental branches can sometimes be attempted to preserve renal function.

II. Arteritis and neurofibromatosis

In pediatric patients, branch vessel stenosis can be seen in association with neurofibromatosis and less frequently with arteritis. These conditions do not respond as well as FMD to angioplasty and recurrences are common. As such, PTA should only be considered after failure of medical treatment.

Technical considerations for renal branch angioplasty:

1. Selective and hyperselective angiography of the renal artery and its branches should be performed with multiple incidences to document the extension of the lesion.

2. A guiding catheter or a guiding sheath should be used with a 0.014 or 0.018 wire system. The guiding catheter should be large enough to accommodate parallel insertion of a safety wire. Administration of nitroglycerine and heparin is strongly recommended at the beginning of the procedure.

3. If the lesion is located at the proximity of a secondary branch, insertion of a safety wire into the latter should be considered.

4. In case of a stenosis involving a bifurcation, alternate kissing balloon inflations should be preferred to simultaneous kissing balloon inflations to avoid the risk of overdilation the proximal artery.

5. Stenting should be reserved for occlusive complications or for angioplasty failures with no alternate therapeutic option. Short low-profile stents should be used.

REFERENCES:

1. Cluzel P, Raynaud A, Beyssen B, Pagny JY, Gaux JC. Stenoses of renal branch arteries in fibromuscular dysplasia: results of percutaneous transluminal angioplasty. Radiology 1994; 193:19-21.
2. Tyagi S, Kaul UA, Satsangi DK, Arora R. Percutaneous transluminal angioplasty for renovascular hypertension in children: initial and long-term results. Pediatrics 1997; 99(1):44-9.
3. Oliva VL, Soulez G, Therasse E. Renal angioplasty and stenting. Can Assoc Radiol J 2001; 52:174-182.

Question 9: What is the role for renal angioplasty/stenting when renal artery stenosis is suspected and the patient has renal insufficiency?

Answer: Renal insufficiency, or ischemic nephropathy is becoming, or should be, the most frequent indication for intervention in renal artery occlusive disease. The clinical, anatomic and physiologic status of the patient must all be integrated and considered in the selection of patients for intervention to yield the best possible risk-benefit for the procedure.

THE INDICATIONS FOR RENAL ARTERY INTERVENTION:

CLINICAL:

1. Recent onset or progressive moderate to severe renal dysfunction
2. Severe or Difficult to Control Hypertension
3. Recurrent Pulmonary Edema
4. Jeopardized Kidney

ANATOMIC:

1. Stenosis ≥60 % Diameter
2. Post Stenotic Dilatation
3. Collateral Circulation
4. Diminished Renal Size (Jeopardized Kidney)

PHYSIOLOGIC:

1. Radionuclide Scan
2. Renal Vein Renin Assay
3. Duplex Ultrasound
4. ***TRANS-STENOTIC PRESSURE GRADIENT***
   ≥ 10 % Peak Systolic or ≥ 5 % Mean Arterial Pressure

WHEN TO INTERVENE AND WHEN NOT!:

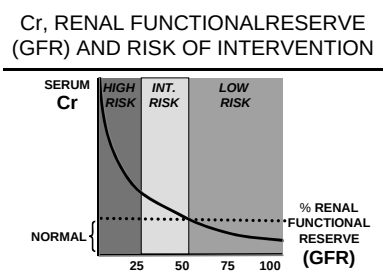
The potential benefits of intervention must be measured against the potential risks and the natural history of the disease. The natural history studies exaggerate the progression of atheromatous renal artery disease. The potential risks of renal artery interventions, especially cholesterol embolization, are under recognized and under reported.

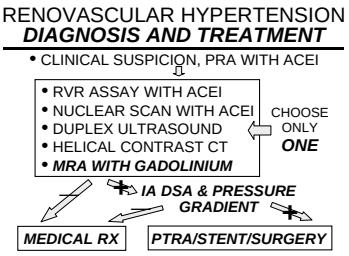
Few physicians performing renal artery interventions are sufficiently familiar with and understand the implications of the **GFR/Serum Cr** curve.

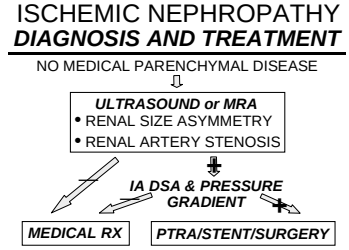
Severe iatrogenic renal parenchymal damage due to diagnostic and therapeutic intravascular procedures in patients with normal pre intervention GLOBAL Serum Cr values can be masked; 50 % of total renal mass, or one of the kidneys can be "destroyed" without any change in global renal function, although the creatinine clearance will be reduced. There is much greater risk when treating patients with elevated Serum Creatinine, whose renal function is at the "knee" of the curve, where there is very diminished renal reserve. In such patients, even an additional 10% loss of renal parenchyma can put the patient on dialysis. For this reason, we believe that it is imperative to confirm the ***physiological*** significance of a stenosis by demonstrating a ***hemodynamically significant trans-stenotic pressure gradient prior to renal artery interventions,*** in addition to adequate ***clinical*** and ***anatomic*** indications**. This is particularly true when treating patients in whom the primary clinical indication is hypertension.**
The initial arteriographic evaluation must begin with an aortogram; NEVER with selective catheterization in a potentially very diseased aorta. If a proximal/ostial renal artery stenosis is found, selective catheterization is contraindicated, ***unless*** an intervention is planned, in which case pressure measurements, as indicated above must be obtained prior to intervention.
The ***minimum*** pressure gradient justifying intervention (using a 4 F catheter) should be:

≥10 % of Peak Systolic Arterial Pressure, or
≥ 5 % of Mean Arterial Pressure

ALGORITHMS FOR DIAGNOSIS AND TREATMENT OF RENOVASCULAR HYPERTENSION AND ISCHEMIC NEPHROPATHY:







THE TECHNIQUES OF RENAL ARTERIOGRAPHY, ANGIOPLASTY AND STENTING:

The techniques described below were developed and evolved over an almost twenty five year experience. They concentrate on two major goals, which are particularly relevant in the patient with compromised renal function:

1. Limiting the amount of nephrotoxic iodinated contrast medium.
2. Limiting and simplifying the manipulations in the diseased abdominal aorta and renal arteries.

AORTOGRAPHY:

Prior to selective renal artery catheterization an aortogram ***must*** be performed. This allows evaluation of the presence, location and extent of atheromatous disease in the aorta and in the renal artery, and the planning of the interventional procedure. We use the **OmniFlush™** (AngioDynamics, Queensbury, NY) catheter for aortography, because its design prevents cephalad reflux into the celiac and superior mesenteric arteries which can overlap the renal arteries and also "steal" contrast from the desired areas of interest. Since the renal arteries originate at the L 1 vertebral body, the sideholes of the catheter are positioned at the T 12-L 1 interspace. Aortography and right renal artery stent deployment is generally performed in the 20-30^{o} LAO projection because the right renal artery usually arises 30^{o} ventrally to the "equator"[13] of the aorta, whereas the left renal artery usually originates directly laterally at the "equator". Axial MRA or CTA images at the level of the renal artery are very helpful in determining the optimal obliquity for aortography.

Since many of these patients have marginal or poor renal function, we try to limit the total amount of iodinated contrast medium. Nephrotoxicity is primarily due to the **iodinated part** of the contrast molecule, therefore we use 30 % concentration (150 mg I/ml) contrast medium, and perform aortography using only 15 ml total volume injected at 15 ml/sec.

SELECTIVE RENAL ARTERY CATHETERIZATION:

We identify the location of the renal artery and the stenosis in relation to the bony landmarks (spine and ribs) and calcifications in the aorta and the renal artery using a non-subtracted aortogram image displayed on a television monitor or as hard copy on a view box. We use a **SoftVue™** (soft tipped) **Sos Omni Selective™** (AngioDynamics, Queensbury, NY) catheter for selective catheterization of the renal artery and for crossing *stenoses*. This "recurve" design is similar to the Simmons type configuration, but has a shorter side arm and is significantly easier and less dangerous to reconstitute its shape. We do not perform contrast test injections during catheterization of the renal artery. Selective catheterization of the stenotic renal artery is performed with the image intensifier in the oblique projection where the origin ("nubbin") of the renal artery is *en face*. The **SoftVue™** (soft tipped) **Sos Omni Selective™** catheter with a very soft floppy **"Bentson" type guidewire** extending approximately one cm from the catheter tip is slowly advanced ***cephalad*** with the catheter tip pointed laterally toward the origin of the renal artery. This maneuver deflects the tip of the wire parallel to the aortic wall, and even slightly pointing toward the

lumen. The wire will readily enter the funnel shaped origin or “nubbin” of the stenotic (or even an occluded) renal artery with a characteristic lateral flick and then it can be gently advanced across the lesion. This maneuver diminishes the volume of contrast used for the diagnostic and therapeutic interventions.

Most ***occluded*** renal arteries have a few millimeter long funnel shaped origin (“nubbin”) proximal to the occlusion, which can be identified and entered as described above; if no “nubbin” is identified, percutaneous recanalization cannot/should not be attempted. For crossing ***occlusions*** we initially use a straight **hydrophilic guidewire** which is forced (pulled) against the funnel shaped nubbin of the origin of the occluded renal artery by the stiffer **AngiOptic™** version of the **Sos Omni Selective™** (AngioDynamics, Queensbury, NY) catheter. The hydrophilic wire should be exchanged out for a non hydrophilic wire as soon as possible, since hydrophilic wires are more likely to produce iatrogenic vessel perforation, or be withdrawn from the vessel inadvertently. Following successfully crossing the lesion, the trans-stenotic pressure gradient must be documented. In the presence of a significant gradient, the soft guidewire is exchanged for a stiffer wire such as the **TAD II™** (Mallinckrodt, St Louis, MO) over which the diagnostic catheter is exchanged for an appropriately sized (usually 6-8 mm diameter) balloon catheter for angioplasty. Prior to stenting, the vessel can be pre-dilated with a relatively small 5mm diameter balloon catheter, and exchanged for a 65 cm long 6 F sheath with a long tapered introducer, such as the **Daig™** (St Jude Medical), **Bright Tip™** (Cordis, Miami, FL), or the **Balkin™** (Cook, Bloomington, IN), Alternatively predilation can be more simply accomplished by advancing the sheath and introducer through the stenosis primarily; this is our currently favored technique. For renal artery stenting only balloon expandable stents should be used. In the past we used the **Palmaz™** (Cordis, Miami, FL) stent but currently prefer the **OmniFlex™** (AngioDynamics, Glenns Falls, NY) because of its MR transparency. For approximate balloon/stent **sizing** we use the length of the curved tip of the **OmniFlush™** (AngioDynamics, Queensbury, NY) catheter; the distance from the top of the curve to the bottom of the tip is always 15mm. The premounted stent is delivered on a balloon catheter through the 6 or 7F guiding catheter (for 0.035” wire based systems) into the stenotic area. Operators should also be familiar with 0.018” wire based systems for renal artery stenting. The guiding sheath is then withdrawn into the aorta, leaving the balloon/stent combination and the guidewire in place and an angiogram is performed through the sheath to aid in the accurate placement of the stent in the renal artery. Contrast injections for stent positioning are performed using only 5ml of 30% contrast injected at 10ml per second. Minor adjustments in the position of the stent can generally be easily performed by advancing or withdrawing the balloon catheter with the mounted stent prior to deployment. The guiding catheter itself can be used if necessary to help in stabilizing the position of the stent during these maneuvers but this should be only used as a last resort since the stent could be damaged by the more rigid guiding catheter. Once the stent is in satisfactory position as evaluated by an angiogram in the appropriate oblique view (the x-ray beam should be perpendicular to the long axis of the origin of the renal artery from the aorta), the balloon is inflated and the stent deployed.

We prefer to deploy the stent with a couple of millimeters extending into the aorta and a few millimeters extending past the stenotic lesion. Palmaz™ and OmniFlex™ stents shorten slightly when expanded. The pulsation of the aorta and the renal artery during the cardiac cycle produces a moderate amount of unpredictable movement of the balloon catheter stent combination. There may also be some unpredictable and difficult to control movement of the balloon catheter stent combination during balloon inflation. For these reasons, we prefer to deploy 15mm long stents for most ostial stenoses. If too short a stent is used or if it is inaccurately placed then a second stent partially overlapping the first one must be deployed to cover the entire lesion. This may decrease long term patency due to extra foreign material and increases the risk of complications. For removing the balloon from the stent after deployment, the sheath should first be gently advanced into the stent as far as it will easily go over the trailing end of the **deflated, but open to air** balloon. This maneuver wraps the balloon to minimize the risk of the balloon “wings” catching in, and inadvertently dislodging the deployed stent.

RISKS OF RENAL ANGIOPLASTY AND STENT PLACEMENT:

During passage of catheters and guidewires through the atheromatous aorta and renal arteries for dilation and stent deployment, the artery can go into spasm, be occluded, perforated, dissected, ruptured or cholesterol crystals may be embolized either into the renal circulation or elsewhere. In-situ thrombosis or thromboembolism from areas of manipulation can also occur. These complications are all very rare; each occurs in fewer than one percent of cases. Many complications are pharmacologically reversible or can be treated by redilatation or stent deployment.

RESULTS:

At New York Presbyterian Hospital Weill Cornell Center,
from May 1989 through January 1997, we attempted to place Palmaz stents in 94 renal arteries in 84 patients. Eighty-seven stents were placed for ostial stenoses. Seventy-seven percent of stents were placed primarily in ostial lesions or total occlusions and 28% after previous failed angioplasties. Indications for intervention were: **hypertension** in 96%; **renal failure** in 60%; (Cr $\geq$ 1.5 mg/dl in 60% ,and $\geq$ 2.0 mg/dl in 45%); and **recurrent flash pulmonary edema** in 30% of patients. Some patients had multiple indications.

Ninety-eight percent of procedures were technically successful. There were seven procedural complications: two thrombosed branch renal arteries partially lysed with urokinase, two puncture site pseudoaneurysms, one puncture site hematoma requiring a transfusion, and three cases of cholesterol embolization (CCE) one with permanent and two with transient renal failure. Angiographic follow-up has been performed in 36% of implanted stents. Seventy-eight percent of stents were widely patent, 22% of stents showed $\geq$60% restenosis. One patient died prior to follow-up from an unrelated cause. Clinical follow-up was available in 100% of patients at a mean of 18 months (0-46); in 22 patients follow-up was at more than 15 months.

The mean blood pressure prior to stenting was 183/91 mm Hg and at the latest clinical follow-up 149/78 mm Hg ($p < .001$). The number of antihypertensive medications was reduced from a mean of 2.93 + 1.4 to 2.08 + 0.9.

Seventy-six percent of patients with Cr > 2.0 mg/dl benefited; 50% had > 20% decrease in Cr, and 25% had stabilized their serum Cr. Eleven of 13 patients with recurrent pulmonary edema and bilateral renal artery stenosis were cured following stenting of one or both renal arteries.

Question 10: What is the role for alternative contrast agents when performing a diagnostic angiogram and/or intervention in a patient with renal insufficiency and suspected renal artery stenosis? What is the role of Fenoldopam, sodium bicarbonate, and Acetylcysteine?

Answer: The question of renal failure during renal interventions is a difficult one. The incidence, mechanism, severity and prevention of contrast-related renal failure are all still unclear. A few aspects of it, however, are clear. First, contrast-related renal failure (CRRF) essentially never occurs in patients with a normal serum creatinine. This is true even though it is also true that serum creatinine is an imprecise measure of renal function: GFR falls with age, as does the amount of creatinine that is produced by the body. That is, a normal serum creatinine(0.5-1.2 or 1.5mgm/dcL) in an 80 year old thin woman probably correlates to a GFR as low as 50-6-ml/min, whereas the same value in a 20 year old indicates a GFR that is probably 80-120ml/min.

Secondly, an elevation in serum creatinine is the best predictor for a bump with the use of iodinated contrast. An elevated creatinine in diabetics is even more ominous. Nonetheless, it is rare for patients to need either short- or long-term dialysis because of CRRF specifically. The likelihood overall in patients with an elevated creatinine who are undergoing cardiac catheterization is about 1.5%.

Third, many other factors come into play in relation to CRRF, including the patient's state of hydration, use of other nephrotoxic drugs (such as Gentamycin), and other co-morbidities, such as CHF or surgery. This is important to consider when scheduling an elective renal intervention.
With this as background, it is clear that the only patients at real risk of CRRF when undergoing renal artery interventions are those with an elevated serum creatinine. How can these patients be identified and how can they be best protected?

It is probably appropriate to have a recent serum creatinine(2 weeks or less) on all patients who are to undergo renal artery interventions. The only possible exceptions are young patients with relatively short duration of hypertension and suspected FMD or vasculitis. Next, it is important that patients, all patients, be as well-hydrated as possible. This can be done orally, with patients encouraged to drink clear liquids for the 24 hours before and after the procedure, or parenterally, generally beginning 12 hours prior to and continuing for 12 hours after the procedure. This must be modified if patients are in CHF.

Various other strategies, including alternative contrast agents and premedications, have been investigated. In patients with normal serum creatinine, the volume of contrast given is not important-increasing volume does not induce renal failure in such patients. In azotemic patients, as well as those with CHF or incipient CHF, volume (and osmotic load) should be limited as much as possible. The use of nonionic agents is common, although conclusive proof that they lower the incidence of renal failure is elusive. The nonionic dimer, Visipaque, is likely to be helpful, as it is isosmolar to blood and causes less alteration in renal blood flow.

The most commonly used alternative contrast agents are carbon dioxide and Gadolinium-based contrast agents. Gadolinium agents should not currently be used in patients with stage III CKD (GFR <= 60 cc/min) because of the widely publicized risk of nephrogenic systemic fibrosis. Carbon dioxide is more widely applicable for several reasons, although it too has limitations. The cost of CO_2 is low, it has very little toxicity if used carefully and there is virtually no limitation on the dose that can be used, and consequently there is really nothing lost if it is tried and fails to provide the necessary information. The major problems with CO_2 are that it is somewhat tricky to use, and the images are generally not as "pretty" as conventional angiographic images. It must be stressed, though, that the quality of information gained with CO_2 is equivalent to that with iodinated contrast agents. Several of the key considerations in using it are:

1. It is compressible, so a 20ml syringe can hold far more than 20ml. It disperses rapidly, so the operator must be very careful to purge the syringe of air, and then to keep the CO_2 in the syringe with a stopcock until it is injected.
2. The more rapidly it is injected and the greater the volume, the more vessel distention occurs, and the more painful the injection becomes. This can cause patient movement, and thus loss of image quality. Images are often improved, counter-intuitively, by using smaller volumes with slower injections.
3. Images are improved with the catheter as close as possible to the area of interest-e.g., a selective renal artery injection will often give better delineation of the contralateral and accessory renal arteries than will an aortic injection.

Various regimens, in addition to hydration, have been investigated as means of decreasing CRRF. The problems inherent in trying to investigate prophylaxis of CRRF are the difficulty in precisely defining what contrast-related renal failure is, the variations in patient risk factors and co-morbidities, and the absence of good understanding of the mechanism of this problem. Further, an elevation in serum creatinine has many different possible etiologies, and it is likely that the negative effect of contrast material will vary with the nature of the underlying renal damage. It has been postulated that CRRF is related to alterations in glomerular and overall renal cortical blood flow. This is based mainly on the finding that contrast agents

cause an initial increase followed by a prolonged decrease in renal blood flow. Also, oxygen free radicals have been implicated in CRRF. This has lead to the use of selective vasodilators, such as adenosine antagonist theophyline. The use of theophyline is limited due to its general toxicity. Other selective vasodilators are also promising, such as prostacyclin analogues, endothelin receptor antagonists and atrial naturietic peptide.

Acetylcysteine acts as an oxygen free radical scavenger, thus preventing cellular toxicity, perhaps toxicity caused by contrast-induced vasoconstriction and resultant cellular hypoxia. It also enhances nitric oxide activity, and this is another possible mechanism of action. As with fenoldapam and Visipaque, proof of the efficacy of acetylcysteine awaits larger randomized studies.

As a bottom line, CRRF is important but is limited to patients with compromised renal function. The best approaches to limiting its incidence and severity are:

- **Intravenous fenoldopam has no role.**
- Ensure good hydration (po or IV) prior to the procedure
- **Sodium bicarbonate, 350 mEq/L of D5w (to avoid excess Na^+ load), infused at 300 ml over an hour prior to the procedure then infused at a maintenance level should be used routinely in patients with renal dysfunction.**
- Limit the dose of the contrast agent used
- Consider Visipaque, particularly if the serum creatinine is greater than 3mgm/dcL.
- Use alternative contrast agents, primarily CO_2-use it enough to develop a familiarity and comfort level with it.
- Consider acetylcysteine 600mgm po bid on the day before and the day of the procedure-but realize that its efficacy is not yet truly proven.

Question 11: How should I work up a patient that I suspect has renal artery stenosis?

Answer: The following criteria are clinical indicators of the presence of renal artery stenosis (RAS):

- Unilateral small kidney
- Epigastric or flank bruit
- Hypertension and extensive arterial disease
- New onset of hypertension at a young age or > 50 years
- Hypertension and unexplained impairment of renal function
- Sudden worsening of renal function in a hypertensive patient
- Impairment of renal function after treatment with ACE inhibitor
- Accelerated or malignant hypertension or hypertension refractory to an appropriate three-drug regimen

The evaluation of patients suspected of having RAS on clinical grounds starts with noninvasive imaging studies. Theses tests can be separated into physiologic (scintigraphy, Doppler sonography) and anatomic (MRA, spiral CTA). These tests are complementary and can be performed in combination (1).
We generally start the imaging evaluation with a physiologic test which serves as screening. We prefer Doppler sonography over scintigraphy because of its better accuracy.

Doppler evaluation of the renal artery consists of both measurement of the peak systolic velocity in the main renal artery and pattern analysis of intrarenal Doppler waveform.

We recommend completing the investigation with an imaging study that will depict the anatomy of the renal arteries. The choice of cross-sectional imaging is somewhat site determined. Gadolinium enhance MRA cannot be performed in patients with stage III CKD, and early angiography (with nephroprotective strategies and small volumes of iso-osmolar contrast) is most likely the best option in these patients if there is a reasonable clinical suspicion of RAS.

After combining the results of noninvasive imaging studies, accurate evaluation of the renal arteries can be obtained in the great majority of cases with the exception of the following limitations: mild forms of fibro-muscular dysplasia (FMD), small accessory renal arteries, branch stenoses, extensive calcifications (CTA); in the rare cases where these situations are considered a possible cause for hypertension in the presence of negative noninvasive studies, catheter angiography is recommended as the final diagnostic examination. For example, we recommend performing bilateral selective catheter angiography instead of MRA or CTA when FMD is suspected. Catheter angiography is also used to solve occasional discrepancies between noninvasive studies, to confirm RAS and accurately determine the percentage of luminal diameter reduction before therapy.

It is generally accepted that RAS less than 50% in diameter are not significant. RAS measuring 70% or greater are considered severe or significant. RAS that measure between 50% and 70% fall into the "moderate" category, and their significance needs to be established with one of the following: abnormal captopril scintigraphy, abnormal intrarenal Doppler waveform pattern, significant pressure gradient measured across stenosis.

Once the hemodynamic significance of RAS has been established, correction of the stenosis should be based on clinical indications (hypertension or renal function). Several imaging and clinical factors are known to affect the outcome of renal revascularization (2). Importantly, a renal resistance-index value of 0.80 or greater reliably identifies patients with RAS in whom angioplasty or surgery will not improve renal function, blood pressure, or kidney survival (3).

REFERENCES:

1. Soulez G, Oliva VL, Turpin S, Lambert R, Nicolet V, Therasse E. Imaging of renovascular hypertension: respective values of renal scintigraphy, renal Doppler US, and MR angiography. RadioGraphics 2000; 20:1355-1368.
2. Giroux MF, Soulez G, Therasse E, Nicolet V, Froment D, Courteau M, Oliva VL. Percutaneous revascularization of the renal arteries: predictors of outcome. JVIR 2000; 11:713-720.
3. Radermacher J, Chavan A, Bleck J, et al. Use of Doppler ultrasonography to predict the outcome of therapy for renal-artery stenosis. N Engl J Med 2001; 344:410-417.

Question 12: How should I follow a patient that I have treated previously for renal artery stenosis with angioplasty/stenting?

Answer: We recommend clinical follow-up as well as renal Doppler sonography at 6 months, 12 months, and q 12 months. Ultrasonographic contrast agents can be used for sub-optimal or inconclusive Doppler examinations (1). If clinical follow-up or Doppler sonography suggests restenosis, anatomic evaluation of the renal artery should be performed. Noninvasive angiographic evaluation can be obtained with MRA or CTA if angioplasty alone has been performed. If a stent has been implanted, MRA is not recommended due to stent-related artefacts whereas CTA can be used for evaluating the renal artery lumen. Although still under evaluation, CTA with multiplanar reformations has been shown to be adequate for determining stent patency (2). Catheter angiography is reserved for sub-optimal or equivocal noninvasive angiographic studies.

REFERENCES:

1. Lacoursiere Y, Levesque J, Onrot JM, et al. Impact of Levovist ultrasonographic contrast agent on the diagnosis and management of hypertensive patients with suspected renal artery stenosis: a Canadian multicentre pilot study. Can Assoc Radiol J 2002; 53:219-227.
2. Behar JV, Nelson RC, Zidar JP, DeLong DM, Smith TP. Thin-section multidetector CT angiography of renal artery stents. AJR 2002; 178:1155-1159.

Question 13: Is there a role for antiplatelet agents before, during or after renal angioplasty/ stenting?

Answer: Antiplatelet agents can be given intravenously during renal artery revascularization procedures, or subsequent to these patients by mouth. Intravascular antiplatelet agents are used presumably to reduce the incidence of acute thrombosis of stents. The oral antiplatelet agents following revascularization parameters may have a role in reducing restenosis. Both acute thrombosis and restenosis are uncommon in renal artery interventions.

The currently available intravenous agents are abciximab, tirofiban, and eptifibatide. There is little peripheral artery literature using these agents; one case series of 14 patients (1) and a case report of abciximab given with balloon angioplasty for acute rethrombosis of a renal artery stent were published(2). These drugs were once routine for carotid artery interventions, but without randomized examination of their results. Because of the risk of intracranial hemorrhage, many high-volume sites have dropped intravenous antiplatelet agents from their carotid stent protocols.

From coronary literature, there is suggestive evidence that the incidence acute thrombosis could be reduced in renal artery stent placement. In the EPIC Study 2,099 patients were randomized to bolus plus infusion of a GP IIb/IIIa inhibitor or placebo (3). Over 30 days post-coronary stent, the GP IIb/IIIa inhibitor group had an 8% incidence of events (death, nonfatal myocardial infarction, unplanned surgical revascularization, unplanned repeat percutaneous procedure, unplanned implantation of a coronary stent, or insertion of an intraaortic balloon pump for refractory ischemia) compared with 13% in the placebo group. In the EPILOG Study, similar reduction in the primary endpoints (death from any cause, myocardial infarction, or urgent revascularization) were observed at 30 days, 5% vs. 12% (4). Very similar numbers were observed for similar events using similar treatment regimens in the EPISTENT Study (5). In this study, 11% of those who received coronary artery stents without abciximab experienced death, myocardial infarction, or need for urgent revascularization within the first 30 days compared to 5% in stented patients who received abciximab. Hemorrhagic complications with GP IIb/IIIa inhibitors are not common, but thrombocytopenia can occur in roughly 1% and should be monitored (5). RESIST data – combined distal embolic protection (Angioguard, Cordis, Warren, NJ) AND abciximab (n=25) was associated with statistically significant BP outcomes and histologic evidence of less captured platelet rich emboli. Interestingly, either of these therapeutic strategies alone (rather than in combination) did not confer benefit.

However, coronary arteries are more prone to acute thrombosis than renal arteries, and the experience above probably would not be reproduced in the renal circulation. Renal thrombosis or analogous events within 30 days of stent placement are rare, certainly not 12-13% as in the coronary arteries. Complications such as guidewire perforation and renal artery rupture may be more frequent, and if these occur platelet inhibitors would not be welcome. In order to conclusively answer the question with regard to renal arteries, one would need a randomized clinical trial with many thousands of patients, given the comparative infrequency of this occurrence. This is unlikely to ever happen. At this time, GP IIb/IIIa inhibitors can not be recommended for all renal stent placements, but rather should be reserved for patients at high-risk for acute thrombosis, such as hypercoaguable patients, those undergoing segmental artery stent placement, or for example, when bailing out an intraprocedural or periprocedural thrombosis. Commonly used oral antiplatelet agents are aspirin and clopidogrel. It has been suggested that cilostazol (Pletal) may also have beneficial effects in reducing restenosis (6). For clopidogrel, it has been suggested that 6 months of therapy is better than 1 month after coronary stenting and radiation (8). Ticlopidine was the first oral antiplatelet agent to show improved patency in coronary stent placement. Clopidogrel was compared with ticlopidine and was found to be equivalent (9). Given the limited risk, there is stronger argument for the routine use of clopidogrel after renal artery stenting than intraprocedural GP IIb/IIIa inhibitors despite the lack of randomized trial data. There is good evidence from the CAPRIE study that patients with peripheral vascular disease should be maintained on clopidogrel and aspirin indefinitely, unless they have contraindications.

REFERENCES:

1. Tepe G, Schott U, Erley CM, Albes J, Claussen CD, Duda SH. Platelet glycoprotein IIb/IIIa receptor antagonist used in conjunction with thrombolysis for peripheral arterial thrombosis. AJR Am J Roentgenol 1999;172(5):1343-6.
2. Berkompas DC. Abciximab combined with angioplasty in a patient with renal artery stent subacute thrombosis. Cathet Cardiovasc Diagn 1998 Nov;45(3):272-4.
3. The EPIC Investigators. Use of a monoclonal antibody directed against the platelet glycoprotein IIb/IIIa receptor in high-risk coronary angioplasty. N Engl J Med 1994;330(14):956-61.
4. The EPILOG Investigators. Platelet glycoprotein IIb/IIIa receptor blockade and low-dose heparin during percutaneous coronary revascularization. N Engl J Med 1997;336(24):1689-96.
5. The EPISTENT Investigators. Randomized placebo-controlled and balloon-angioplasty-controlled trial to assess safety of coronary stenting with use of platelet glycoprotein-IIb/IIIa blockade. Evaluation of Platelet IIb/IIIa Inhibitor for Stenting. Lancet 1998 Jul 11;352(9122):87-92.
6. El-Beyrouty C, Spinler SA. Cilostazol for prevention of thrombosis and restenosis after intracoronary stenting. Ann Pharmacother 2001;35(9):1108-13.
7. Park SW, Lee CW, Kim HS, Lee HJ, Park HK, Hong MK, Kim JJ, Park SJ. Comparison of cilostazol versus ticlopidine therapy after stent implantation. Am J Cardiol 1999;84(5):511-4.
8. Waksman R, Ajani AE, White RL, Pinnow E, Dieble R, Bui AB, Taaffe M, Gruberg L, Mintz GS, Satler LF, Pichard AD, Kent KK, Lindsay J. Prolonged antiplatelet therapy to prevent late thrombosis after intracoronary gamma-radiation in patients with in-stent restenosis: Washington Radiation for In-Stent Restenosis Trial plus 6 months of clopidogrel (WRIST PLUS). Circulation 2001;103(19):2332-5.
9. Berger PB, Bell MR, Rihal CS, Ting H, Barsness G, Garratt K, Bellot V, Mathew V, Melby S, Hammes L, Grill D, Holmes DR Jr. Clopidogrel versus ticlopidine after intracoronary stent placement. J Am Coll Cardiol. 1999;34(7):1891-4.

Question 14: Is there a role for filtration devices during renal angioplasty/ stenting?

Answer: The answer to this question depends on the patient's renal function. It is probably not justified in patients with adequate renal reserve unless you are planning on giving them a serious amount of emboli. While in young patients the Serum Creatinine is a good indicator of renal function, in elderly patients the Glomerular Filtration Rate (GFR) is more accurate as older patients have less body mass than younger ones. Each time a plaque is disrupted by a balloon or stent there is probably a shower of emboli comprising cholesterol debris and plaque fragments to the distal vessels. If the renal function is normal this will likely have no measurable effect. However in cases of renal impairment, such a shower of emboli may tip the patient into overt renal failure. There is no effective treatment of "trash kidney". Radical treatments like plasmaphoresis have in my experience been useless.

A meta-analyses of renal angioplasty (1) showed significant decline in renal function after angioplasty in those patients with pre-existing impairment of renal function. Our own experience (2) indicated that almost 35% of patients overall showed an increase in serum creatinine from basal levels and in those with pre-existing renal impairment the percentage of worsening renal function was 62%! Emboli were only recognized in a small number of these patients and it is possible that contrast media toxicity was also a contributor. However in most cases of renal impairment we would now use carbon dioxide instead of iodinated contrast. Dr Andrew Holden in Auckland, New Zealand, has pioneered the concept of using renal filtration devices to protect patients from renal microemboli. His data which was presented (at the IRSA meeting in 2002 in Cairns, Far North Queensland) in 24 patients (30 renal arteries) showed a zero incidence of decline in renal function in azotemic patients and 80% of the filters contained significant debris of cholesterol clefts and plaque fragments after the procedure.

Apart from the additional cost to consider, there are significant technical issues using current filters, which are designed for a long vessel, in the renal artery. The average renal artery bifurcates about 40mm from its origin and the current combination of balloon, stent and filter device is about 50mm. A recent development is the “Spider” embolic protection device (ev3, Plymouth, Mn) which is a nitinol mesh filter designed to be deployed through a 3.2Fr microcatheter after the lesion has been crossed by your choice

of wire. This overcomes the problem of getting across the lesion with a short tip guide wire seen on other filters but it is still a relatively long system at 6 and 7mm filter diameters.

Use of the filter is easier when a monorail or rapid exchange system is used as the filter wire can be used to cross the lesion without the use of interchange catheters or pre-dilatation.

In a patient with borderline renal impairment and low renal reserve a case can be made for use of renal artery filtration during renal angioplasty and stenting.

There is developing experience using a distal balloon occlusion device (Guardwire, Medtronic Inc.) during renal protection (Holden, Edwards JVS 2007, Rundback personal experience). These devices have very limited purchase in the renal arteries and are therefore suitable in almost all cases. Main renal artery protection can be achieved in 80-95% of cases, with partial protection possible in nearly all of the rest of cases. The balloon inflation is volume rather than pressure mediated; despite this, the occlusion balloon wire provides an extremely secure platform for subsequent stent insertion and positioning. No cases of clinical relevant renal decline due to “warm ischemia” have been described, and occlusion times are almost always <15 minutes, and usually less than 10 minutes for each kidney.Early clinical experience has shown reduced rates of renal function decline using balloon occlusion embolic protection when treating azotemic patients than expected from historical controls. Further data and more trials are needed. Another interesting device in phase 1 trials is the Fibernet filter (Lumend Medical). This is a fiber mesh with very small pore size and a deployed width of mm with diameters up to 8 mm. Again, data is pending.

REFERENCES:

1. Palmaz JC. The current status of vascular intervention in ischemic nephropathy. JVIR. 1998 Jul-Aug;9(4):539-43.
2. Perkovic V, Thomson KR, Mitchell PJ, Gibson RN, Atkinson N, Field PL, Becker GJ. Treatment of renovascular disease with percutaneous stent insertion; Longterm outcomes. Australas Radiol 2001; 45: 438 - 443
3. Holden A, Hill A Renal angioplasty and stenting with distal protection of the main renal artery in ischemic nephropathy: early experience. J Vasc Surg. 2003 Nov;38(5):962-8.