

*Medical Progress***RENAL-ARTERY STENOSIS**

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PRI-MARY diseases of the renal arteries often involve the large renal arteries, whereas secondary diseases are frequently characterized by small-vessel and intrarenal vascular disease. In this article, we will concentrate on the two most common primary diseases of the renal arteries — atherosclerotic renal-artery stenosis and fibromuscular dysplasia — and their association with two common clinical syndromes, hypertension and ischemic nephropathy. The relations among renal-artery stenosis, hypertension, and renal excretory dysfunction are complex (Fig. 1). Renal-artery stenosis may occur alone (isolated anatomical renal-artery stenosis) or in association with hypertension, renal insufficiency (ischemic nephropathy), or both.

PREVALENCE AND NATURAL HISTORY

Fibromuscular dysplasia is a collection of vascular diseases that affects the intima, media, and adventitia (periarterial fibromuscular dysplasia). Fibromuscular dysplasia accounts for less than 10 percent of cases of renal-artery stenosis, and 90 percent of cases of fibromuscular dysplasia involve the media. Fibromuscular dysplasia tends to affect girls and women between 15 and 50 years of age, frequently involves the distal two thirds of the renal artery and its branches, and is characterized by a beaded, aneurysmal appearance on angiography (Fig. 2). Intimal and periarterial fibromuscular dysplasia is commonly associated with progressive dissection and thrombosis, whereas medial fibromuscular dysplasia progresses in 30 percent of patients and is rarely associated with dissection or thrombosis. In contrast to atherosclerotic renal-artery stenosis, fibromuscular dysplasia rarely leads to renal-artery occlusion. The cause of fibromuscular dysplasia is unknown, although many theories have been advanced, including those involving a genetic predisposition, smoking,

hormonal factors, and disorders of the vasa vasorum as risk factors.

Atherosclerosis accounts for 90 percent of cases of renal-artery stenosis and usually involves the ostium and proximal third of the main renal artery and the perirenal aorta (Fig. 2C). In advanced cases, segmental and diffuse intrarenal atherosclerosis may also be observed, particularly in patients with ischemic nephropathy (Fig. 3). The prevalence of atherosclerotic renal-artery stenosis increases with age, particularly in patients with diabetes, aortoiliac occlusive disease, coronary artery disease, or hypertension.²⁻⁵ Among patients with atherosclerotic renal-artery stenosis, progressive stenosis was reported in 51 percent of renal arteries five years after diagnosis (including 18 percent of initially normal vessels),^{6,7} only 3 to 16 percent of renal arteries became totally occluded,^{3,4,6,8} and renal atrophy developed in 21 percent of patients with renal-artery stenosis of more than 60 percent. Thus, atherosclerotic renal-artery stenosis is a common and progressive disease, particularly in patients with diabetes or other manifestations of atherosclerosis. Nevertheless, it is likely that many cases of atherosclerotic renal-artery stenosis are never detected because refractory hypertension or renal failure does not develop.

RENAL-ARTERY STENOSIS AND HYPERTENSION**Pathophysiology**

The risk of cardiovascular events in adults depends more on the degree of hypertension than on its cause. A decrease in renal perfusion pressure activates the renin-angiotensin system, which leads to the release of renin and the production of angiotensin II; has direct effects on sodium excretion, sympathetic nerve activity, intrarenal prostaglandin concentrations, and nitric oxide production; and causes renovascular hypertension.^{9,10} When hypertension is sustained, plasma renin activity decreases (referred to as “reverse tachyphylaxis”), partially explaining the limitations of renin measurements for identifying patients with renovascular hypertension.

Although renovascular hypertension often contributes to accelerated or malignant hypertension, it is not readily distinguishable from essential hypertension. Certain classic features, such as hypokalemia, an abdominal bruit, the absence of a family history of essential hypertension, a duration of hypertension of less than one year, and the onset of hypertension before the age of 50 years, are more suggestive of renovascular hypertension than of other types of hypertension,¹¹ but none have strong predictive value. In fact, the ma-

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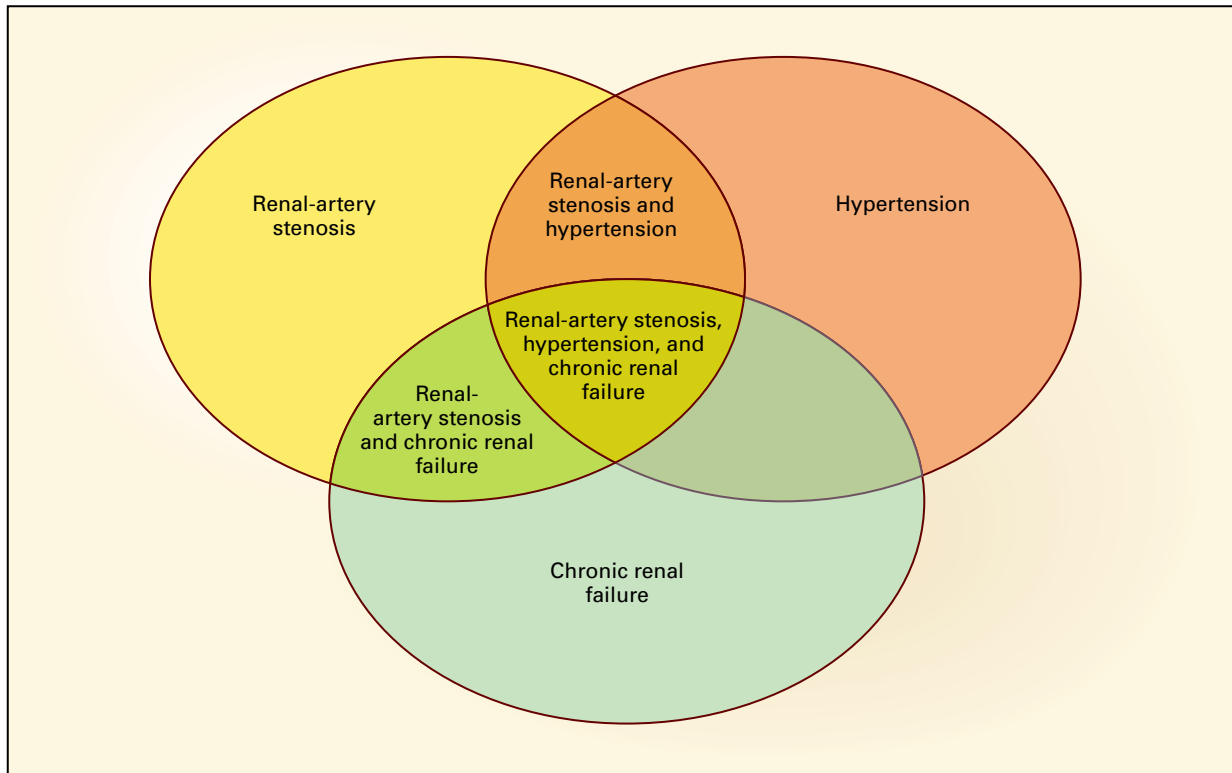


Figure 1. Interrelation among Renal-Artery Stenosis, Hypertension, and Chronic Renal Failure.

Renal-artery stenosis may occur alone (isolated anatomical renal-artery stenosis) or in combination with hypertension (renovascular or essential hypertension), renal insufficiency (ischemic nephropathy), or both. Patients with renal-artery stenosis alone may benefit from revascularization to prevent loss of renal mass. In patients with renal-artery stenosis and hypertension, hypertension is seldom cured by revascularization, except in those with fibromuscular dysplasia. In patients with renal-artery stenosis and chronic renal failure, renal revascularization may improve or stabilize renal function.

majority of patients with renal-artery stenosis who have hypertension have essential hypertension, as suggested by the fact that the hypertension usually persists despite successful revascularization.

Noninvasive Evaluation

Patients with certain clinical features associated with renal-artery stenosis are often considered for further evaluation (Table 1). The evaluation may include studies to assess overall renal function, physiological studies to assess the renin-angiotensin system, perfusion studies to assess differential renal blood flow, and imaging studies to identify renal-artery stenosis (Table 2). Methods of measuring the response of the renin-angiotensin system include renin-sodium profiling, assessment of plasma renin activity before and after the administration of captopril, assessment of the effect on blood pressure and renal function of an angiotensin-converting-enzyme (ACE) inhibitor, and captopril renography to assess differential renal perfusion. The tests are not recommended in most elderly patients with atherosclerotic renal-artery stenosis and hyperten-

sion, since hypertension in these patients is not renin-dependent and the results do not reliably predict the course of hypertension after revascularization. In contrast, these studies are more useful for identifying patients with fibromuscular dysplasia in whom hypertension is likely to be cured by revascularization, since this disorder is frequently renin-dependent.^{12,13}

Because of the limited usefulness of physiological studies in elderly patients with atherosclerotic renal-artery stenosis, imaging techniques are preferable as a means to identify stenosis in such patients (Fig. 4). Duplex ultrasonography can provide images of the renal arteries and assess blood-flow velocity and pressure waveforms, but there is a 10 to 20 percent rate of failure due to the operator's inexperience or the presence of obesity or bowel gas.¹⁴ Gadolinium-enhanced magnetic resonance angiography and computed tomographic angiography are useful for evaluating the renal circulation and aorta, but they are less reliable for visualizing distal segments and small accessory arteries.^{15,16} Gadolinium is not nephrotoxic and is useful in patients with renal insufficiency.

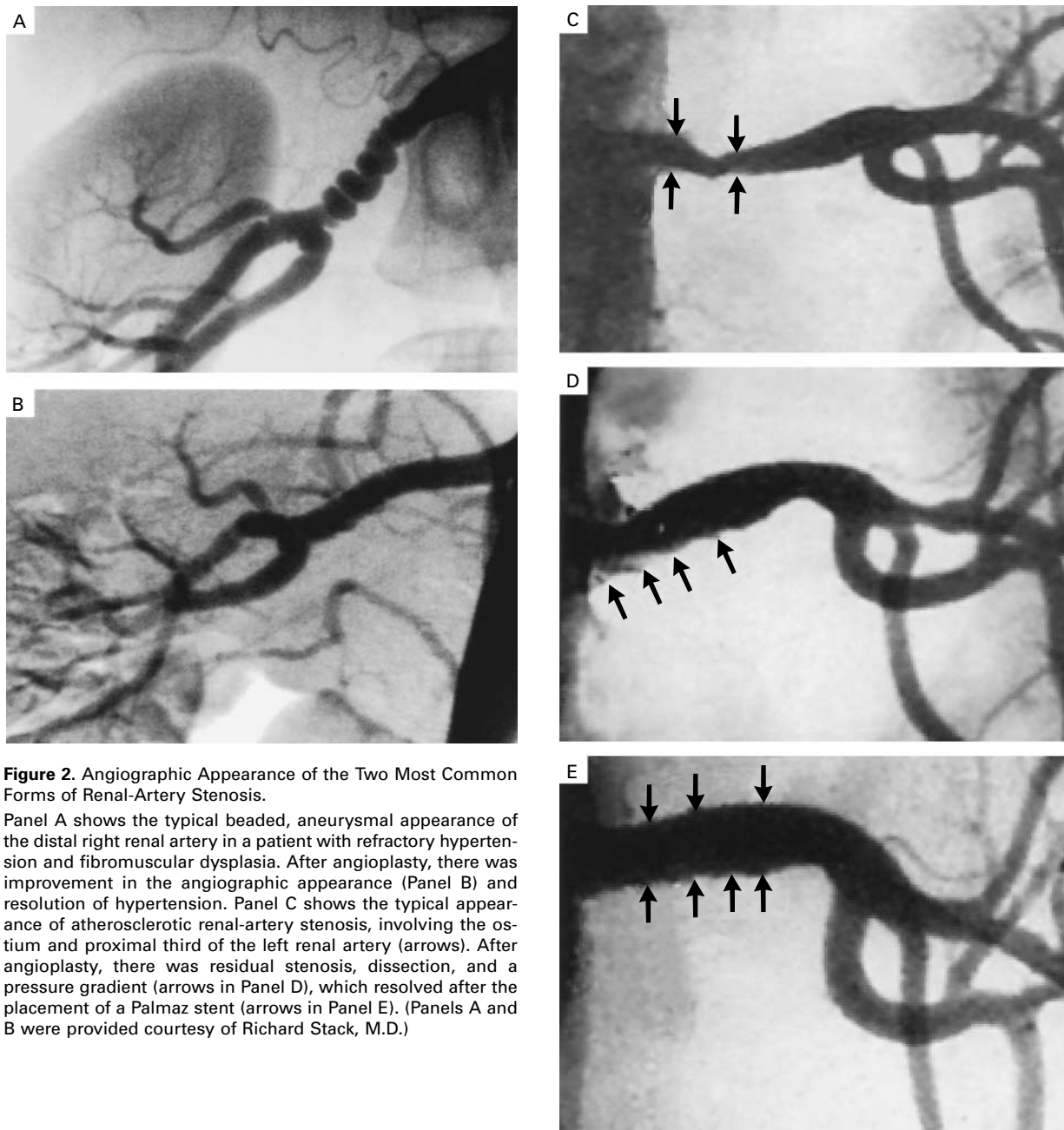


Figure 2. Angiographic Appearance of the Two Most Common Forms of Renal-Artery Stenosis.

Panel A shows the typical beaded, aneurysmal appearance of the distal right renal artery in a patient with refractory hypertension and fibromuscular dysplasia. After angioplasty, there was improvement in the angiographic appearance (Panel B) and resolution of hypertension. Panel C shows the typical appearance of atherosclerotic renal-artery stenosis, involving the ostium and proximal third of the left renal artery (arrows). After angioplasty, there was residual stenosis, dissection, and a pressure gradient (arrows in Panel D), which resolved after the placement of a Palmaz stent (arrows in Panel E). (Panels A and B were provided courtesy of Richard Stack, M.D.)

Invasive Evaluation

The goals of contrast-enhanced angiography are to confirm the diagnosis and cause of renal-artery stenosis and to evaluate the extent of intrarenal vascular disease, determine the dimensions of the kidneys, and identify associated aneurysmal or occlusive diseases of the aorta. Low-osmolar contrast material is recommended to minimize the discomfort of injections of contrast mediums, but it must be used cautiously in patients with renal failure because of its nephrotoxicity. Intraarterial digital subtraction techniques may reduce

the volume of contrast medium needed to 15 to 20 ml, an amount that would not be expected to lead to worsening of base-line renal function in most patients. In patients with advanced oliguric renal failure, the use of noniodinated contrast agents such as carbon dioxide or gadolinium may obviate the risk of contrast-medium-induced nephropathy.¹⁷

Medical Therapy

Patients with fibromuscular dysplasia rarely have excretory dysfunction, and hypertension in these patients

generally responds to ACE inhibitors or — in patients with refractory hypertension — to balloon angioplasty. For patients with hypertension and atherosclerotic renal-artery stenosis, aspirin, cholesterol-lowering drugs, and smoking cessation are essential to limit atherosclerosis. ACE inhibitors and angiotensin-receptor blockers are effective in 86 to 92 percent of these patients,¹⁸ but the loss of renal mass and reduction in transcapillary filtration pressure can produce acute or chronic renal insufficiency, especially if renal-artery stenosis affects both kidneys or the sole functional kidney.^{19,20} ACE-inhibitor-induced renal insufficiency is potentiated by sodium depletion and preexisting renal dysfunction, is usually reversible if detected promptly, and often provides an indication that critical renovascular disease is present. When the serum creatinine concentration is normal, potential loss of renal mass can be predicted on the basis of the finding on nuclear imaging that fractional flow to the stenotic kidney is impaired (Table 2), and this finding may provide further justification for renal revascularization.^{4,8,21,22}

Surgical Revascularization

Before ACE inhibitors and balloon angioplasty became available, unilateral aortorenal bypass surgery was the most common surgical technique.^{23,24} The use of aortorenal bypass has declined in many centers, and extra-anatomical bypass (in which the bypass originates from the celiac or mesenteric branches rather than the aorta) now accounts for 80 percent of renal bypass operations in some centers.^{23,25} Perioperative mortality rates range from 2.1 percent to 6.1 percent for extra-anatomical bypass²³⁻²⁷ and from 1 percent to 4.7 per-

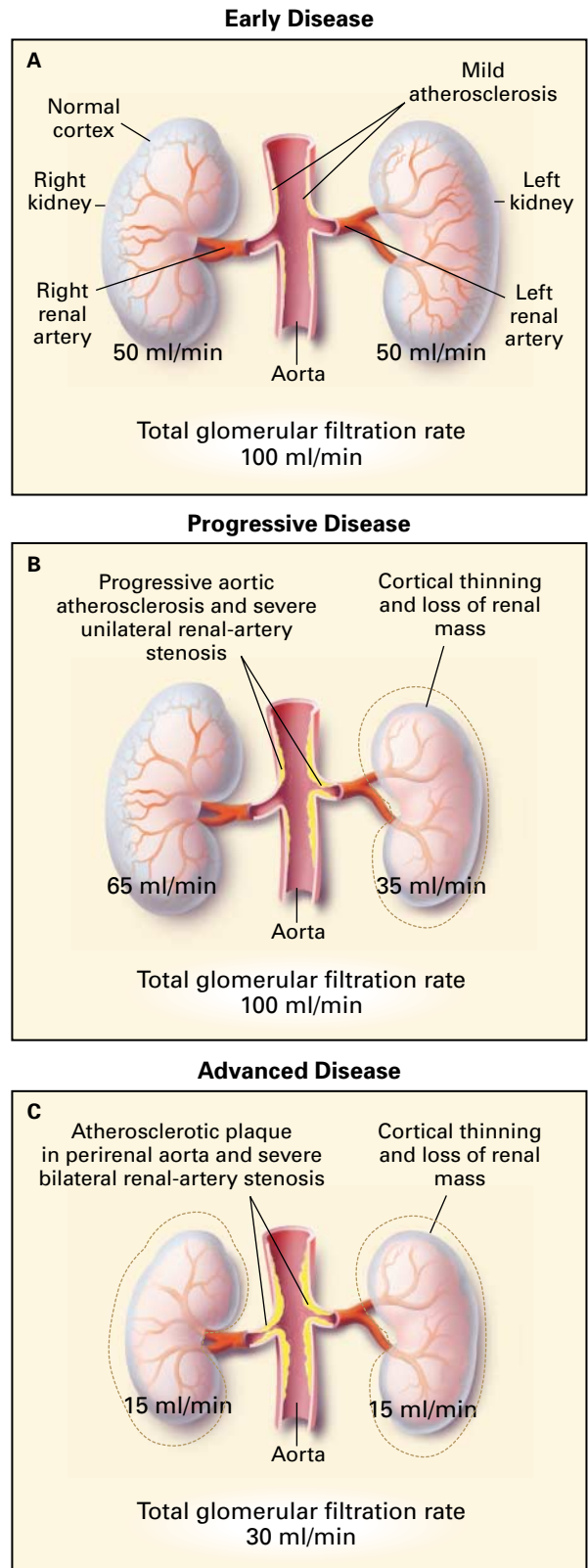


Figure 3. Progressive Atherosclerosis, Renal-Artery Stenosis, and Ischemic Nephropathy.

In the early phase (Panel A), there is mild atherosclerosis of the perirenal abdominal aorta and normal renal function. Renal blood flow, renal mass, and the serum creatinine concentration are normal. The dimensions of the kidneys are normal, and there is no cortical atrophy. The total glomerular filtration rate (100 ml per minute) and the glomerular filtration rate in each kidney (50 ml per minute) are normal. As the disease progresses (Panel B), there is progressive aortic atherosclerosis and severe unilateral renal-artery stenosis. The left kidney is smaller than the right kidney, and there may be cortical thinning and asymmetry in renal blood flow. The serum creatinine concentration remains normal as long as the right kidney is normal, despite the loss of renal mass. The total glomerular filtration rate may be normal (100 ml per minute) or only slightly depressed owing to compensatory changes in the right kidney, but renal blood flow is decreased in the left kidney (35 ml per minute). In advanced disease (Panel C), there is bulky atherosclerotic plaque in the perirenal aorta and severe bilateral renal-artery stenosis. Both kidneys are small, and there is marked cortical thinning and irregularity. Loss of more than 50 percent of renal mass is usually associated with an elevation in the serum creatinine concentration (ischemic nephropathy), which may not be reversible. The total glomerular filtration rate (30 ml per minute) and the glomerular filtration rate in each kidney (15 ml per minute) are depressed.

TABLE 1. CLINICAL FINDINGS ASSOCIATED WITH RENAL-ARTERY STENOSIS.

Hypertension	
	Abrupt onset of hypertension before the age of 50 years (suggestive of fibromuscular dysplasia)
	Abrupt onset of hypertension at or after the age of 50 years (suggestive of atherosclerotic renal-artery stenosis)
	Accelerated or malignant hypertension
	Refractory hypertension (not responsive to therapy with ≥ 3 drugs)
Renal abnormalities	
	Unexplained azotemia (suggestive of atherosclerotic renal-artery stenosis)
	Azotemia induced by treatment with an angiotensin-converting-enzyme inhibitor
	Unilateral small kidney
	Unexplained hypokalemia
Other findings	
	Abdominal bruit, flank bruit, or both
	Severe retinopathy
	Carotid, coronary, or peripheral vascular disease
	Unexplained congestive heart failure or acute pulmonary edema

cent for renal endarterectomy.^{26,28} Factors that increase perioperative mortality include the need for aortic reconstruction, the presence of severe preoperative azotemia, the need for bilateral renal bypass, and the use of an aortic graft as the source of aortorenal bypass.^{21,26,29-34} Independent predictors of an increased likelihood of death in the perioperative period include early graft failure, the presence of coronary artery disease, the presence of uncontrolled hypertension, and the need for abdominal aortic-aneurysm repair.²⁶ Other complications include myocardial infarction (in 2.0 to 9.0 percent of patients),^{23,28,29} stroke (in 0 to 3.3 percent),²⁵ hemorrhage requiring surgical exploration (in 2.0 to 3.0 percent),^{29,35} and cholesterol embolization (in 1.0 to 4.3 percent).^{22,25,29}

Early graft failure has been reported in 1.4 to 10 percent of patients,^{24,25,27,30,35} is usually due to graft thrombosis associated with technical problems, and is the strongest independent predictor of perioperative death.²⁶ In contrast, late graft failure is usually due to the presence of organized thrombus, intimal proliferation, and progressive atherosclerosis. At five years, the rate of graft failure ranges from 6 percent to 18 percent,^{24,26,30,32} repeated operation or angioplasty is required in 5 to 15 percent of patients,²³ and the survival rate is 65 to 81 percent.^{23,29,30,36} Independent predictors of increased late mortality include an age of more than 70 years at the time of the bypass, the presence of coronary artery disease, and preoperative uncontrolled hypertension.^{26,32} Follow-up imaging studies are recommended after revascularization, particularly if conditions suggesting graft failure, such as hypertension or renal dysfunction, develop.

Percutaneous Intervention

Percutaneous revascularization of renal-artery stenosis involves conventional balloon angioplasty, with

or without stenting. Guiding-catheter techniques are commonly employed, which involve the use of coronary or peripheral guide wires and balloon catheters. Treatment with aspirin before the procedure and the use of a low-osmolar contrast medium and heparin during the procedure are recommended. Conventional balloon angioplasty is considered the treatment of choice for patients with uncontrolled hypertension and fibromuscular dysplasia (Fig. 2). The procedure is successful in 82 to 100 percent of patients,^{37,38} and stenosis recurs in 10 to 11 percent.^{39,40}

In contrast, conventional balloon angioplasty is less effective for atherosclerotic renal-artery stenosis,⁴⁰ because of the potential for dissection and the elastic recoil and rigidity of the lesions.^{41,42} These limitations account for the incidence of restenosis of 10 to 47 percent after renal angioplasty. An analysis of the pooled results of studies of conventional balloon angioplasty in 1118 patients showed that 0.5 percent died in the hospital, 0.3 percent underwent nephrectomy, 2.0 percent required renal surgery,^{37,38} 2.2 percent had occlusion of a side branch of the renal artery, 1.1 percent had cholesterol embolization, and 2.3 percent sustained an injury at the site of vascular access.^{37,38} The rate of immediate success of conventional balloon angioplasty is higher for nonostial atherosclerotic renal-artery stenosis (72 to 82 percent) than for ostial atherosclerotic renal-artery stenosis (60 to 62 percent).^{43,44} As compared with patients with fibromuscular dysplasia, patients with atherosclerotic renal-artery stenosis have much lower rates of event-free survival⁴³ and late vessel patency.⁴⁵

Although the results of randomized studies have not yet been reported, stenting is an attractive alternative to conventional balloon angioplasty for atherosclerotic renal-artery stenosis, because of its efficacy in resolving dissections, elastic recoil, residual stenoses, and translesional pressure gradients after conventional balloon angioplasty (Fig. 2E).^{46,47} No stents have yet been approved by the Food and Drug Administration for this indication, so stents designed for the biliary tract, coronary arteries, and iliac arteries have been applied to the renal circulation. Limitations of published studies include the short duration of follow-up (commonly, 6 to 16 months) and the inconsistent use of angiography and duplex ultrasonography to assess the patency of the stents. Despite these limitations, most studies have reported success rates of 94 to 100 percent, residual-diameter stenoses of less than 10 percent, and rates of angiographically evident restenosis of 11 to 23 percent at one year.^{42,47-49}

The dramatic improvement in the diameter and contour of the lumen after stenting is not merely cosmetic, since the final diameter after intervention is an important predictor of the risk of restenosis.⁴⁸ Among 700 patients who received a stent between 1995 and 1998, 0.5 percent died and 0.7 percent had thrombosis of the stent.^{42,47-52} Three-year survival was heavi-

TABLE 2. NONINVASIVE ASSESSMENT OF RENAL-ARTERY STENOSIS.

STUDY	RATIONALE	STRENGTHS	LIMITATIONS
Physiological studies to assess the renin-angiotensin system			
Measurement of peripheral plasma renin activity	Reflects the adequacy of sodium excretion	Measures the level of activation of the renin-angiotensin system	Low predictive accuracy for renovascular hypertension; results influenced by medications and many other conditions
Measurement of captopril-stimulated renin activity	Produces a fall in pressure distal to the stenosis	Enhances the release of renin from the stenotic kidney	Low predictive accuracy for renovascular hypertension; results influenced by many other conditions
Measurement of renal-vein renin activity	Compares renin release from the two kidneys	Lateralization predictive of improvement in blood pressure with revascularization	Nonlateralization not predictive of the failure of blood pressure to improve with revascularization; results influenced by medications and many other conditions
Functional studies to assess overall renal function			
Measurement of serum creatinine	Measures overall renal function	Readily available; inexpensive	Not sensitive to early changes in renal mass or single-kidney function
Urinalysis	Assesses urinary sediment and proteinuria	Readily available; inexpensive	Results are nonspecific and influenced by many other diseases
Nuclear imaging with [¹²⁵ I]iothalamate or chromium Cr 51-labeled pentetic acid (DTPA) to determine the glomerular filtration rate	Measures overall glomerular filtration rate	Useful for estimating glomerular filtration rate in patients with normal and abnormal renal function	Expensive; not widely available
Perfusion studies to assess differential renal blood flow			
Captopril renography with technetium ^{99m} Tc mertiatide (^{99m} Tc MAG3)	Captopril-mediated fall in filtration pressure amplifies differences in renal perfusion	Normal study excludes renovascular hypertension	Multiple limitations in patients with advanced atherosclerosis or creatinine >2.0 mg/dl (177 μmol/liter)
Nuclear imaging with technetium mertiatide or technetium-labeled pentetic acid (DTPA) to estimate fractional flow to each kidney	Estimates fractional flow to each kidney	Allows calculation of single-kidney glomerular filtration rate	Results may be influenced by the presence of obstructive uropathy
Vascular studies to evaluate the renal arteries			
Duplex ultrasonography	Shows the renal arteries and measures flow velocity as a means of assessing the severity of stenosis	Inexpensive; widely available	Heavily dependent on operator's experience; less useful than invasive angiography for the diagnosis of fibromuscular dysplasia and abnormalities in accessory renal arteries
Magnetic resonance angiography	Shows the renal arteries and perirenal aorta	Not nephrotoxic; useful in patients with renal failure; provides excellent images	Expensive; less useful than invasive angiography for the diagnosis of fibromuscular dysplasia; stents result in imaging artifacts
Computed tomographic angiography	Shows the renal arteries and perirenal aorta	Provides excellent images; stents do not cause artifacts	Not widely available; the large volume of contrast medium required is potentially nephrotoxic

ly influenced by base-line renal function: it was 94 percent among patients with normal renal function at base line, 74 percent among those with a serum creatinine concentration of 1.5 to 2.0 mg per deciliter (133 to 177 μmol per liter), and 52 percent among those with a serum creatinine concentration of more than 2.0 mg per deciliter. A base-line serum creatinine concentration of more than 1.5 mg per deciliter was the strongest independent predictor of late death (relative risk, 5.0).⁵²

One small prospective, randomized comparison of conventional balloon angioplasty and surgical revascularization in patients with hypertension and athero-

sclerotic renal-artery stenosis found a higher rate of primary patency among patients treated surgically at four years (96 percent vs. 75 percent), as assessed by angiography; similar rates of secondary patency (97 percent and 90 percent); and no cost advantage for conventional balloon angioplasty.^{53,54} The findings in another study suggested that stenting was substantially cheaper than conventional balloon angioplasty or bypass.⁵⁵

Effect of Revascularization on Hypertension

Published studies of the outcome of revascularization for renal-artery stenosis have had numerous lim-

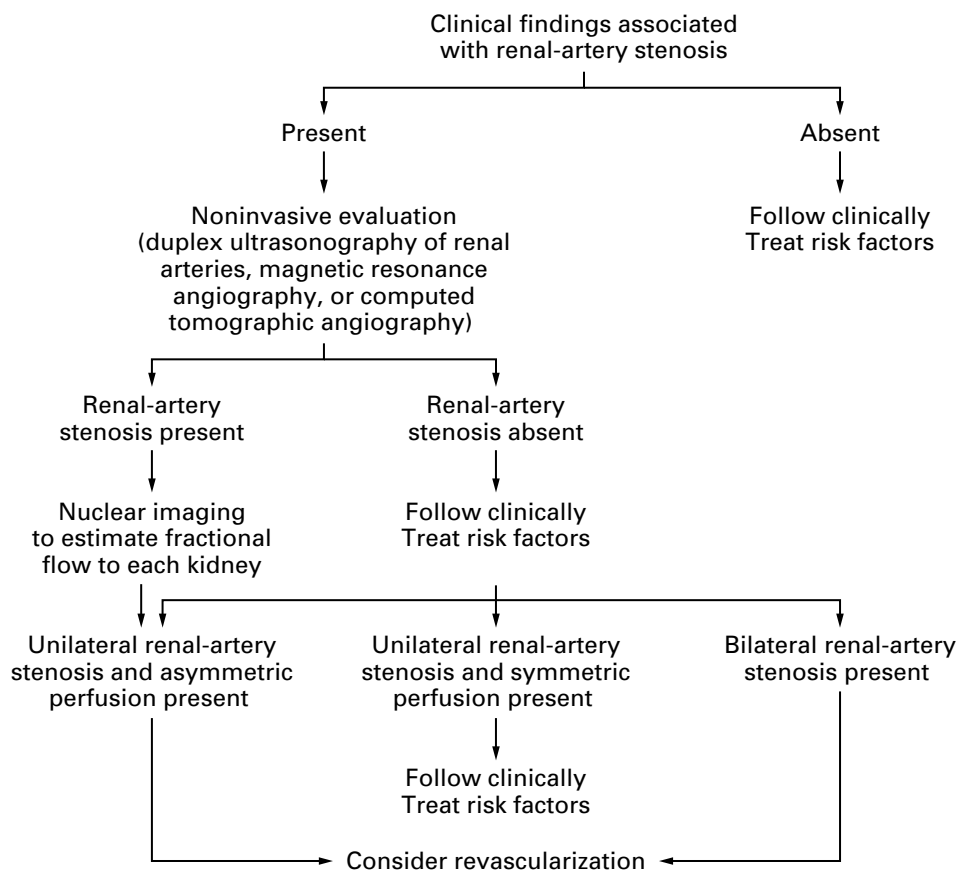


Figure 4. Algorithm for Evaluating Patients in Whom Renal-Artery Stenosis Is Suspected.

The clinical findings associated with renal-artery stenosis are listed in Table 1. Clinical follow-up includes periodic re-assessment with duplex ultrasonography, magnetic resonance angiography, and nuclear imaging to estimate fractional blood flow to each kidney. The treatment of risk factors includes smoking cessation and the use of aspirin, lipid-lowering agents, and antihypertensive therapy.

itations. Hypertension has been classified as “cured” (i.e., the blood pressure is normal without a need for medication), improved (the number or dose of medications is reduced, blood pressure is better controlled, or both), or unchanged, but the ability to make direct comparisons among studies is limited because of differences in medical therapy, target blood pressure, and criteria for improvement. Interpretation of the data is further limited by the uncertain clinical relevance of these classification groups, since statistically significant differences in blood pressure and medications may not be clinically significant. Finally, the effects on renal-artery stenosis of aggressive lipid-lowering therapy, risk-factor modification, antihypertensive therapy, and aspirin have not been studied. These important limitations may partially explain the lack of enthusiasm of some physicians for further studies of the use of renal angiography and revascularization to control hypertension.

Despite these limitations, it is apparent that hypertension is more likely to be cured after revascularization in patients with fibromuscular dysplasia than in those with atherosclerotic renal-artery stenosis (60 percent vs. <30 percent), regardless of the type of revascularization.^{21,24,27,28,36-38,40,43} Recurrent hypertension after initial improvement is unusual,^{56,57} but if it occurs, it may be due to restenosis, atherosclerosis, or both. Two small randomized trials of conventional balloon angioplasty and medical therapy demonstrated a significant decrease in blood pressure and a reduced need for medication in the conventional angioplasty group, but cure of hypertension was rare.^{58,59} A recent randomized trial involving patients with hypertension and atherosclerotic renal-artery stenosis showed no significant difference in outcomes between angioplasty and medical therapy.⁶⁰ Like other means of revascularization, stenting has been associated with a small but statistically significant decrease in blood pressure and in

the need for medication at four years.^{48,52} The rates of cure of hypertension after stenting are low and are similar to those associated with surgery and conventional balloon angioplasty.^{47,49,52}

ISCHEMIC NEPHROPATHY

Pathophysiology

Ischemic nephropathy is defined as an obstruction of renal blood flow that leads to ischemia and excretory dysfunction (Fig. 3).²¹ The causation is not fully understood, since normal kidneys receive more blood and oxygen than are necessary for metabolic requirements and markers of renal ischemia are not altered in underperfused kidneys.⁶¹ However, autoregulation of blood flow is ineffective when systolic blood pressure falls below 70 or 80 mm Hg, and factors such as reduced shear stress and decreased production of nitric oxide,⁶² increased production of endothelins, and activation of the renin-angiotensin system may create localized areas of ischemia, tubular injury, epithelial-cell disruption, and interstitial fibrosis.⁶³ Renal dysfunction is less common with fibromuscular dysplasia than atherosclerotic renal-artery stenosis, suggesting that atherogenic factors serve to increase the renal injury.

Clinical Characteristics

Atherosclerotic renal-artery stenosis may be overlooked as a cause of renal insufficiency,⁶⁴⁻⁶⁷ but it should be considered, since it is potentially reversible when treated early.^{21,24,25,27,66} The absence of hypertension does not preclude the possibility of renal-artery stenosis.⁶⁴⁻⁶⁷ Two important ischemic renal syndromes are acute renal failure and unexplained chronic or progressive azotemia. Renal-artery stenosis should be considered in the differential diagnosis of acute renal failure, particularly if the analysis of urinary sediment has unremarkable results and there are no signs of acute tubular necrosis, glomerulonephritis, or interstitial nephritis.⁶⁴ Among patients with renal-artery stenosis, acute renal failure may occur 1 to 14 days after the initiation of treatment with ACE inhibitors,²⁰ but acute ischemic nephropathy may also occur after the use of diuretics or other antihypertensive drugs,^{61,63,64,68-70} after major surgery, and after the spontaneous progression of renal-artery stenosis to occlusion.⁷⁰⁻⁷² When acute renal failure and oliguria are due to bilateral occlusion of the renal arteries, urinary findings may mimic those of acute tubular necrosis.

Patients with unexplained chronic or progressive renal failure represent a diverse group, and occult ischemic nephropathy may be present in up to 24 percent of such patients who are 50 years of age or older,^{73,74} particularly among those with generalized atherosclerosis, recurrent pulmonary edema, or uncontrolled hypertension (Table 1).⁶⁵ Ischemic nephropathy is an important cause of end-stage renal disease,^{8,66,67,73} and among patients who are receiving dialysis, those with renovascular disease have the lowest survival rate (me-

dian survival, 25 to 34 months) and a 5-year mortality rate of more than 80 percent.^{8,24,65,75} Unilateral renal-artery stenosis is not associated with elevated serum creatinine concentrations, and an increase in the serum creatinine concentration to more than 2.0 mg per deciliter in a patient who is known to have atherosclerotic stenosis of one renal artery suggests the development of bilateral stenosis, parenchymal disease, or both.

Noninvasive Evaluation

Ideally, a noninvasive test for ischemic nephropathy would identify patients with severe renal-artery stenosis and reversible ischemic dysfunction; unfortunately, no such test is available. Patients with severe stenosis can be identified on the basis of the ability of sodium nitroprusside or ACE inhibitors to induce controlled hypotension,⁷⁶ but the sensitivity and specificity of this method are unknown. A finding of asymmetric renal size is consistent with the presence of ischemic nephropathy but is nonspecific.^{3,7,8,22} Most physicians rely on the serum creatinine concentration as a surrogate for the glomerular filtration rate because this measure is convenient and inexpensive to determine and also reflects overall renal function. However, the serum creatinine concentration is not ideal because of its sensitivity to changes in muscle mass, dietary protein intake, tubular secretion, and extrarenal metabolism.⁷⁷

These limitations also apply to other measurements that rely on the serum creatinine concentration, including creatinine clearance, inverse creatinine slopes, and the Cockcroft formula for estimating the glomerular filtration rate. Also, the serum creatinine concentration is a poor index of the function of individual kidneys and renal mass, since unilateral renal-artery stenosis of more than 70 percent is often associated with a reduction in the glomerular filtration rate in one kidney,⁶⁴ but there may be no change in the creatinine concentration until 50 percent of the total renal mass is lost (Fig. 3).^{3,4,7}

Although patients without atherosclerosis who have one kidney (such as those who have undergone nephrectomy for renal transplantation, those with renal-cell carcinoma, and those with injuries related to trauma) can tolerate such a loss of renal mass without long-term consequences, bilateral stenosis develops within two years in 18 percent of patients with unilateral atherosclerotic renal-artery stenosis.⁴ Hence, patients with unilateral atherosclerotic renal-artery stenosis have less renal reserve than patients without atherosclerosis, and early recognition of renal vascular disease is essential to avert the development of advanced renal dysfunction.

As a practical matter, to detect ischemic nephropathy one must have a high index of suspicion and use vascular imaging techniques.⁶⁴ Once renal-artery stenosis is identified, some centers⁷⁸ (including our own) use [¹²⁵I]iothalamate to estimate the total glomerular filtration rate; we assess the fractional flow to each kidney

with technetium ^{99m}Tc -labeled pentetic acid (DTPA) or technetium ^{99m}Tc mertiatide (^{99m}Tc -MAG3) (Table 2). The total glomerular filtration rate and the rate in each kidney can be used to assess base-line and serial function, before and after renal revascularization (Fig. 3).^{3,78}

Medical Therapy

Little is known about the efficacy of medical therapy targeted to ischemic nephropathy. Progressive renal failure may occur despite successful revascularization, suggesting that ischemic nephropathy may be multifactorial,⁷⁹ and efforts to limit atherosclerosis are essential. The long-term effect of conservative therapy on renal dysfunction remains controversial: two studies found that serum creatinine concentrations rose in only 5 to 10 percent of patients,^{3,7} whereas another study showed clear deterioration of renal function, which stabilized or improved only after successful revascularization.⁸⁰

For patients with advanced renal failure, reported predictors of functional recovery after revascularization include the following findings: filling of the distal renal arterial bed by collateral vessels, visualization of an excretory pyelogram after angiography, intact glomeruli on renal biopsy,²⁷ a renal length of more than 7 to 9 cm,^{64,81} and a serum creatinine concentration of less than 4.0 mg per deciliter (354 μmol per liter).⁸¹ However, these variables may not be reliable indicators in a given patient, and several studies have reported the reversal of renal failure after successful revascularization, even among patients who had been receiving dialysis for as long as one year^{73,82-84} and those with bilateral renal-artery occlusion.^{44,65,71,82} In our experience, however, patients with diffuse intrarenal vascular disease and poor cortical blood flow are likely to have irreversible ischemic nephropathy, and in such patients, revascularization of the renal arteries rarely improves excretory function.

Renal Revascularization

There is no consensus about which patients should undergo revascularization or the type of revascularization that should be used. The decision to revascularize the kidney to preserve renal function is based on the assumptions that the stenosis is hemodynamically important and contributes to renal insufficiency and that correction of the stenosis will stabilize or improve renal function. The timing of revascularization remains controversial; many clinicians do not advocate its use unless there is bilateral renal-artery stenosis and the creatinine concentration is elevated. However, several types of evidence suggest that performing revascularization before the serum creatinine concentration becomes elevated is a better approach. First, surgical studies report that the risk of perioperative and late death (within four years) and renal failure rises by a factor of 2 to 3 for each increment of 1.0 mg per deci-

liter (88 μmol per liter) in the base-line creatinine concentration^{33,85,86} and that the incidence and severity of postoperative renal failure are highly dependent on the base-line creatinine concentration.^{30,31,34} Second, late outcomes after surgical^{33,36,85} and percutaneous⁵² intervention are better when base-line renal function is normal. Third, a base-line creatinine concentration of more than 1.5 mg per deciliter is the strongest independent predictor of the risk of death within four years after renal stenting and is associated with a risk that is five times as high as that among patients with a base-line creatinine concentration of 1.5 mg per deciliter or less.⁵²

Effect of Revascularization on Renal Function

Studies of the ability of revascularization to preserve renal function are severely limited by the small numbers of patients studied, the brevity of follow-up, and the lack of a control group of patients who were treated with optimal medical management. The studies have classified renal function as improved, unchanged, or worse, but the definitions of these terms have been inconsistent. For example, it is unclear whether the term "unchanged" means that renal function stabilized or that the treatment had no effect. After surgical or percutaneous revascularization, renal function improves in 40 to 55 percent of patients and deteriorates further in 14 to 30 percent.^{23-25,27,28,44,52,57,87-89} In one study, surgical revascularization slowed the rate of decline in the glomerular filtration rate to 0.94 percent per week, as compared with a rate of 3.25 percent per week at base line.²¹ Causes of renal deterioration after successful revascularization include volume depletion, nephropathy induced by the use of contrast medium, and renal embolization. These potential complications, particularly in patients with renal failure, often temper physicians' enthusiasm for renal revascularization. In the future, the use of devices designed to protect the distal portion of the arteries, such as balloons and filters, may reduce the risk of renal embolization and improve the outcome of percutaneous intervention.

RECOMMENDATIONS

The evaluation and treatment of patients with renal-artery stenosis must be individualized on the basis of clinical factors such as age, existing medical conditions, the likelihood that the correction of renal-artery stenosis will improve blood-pressure control and renal function, and the risk entailed by invasive procedures. Our recommendations (Fig. 4) are chiefly based on clinical characteristics, an assessment of risk factors for renal-artery stenosis (Table 1), base-line renal function, and the degree of asymmetry in renal blood flow on nuclear imaging (Table 2); the primary goal is to preserve renal function.

The base-line assessment of renal function should include measurement of the serum creatinine concen-

tration and urinalysis. For patients who have no clinical findings suggestive of renal-artery stenosis, we recommend medical therapy, periodic follow-up, and aggressive modification of risk factors for atherosclerosis. Patients who have one or more clinical findings should be considered for further evaluation. For patients with normal renal function who have at least one clinical finding and who require coronary or peripheral arteriography for other reasons, we recommend abdominal aortography, since it adds little or no risk to the angiographic procedure. For patients with base-line renal insufficiency or those who do not require invasive angiography, we prefer magnetic resonance angiography, because it provides information about the anatomy of renal arteries, kidneys, and aorta.

If the results of noninvasive studies suggest the presence of renal-artery stenosis, we recommend nuclear imaging studies to determine the total glomerular filtration rate and the glomerular filtration rate of each kidney. If the patient has unilateral renal-artery stenosis and normal renal function, and the blood flow to both kidneys is symmetric, we recommend continued close follow-up without intervention. Noninvasive vascular imaging or studies of the glomerular filtration rate in each kidney should be repeated periodically to monitor the progression of the disease.

The indications for revascularization of the renal arteries are the subject of controversy. In the presence of unilateral renal-artery stenosis and asymmetric blood flow, or of bilateral renal-artery stenosis, we recommend angiography and revascularization for patients with normal or mildly impaired renal function. In patients with refractory hypertension and renal-artery stenosis, the likelihood of cure of hypertension is highest among those with fibromuscular dysplasia, and conventional balloon angioplasty is the treatment of choice. In patients with atherosclerotic renal-artery stenosis, control of hypertension is facilitated by revascularization, cure of hypertension is unusual, and preservation of renal function may be more important. However, we consider chronic hypertension a weak indication for renal revascularization (because most studies suggest that such an approach has only a small effect on hypertension), unless accelerating or malignant hypertension develops, suggesting the presence of a renovascular component.

The revascularization technique to be used depends on the presence or absence of associated aortoiliac diseases. Stenting is reasonable in cases of unilateral or bilateral atherosclerotic renal-artery stenosis that are not associated with disease of the aorta. For complicated cases involving renal-artery stenosis and aortic aneurysmal or occlusive disease, surgical revascularization and renal bypass are both reasonable approaches. Some surgeons prefer to perform aortic replacement, followed by percutaneous treatment of renal-artery stenosis. Serial studies of the glomerular filtration rate of each kidney and magnetic resonance angiography

or duplex ultrasonography should be performed yearly after revascularization to monitor renal perfusion and vessel patency.

For patients with advanced renal dysfunction, revascularization of both renal arteries (or of one in patients with a single functional kidney) may be considered, but the decision to intervene is heavily dependent on the presence of other known renal and extrarenal diseases. We believe that the presence of diabetic nephropathy, severe proteinuria, and poor cortical blood flow would argue against the possibility that the ischemic nephropathy is reversible. The presence of unilateral renal-artery stenosis and severe renal failure indicates advanced parenchymal disease and thus that the risk entailed by revascularization is not justified.

CONCLUSIONS

Atherosclerotic renal-artery stenosis is a common manifestation of generalized atherosclerosis and is frequently associated with hypertension and excretory dysfunction. However, the association of renal-artery stenosis with hypertension or renal insufficiency does not establish causation, and although the methods for the diagnosis and treatment of renal-artery stenosis have improved, the use of invasive diagnostic techniques and treatment early in the course of the disease still has no proven benefit. Furthermore, there seems to be a shift away from identifying patients with renovascular hypertension, because of the known benefits of medical therapy and the lack of sustained cure after percutaneous or surgical revascularization, and a shift toward identifying patients with renal-artery stenosis who are at risk for excretory dysfunction. Because of this shift, medical therapy and modification of risk factors to limit atherosclerosis are essential in all patients, regardless of whether they have undergone revascularization. In patients with atherosclerotic renal-artery stenosis who are at risk for excretory dysfunction, percutaneous and surgical techniques may improve or stabilize renal function.

The long-term results are better in patients who have better renal function at base line, suggesting that deferring revascularization until renal function deteriorates may not be the best approach; further study is clearly needed. A multicenter, randomized trial is being organized to compare the efficacy of renal stenting and of aggressive medical therapy in preserving renal function.

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