Ischemic nephropathy

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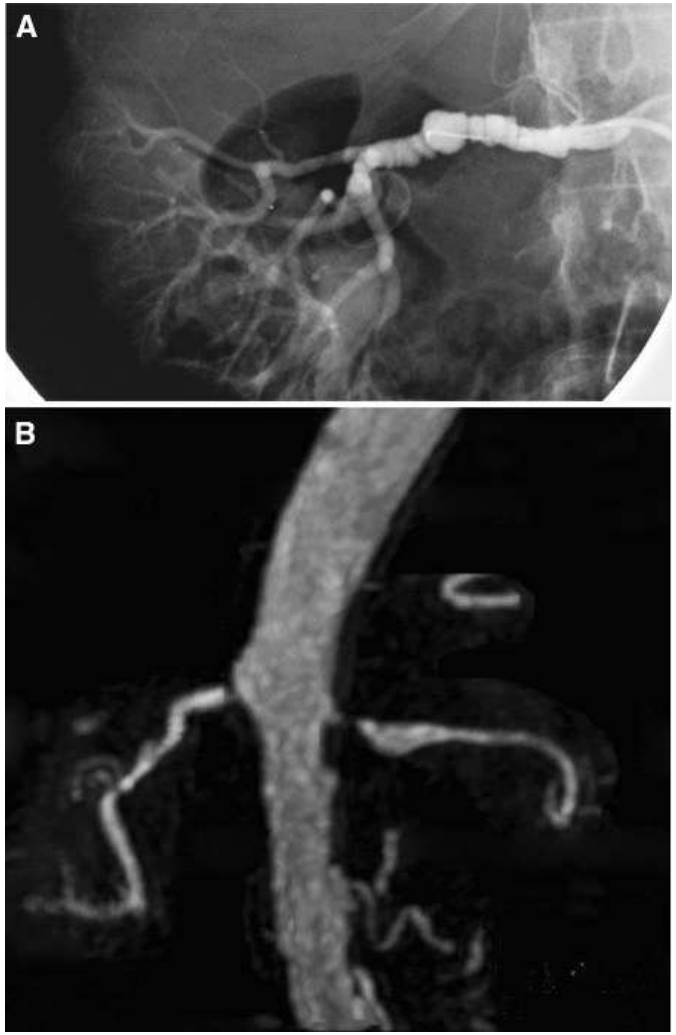
I have no relevant financial relationship to disclose

Andrzej Wiecek

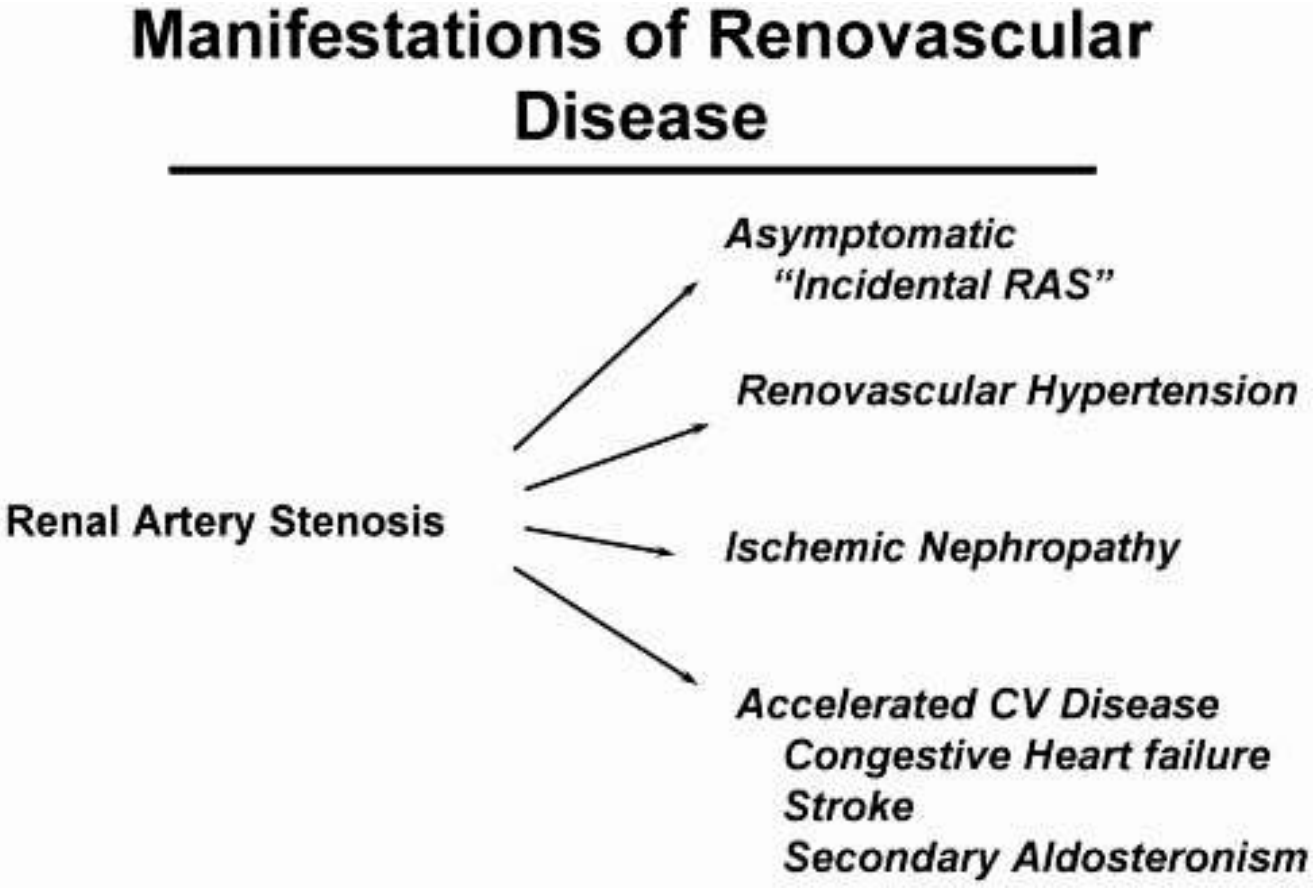


A, Angiogram from a patient with FMD with lesions characteristic of medial fibroplasia. The "string-of-beads" appearance typically develops in the mid portion of the vessel from circumferential webs within the vessel. These lesions may progress, particularly in smokers.

B, MRA from an individual with atherosclerotic disease affecting the renal arteries. These lesions commonly arise near the ostium of the vessel and may be an extension of aortic plaques.

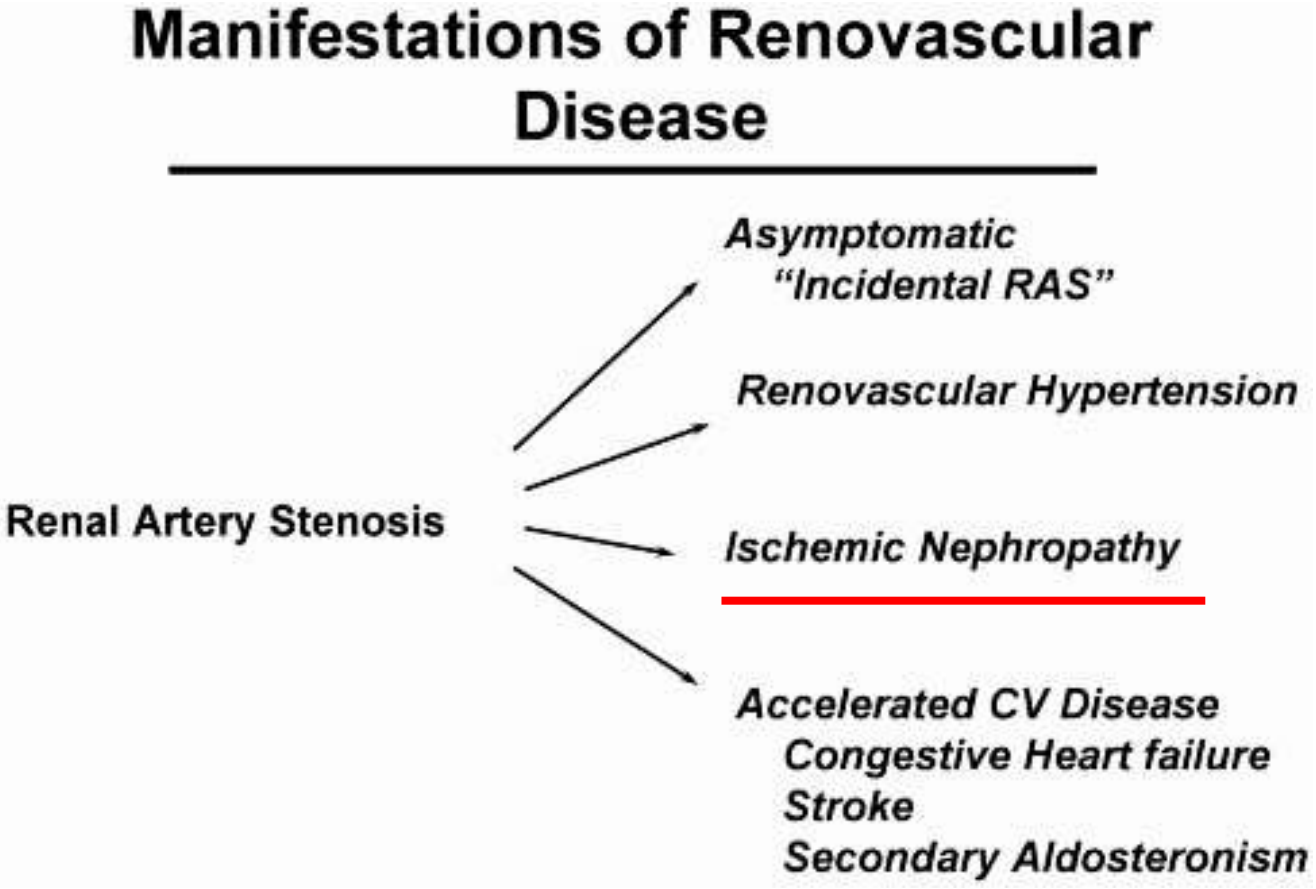
Garovic V.D. and Textor S.C., Circulation. 2005; 112: 1362-1374

Schematic summary of the clinical manifestations of renovascular disease



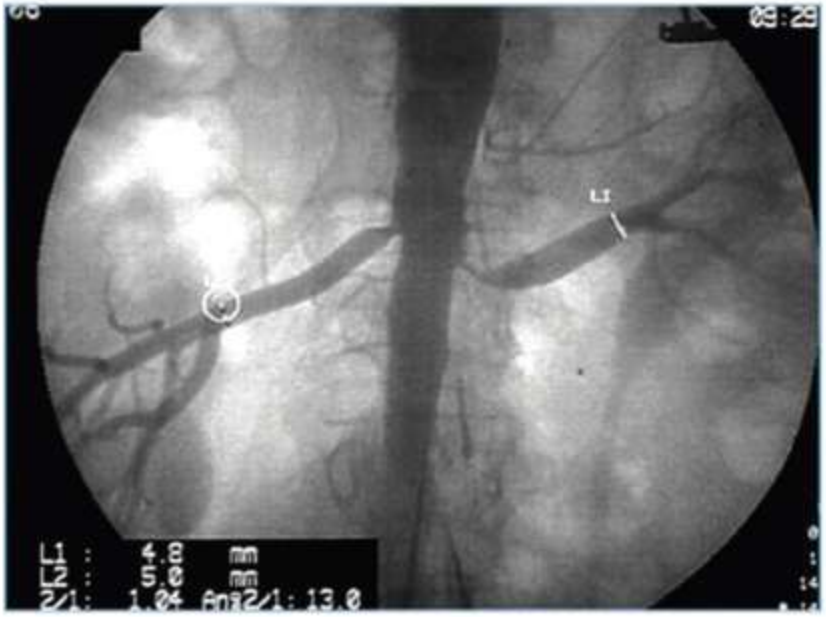
Garovic V.D. and Textor S.C., Circulation. 2005; 112: 1362-1374

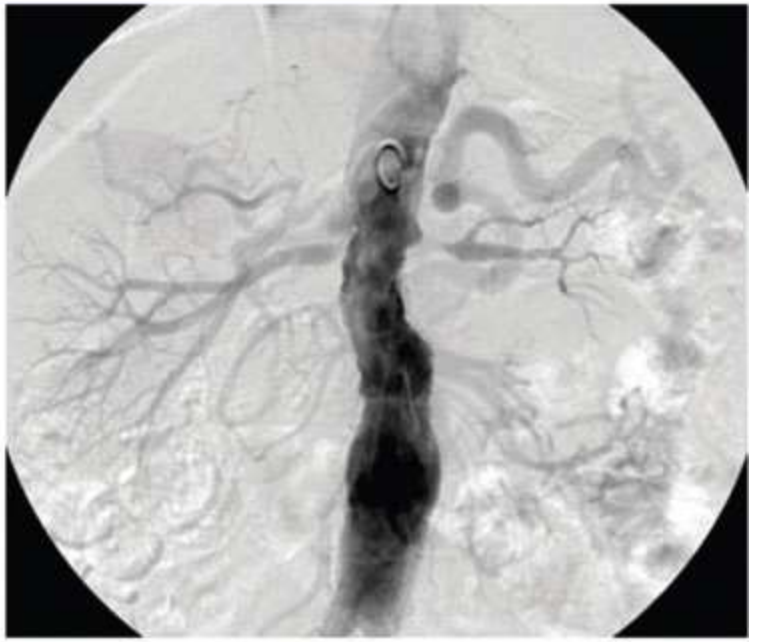
Schematic summary of the clinical manifestations of renovascular disease



Garovic V.D. and Textor S.C., Circulation. 2005; 112: 1362-1374

Spectrum of Renovascular Disease Manifestations





Asymptomatic "Incidental RAS"

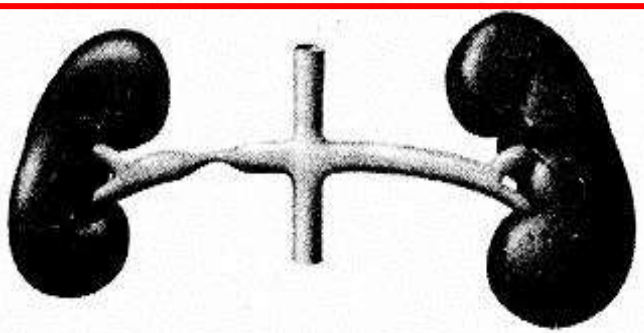
Renovascular Hypertension

Accelerated CV Disease
Congestive Heart failure
Stroke

Ischemic Nephropathy

Herrmann S.M.S., Saad A., Stephen C. Textor S.C, Nephrol. Dial. Transplant., 2015, 30: 366–375

UNILATERAL RENAL ARTERY STENOSIS



Reduced renal perfusion

↑ Renin-angiotensin system (RAS)
↑ Renin
↑ Angiotensin II
↑ Aldosterone

Angiotensin II–dependent hypertension

Increased renal perfusion

Suppressed RAS

Increased Na^+ excretion (pressure natriuresis)

Effect of blockade of RAS

Reduced arterial pressure

Enhanced lateralization of diagnostic tests

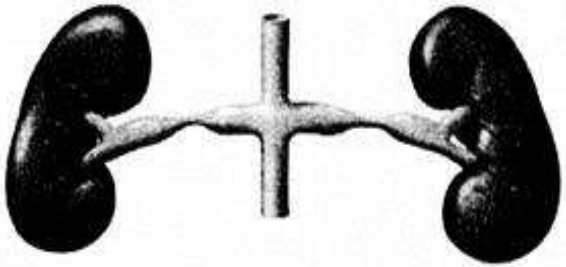
Glomerular filtration rate (GFR) in stenotic kidney may fall

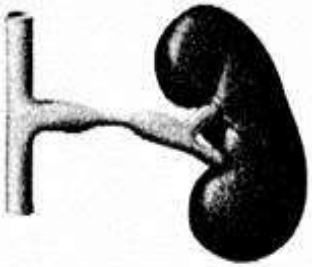
Diagnostic tests

Plasma renin activity elevated

Lateralized features, e.g., renin levels in renal veins, captopril-enhanced renography

BILATERAL RENAL ARTERY STENOSIS





Bilateral

Stenosis of solitary kidney

Reduced renal perfusion

↑ Renin-angiotensin system (RAS)
↑ Renin
↑ Angiotensin II
↑ Aldosterone

Impaired Na^+ and water excretion

Inhibit RAS

Volume expansion

Normal or low angiotensin II

Increased arterial pressure

Effect of blockade of RAS

Reduced arterial pressure only after volume depletion

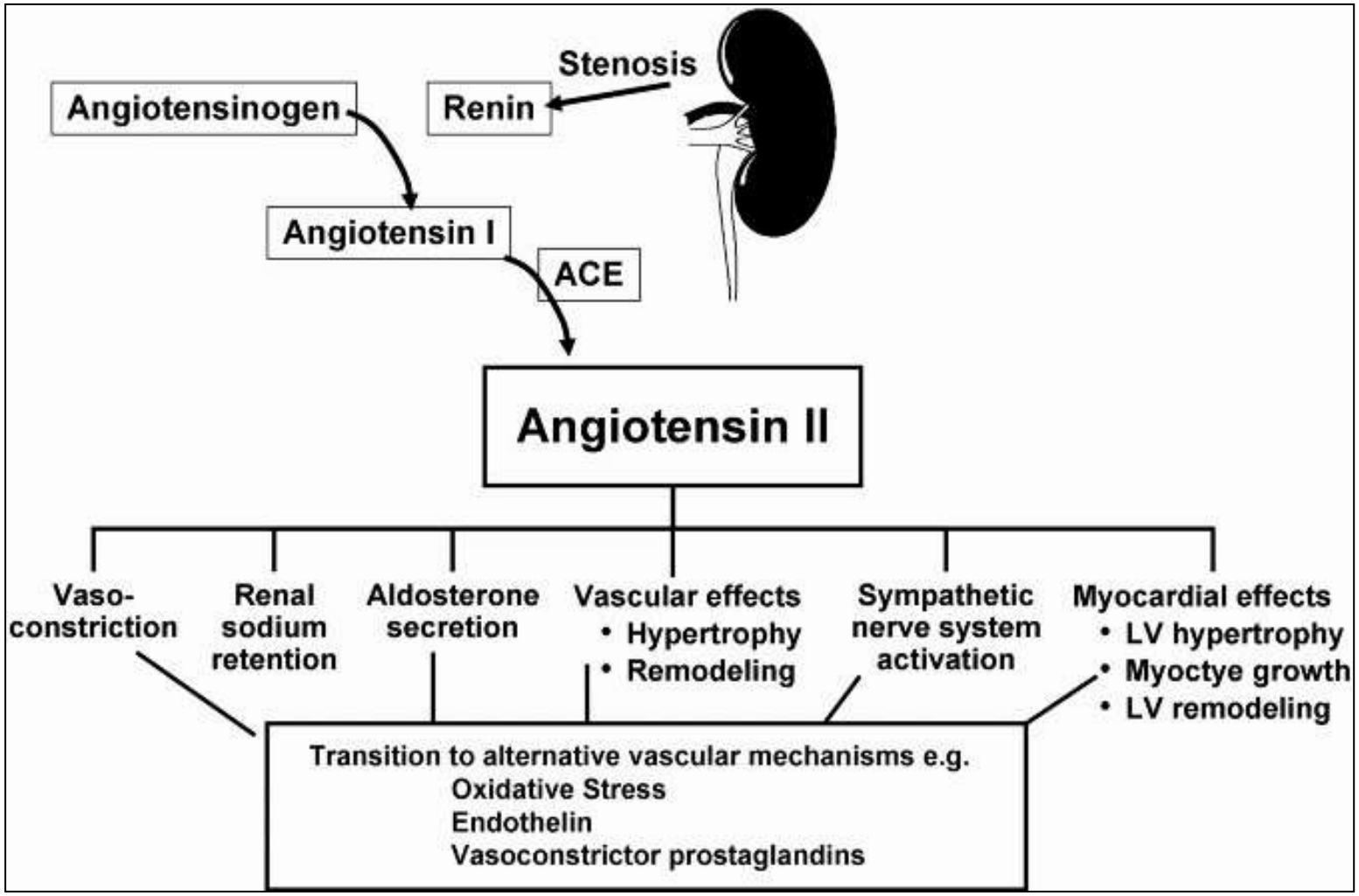
May lower GFR

Diagnostic tests

Plasma renin activity normal or low

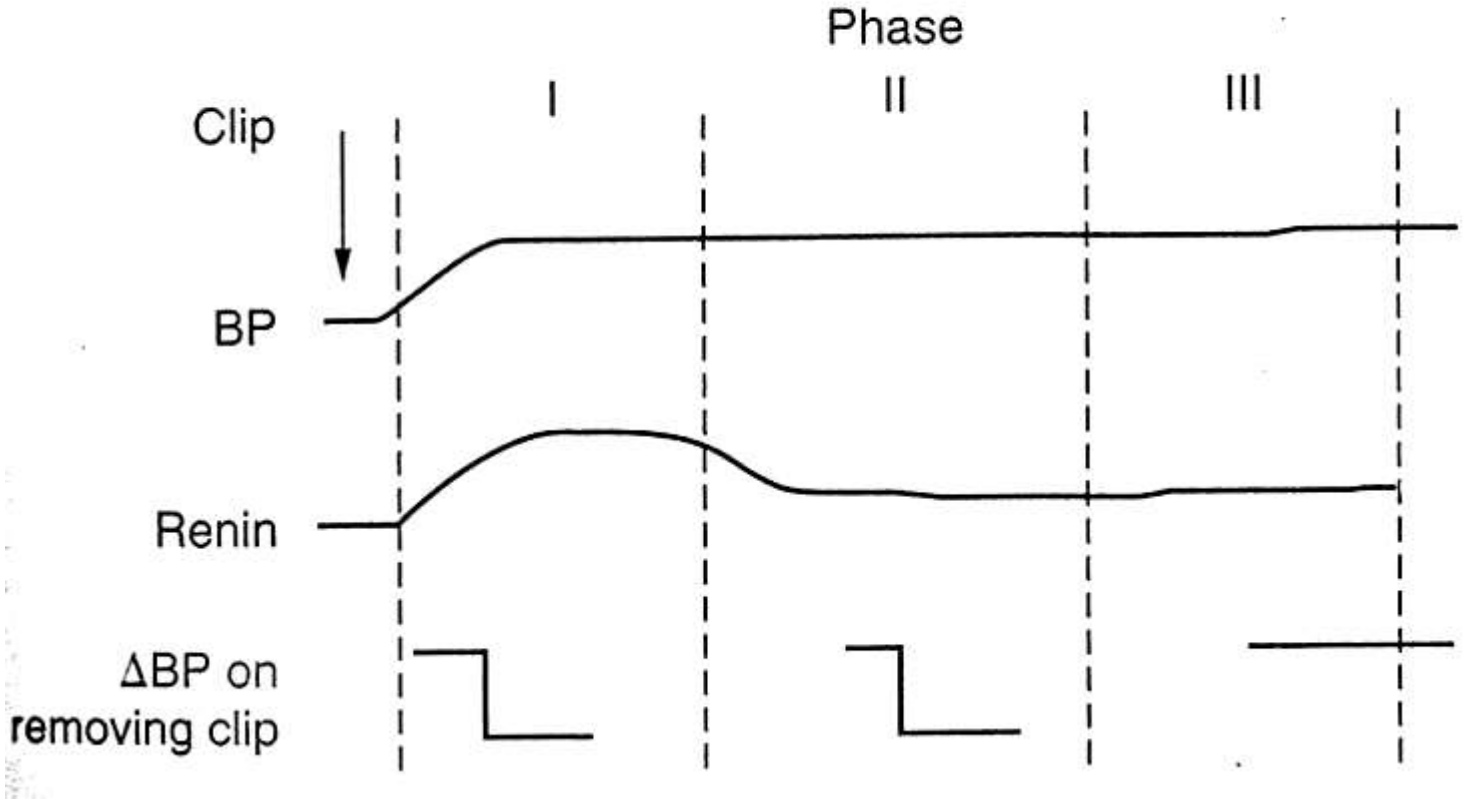
Lateralized features: none

Pressor mechanisms identified in renovascular hypertension



Garovic V.D. and Textor S.C., Circulation. 2005; 112: 1362-1374

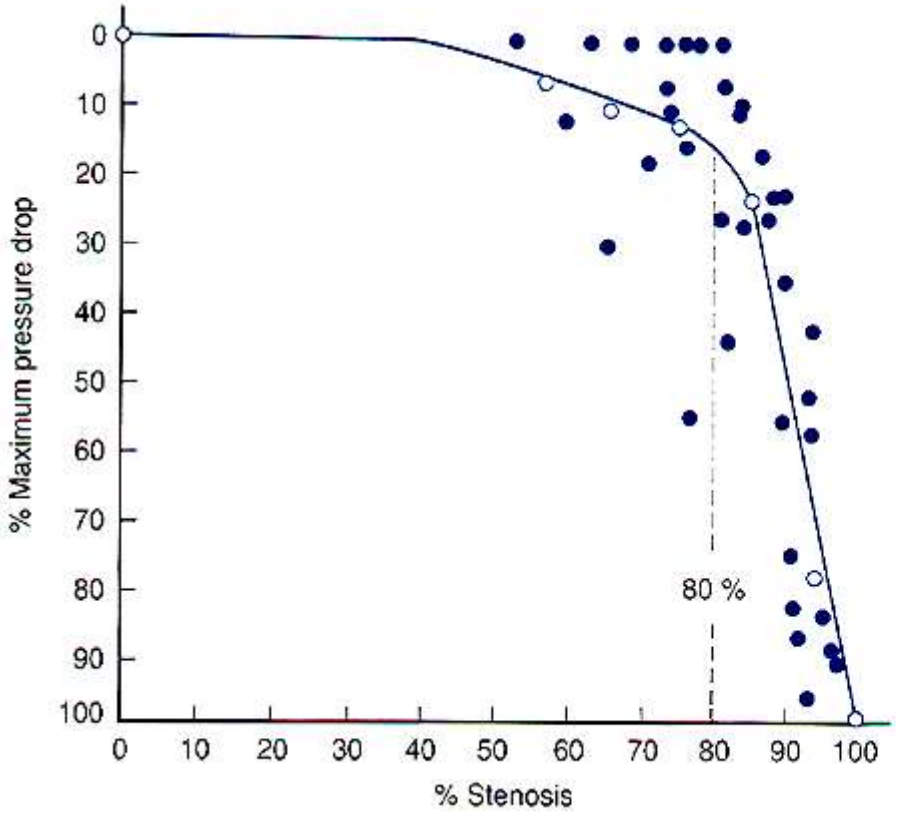
Depiction of phases observed in experimental renovascular hypertension

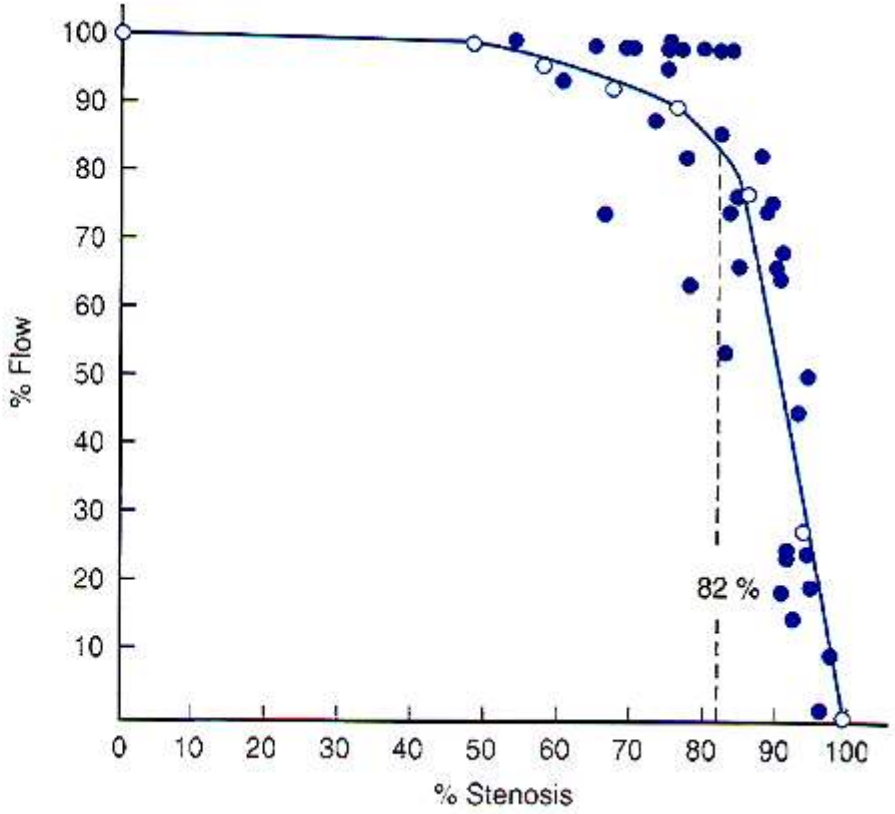


Brown J.J. et al., Lancet, 1976, 1, 1219-1221

Measured fall in arterial pressure and blood flow across stenotic vascular lesion induced in experimental animals

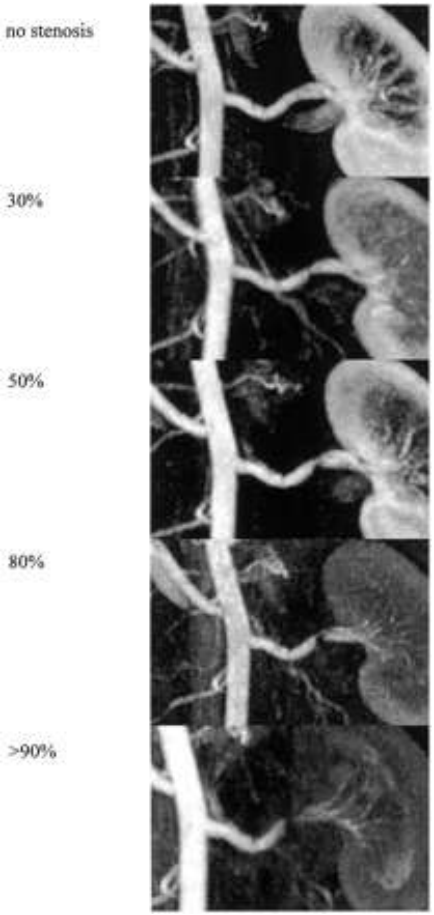
These data indicate that „critical” lesions require 70-80% luminal obstruction before hemodynamic effects can be detected

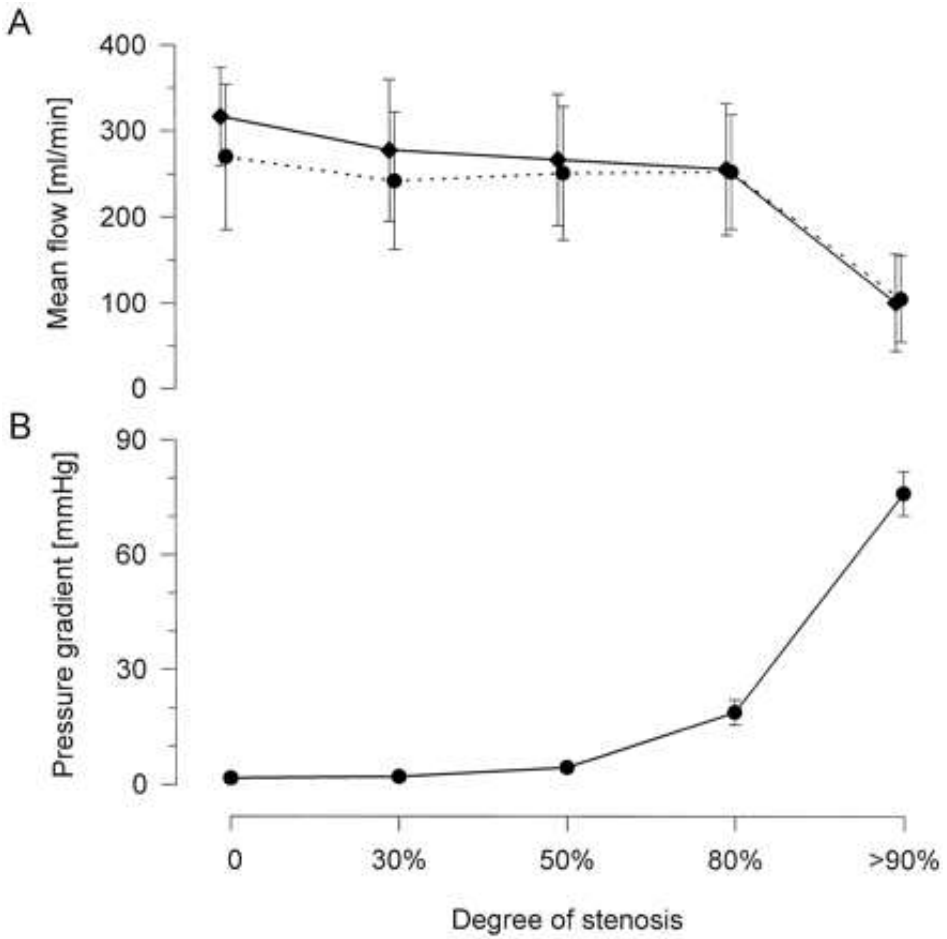




May AG. et al.: Surgery, 1963, 54, 250-259

Hemodynamic consequences of renal artery stenosis





Schoenberg SO, Bock M, Kallinowski F, Just A. J Am Soc Nephrol. 2000 ;12::2190-8

revisión corta

http://www.revistanefrologia.com

Ischemic nephropathy – pathogenesis and treatment

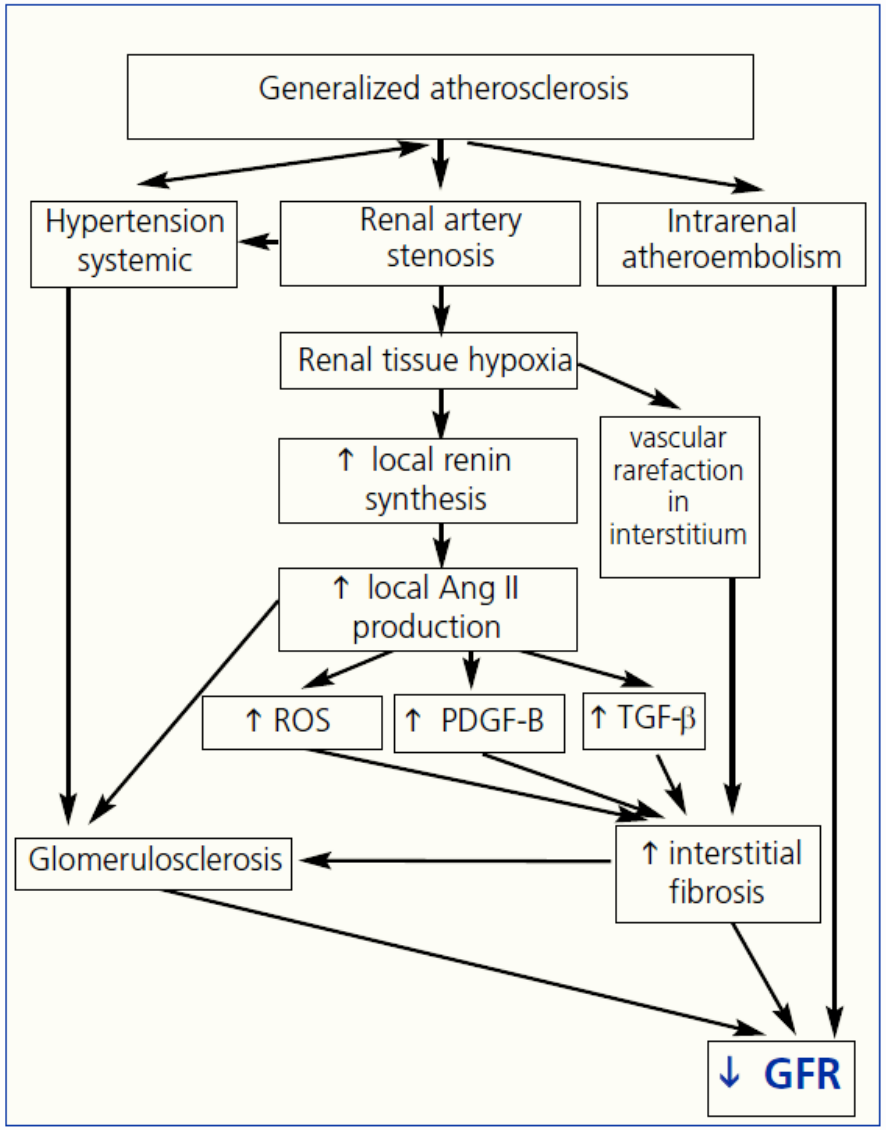
Marcin Adamczak, Andrzej Wiecek

Department of Nephrology, Endocrinology and Metabolic Diseases. Medical University of Silesia, Katowice (Poland)

Nefrologia 2012;32(4):432-38

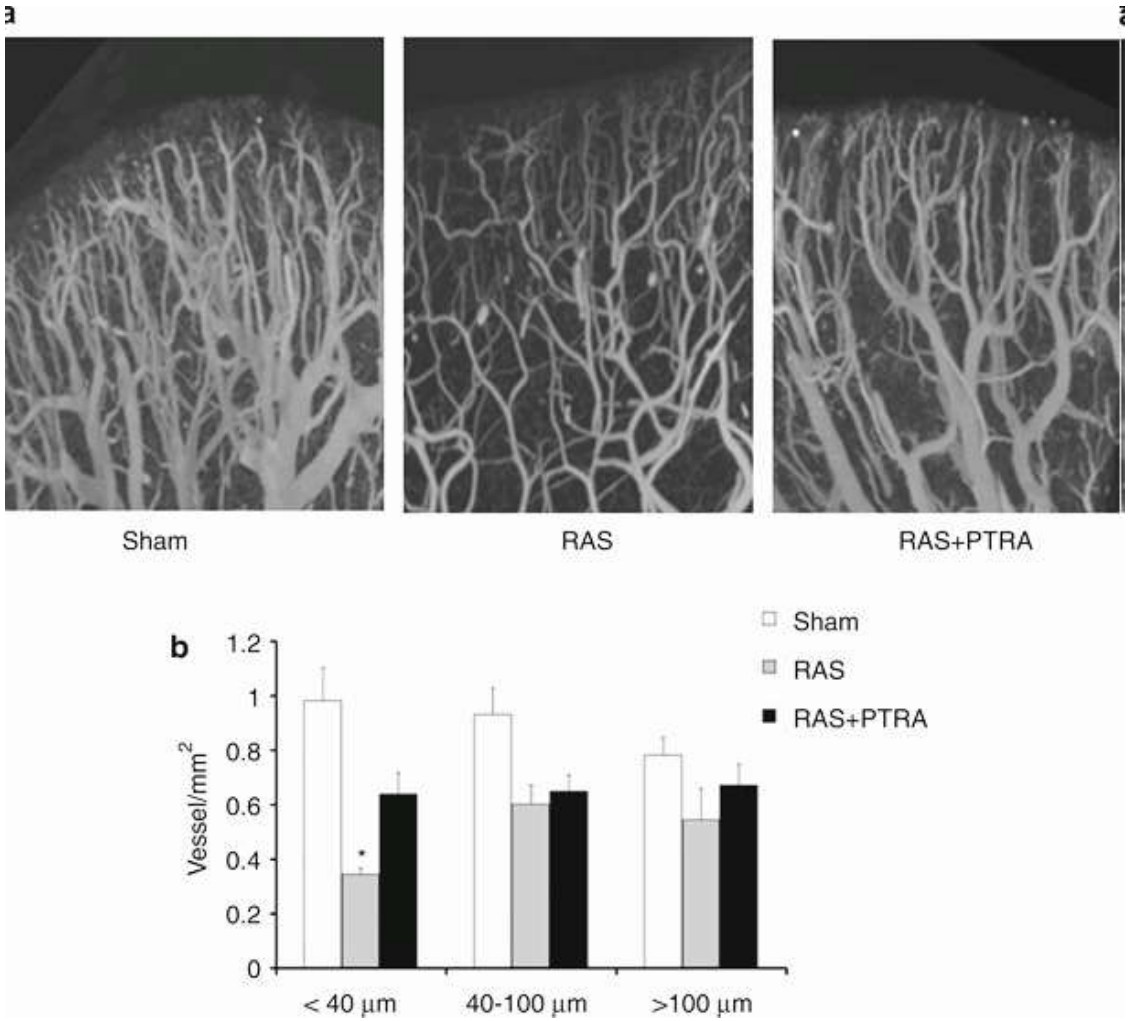
doi:10.3265/Nefrologia.pre2012.Apr.11472

Pathogenesis of ischemic nephropathy



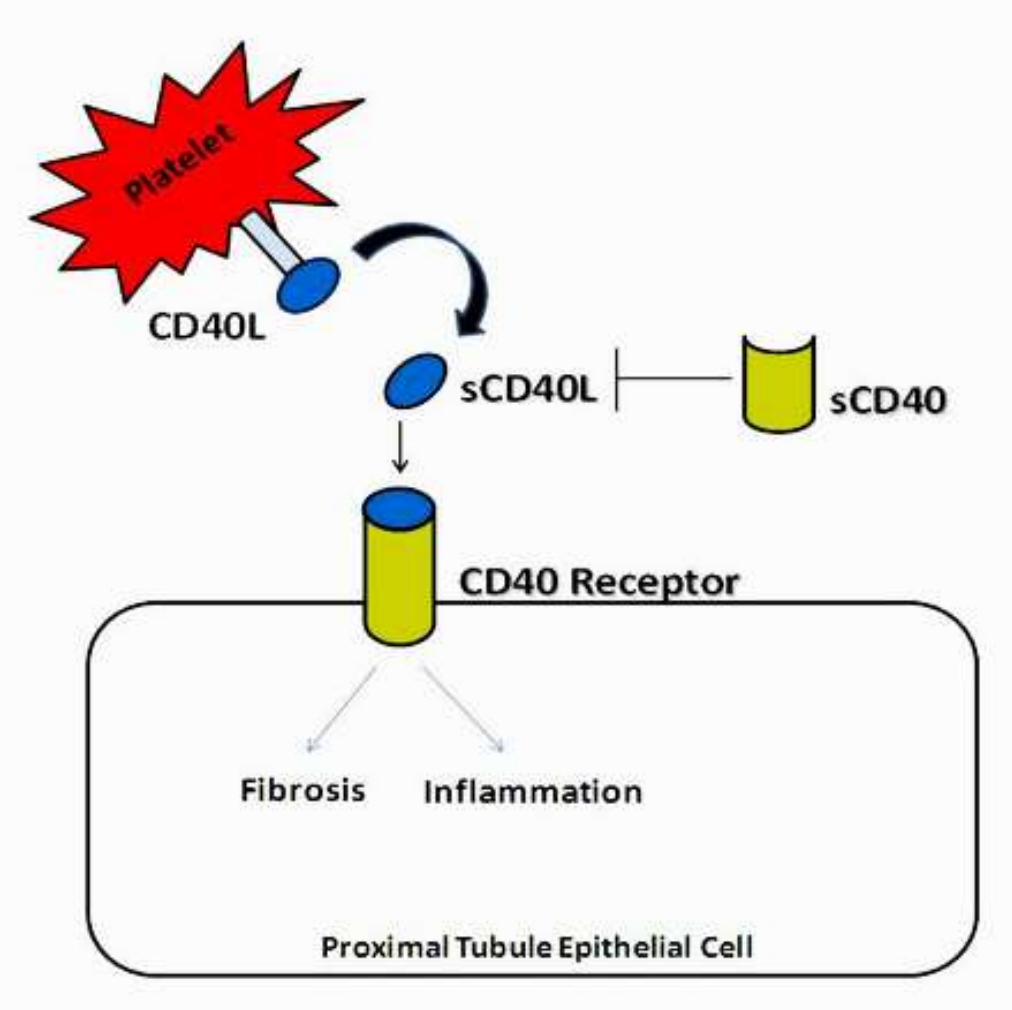
Adamczak M., Wiecek A., Nefrologia, 2012;32:432-438

Three-dimensional tomographic images of the **cortical microcirculation** in sham, RAS, and RAS + PTRA pigs



Favreau F.D. et al., Kidney Int.;2010 78: 1110–1118

Proposed mechanisms for **CD40/sCD40L signaling** in the proximal tubule contributing to the development of renal injury in atherosclerotic renal artery stenosis



Haller S.T., Discov. Med., 2013, 16: 255-260

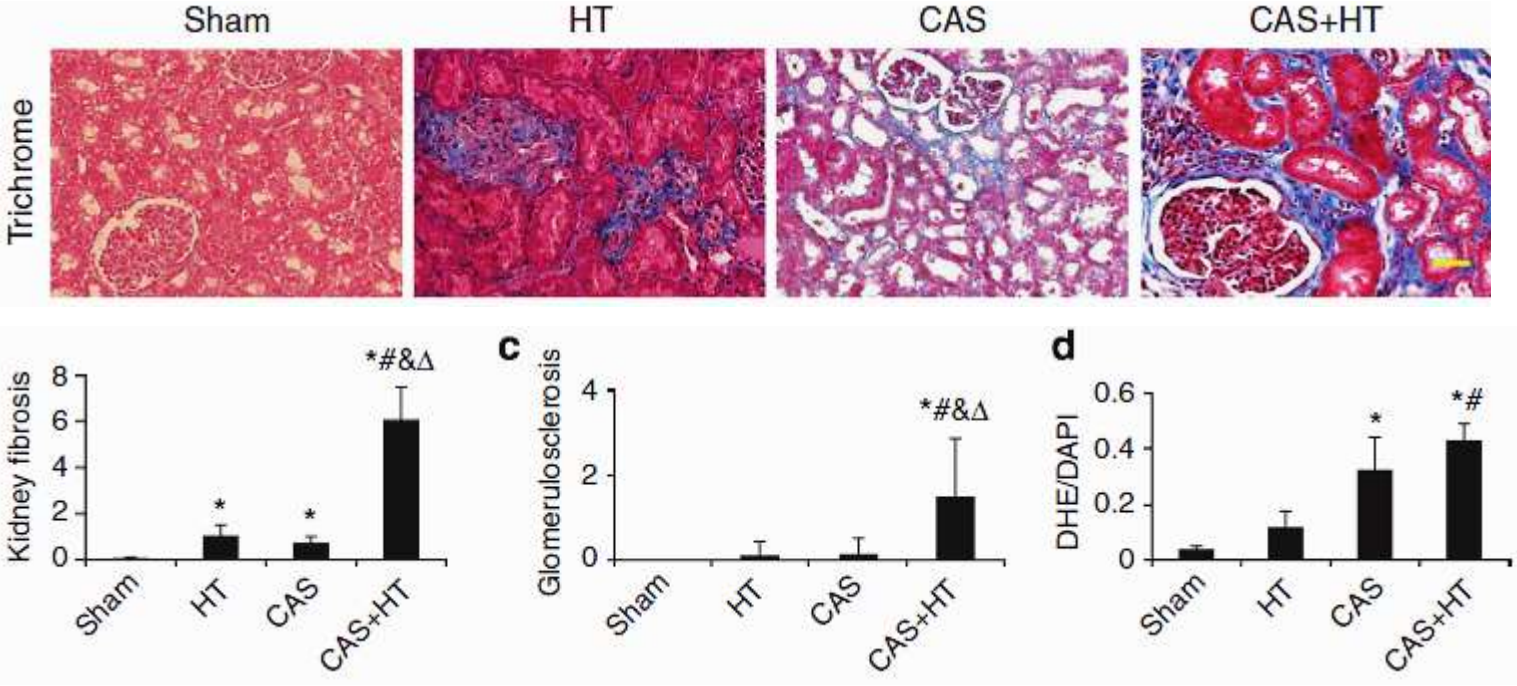
http://www.kidney-international.org

see commentary on page 676

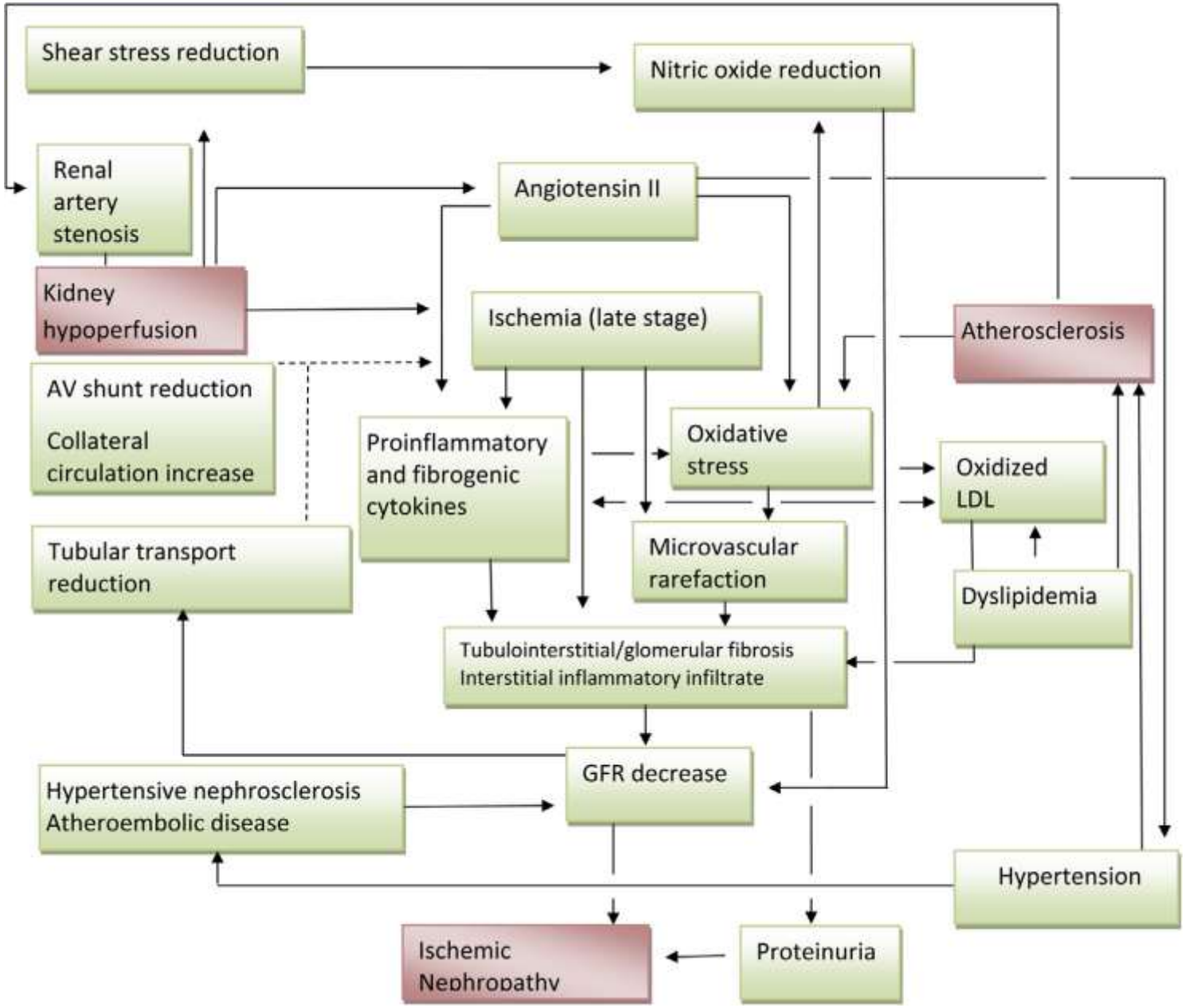
Experimental coronary artery stenosis accelerates kidney damage in renovascular hypertensive swine

Dong Sun[1,2], Alfonso Eirin[1], Xiang-Yang Zhu[1], Xin Zhang[1], John A. Crane[1], John R. Woollard[1], Amir Lerman[3] and Lilach O. Lerman[1,3]

[1]Division of Nephrology and Hypertension, Mayo Clinic, Rochester, Minnesota, USA; [2]Department of Nephrology, The Affiliated Hospital of Xuzhou Medical College, Xuzhou, China and [3]Division Cardiovascular Disease, Mayo Clinic, Rochester, Minnesota, USA



Pathophysiology of ischemic nephropathy



Boehlke M. and Correa Barcellos F., Am. J. Kidney Dis., 2015, 65: 611-622

Blood Oxygen Level–Dependent (BOLD) magnetic resonance imaging technique

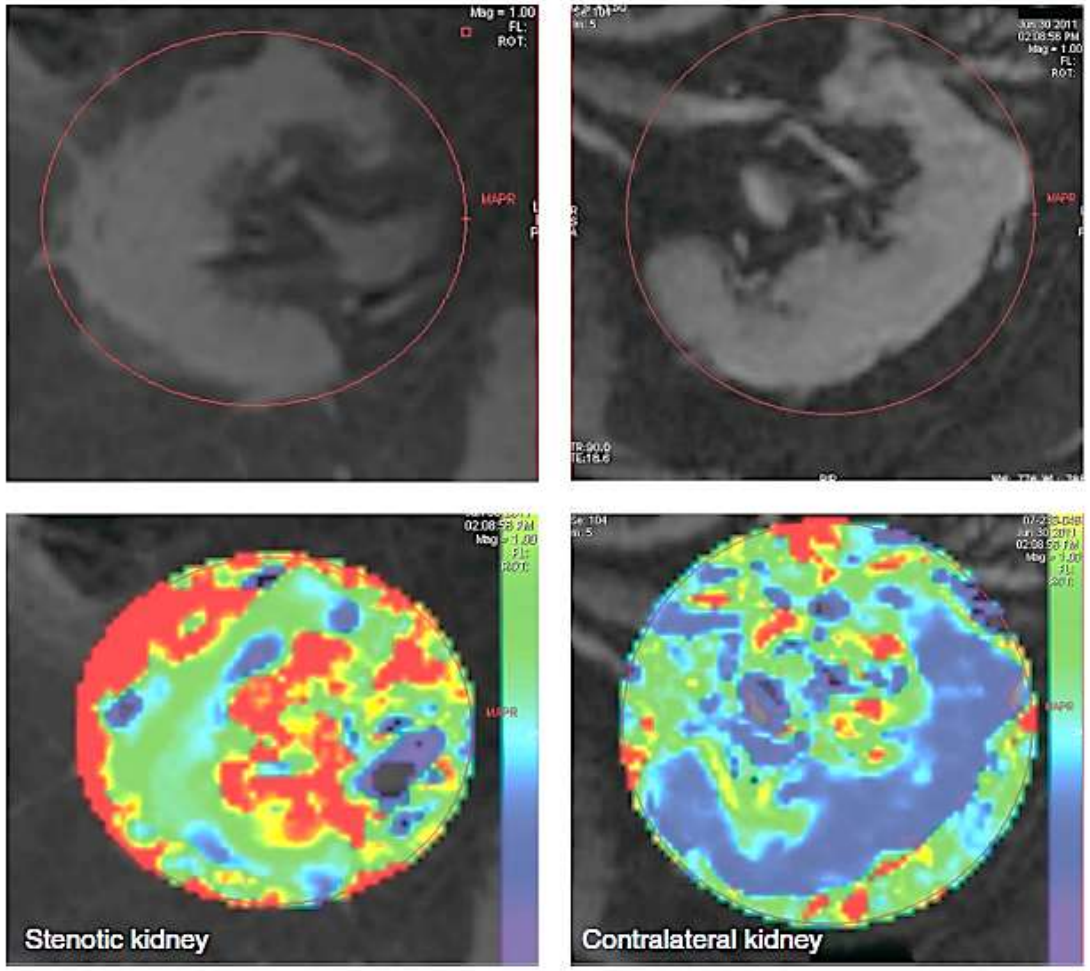
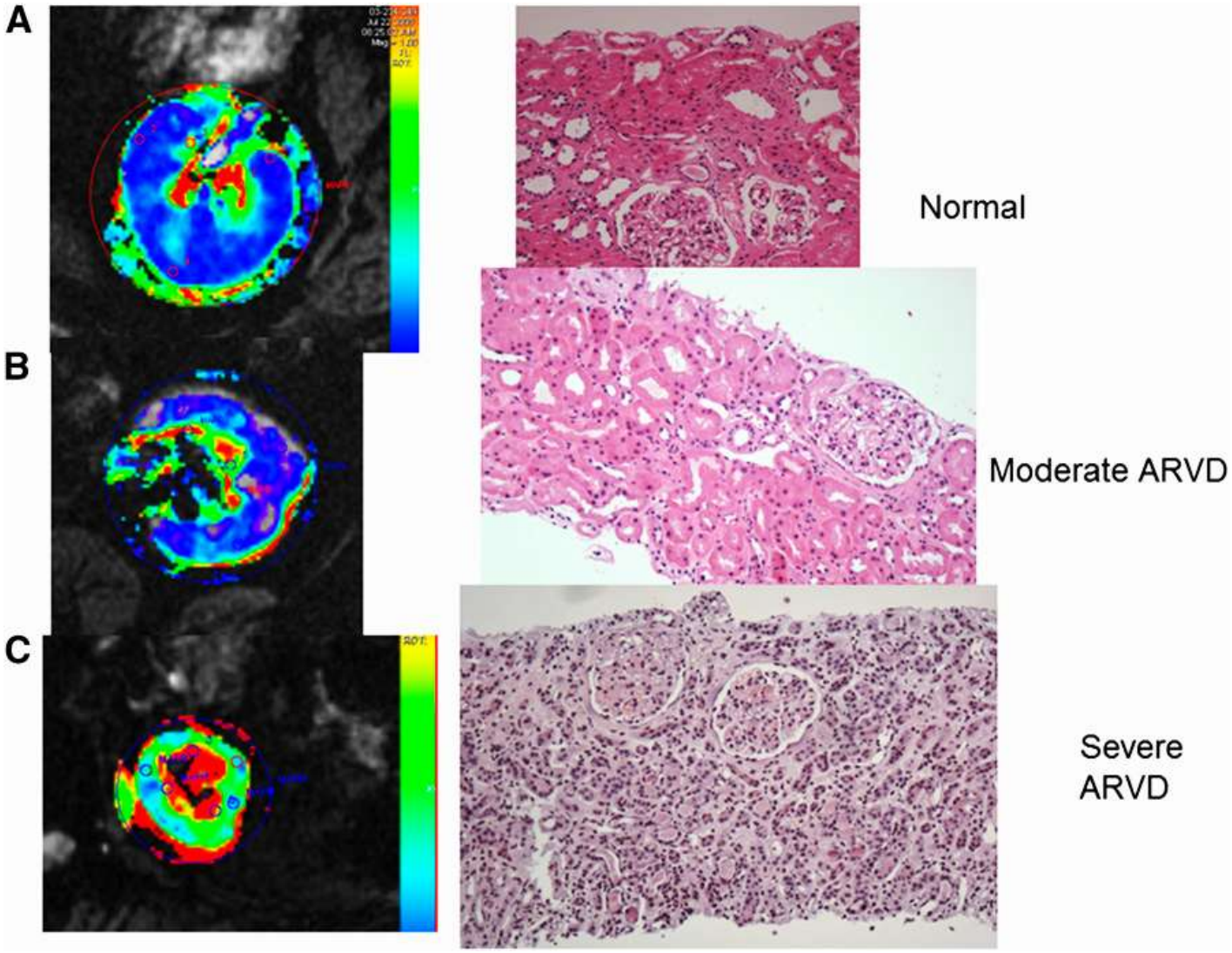


Figure 5 | Blood-oxygen-level-dependent (BOLD) magnetic resonance (MR) images with parametric maps depicting R2* levels that correspond to tissue levels of deoxyhemoglobin in axial images of the kidneys. Both of these kidneys had high-grade renal arterial stenosis with velocities >400 cm/s. Serum creatinine was >3.6 mg/dl, although the patient was treated with angiotensin receptor blockers and diuretics. The larger kidney (right panel, left kidney) has well-preserved cortical oxygenation (blue zone) and a normal corticomedullary oxygen gradient. The smaller kidney (left panels) is developing overt cortical hypoxia with rising R2* levels and expanding zone of medullary hypoxia (inner red zone). These functional imaging tools may assist in defining kidneys that are 'at risk' from critical vascular occlusion, yet remain 'salvageable' from the point of view of restoring renal blood flow (see text).

Textor S.C. et al. Kidney Int., 2012, 83, 28-40

Cortical hypoxia and inflammation develop in severe Atherosclerotic Renovascular Disease (ARVD)



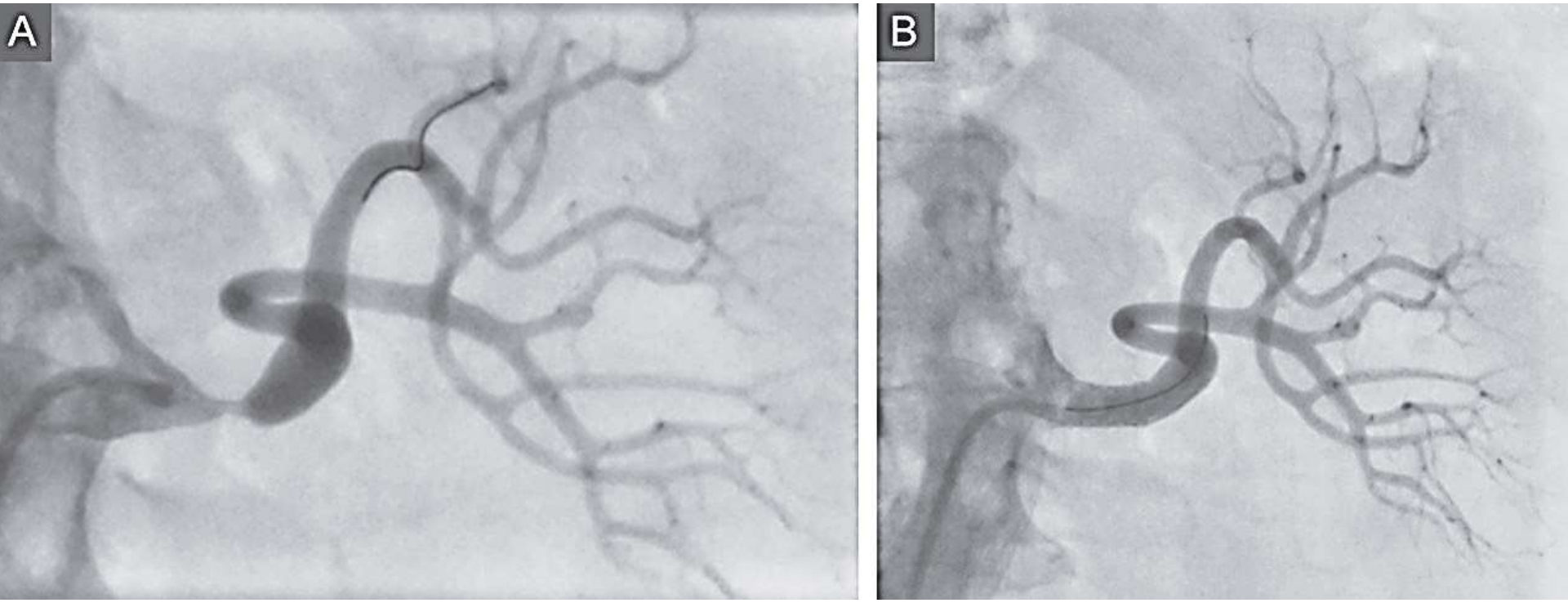
Textor S.C., and Lerman L.O., J. Am. Soc. Nephrol., 2015, 26: 2074–2080

Table 1. Prevalence of Atherosclerotic Renal Artery Stenosis in Different Subgroups

Subgroups	Prevalence of Atherosclerotic Renal Artery Stenosis (>60% of renal artery lumen)
General population	0.5%
Age > 65 years (Doppler)	7%
Healthy kidney donors	3-5%
Chronic kidney disease	5.5%
Suspicion of renovascular hypertension	14%
Coronary angiography	19%-24% (7% bilateral)
ESRD	12%-14% (2%-5% as cause of CKD)
Peripheral arterial disease	28%-59%
Abdominal aortic aneurysm	33%
Eldery with CHF	34%
Refractory CHF	40%-50%
Diffuse arterial disease	50%

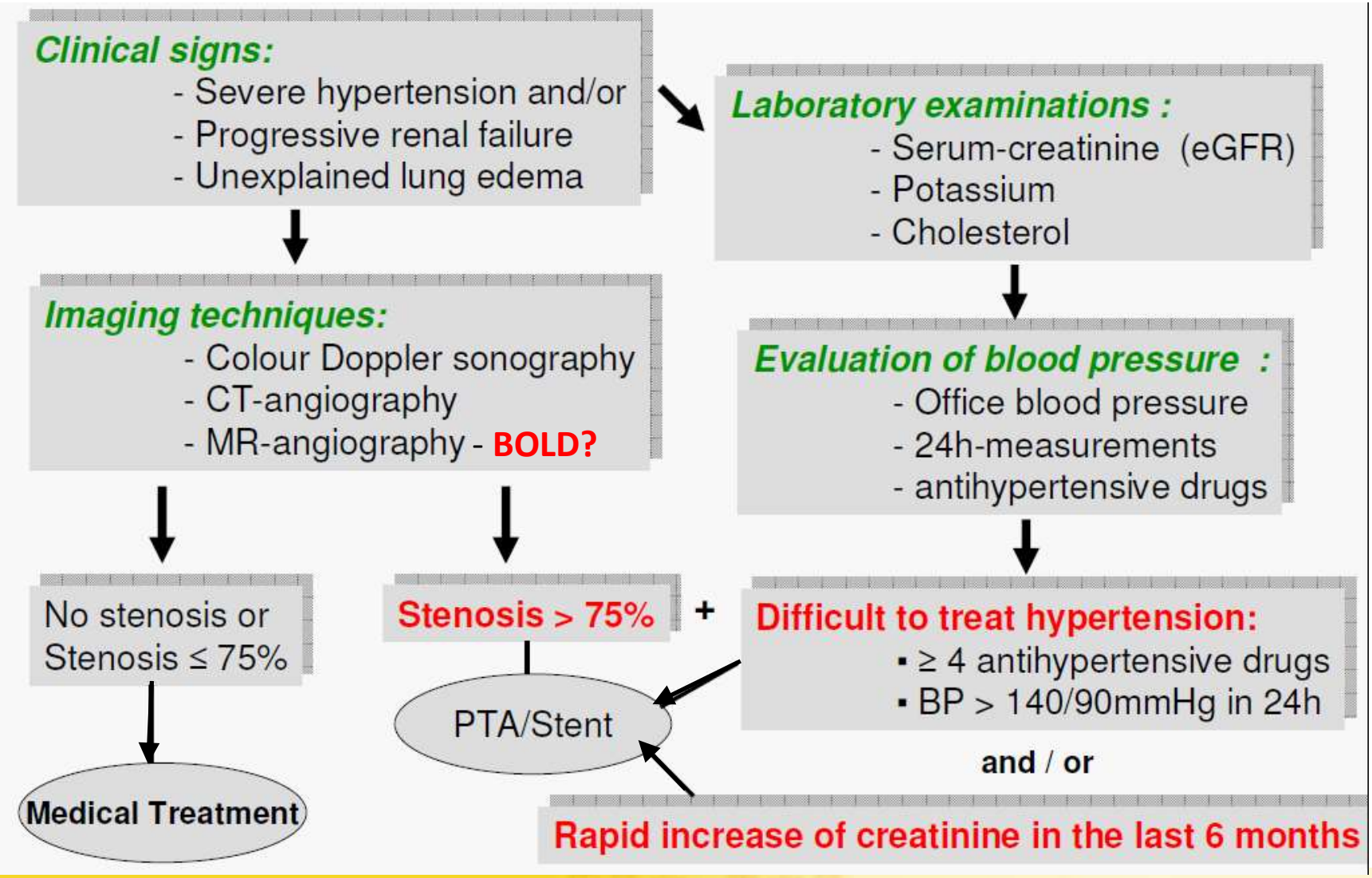
Boehlke M. and Correa Barcellos F., Am. J. Kidney Dis., 2015, 65: 611-622

High grade atherosclerotic stenosis of left renal artery (A); result after stent placement (B)

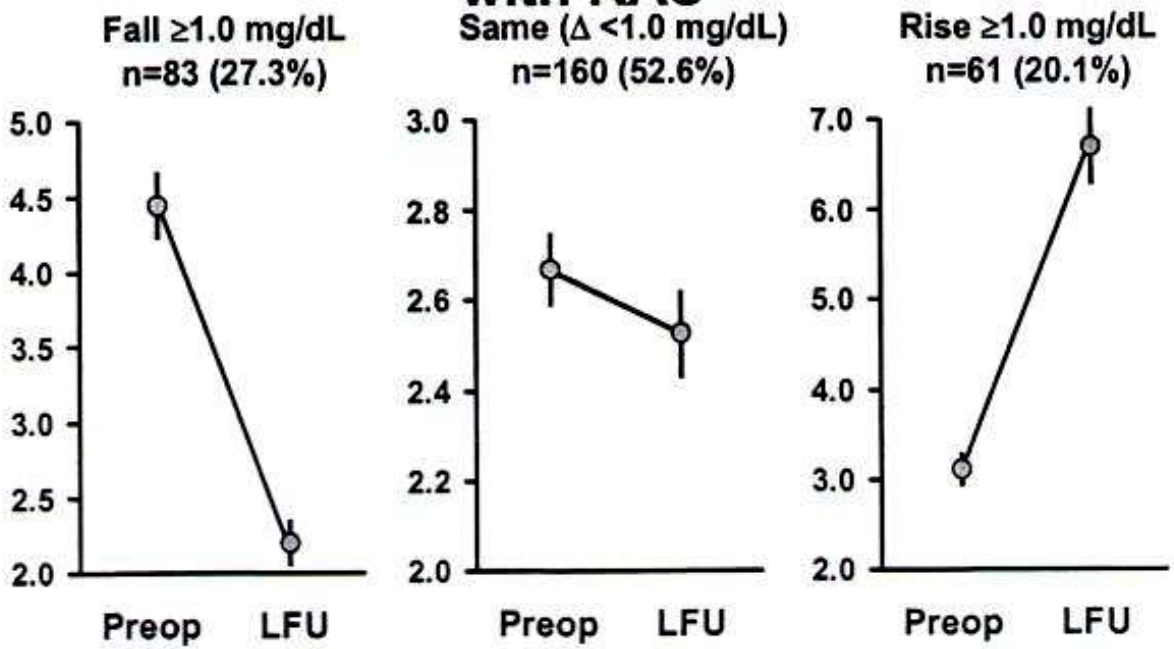


Zeller T. et al., Vasa 2014, 43, 27 – 38

Diagnostic work up of patients with suspected renal artery stenosis in 2015

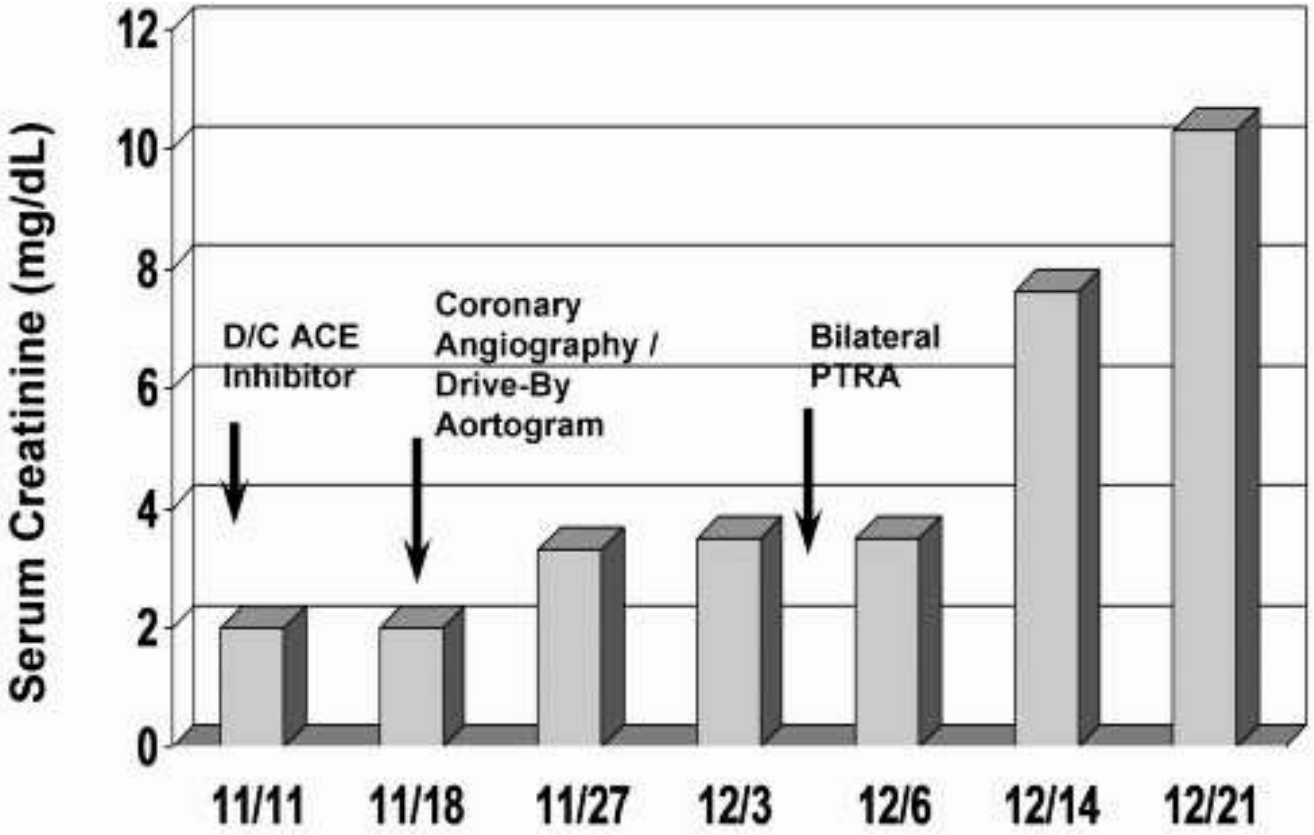


Creatinine in Azotemic Patients with RAS

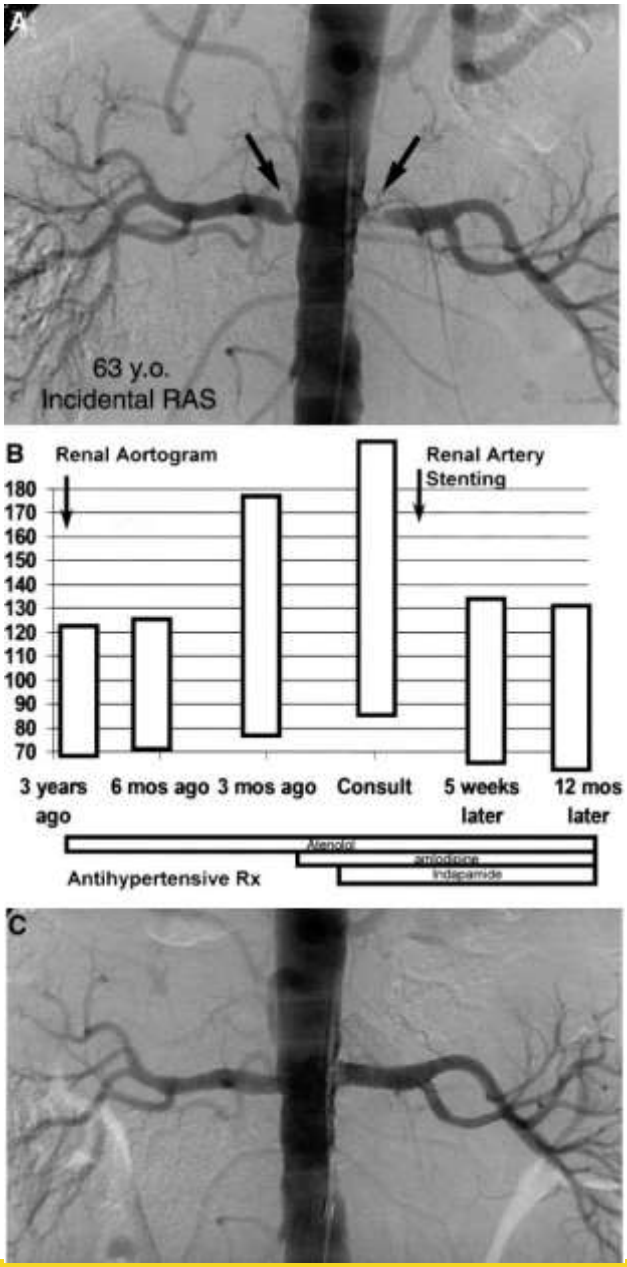


Levels of serum creatinine in 304 azotemic patients (initial serum creatinine ≥2.0 mg/dl) who successfully underwent surgical renal revascularization. The mean follow-up was >3 yr for the group. When considered as a large group, overall mean serum creatinine did not change from baseline (3.3 *versus* 3.4 mg/dl). Clinical outcomes differed markedly, however, between those with a meaningful fall in creatinine (left, defined here as a fall ≥1.0 mg/dl) or no change (middle), as compared with those with a rise in serum creatinine (right).

Serum creatinine values in a 63-year-old man with coronary disease and congestive cardiac failure subjected to bilateral PTRA



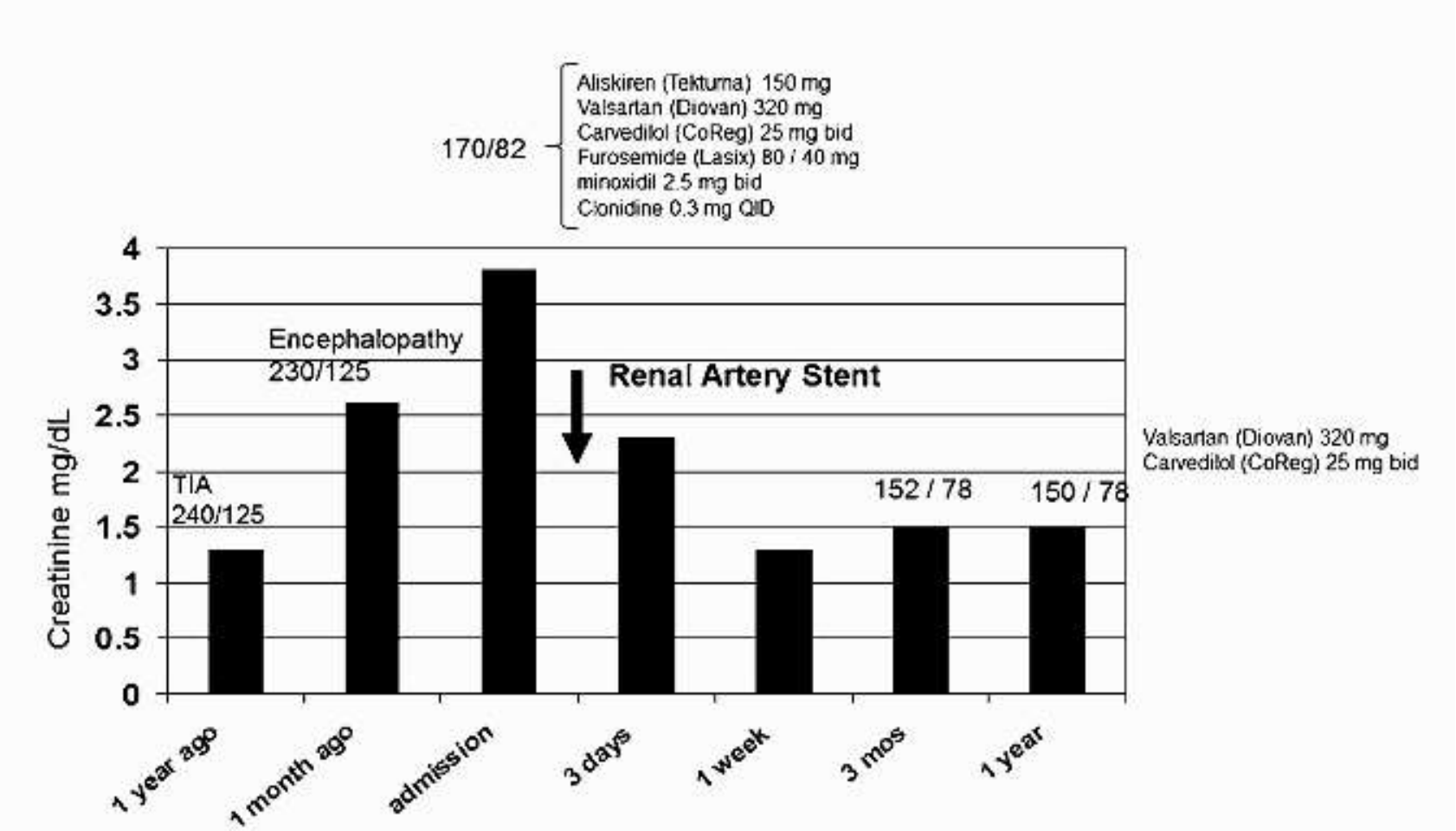
Garovic V.D. and Textor S.C., Circulation. 2005; 112: 1362-1374



Angiograms and blood pressures in a 63-year old man with incidentally identified renal artery stenosis during coronary angiography

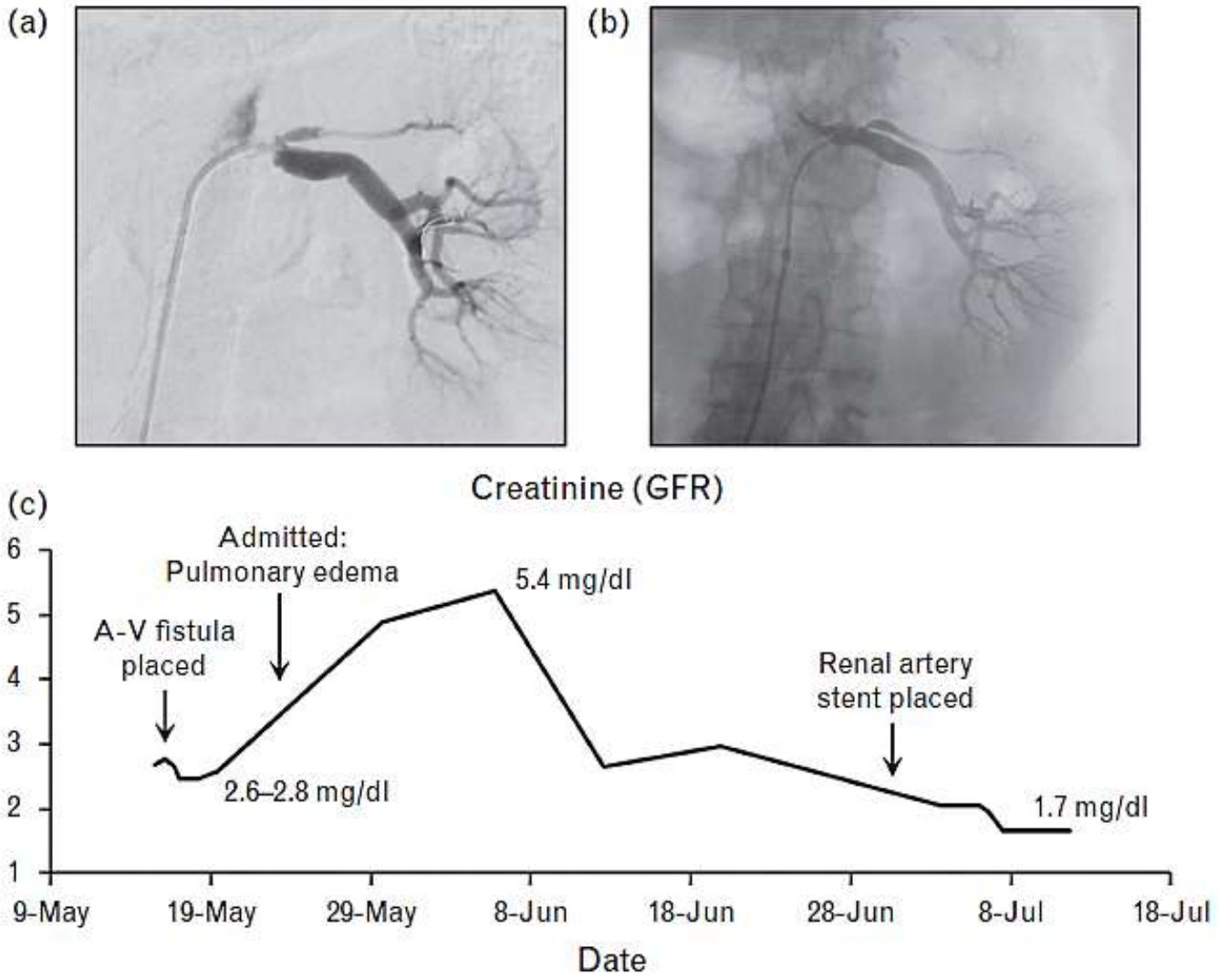
Garovic V.D. and Textor S.C., Circulation. 2005; 112: 1362-1374

Serum creatinine levels from 1 year before to 1 year after renal revascularization

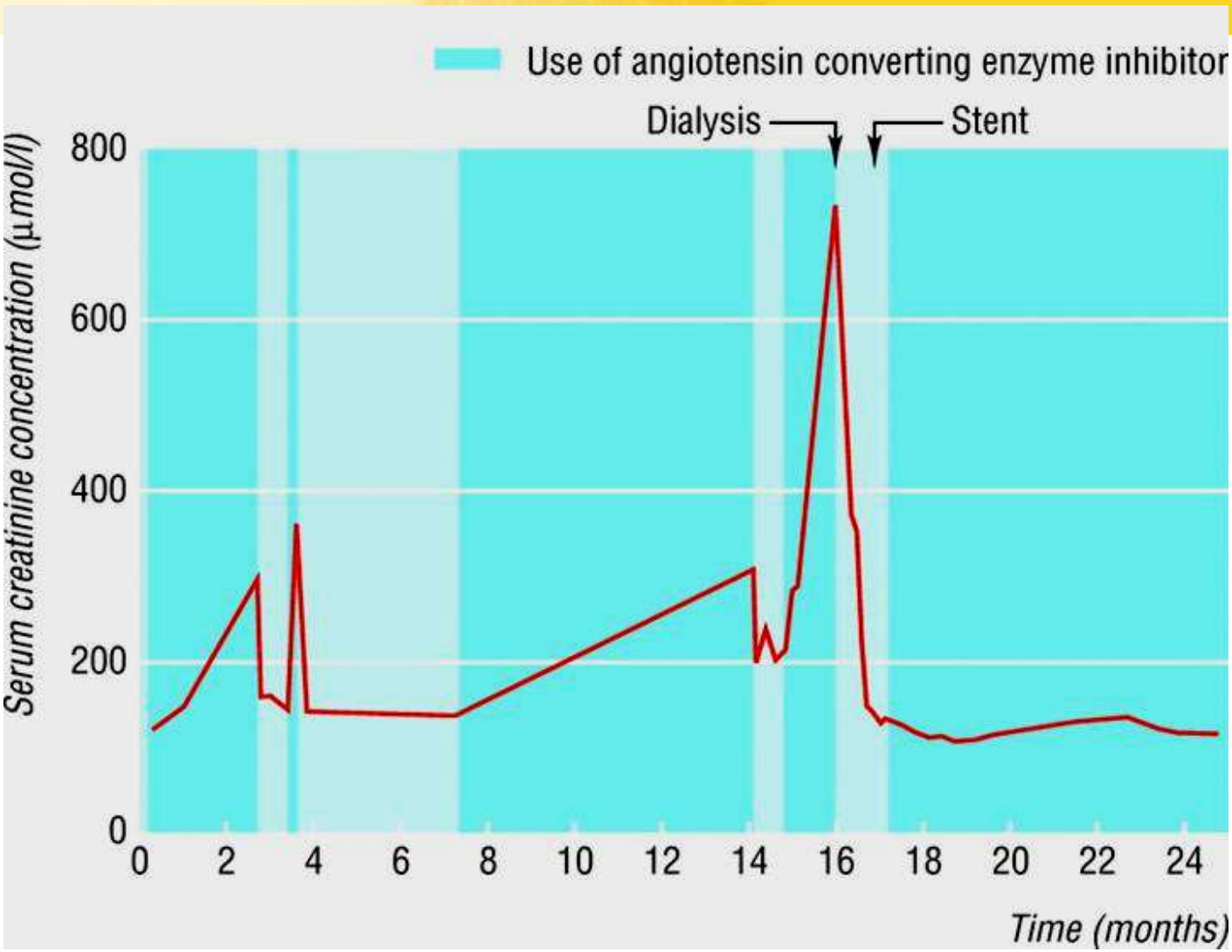


Textor S.C., Clin J Am Soc Nephrol., 2014, 9: 1117–1123

Renal angiograms and serial serum creatinine values during a 6-week time period obtained for a 62-year-old diabetic patient

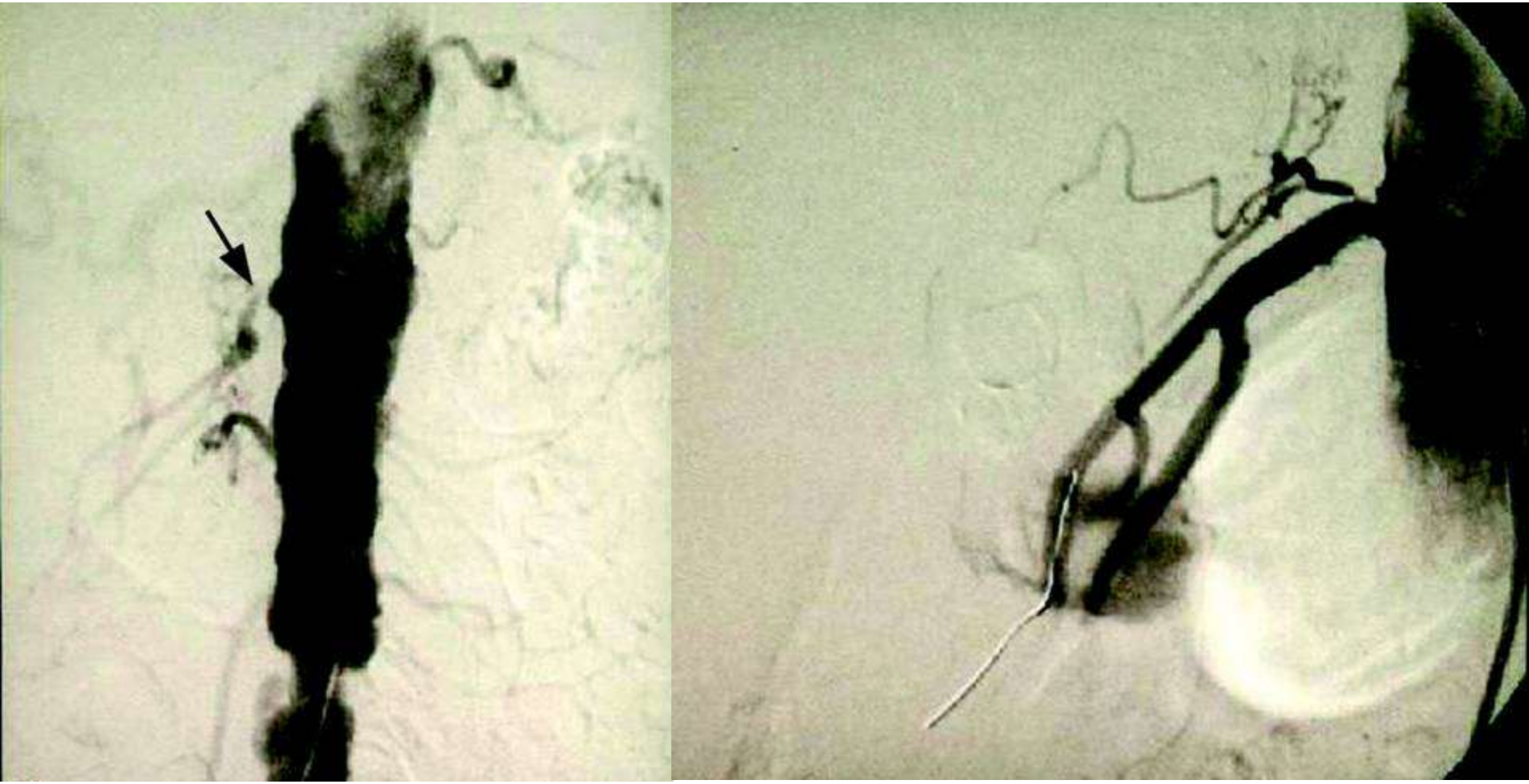


Textor S.C., Curr. Opin. Nephrol .Hypertens., 2013, 22,525–530



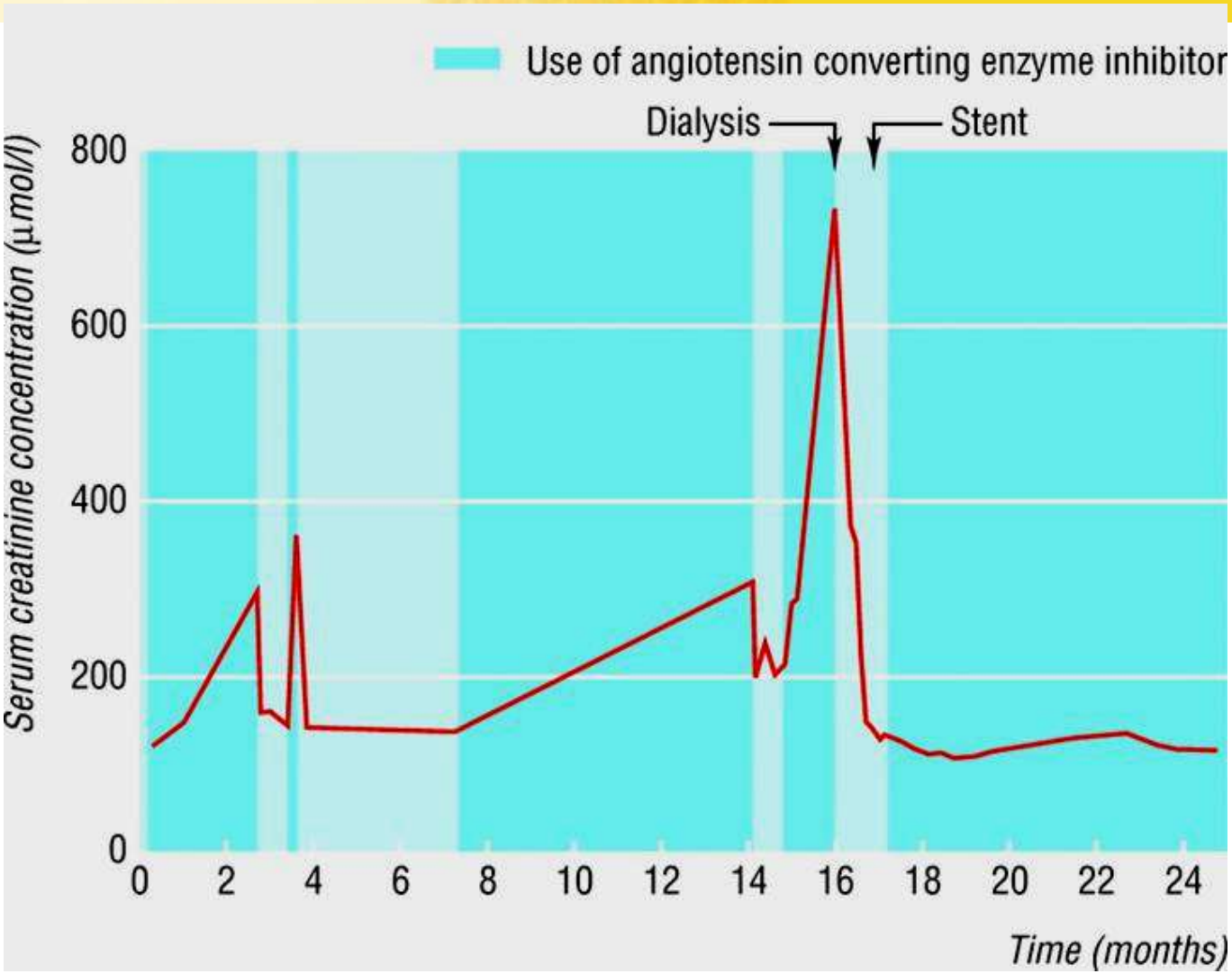
Serum creatinine concentration increased on four occasions in association with angiotensin converting enzyme inhibition, leading to dialysis, then remained stable despite patient taking angiotensin converting enzyme inhibitor after dilation and stenting of right renal artery.

Brit. Med. J. 2003, 326,489-491



Renal arteriogram showing occlusion of left renal artery (*left*) and tight stenosis of right renal artery before (arrowed) and after stenting (*right*)

Brit. Med. J. 2003, 326,489-491



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Brit. Med. J., 2003, 326, 489-491

CURRENT OPINION

Where now in the management of renal artery stenosis? Implications of the ASTRAL and CORAL trials

James Ritchie, Helen V. Alderson, and Philip A. Kalra

Purpose of review

The neutral findings of Angioplasty and Stenting for Renal Artery Lesions and Cardiovascular Outcomes in Renal Artery Lesions trials have shown that unselected revascularization does not improve outcomes in atherosclerotic renovascular disease (ARVD). This review highlights recent translational, clinical and epidemiological studies and suggests directions for future research.

Recent findings

Imaging studies show that the degree of renal artery stenosis is not the most important determinant of outcome and response to therapies in ARVD. Porcine models have established a better understanding of the microvascular and inflammatory changes that occur in ARVD. Biomarkers of inflammation and cardiovascular dysfunction may be informative but do not yet help assess prognosis or response to treatment. Stem cell therapies show promise in animal models but have yet to translate into clinical practice. Analysis of patient subgroups with high-risk presentations of ARVD has provided new insights into treatment response and may guide future studies.

Summary

It is time to reframe thinking and research in ARVD. We need better ways to identify patients likely to benefit from revascularization and to improve response to treatment in these individuals. Many preclinical studies show promise, but these are often small scale and difficult to replicate. Future work should focus on establishing an international disease registry as a foundation for collaborative research.

Cur. Opin. Nephrol. Hypertens., 2014, 23, 525-532

European Review for Medical and Pharmacological Sciences 2013; 17: 507-512

Predictor factors for renal outcome in renal artery stenosis

R. CIANCI, P. MARTINA, A. GIGANTE, D. DI DONATO, L. POLIDORI, P. PRESTA**, R. LABBADIA, D. AMOROSO, A. ZACCARIA*, B. BARBANO, G. FUIANO**

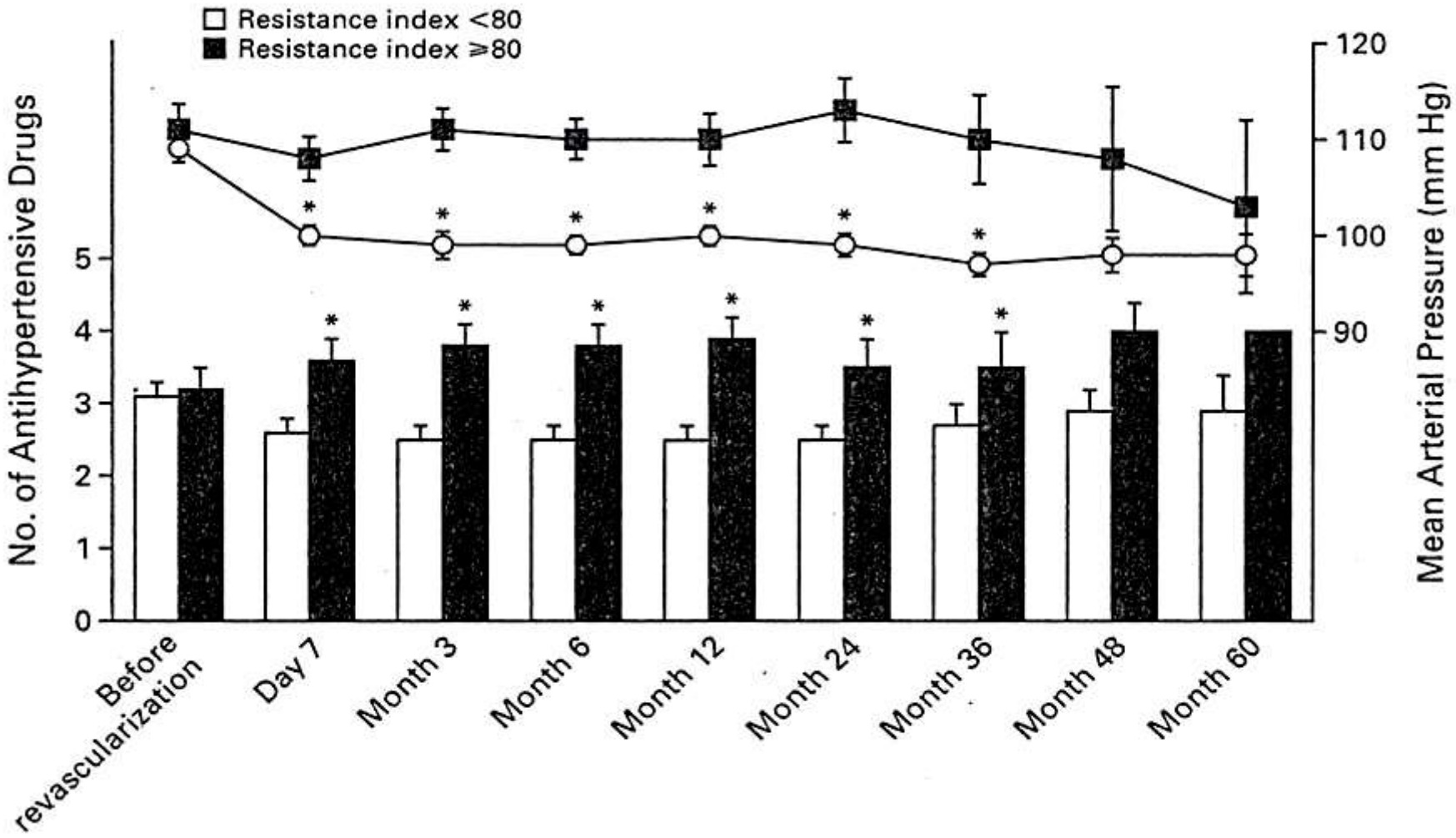
Department of Nephrology, School of Medicine, Sapienza University, Rome, Italy
*Department of Vascular and Endovascular Surgery, San Pietro-Fatebenefratelli Hospital, Rome, Italy
**Department of Nephrology, School of Medicine, Magna Graecia University of Catanzaro, Catanzaro, Italy

MATERIALS AND METHODS: we performed an observational study on a total of 55 patients to find predictive factors of the outcome of renal function after renal percutaneous transluminal angioplasty and stenting (RPTAs).

RESULTS: We found that uricemia, proteinuria and IR were higher at baseline in patients who worsened renal function after revascularization.

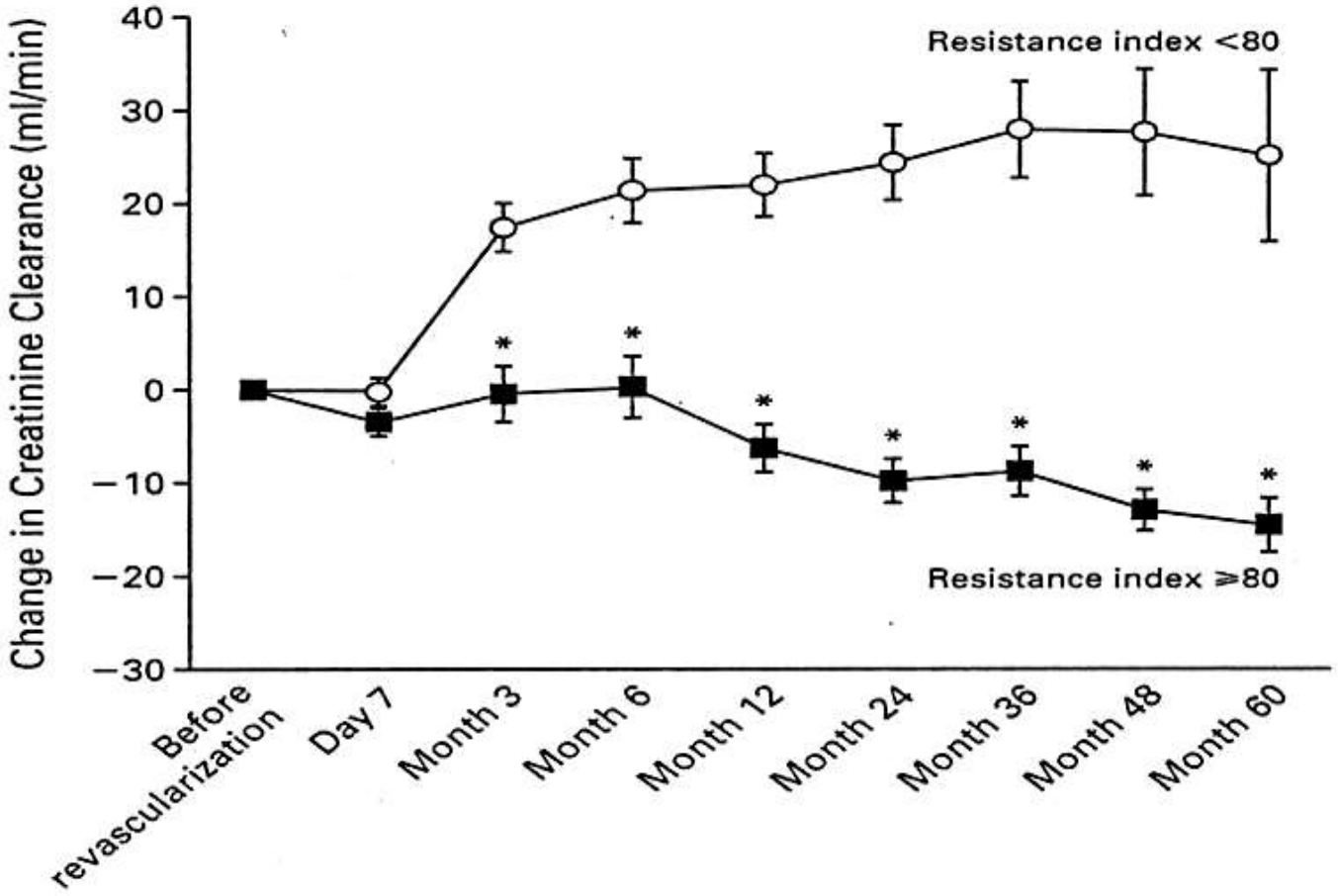
CONCLUSIONS: The identification of predictive factors (uricemia; proteinuria and RI) of chronic kidney disease (CKD) progression in patients with RAS undergone revascularization could be useful to predict renal long term outcome and to select patients that really could benefit of this.

Mean (±SEM) change in MAP and the number of antihypertensive drugs taken after the correction of RAS, according to resistance index values before revascularization



Radermacher J. et al N. Eng. J. Med., 2001, 344, 410-417

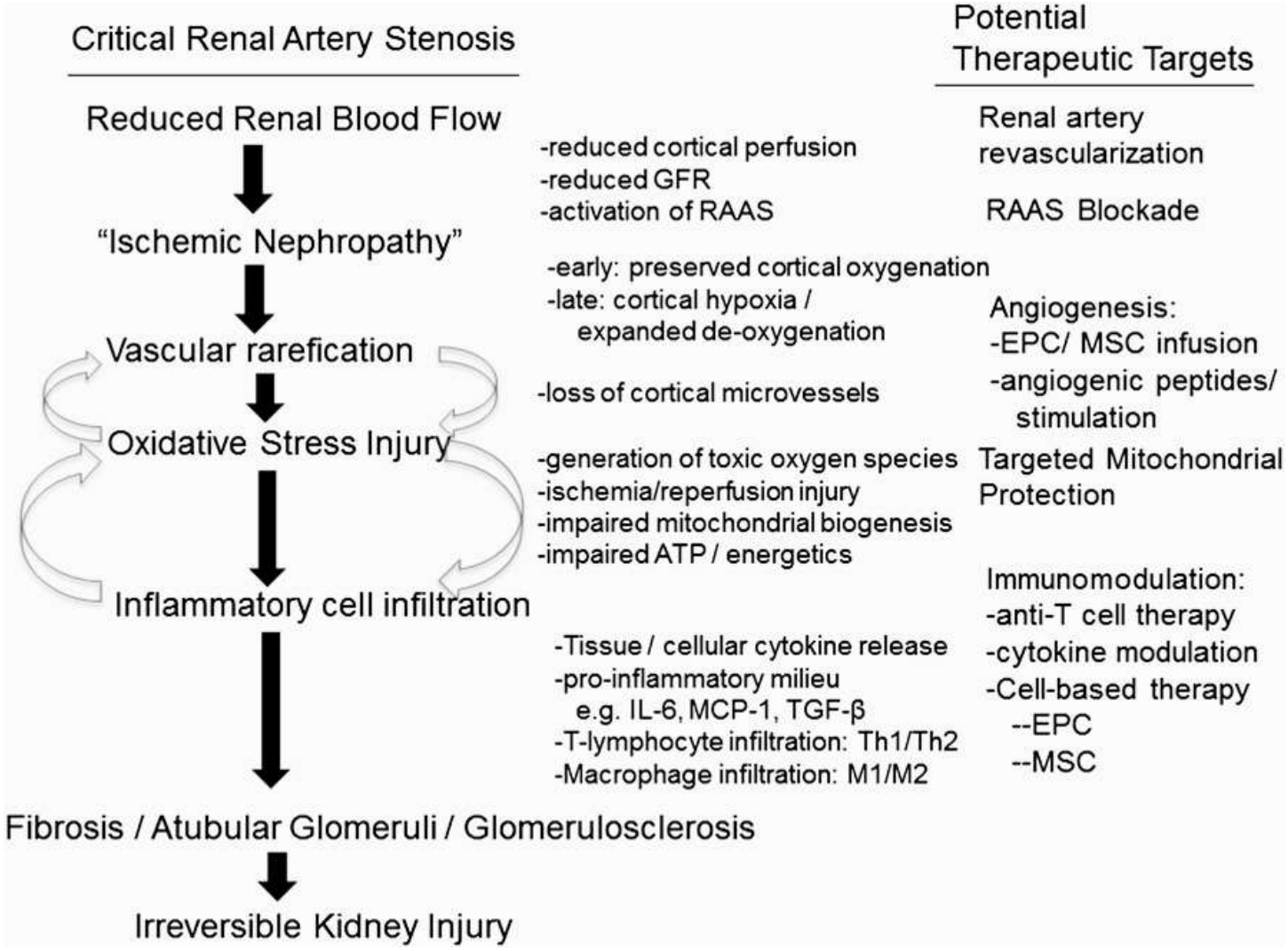
Mean changes in creatinine clearance after the correction of RAS, according to resistance index values before revascularization



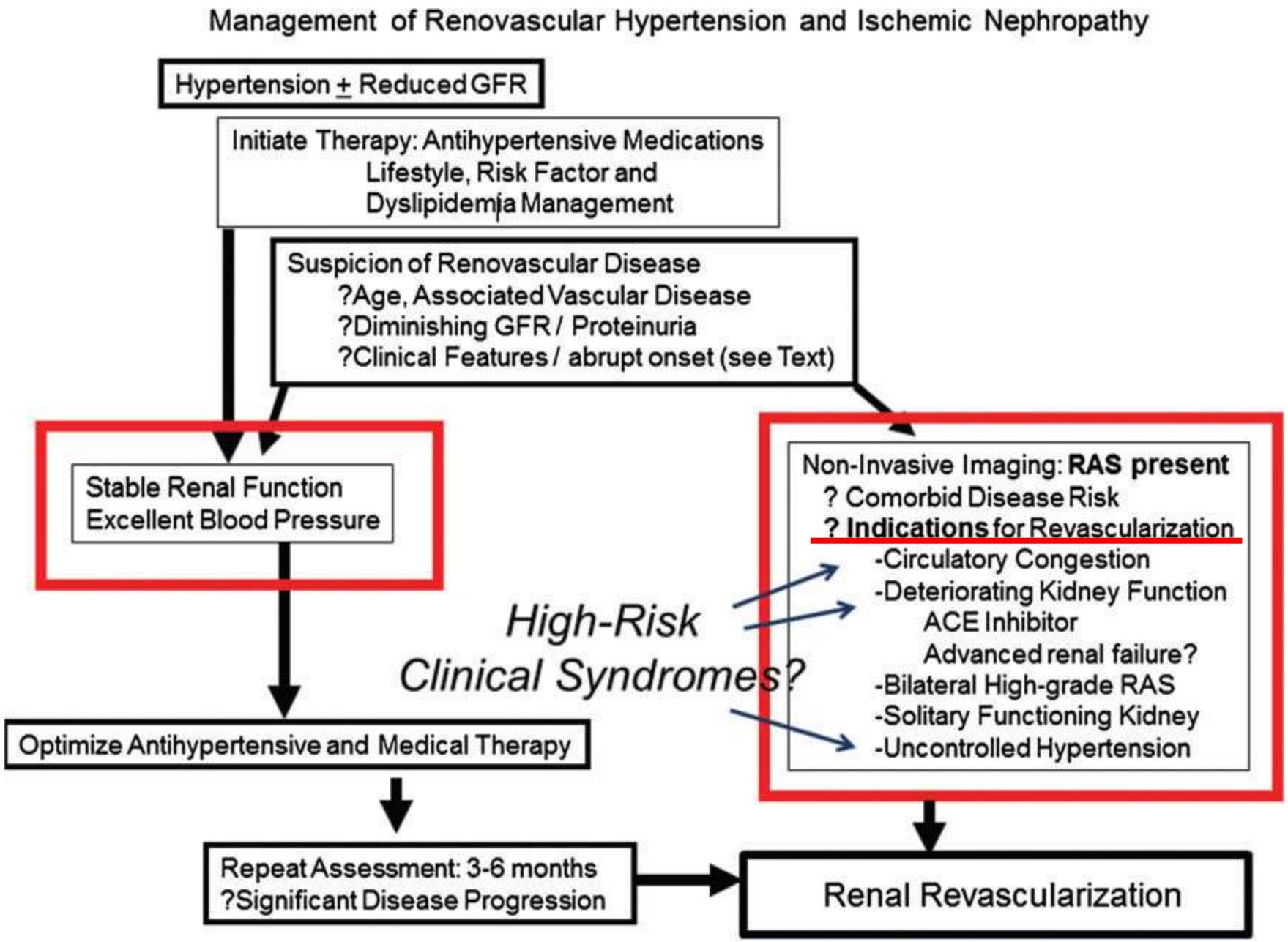
No. with Follow-up Data									
Resistance index <80	96	96	95	83	73	59	43	34	21
Resistance index ⩾80	35	35	33	31	26	21	16	8	5

Radermacher J. et al N.Eng. J. Med., 2001, 344, 410-417

Injury pathways and targets in Atherosclerotic Renovascular Disease (ARVD)



Textor S.C., and Lerman L.O., J. Am. Soc. Nephrol., 2015, 26: 2074–2080



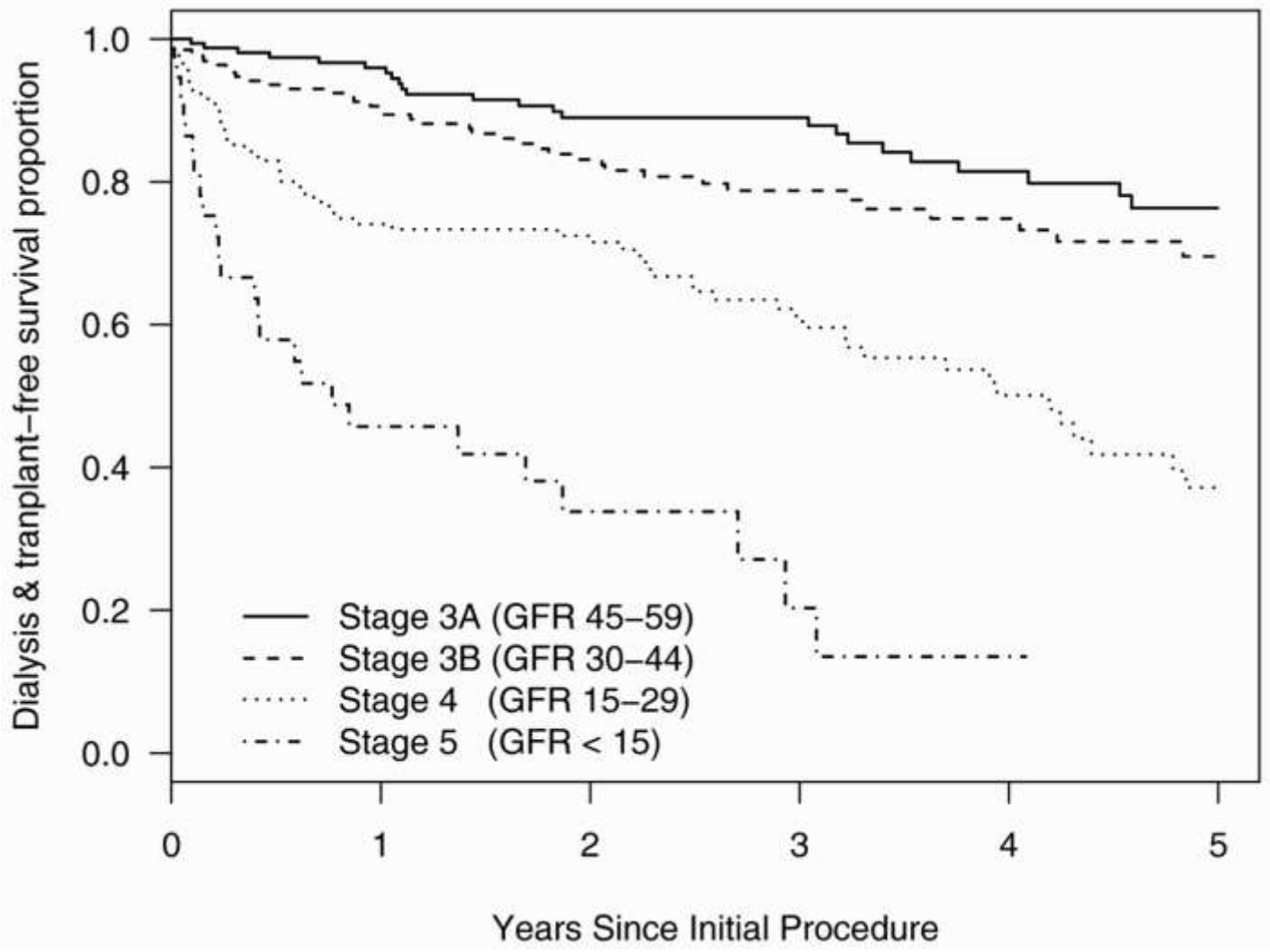
Herrmann S.M.S., Saad A., Stephen C. Textor S.C, Nephrol. Dial. Transplant., 2015, 30: 366–375

Thank you very much for your attention !

Andrzej Wiecek

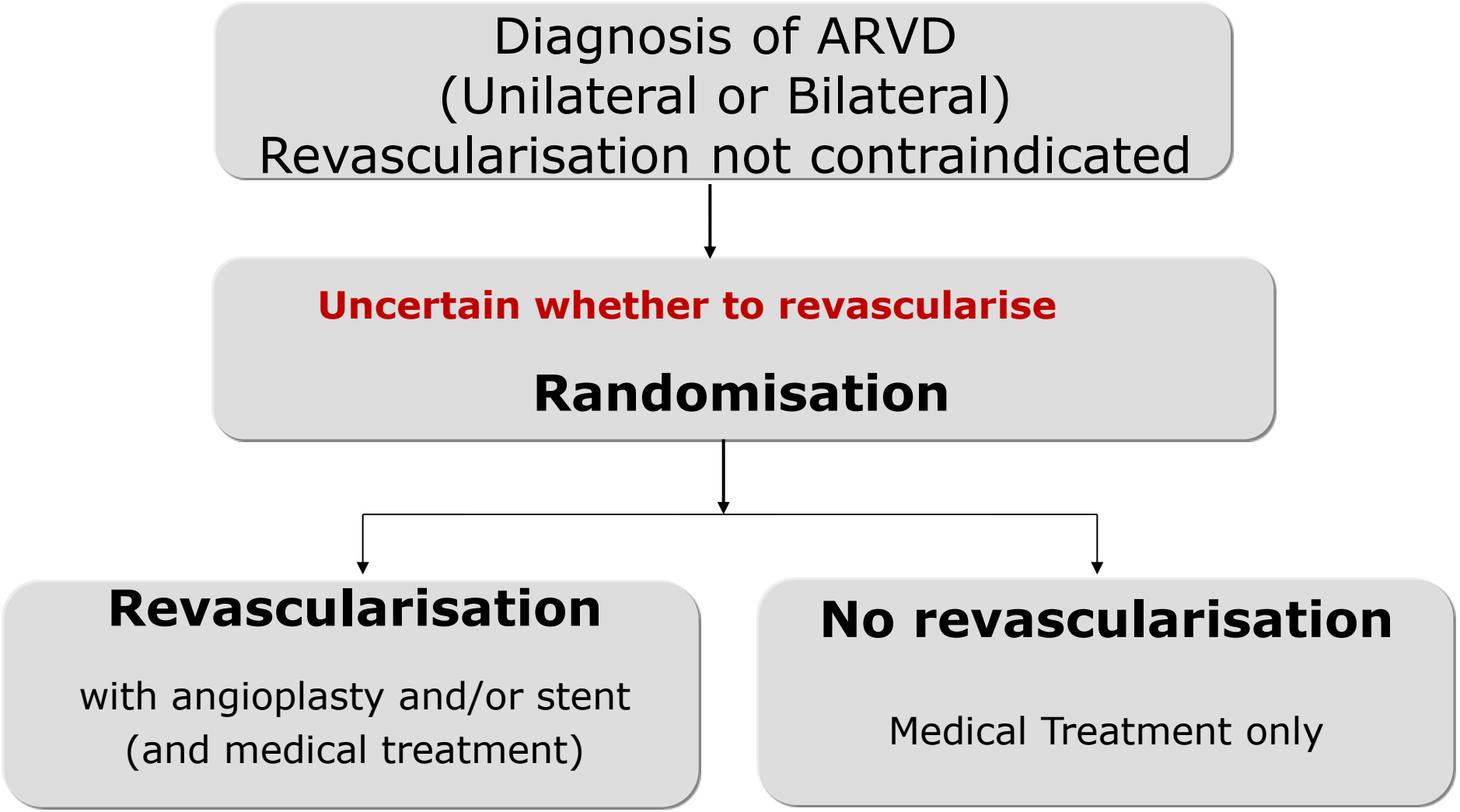
Katowice
Poland

Kaplan-Meier plots of freedom from requiring renal replacement therapy for 550 patients with variable pre-treatment levels of estimated GFR after technically successful renal artery angioplasty and stenting



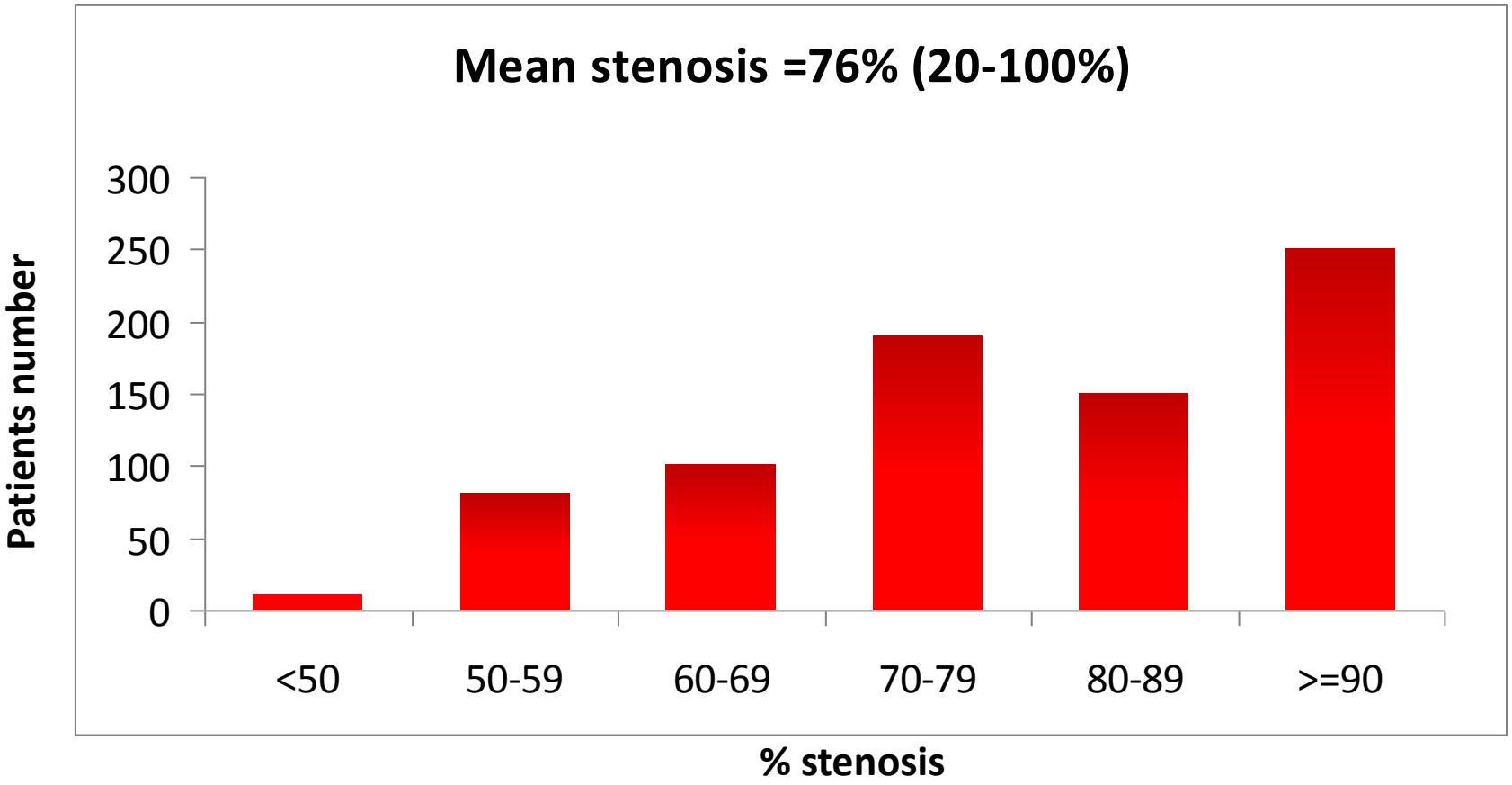
Textor S.C. et al., Kidney Int., 2013; 83: 28–40

ASTRAL Trial protocol



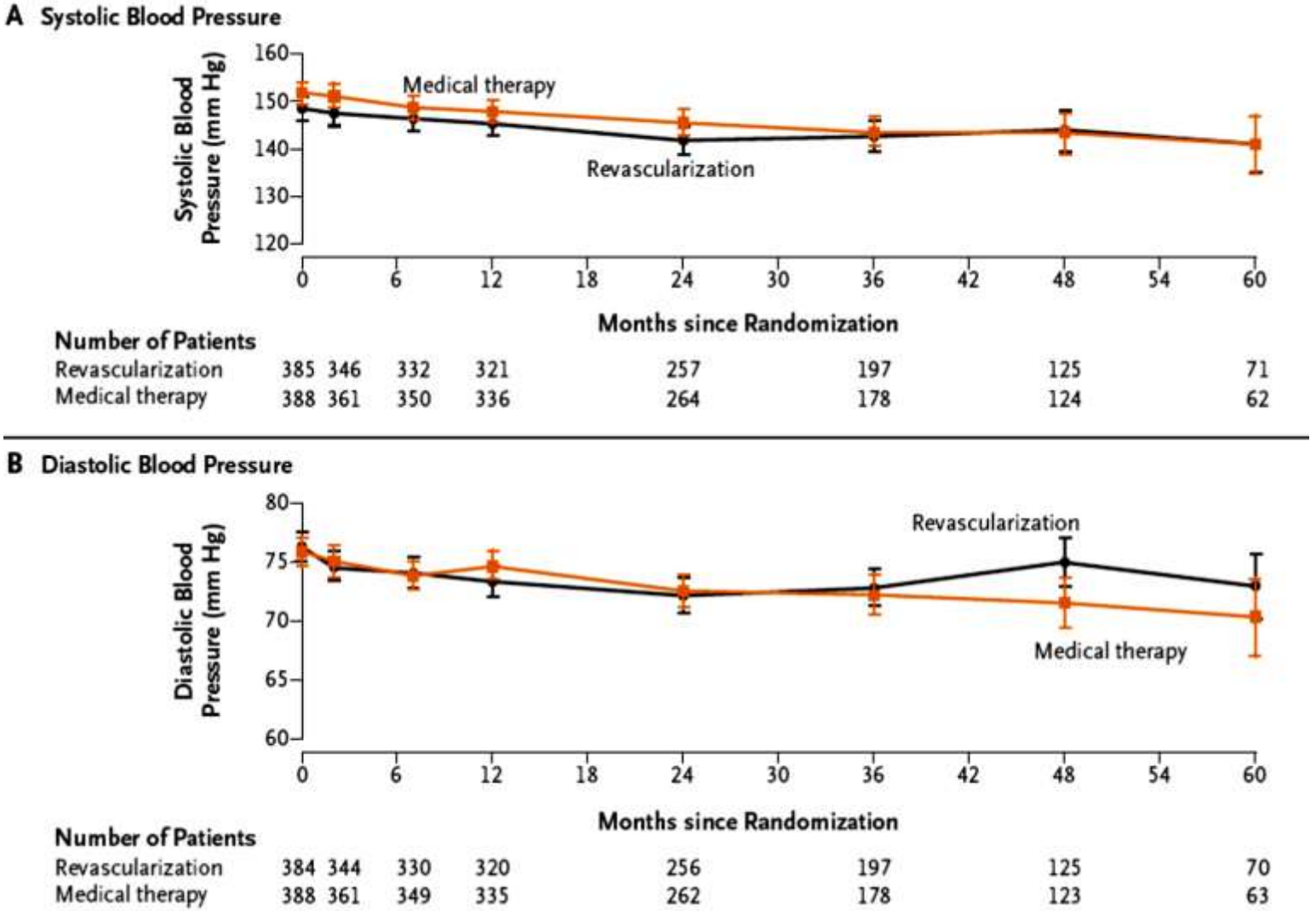
Kalra P. N. Engl. J. Med., 2009, 361,1953-62

ASTRAL - Patients characteristic – percent of lumen stenosis



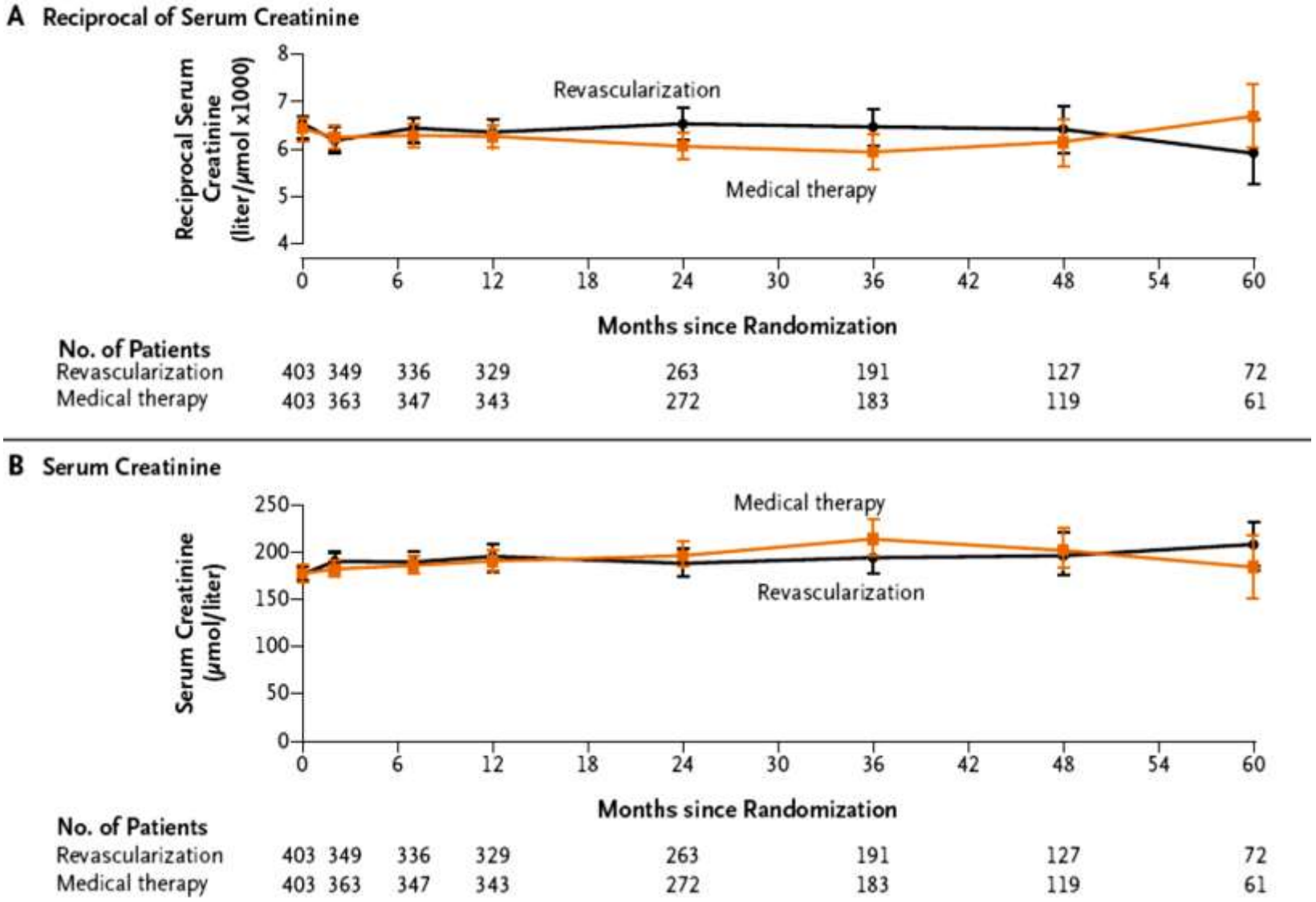
Kalra P. N. Engl. J. Med., 2009, 361,1953-62

ASTRAL - Systolic and diastolic blood pressure in patients with renal artery stenosis treated with revascularization or medical therapy alone



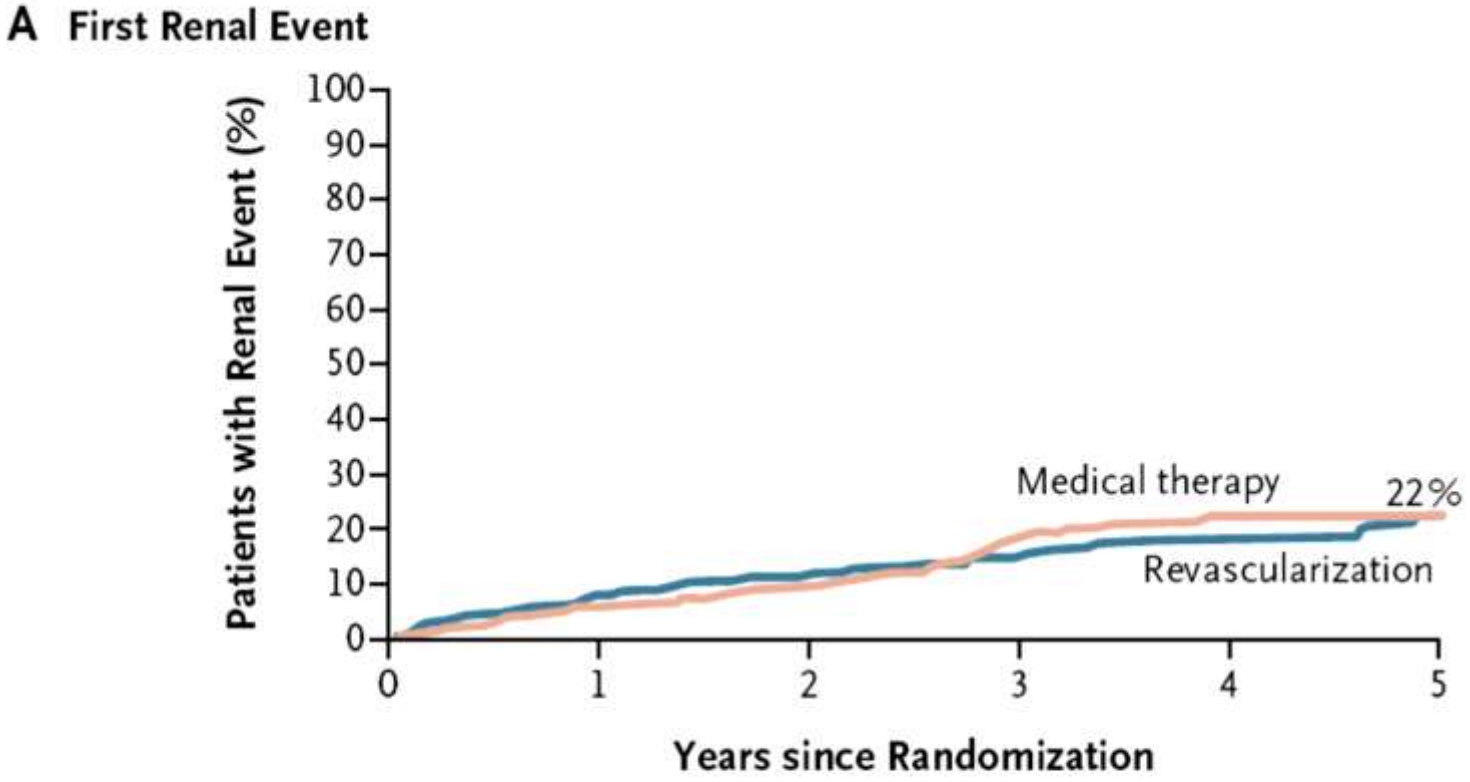
Kalra P. N. Engl. J. Med., 2009, 361,1953-62

ASTRAL - Renal function in patients with renal-artery stenosis treated with revascularization or medical therapy alone



Kalra P. N. Engl. J. Med., 2009, 361,1953-62

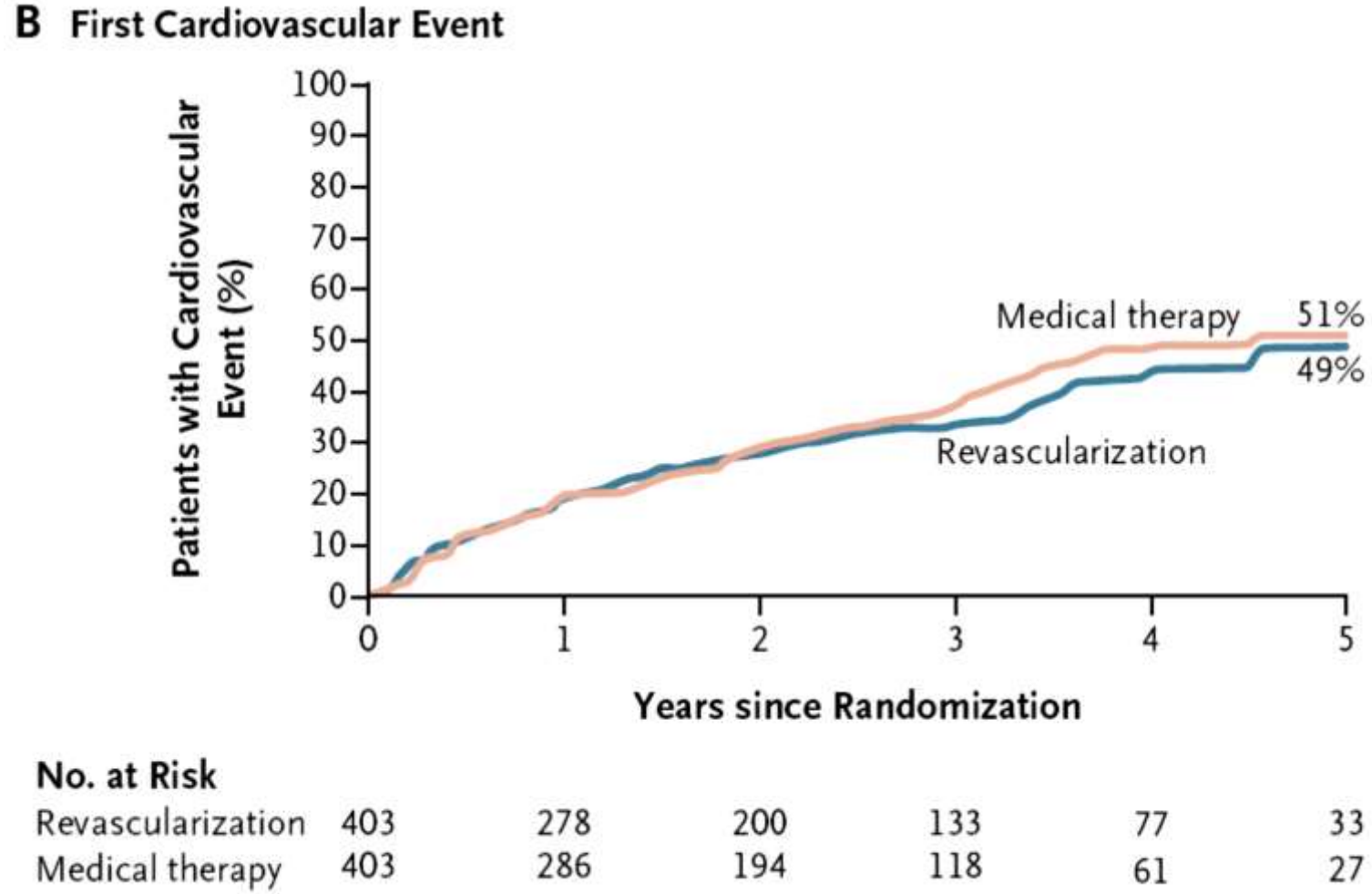
ASTRAL - Kaplan–Meier curves for the time to the first renal events



No. at Risk						
Revascularization	403	315	236	157	99	39
Medical therapy	403	319	233	145	84	37

Kalra P. N. Engl. J. Med., 2009, 361,1953-62

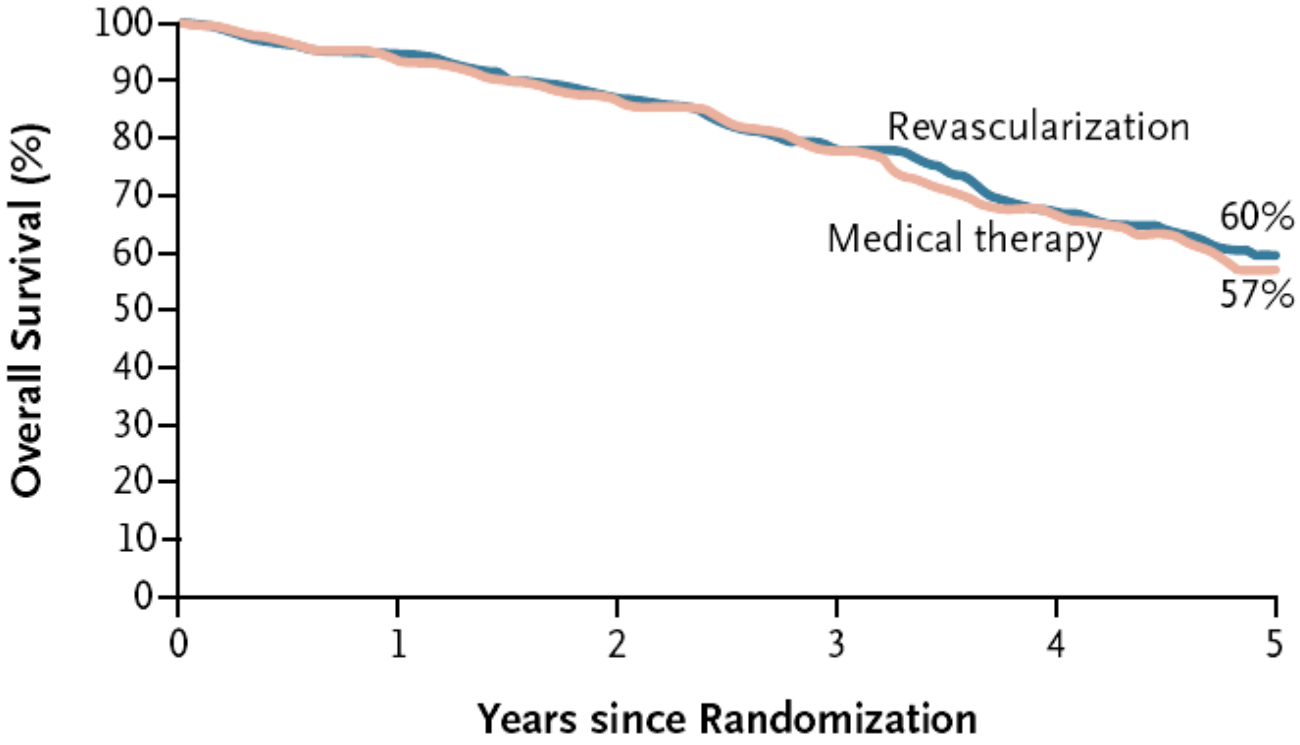
ASTRAL - Kaplan–Meier curves for the time to the first cardiovascular events



Kalra P. N. Engl. J. Med., 2009, 361,1953-62

ASTRAL

Kaplan–Meier curves for overall survival



No. at Risk

Revascularization	403	337	257	178	109	46
Medical therapy	403	332	248	165	96	40

Kalra P. N. Engl. J. Med., 2009, 361,1953-62

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JANUARY 2, 2014 VOL. 370 NO. 1

Stenting and Medical Therapy for Atherosclerotic Renal-Artery Stenosis

Christopher J. Cooper, M.D., Timothy P. Murphy, M.D., Donald E. Cutlip, M.D., Kenneth Jamerson, M.D., William Henrich, M.D., Diane M. Reid, M.D., David J. Cohen, M.D., Alan H. Matsumoto, M.D., Michael Steffes, M.D., Michael R. Jaff, D.O., Martin R. Prince, M.D., Ph.D., Eldrin F. Lewis, M.D., Katherine R. Tuttle, M.D., Joseph I. Shapiro, M.D., M.P.H., John H. Rundback, M.D., Joseph M. Massaro, Ph.D., Ralph B. D'Agostino, Sr., Ph.D., and Lance D. Dworkin, M.D., for the CORAL Investigators*

From the University of Toledo, Toledo, OH (C.J.C.); Rhode Island Hospital (T.P.M., L.D.D.) and Alpert Medical School of Brown University (T.P.M., L.D.D.) — both in Providence; Harvard Clinical Research Institute (D.E.C., J.M.M., R.B.D.), Beth Israel Deaconess Medical Center (D.E.C.),

ABSTRACT

BACKGROUND

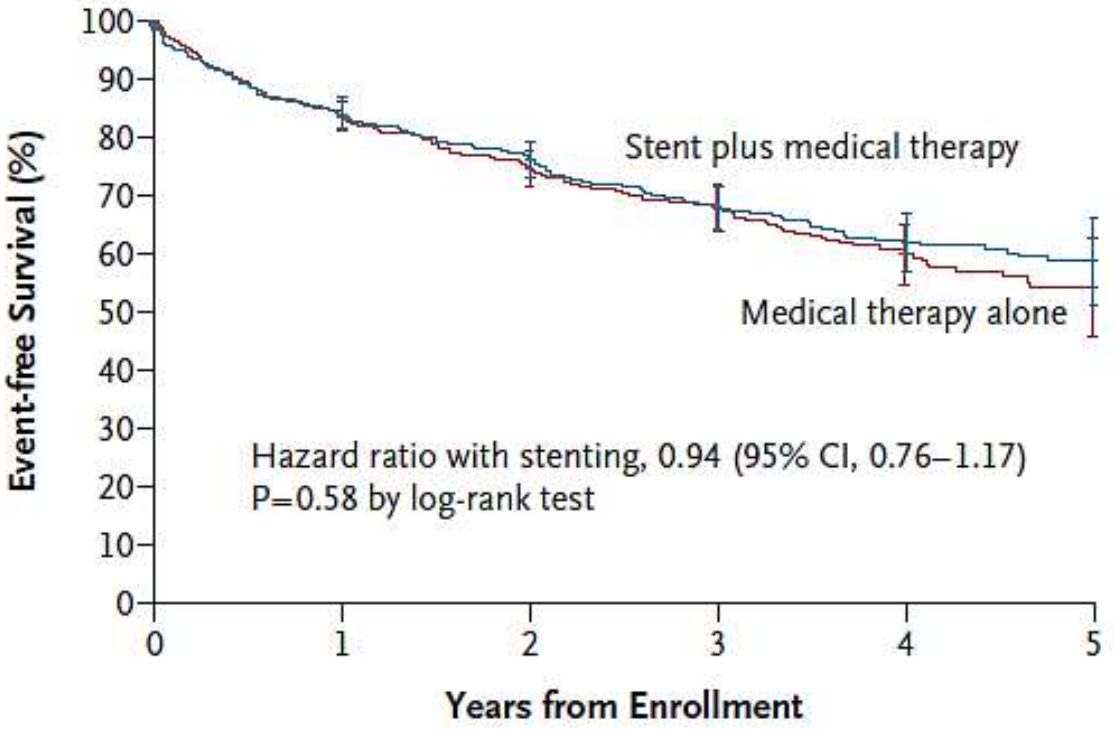
Atherosclerotic renal-artery stenosis is a common problem in the elderly. Despite two randomized trials that did not show a benefit of renal-artery stenting with respect to kidney function, the usefulness of stenting for the prevention of major adverse renal and cardiovascular events is uncertain.

METHODS

We randomly assigned 947 participants who had atherosclerotic renal-artery stenosis and either systolic hypertension while taking two or more antihypertensive drugs or chronic kidney disease to medical therapy plus renal-artery stenting or medical therapy alone. Participants were followed for the occurrence of adverse cardiovascular and renal events (a composite end point of death from cardiovascular or renal causes, myocardial infarction, stroke, hospitalization for congestive heart failure, progressive renal insufficiency, or the need for renal-replacement therapy).

The CORAL Study

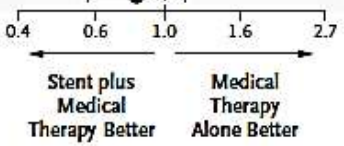
Kaplan–Meier Curves for the Primary Outcome



No. at Risk						
Medical therapy alone	472	371	314	214	115	40
Stent plus medical therapy	459	362	318	224	131	59

The CORAL Study:
Forest Plot of Treatment Effects within Subgroups

Subgroup	Stent plus Medical Therapy	Medical Therapy Alone	Hazard Ratio (95% CI)	P Value for Interaction
	no. of patients/total no. (%)			
Overall	161/459 (35.1)	169/472 (35.8)	0.94 (0.76–1.17)	
Creatinine level				0.09
>1.6 mg/dl	43/84 (51.2)	34/87 (39.1)	1.35 (0.86–2.11)	
≤1.6 mg/dl	112/352 (31.8)	128/367 (34.9)	0.87 (0.67–1.12)	
Estimated GFR				0.80
≥45 ml/min/1.73 m^2	91/288 (31.6)	105/311 (33.8)	0.93 (0.70–1.23)	
<45 ml/min/1.73 m^2	64/148 (43.2)	57/143 (39.9)	0.98 (0.68–1.40)	
Diabetes				0.17
Yes	69/148 (46.6)	66/162 (40.7)	1.15 (0.82–1.61)	
No	92/309 (29.8)	103/310 (33.2)	0.84 (0.64–1.12)	
Sex				0.64
Male	75/234 (32.1)	78/231 (33.8)	0.89 (0.65–1.22)	
Female	86/225 (38.2)	91/241 (37.8)	0.99 (0.74–1.33)	
Global ischemia				0.32
Yes	39/89 (43.8)	20/51 (39.2)	1.07 (0.62–1.83)	
No	119/356 (33.4)	106/264 (40.2)	0.78 (0.60–1.01)	
Race				0.62
Black	11/29 (37.9)	10/30 (33.3)	1.01 (0.42–2.43)	
Other	126/356 (35.4)	136/357 (38.1)	0.88 (0.69–1.13)	
Baseline systolic blood pressure				0.55
>160 mm Hg	66/148 (44.6)	58/139 (41.7)	1.02 (0.71–1.45)	
≤160 mm Hg	95/309 (30.7)	108/328 (32.9)	0.90 (0.68–1.18)	
Age				0.56
>70 yr	91/226 (40.3)	94/220 (42.7)	0.87 (0.65–1.16)	
≤70 yr	70/233 (30.0)	75/252 (29.8)	1.00 (0.72–1.39)	
U.S. sites				0.38
Yes	137/385 (35.6)	146/387 (37.7)	0.90 (0.71–1.14)	
No	24/74 (32.4)	23/85 (27.1)	1.22 (0.69–2.16)	
Maximal diameter stenosis				0.66
≥80%	77/198 (38.9)	64/166 (38.6)	0.93 (0.67–1.30)	
<80%	77/231 (33.3)	79/208 (38.0)	0.84 (0.61–1.14)	



Cooper C. J. et al., N. Engl. J. Med., 2014, 370, 13 - 22

The NEW ENGLAND JOURNAL of MEDICINE

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Stenting and Medical Therapy for Atherosclerotic Renal-Artery Stenosis

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ABSTRACT

BACKGROUND

Atherosclerotic renal-artery stenosis is a common problem in the elderly. Despite two randomized trials that did not show a benefit of renal-artery stenting with respect to kidney function, the usefulness of stenting for the prevention of major adverse renal and cardiovascular events is uncertain.

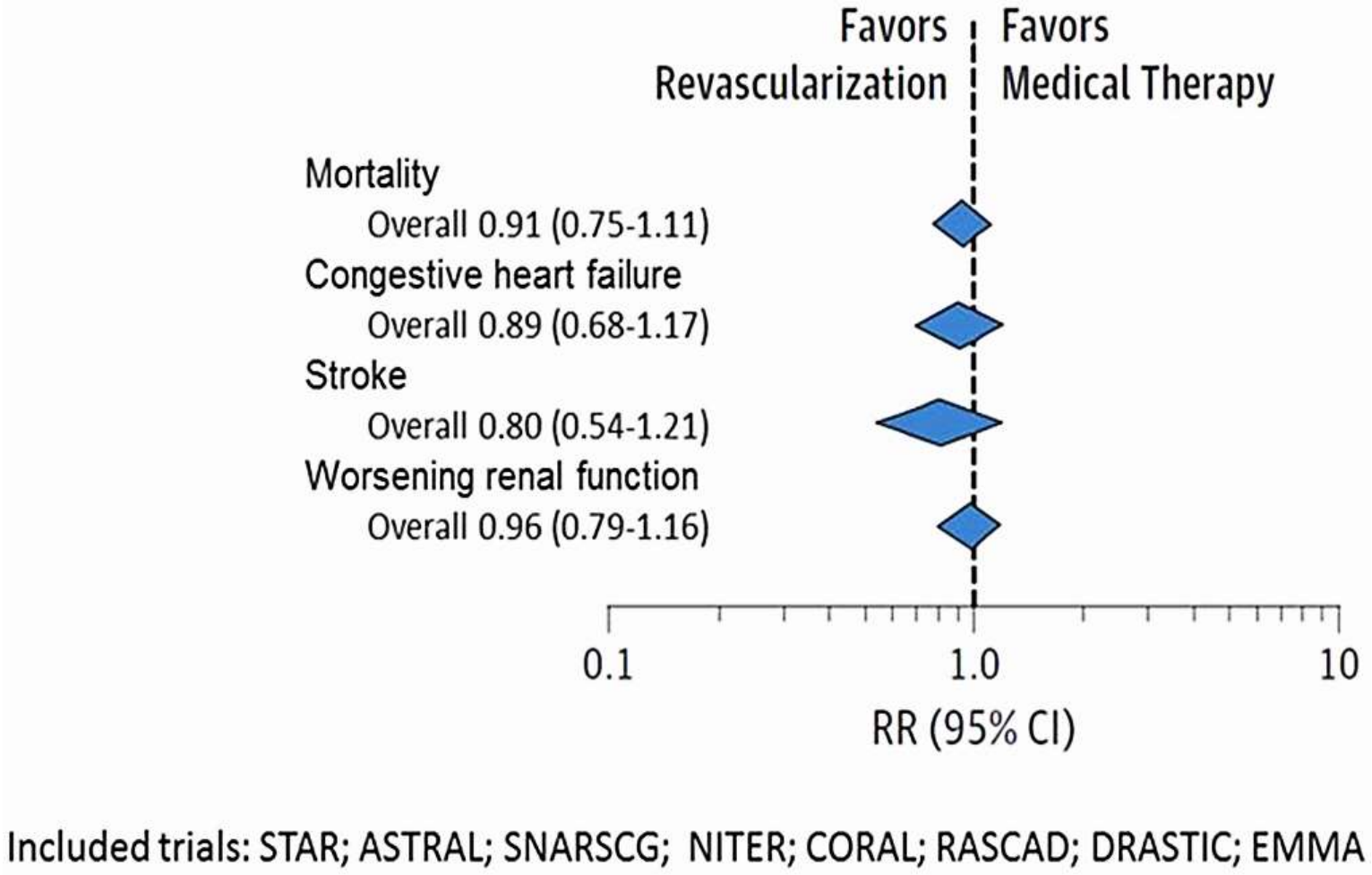
CONCLUSIONS

Renal-artery stenting did not confer a significant benefit with respect to the prevention of clinical events when added to comprehensive, multifactorial medical therapy in people with atherosclerotic renal-artery stenosis and hypertension or chronic kidney disease. (Funded by the National Heart, Lung and Blood Institute and others; ClinicalTrials.gov number, NCT00081731.)

From the University of Toledo, Toledo, OH (C.J.C.); Rhode Island Hospital (T.P.M., L.D.D.) and Alpert Medical School of Brown University (T.P.M., L.D.D.) — both in Providence; Harvard Clinical Research Institute (D.E.C., J.M.M., R.B.D.), Beth Israel Deaconess Medical Center (D.E.C.),

Renal artery revascularization:

updated metaanalysis with the CORAL trial summary estimates of cardiovascular outcomes for revascularization vs medical therapy



Included trials: STAR; ASTRAL; SNARSCG; NITER; CORAL; RASCAD; DRASTIC; EMMA

Renovascular Hypertension Revisited: To intervene or not?

- The decision to revascularize the renal artery in atherosclerotic renal artery stenosis usually is made with the assumption that ischemia is partially responsible for the decrease in kidney function and that correcting the stenosis and restoring kidney perfusion will stabilize or improve glomerular filtration

- The aim with this type of treatment ultimately is to avoid or at least delay the need for RRT. However, kidney function may continue to decrease even if revascularization is successful. This highlights how complex the physiopathology of ischemic nephropathy is because it includes an important intrarenal (parenchymal) component that is affected by risk factors for atherosclerosis

Renovascular Hypertension Revisited: To intervene or not?

- Therefore, the assumption that restoring renal artery patency always protects the kidney is false. In addition, sometimes the revascularization procedure causes a worsening of kidney function, in addition to the high risk of major complications and increased economic costs associated with the procedure

Renovascular Hypertension Revisited: To intervene or not?

- Based on current evidence, patients with good BP control, stable kidney function, and no recurrent flash pulmonary edema should be treated with medical therapy only. The medical therapy should include ACE inhibitors or ARBs, with additional antihypertensive drugs aimed at adequate BP control, antiplatelet therapy, HMG-CoA (3-hydroxy-3-methylglutaryl coenzyme A) reductase inhibitors, antidiabetic therapy if indicated, and smoking cessation.

- In addition, there seems to be little value in screening for atherosclerotic renal artery stenosis in asymptomatic patients who have atherosclerosis and CKD or hypertension, including the current practice of “drive-by” angiography, or even screening low-risk symptomatic patients who have a good response to medical therapy

Boehlke M. and Correa Barcellos F., Am J Kidney Dis., 2015, 65: 611-622

Renovascular Hypertension Revisited: To intervene or not?

- High-risk patients, such those with recurrent flash pulmonary edema, rapidly declining kidney function, or refractory hypertension, may benefit from revascularization, but there is no definitive evidence.

- Each case must be discussed with the patient and his or her family, weighing the potential benefits with the procedure risks. If revascularization is chosen, angioplasty with stent placement is the preferred method, considering its similar results when compared with surgery, with fewer complications and less costs and the lower rate of restenosis after stent placement.

Factors favoring medical therapy plus revascularization for renal artery stenosis:

- Progressive decline in GFR during treatment of hypertension
- Failure to achieve adequate BP control with optimal medical therapy
- Rapid or recurrent decline in GFR in association with a reduction in systemic pressure
- Decline inGFR during therapy with ACE inhibitors or ARBs
- Recurrent congestive heart failure in a patient in whom left ventricular failure does not explain the cause (flash pulmonary edema)

Textor S.C., Clin J Am Soc Nephrol., 2014, 9: 1117–1123

Factors favoring medical therapy and surveillance of renal artery disease

- Controlled BP with stable renal function
- Stable renal artery stenosis without progression on surveillance studies (e.g., serial duplex ultrasound)
- Advanced age and/or limited life expectancy
- Extensive comorbidities that make revascularization too risky
- High risk for or previous experience with atheroembolic disease
- Other concomitant renal parenchymal diseases that cause progressive renal dysfunction (e.g., diabetic nephropathy) or severely reduced kidney size (< 7.0 cm)

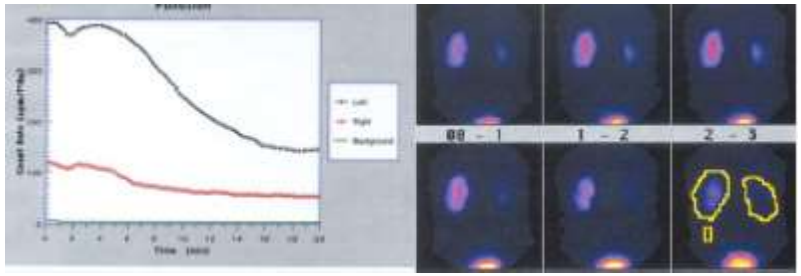
Textor S.C., Clin J Am Soc Nephrol., 2014, 9: 1117–1123

Indications for Renal Revascularization

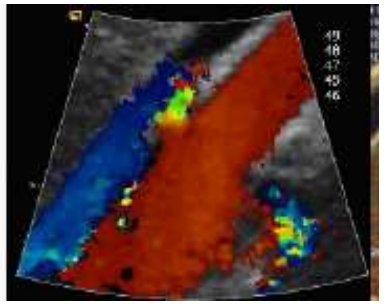
- Resistant hypertension
  - Failure of medical therapy despite full doses of ≥3 drugs, including diuretic
  - Compelling need for ACE inhibition/angiotensin blockade with angiotensin-dependent GFR
- Progressive renal insufficiency
  - Salvageable kidneys
    - Recent rise in serum creatinine
    - Loss of GFR during antihypertensive therapy, eg, with ACE inhibition/ARB therapy
    - Evidence of preserved diastolic blood flow (low resistive index; see text)
- Circulatory congestion, recurrent "flash" pulmonary edema
- Refractory congestive heart failure with bilateral renal arterial stenosis

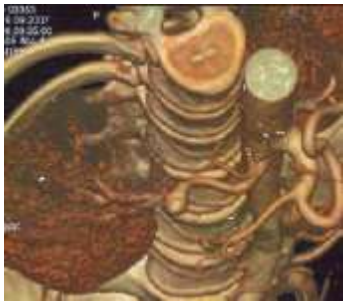
Garovic V.D. and Textor S.C., Circulation. 2005; 112: 1362-1374

Diagnostic procedure in patients with suspected renal artery stenosis

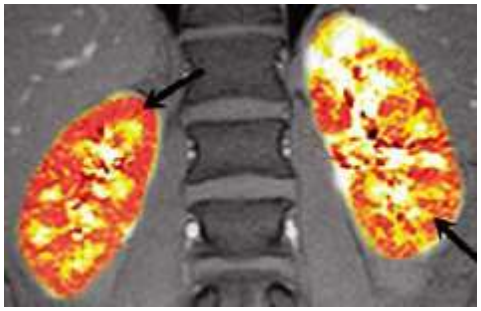


- **The past:**
  - Captopril test
  - Captopril renogram





- **The present time:**
  - Colour Doppler Sonography (CDS)
  - Computed Tomography Angiography (CTA)
  - Magnetic Resonance Tomography Angiography (MRA)



- **The future**
  - BOLD- Magnetic Resonance Imaging (MRI)

Figure 1. Proposed mechanism for CD40/sCD40L signaling in the proximal tubule contributing to the development of renal injury in atherosclerotic renal artery stenosis. In the setting of atherosclerotic renal artery stenosis, increased platelet activation leads to the expression of CD40 ligand (CD40L), which is subsequently cleaved producing soluble CD40 ligand (sCD40L) (Antoniades *et al.*, 2009; Haller *et al.*, 2011). Soluble CD40L may signal through the CD40 receptor expressed on proximal tubular epithelial cells causing fibrosis and inflammation (Pontrelli *et al.*, 2006). CD40 also exists in a soluble form (sCD40), which may act as an antagonist preventing activation (Contin *et al.*, 2003).

We have reported a substantial increase in sCD40L in patients with renal artery stenosis compared to normal control subjects, which significantly decreased following antiplatelet therapy (Haller *et al.*, 2011). Recently, we have shown that low baseline levels of the soluble CD40 receptor are associated with a loss of renal function in patients with renal artery stenosis at one-year follow-up (Haller *et al.*, 2013). Others have also seen interactions between circulating levels of CD40 and clinical outcomes, and have suggested that high circulating levels of circulating CD40 inhibit activation of receptor-bound CD40 (Contin *et al.*, 2003). It is possible that in atherosclerotic renal artery stenosis platelet-derived sCD40L travels from the atherosclerotic lesion to the kidney and activates CD40 on the proximal tubules resulting in inflammation, injury, and renal fibrosis (**Figure 1**).

CD40, a type-I transmembrane receptor and a member of the tumor necrosis factor (TNF) receptor superfamily, is expressed on a wide range of cells and critically links thrombosis, inflammation, immunity, and fibrosis (Antoniades *et al.*, 2009). Recent work in renal disease models suggests that an important mediator of renal fibrosis and inflammatory cell infiltration is CD40 that resides on the surface of the proximal tubular epithelium. Specifically, CD40 is up-regulated after renal injury (Gaweco *et al.*, 1999) and activation of the receptor results in 1) infiltration of inflammatory cells into the interstitium of the kidney through monocyte chemo-attractant protein-1 (MCP-1), and intracellular adhesion molecule-1 (ICAM-1) expression (Li and Nord, 2009), and 2) increase of plasminogen activator inhibitor type 1 (PAI-1) and interstitial fibrosis (Pontrelli *et al.*, 2008; Rerolle *et al.*, 2000; Starke *et al.*, 2007). Importantly, angiotensin II, whose release is increased during renal ischemia, increases TGF-β, which in turn increases expression of CD40 (Starke *et al.*, 2007). Finally, CD40 activation increases antigen-specific recognition and killing of tubular epithelial cells by cytotoxic CD8+ T cells (Starke *et al.*, 2007). Inhibition of CD40 significantly decreased the severity of renal injury in an animal model of chronic proteinuric renal disease (Kairaitis *et al.*, 2003).

Potential markers of cardiovascular-renal events (CVRE) in patients with renal artery stenosis

Table 1. Result of a Cox Regression Analysis Using CVREs as the Dependent Variable, and SBP, IMT, BNP, RAAS and LVH as the Independent Variables

CVREs	Haz.Ratio	Std.Err.	Z	P	95% Conf. Interval	
SBP	1.017796	0.0071446	2.51	0.012	1.003889	1.03190
IMT	0.764413	0.1772249	−1.16	0.247	0.485268	1.20413
BNP	1.003115	0.0017999	1.73	0.083	0.999593	1.00665
RAAS	3.526322	0.7229337	6.15	0.000	2.359481	5.27020
LVH	1.686646	0.5998832	1.47	0.142	0.840002	3.38663

SBP, systolic blood pressure; IMT, intima-media thickness; baPWV, brachial-ankle pulse wave velocity; BNP, brain natriuretic peptide; RAAS, renal artery arteriosclerosis; LVH, left ventricular hypertrophy; Haz. Ratio, hazard ratio; Std. Err., standared error; Conf., confidence.

Table 2. Result of a Cox Regression Analysis Using CVREs as the Dependent Variable, and MCP-1, IP10, 8-OHdG, and AGP2 as the Independent Variables

CVREs	Haz.Ratio	Std.Err.	Z	P	95% Conf. Interval	
MCP-1	1.00198	0.00267	0.74	0.458	0.996759	1.007226
IP-10	1.00169	0.00134	1.26	0.207	0.999069	1.004319
8-OHdG	1.04970	0.03117	1.63	0.102	0.990339	1.112608
AGP2	1.00079	0.00011	7.01	0.000	1.000565	1.001005

CVRE, cardiovascular-renal events; MCP-1, monocyte chemoattractant protein 1; IP-10, interferon-inducible protein 10; 8-OHdG, urinary 8-hydroxydeoxyguanosine; AGP2, angiopoietin-2. Haz. Ratio, hazard ratio; Std.Err., standared error; Conf., confidence.

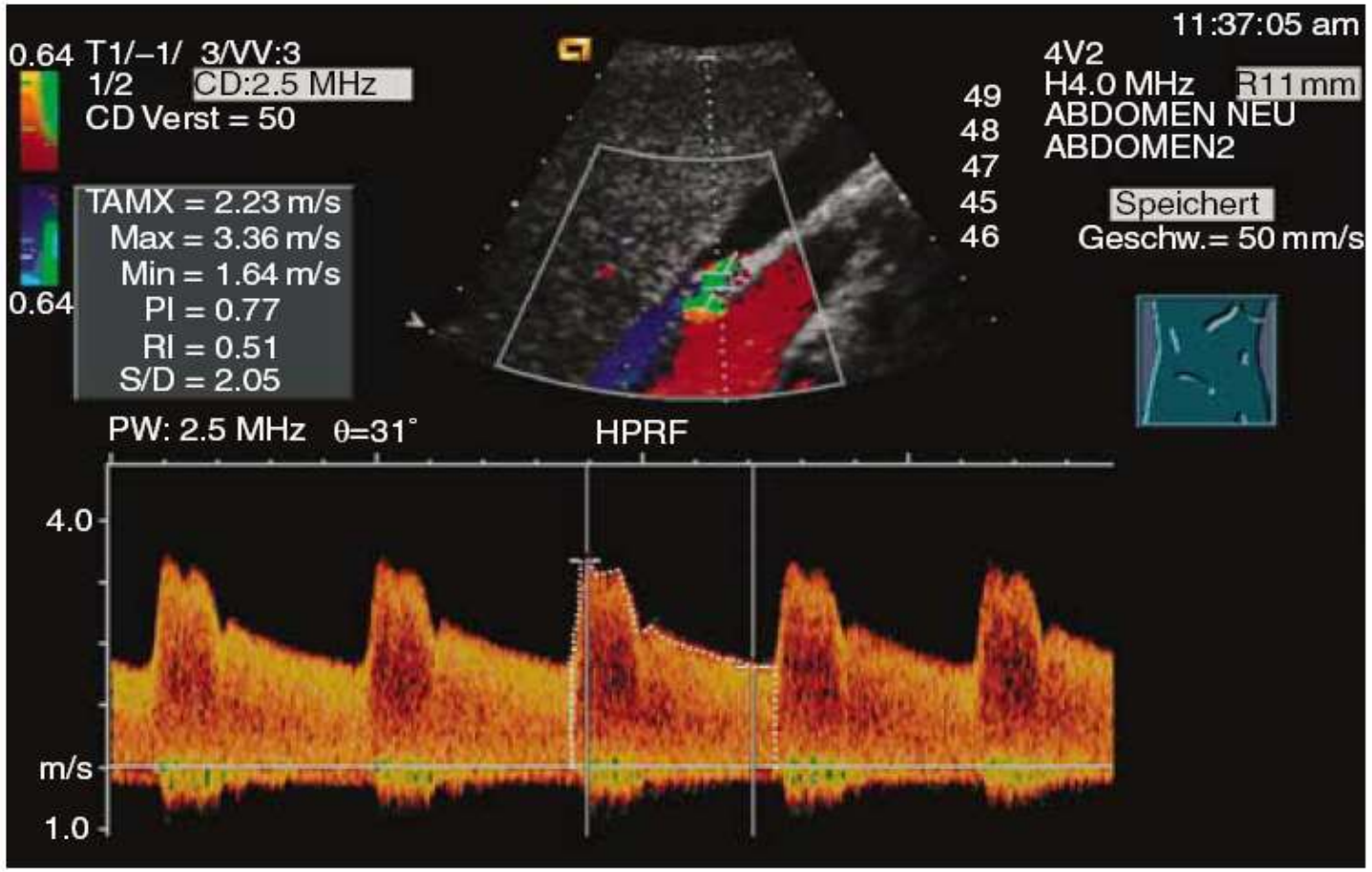
Ogawa S. et al.,Circ. J., 2013; 77: 2816 – 2822

Potential causes of renal artery stenosis

- **Atherosclerosis**
- **Fibromuscular dysplasia**
  - Medial (string-of-beads appearance)
  - Nonmedial (unifocal or tubular lesions)
- **Arteritis**
  - Takayasu arteritis
  - Polyarteritis nodosa
  - Kawasaki disease
- **Rare diseases (mostly reported in children)**
  - Familial diseases: type 1 neurofibromatosis, tuberous sclerosis, pseudoxanthoma elasticum, vascular Ehlers–Danlos syndrome, Alagille syndrome, Marfan syndrome, Williams syndrome, Turner syndrome
  - Idiopathic mid-aortic syndrome
- **Miscellaneous causes**
  - Renal artery spasms induced by sympathomimetic agent or ergot alkaloid abuse
  - Segmental arterial mediolysis
  - Extrinsic compression

Plouin P. et al. Nat. Rev. Nephrol., 2011, 6, 151-159

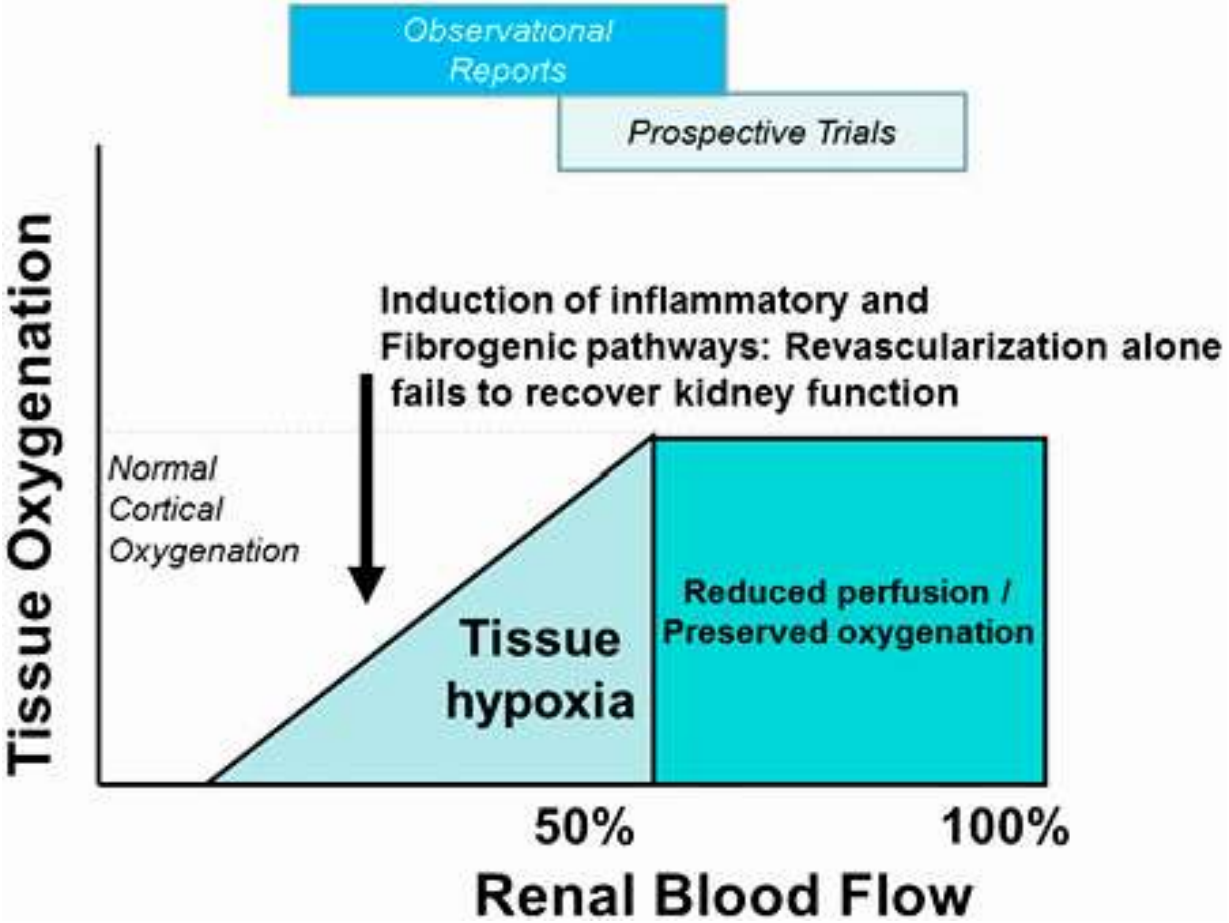
Color duplex sonography of right-sided ostial renal artery stenosis



High peak systolic velocity of 3.36 m/s is obtained within in the stenosis. The green color indicates high blood flow velocity with turbulences near the stenosis. Low mean resistive index(RI=47) of the right kidney is an indirect sign of significant stenosis

Krumme B. and Donauer J. Kidney Int. 2006: 70:1543-7

Clinical results depend on the degree of blood flow reduction tissue hypoxia and the level of inflammatory and fibrotic injury



Textor S.C., and Lerman L.O., J. Am. Soc. Nephrol., 2015, 26: 2074–2080

Nephrol Dial Transplant (2015) 30: 366–375
doi: 10.1093/ndt/gfu067
Advance Access publication 9 April 2014

Management of atherosclerotic renovascular disease after Cardiovascular Outcomes in Renal Atherosclerotic Lesions (CORAL)

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ABSTRACT

Many patients with occlusive atherosclerotic renovascular disease (ARVD) may be managed effectively with medical therapy for several years without endovascular stenting, as demonstrated by randomized, prospective trials including the Cardiovascular Outcomes in Renal Atherosclerotic Lesions (CORAL) trial, the Angioplasty and Stenting for Renal Artery Lesions (ASTRAL) trial and the Stent Placement and Blood

over a wide range of vascular occlusion. Progression of ARVD to severe vascular compromise eventually produces cortical hypoxia, however, associated with active inflammatory cytokine release and cellular infiltration of the renal parenchyma. In such cases ARVD produces a loss of glomerular filtration rate that no longer is reversible simply by restoring vessel patency with technically successful renal revascularization. Each of these trials reported adverse renal functional outcomes ranging between 16 and 22% over periods of 2–5 years of follow-up. Blood pressure control and medication adjustment

AJKD

Narrative Review

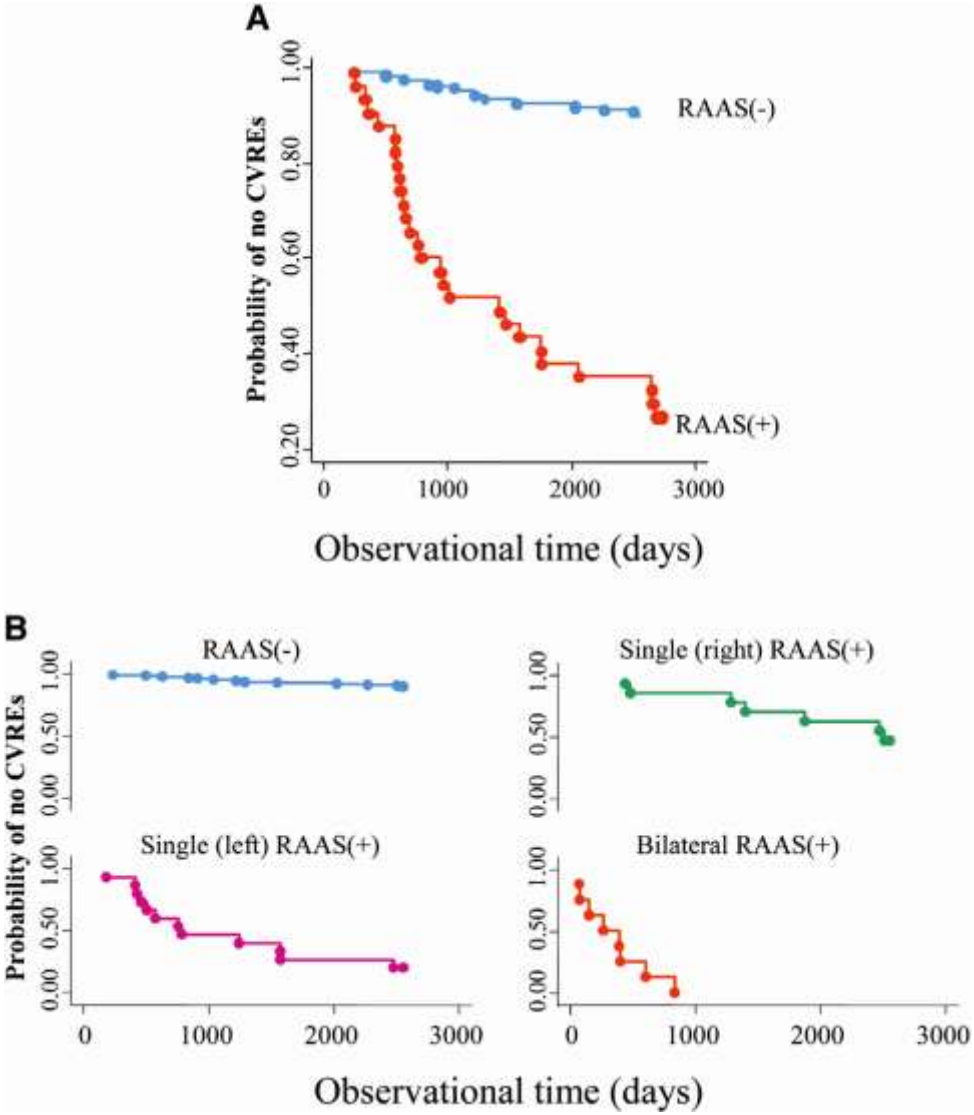
From the 1990s to CORAL (Cardiovascular Outcomes in Renal Atherosclerotic Lesions) Trial Results and Beyond: Does Stenting Have a Role in Ischemic Nephropathy?

Maristela Böhlke, MD, PhD, and Franklin Correa Barcellos, MD, PhD

The prevalence of atherosclerotic renal artery stenosis is high, ~7% in individuals older than 65 years and ~50% in patients with diffuse arterial disease, and it is increasingly frequent in an aging population. About 10% to 15% of atherosclerotic renal artery stenosis cases lead to the development of resistant hypertension and/or ischemic nephropathy. The management of ischemic nephropathy may include medical therapy and/or revascularization. In the past, revascularization required surgical bypass or endarterectomy, accompanied by the morbidity and mortality associated with a major surgical procedure. During the last few decades, less invasive endovascular procedures such as percutaneous transluminal renal artery angioplasty with stent placement have become available. At the same time, new antihypertensive and cardiovascular drugs have been developed, which may preclude revascularization, at least in some cases. The indications of each of these therapeutic options have changed over time. This review offers a temporal perspective on the course of technical and scientific advances and the accompanying change in clinical practice for the treatment of ischemic nephropathy. The latest randomized clinical trials, including the CORAL (Cardiovascular Outcomes in Renal Atherosclerotic Lesions) trial, the largest on the subject, as well as a meta-analysis of these studies, have indicated that the best approach is medical therapy alone. There is evidence that revascularization brings no additional benefit, at least in low-risk and stable atherosclerotic renal artery stenosis. High-risk patients, especially those with recurrent flash pulmonary edema, could benefit from percutaneous transluminal renal artery angioplasty and stent placement, but there is no definitive evidence and the treatment choice should take into account the risks and potential benefits of the procedure.

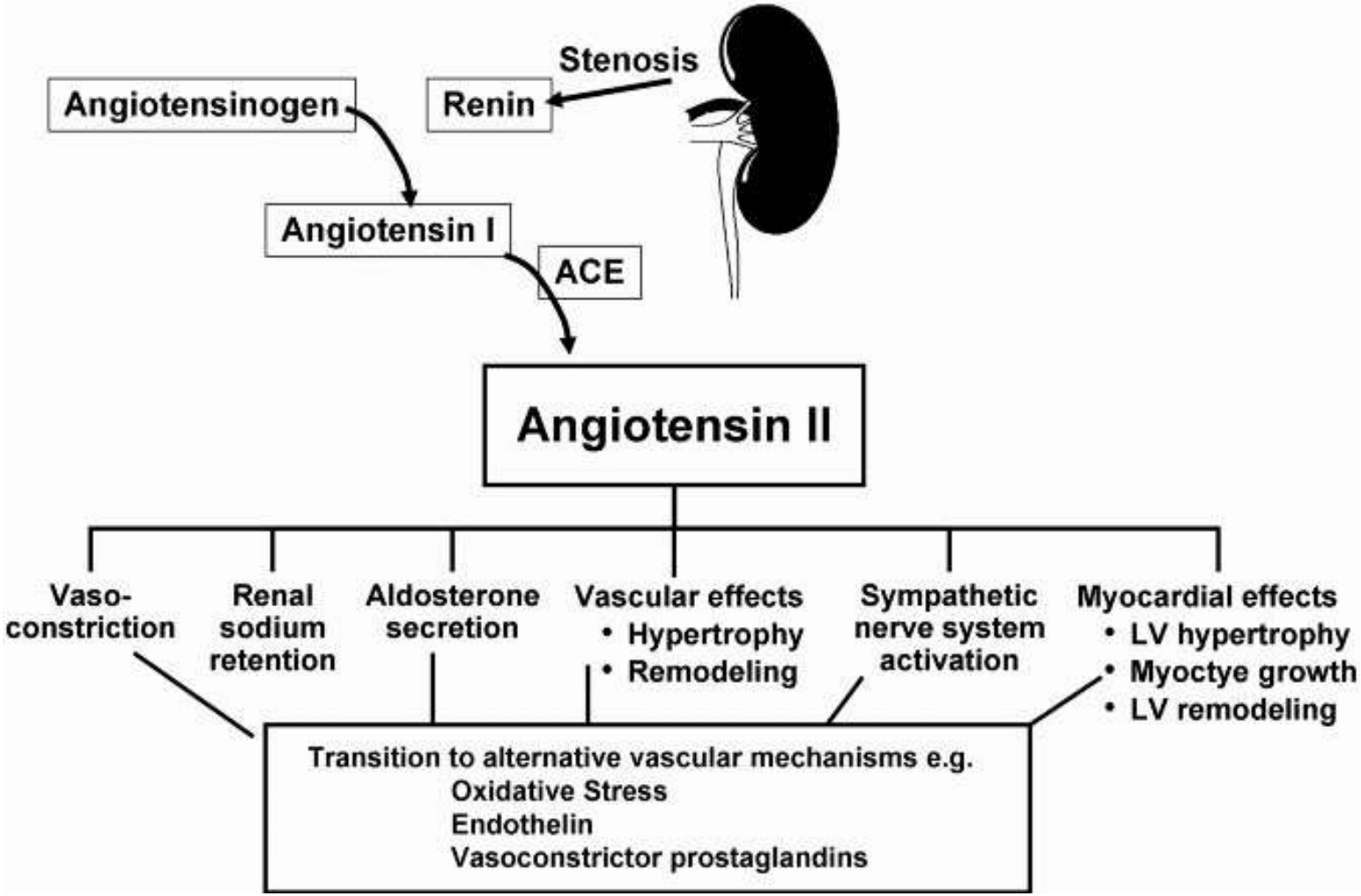
Am J Kidney Dis. ■(■):■-■.

Probability of not experiencing a cardiovascular-renal events (CVRE) over time



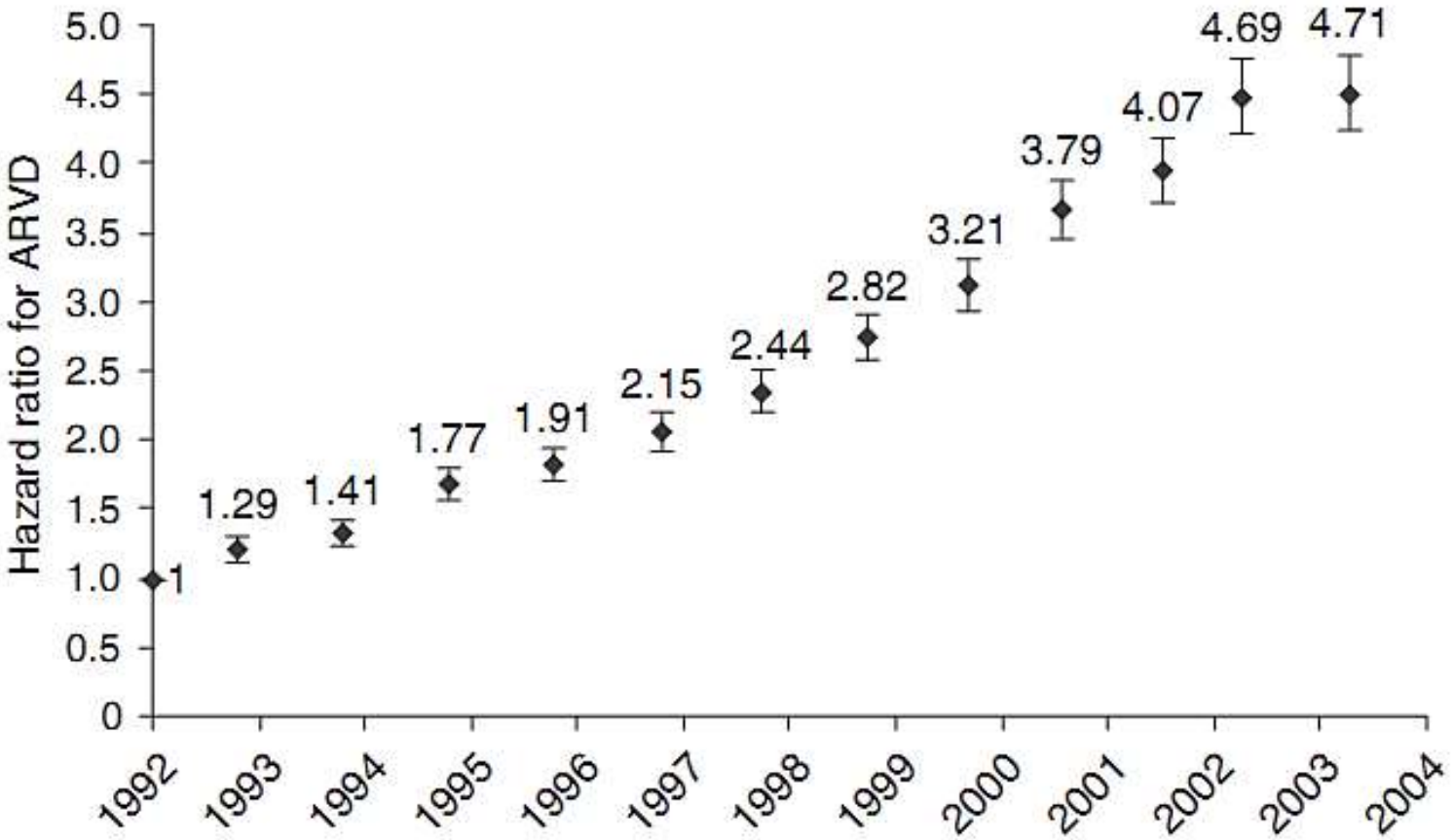
Ogawa S. et al.,Circ. J., 2013; 77: 2816 – 2822

Schematic of pressor mechanisms identified in renovascular hypertension



Garovic V.D. and Textor S.C., Circulation. 2005; 112: 1362-1374

Unadjusted hazard ratios, with 95% confidence intervals, for atherosclerotic renovascular disease (ARVD) by calendar year, with 1992 as reference category



Kalra P. et al., Kidney Int., 2010, 77, 37–43

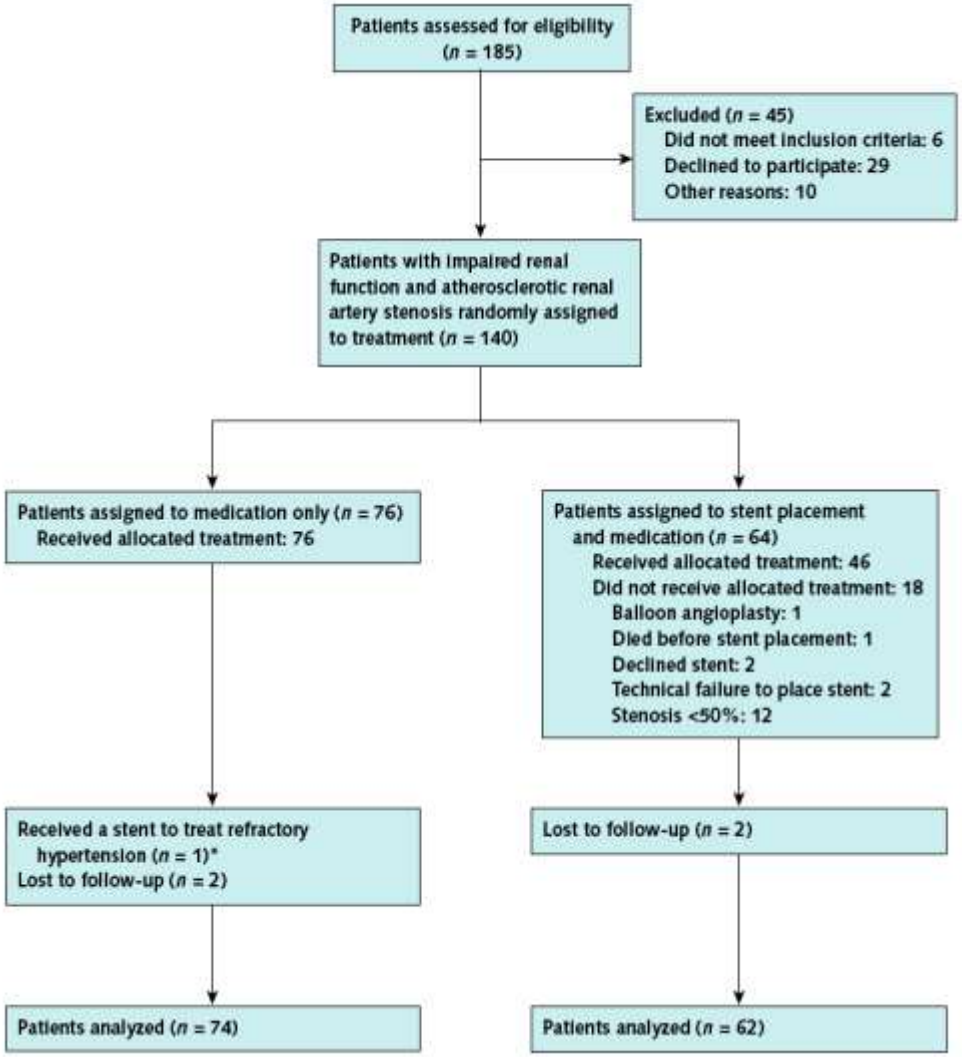
Overview of clinical trials

PTRA vs medical treatment

	EMMA [1]	Scottish [2]	DRASTIC [3]
No. randomized	49	55	106
Stenosis grade	≥ 60 %	≥ 50 %	≥ 50 %
% bilateral	0	51	25
Main outcome	6 mo ABP	6 mo OBP	12 mo OBP
Differences			
- in final BP	NS	NS	NS
- in Rx score	p<0.01	p<0.01	p<0.01

1 Plouin et al., Hypertension 1998. 2 Webster et al., J Human Hypertens 1998
3 van Jaarsveld et al.,N Engl J Med 2000

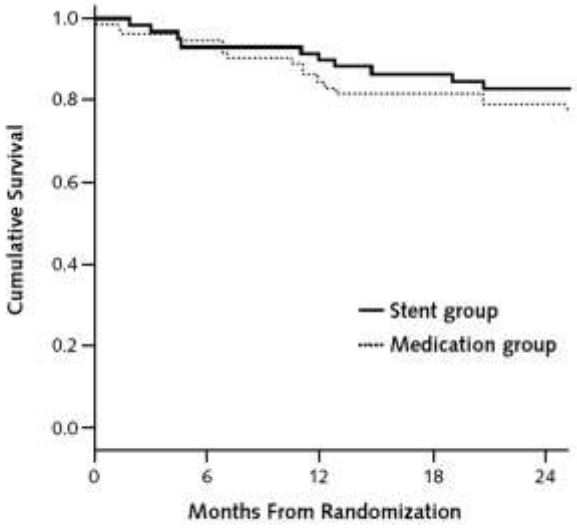
Stent placement in patients with atherosclerotic renal artery stenosis and impaired renal function – STAR Trial



140 patients with creatinine clearance
less than 80 mL/min
per 1.73 m^2
and ARAS of 50% or greater

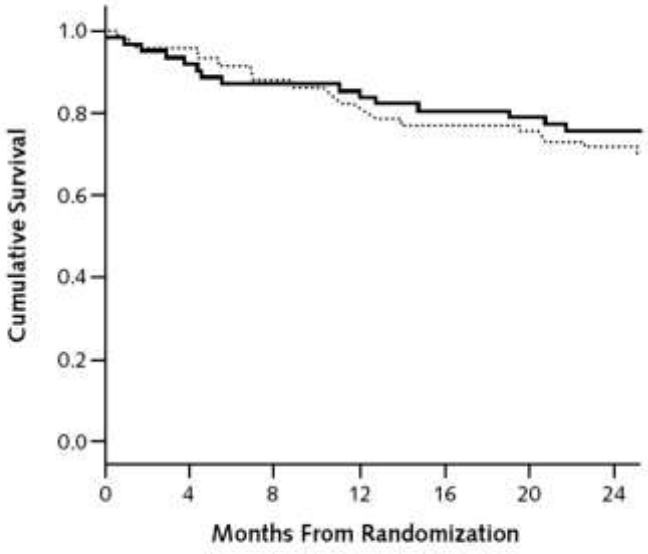
Bax L et al. Ann Intern Med. 2009;150:840-848

STAR -Trial



Patients remaining, *n*					
Medication group	76	68	60	57	53
Stent group	64	54	52	50	46

Survival curves for the primary end point during 2 years of follow-up



Patients remaining, *n*					
Medication group	76	68	60	57	53
Stent group	64	54	52	50	46

Survival curves for the primary end point plus death during 2 years of follow-up

Bax L et al. Ann Intern Med. 2009;150:840-848

http://www.kidney-international.org basic research

see commentary on page 676

Experimental coronary artery stenosis accelerates kidney damage in renovascular hypertensive swine

Dong Sun[1,2], Alfonso Eirin[1], Xiang-Yang Zhu[1], Xin Zhang[1], John A. Crane[1], John R. Woollard[1], Amir Lerman[3] and Lilach O. Lerman[1,3]

[1]Division of Nephrology and Hypertension, Mayo Clinic, Rochester, Minnesota, USA; [2]Department of Nephrology, The Affiliated Hospital of Xuzhou Medical College, Xuzhou, China and [3]Division Cardiovascular Disease, Mayo Clinic, Rochester, Minnesota, USA

In conclusion, this study demonstrates that nonatherosclerotic CAS alone augments renal inflammation, increases systemic and renal oxidative stress, and elicits renal injury and dysfunction. Coexistence of CAS and HT aggravates renal microvascular injury and consequently tissue hypoxia, it synergistically magnifies kidney fibrosis, and it may thereby contribute to increased incidence of renal failure seen when CAS and HT coexist. These observations underscore the cross talk between the myocardium and the kidney and the need for careful screening in order to assess the relative risk and to ensure adequacy of management in patients with concurrent CAS and HT, regardless of the atherosclerosis burden.

Sun D. et al., Kidney Int., 2015, 87, 719–727

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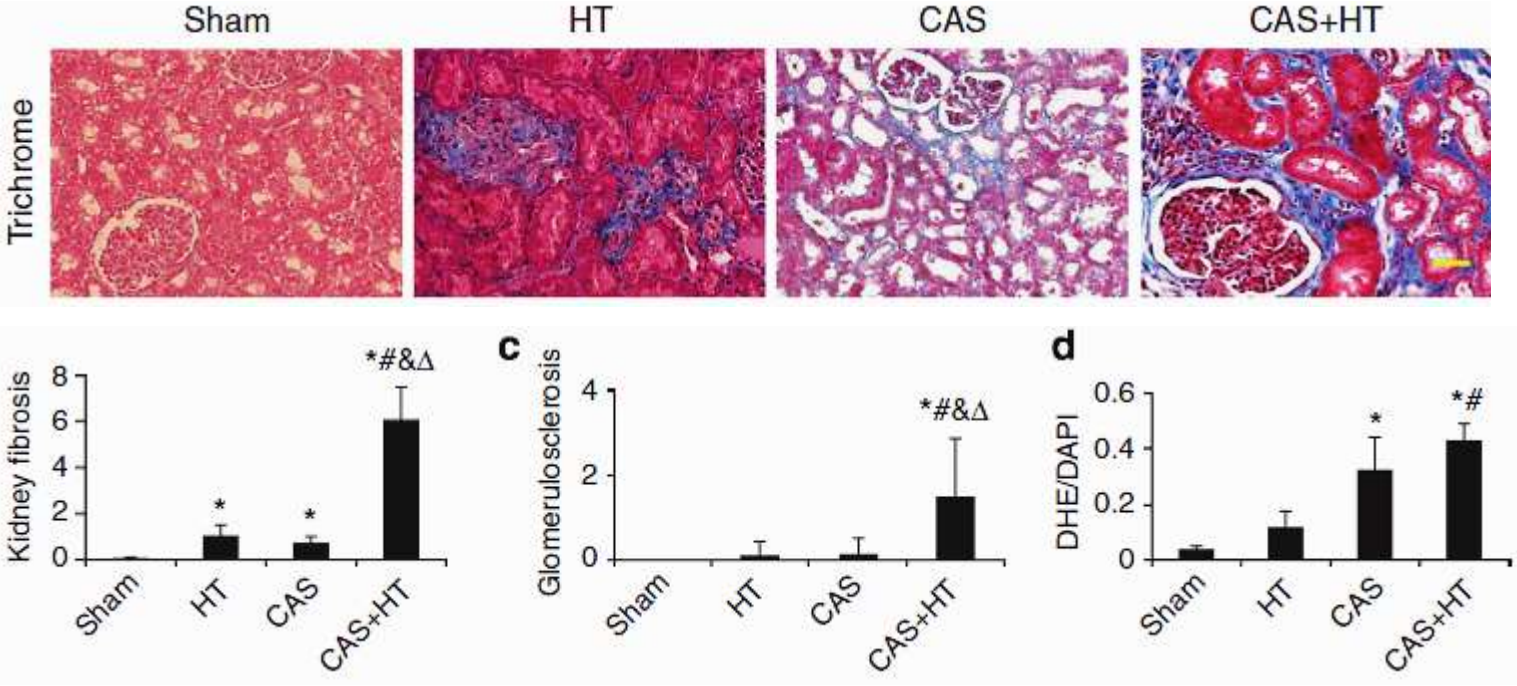


Prevalence of high-risk presentations of atherosclerotic renovascular disease

Table 1. Prevalence of high-risk presentations of atherosclerotic renovascular disease

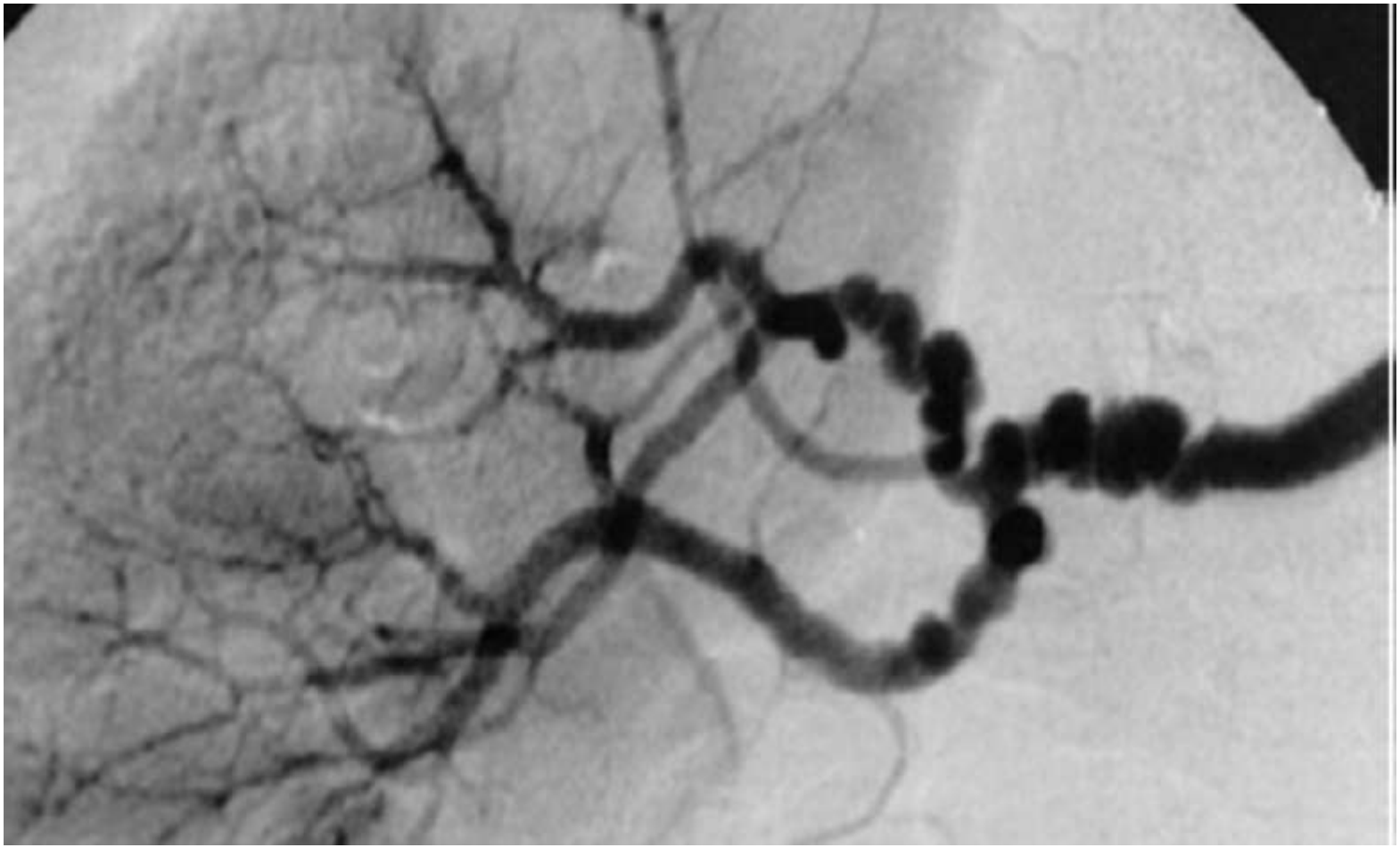
Rapidly declining renal function*	Refractory hypertension**	Flash pulmonary edema
12–17% [1,4▪▪]	Present in 33% of patients at time of diagnosis of atherosclerotic renovascular disease (ARVD) [4▪▪]	5–8% [4▪▪,46]
	8–24% of patients with uncontrolled hypertension have ARVD [44,45▪].	

*Rapidly declining renal function defined as an increase in serum creatinine of greater than or equal to 100 μmol/l or 20% in the 12 months prior to randomization [1].

**Refractory hypertension defined as systolic blood pressure greater than 140 mmHg and/or diastolic blood pressure greater than 90 mmHg despite use of three different classes of antihypertensive of which at least one is a diuretic [47].

Ritchie J., Alderson H.V., Kalra Ph. A. Curr. Opin. Nephrol. Hypertens. 2014, 23:525–532

The "string-of-beads" feature in medial fibromuscular dysplasia



Plouin P. et al., Orphanet Journal of Rare Diseases 2007, 2, 28

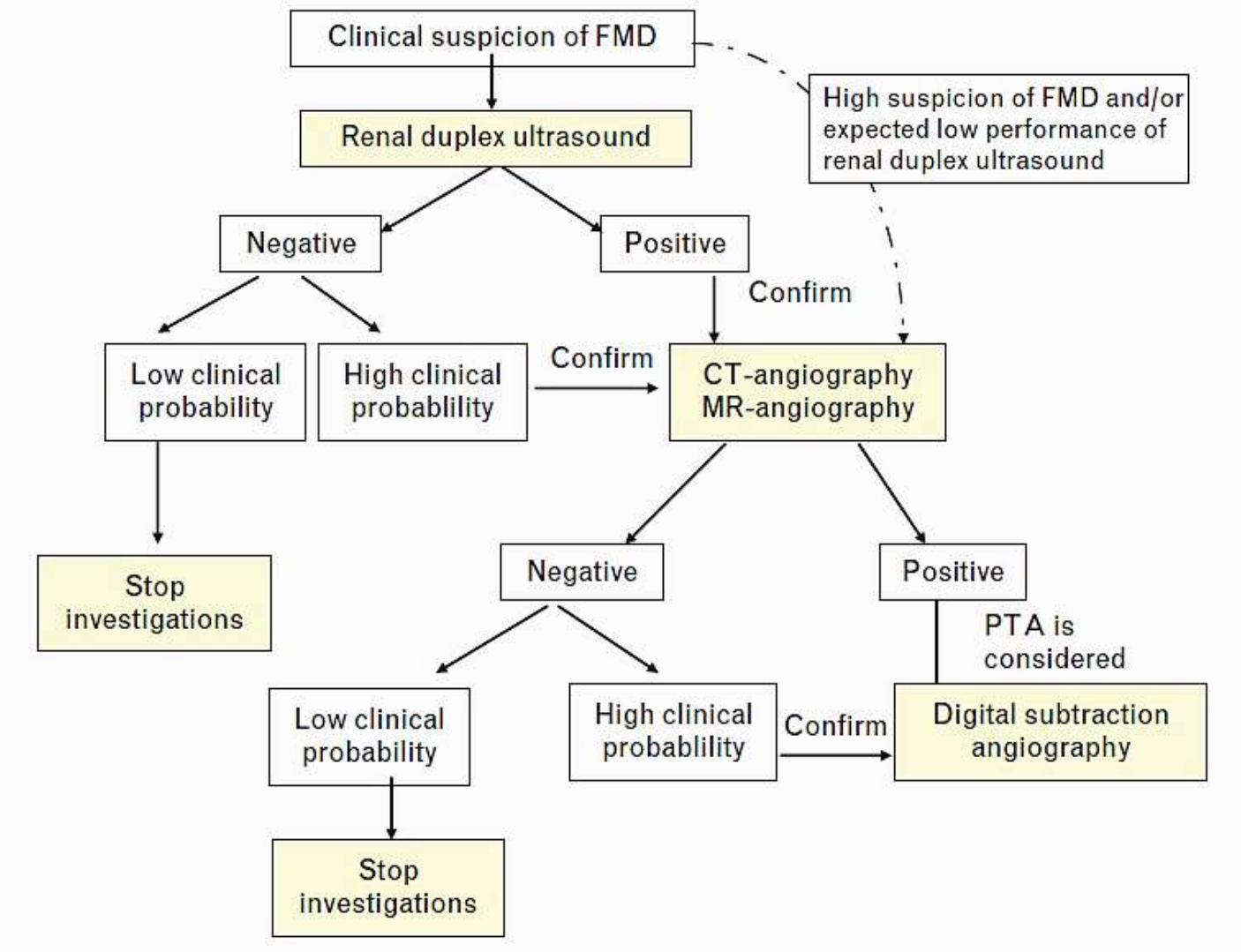
Consensus Document

European consensus on the diagnosis and management of fibromuscular dysplasia

Alexandre Persu[a,b], Alessandra Giavarini[c,d], Emmanuel Touzé[e], Andrzej Januszewicz[f], Marc Sapoval[g,h], Michel Azizi[c,h], Xavier Barral[i], Xavier Jeunemaitre[h,j], Alberto Morganti[d], Pierre-François Plouin[c,h], Peter de Leeuw[k], on behalf of the ESH Working Group 'Hypertension and the Kidney'

J. Hypertens., 2014 , 32: 1367-1378,

Proposed algorithm for establishing the diagnosis of fibromuscular dysplasia (FMD) of the renal arteries



Persu A. et al., J. Hypertens., 2014, 32: 1367-1378

Fibromuscular Dysplasia

- In contrast to atherosclerotic renal artery stenosis, a systematic review and meta-analysis of patients with fibromuscular dysplasia as cause of renal artery stenosis revealed that percutaneous transluminal angioplasty alone (without stenting) improves BP control or even cures hypertension.

- Further, BP outcome was inversely associated with age. Hence, the European consensus on the diagnosis and management of fibromuscular dysplasia proposes revascularization for hypertension because of fibromuscular dysplasia, especially in patients with recent onset hypertension or TRH.