

Cor>Sag -30

R A

Renal Artery Stenosis

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- ❑ Defined as a narrowing of one or both renal arteries or their branches
 - ❑ Most commonly caused by atherosclerosis
 - ❑ Less frequently caused by fibromuscular dysplasia
 - ❑ 90% of lesions are ostial
 - ❑ Prevalence increases with age

Table 1. Characteristics of Atherosclerotic Renal-Artery Stenosis and Fibromuscular Dysplasia.

Variable	Atherosclerosis	Fibromuscular Dysplasia
Age at presentation	Older (>50 yr)	Usually young (<40 yr)
Sex	Either	Usually female
Lesion location	Ostial, proximal, middle*	Middle or distal
Blood-pressure response to revascularization	Unclear	Normotension in most patients

* Locations are listed in descending order of likelihood (i.e., ostial is more likely than proximal, which is more likely than middle).

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- Prevalence of clinically manifested atherosclerotic renal-artery stenosis in the Medicare population is 0.5% overall and 5.5% among patients with chronic kidney disease
 - patients with renal-artery stenosis had significantly increased rates of CKD (25%, vs. 2%), CAD (67% vs. 25%), stroke (37% vs. 12%), and PVD (56% vs. 13%),

Increased risk of cardiovascular events may be due to:

- concomitant atherosclerosis in other vascular beds
- activation of the renin–angiotensin–aldosterone and sympathetic nervous systems
- associated renal insufficiency

Classic clues suggestive of RAS

- ❑ The onset of stage 2 hypertension after 50 years of age
- ❑ Hypertension associated with renal insufficiency
- ❑ Hypertension with repeated hospital admissions for heart failure
- ❑ Drug-resistant hypertension

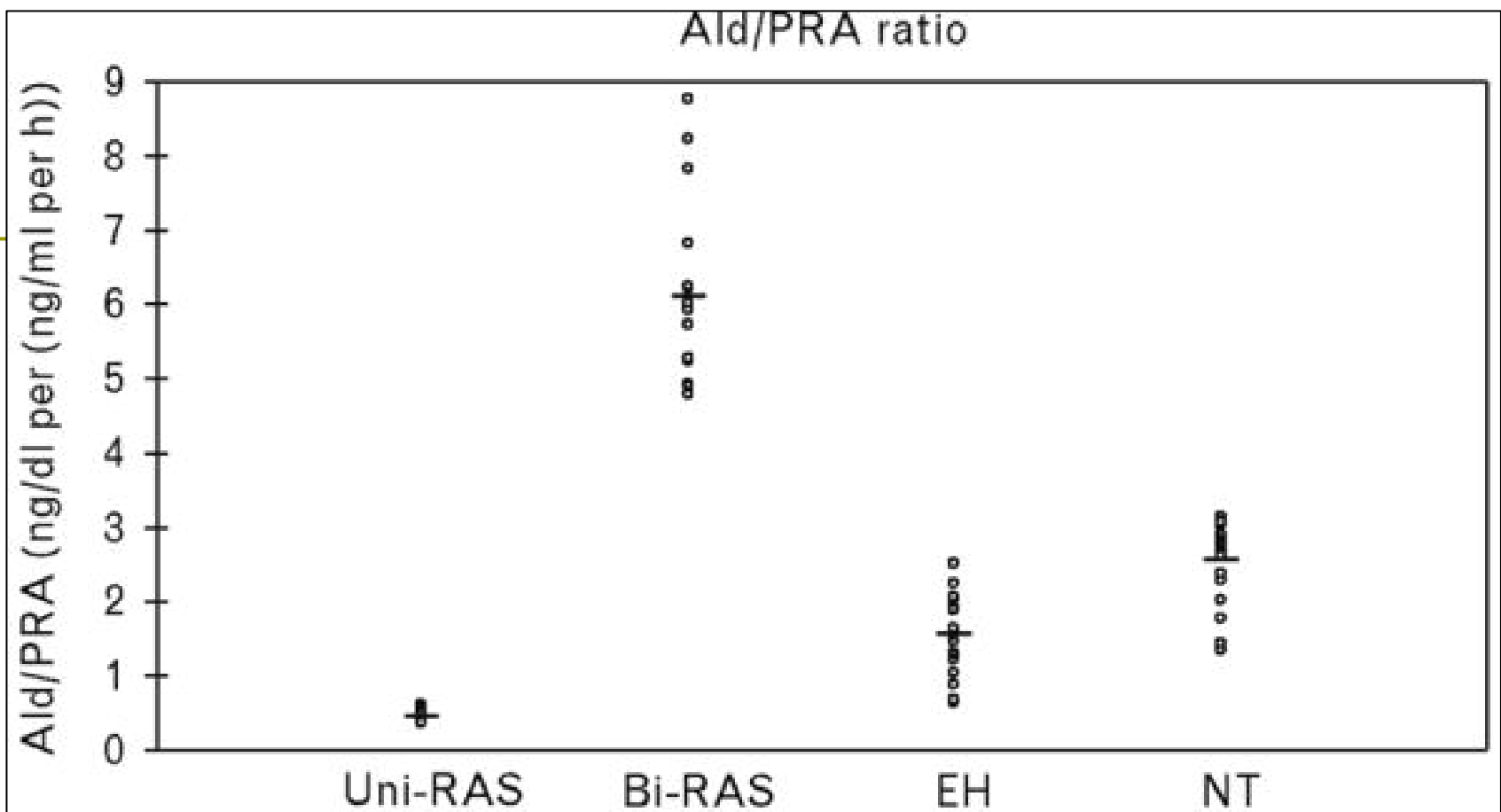
Diagnosis



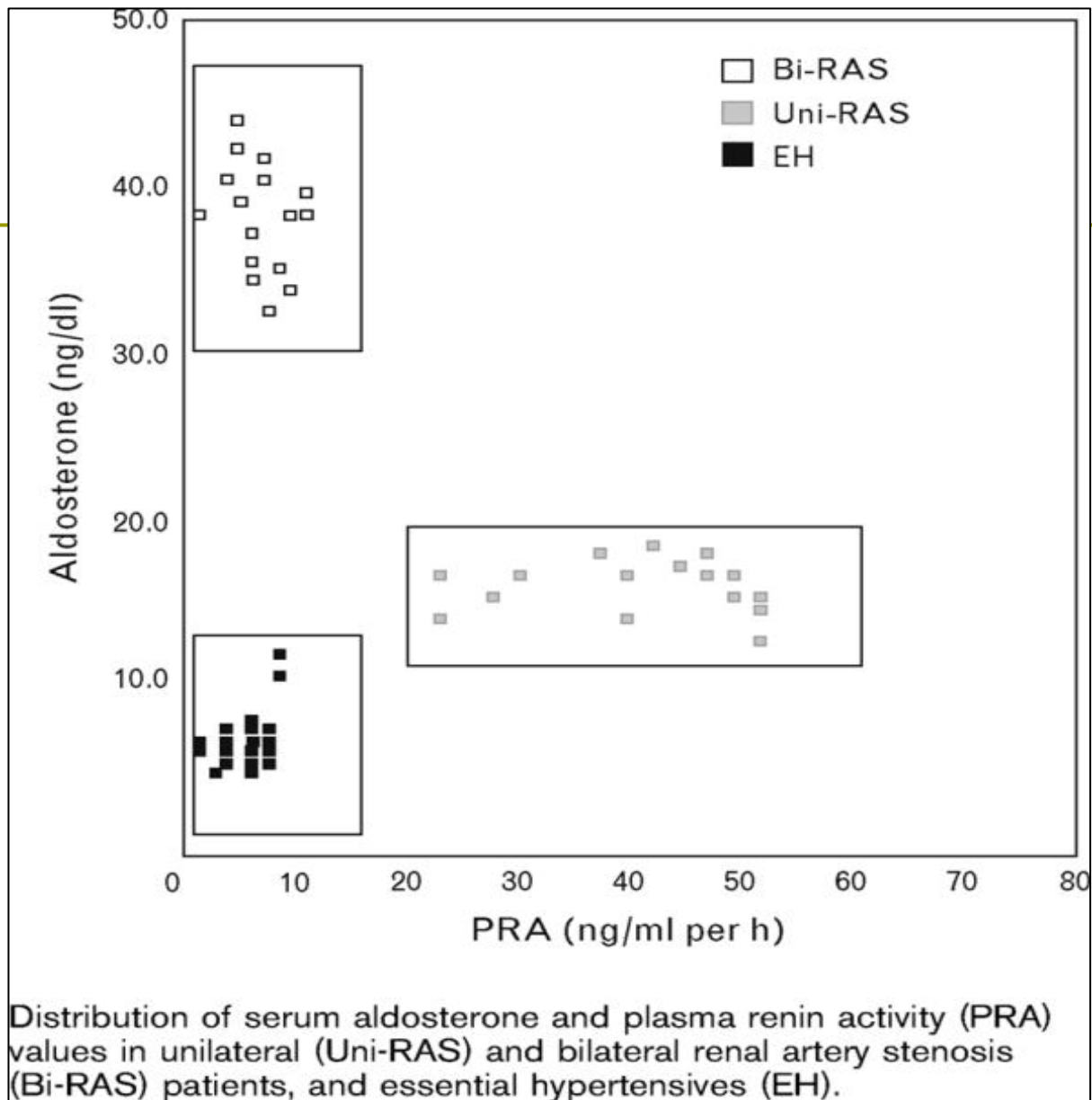
Table 2. Diagnostic Imaging Tests for Renal-Artery Stenosis.

Test	Advantages	Disadvantages
Duplex ultrasonography	Noninvasive	Requires a skilled technician; limited by obesity or bowel gas
Magnetic resonance angiography	Noninvasive	Risk of nephrogenic systemic sclerosis among patients with chronic kidney disease
Computed tomographic angiography	Noninvasive	Risk of contrast nephropathy among patients with chronic kidney disease; radiation exposure
Digital-subtraction angiography	Best image quality and anatomical information	Invasive, risk of contrast nephropathy among patients with chronic kidney disease, risk of atheroembolic events, risk of vascular complications at puncture site; radiation exposure

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- 51 hypertensive patients were studied:
 - 16 with Uni-RAS
 - 16 with Bi-RAS
 - 19 essential hypertensive pts with normal arteries
 - Nineteen normotensive individuals were also studied
 - Ald/PRA lower than 0.5 and Ald/PRA higher than 3.7 to have the best sensitivity and specificity to detect Uni-RAS and Bi-RAS, respectively



Distribution of Ald/PRA ratios in unilateral (Uni-RAS) and bilateral renal artery stenosis (Bi-RAS) patients, essential hypertensives (EH) and normotensive individuals (NT).





Mechanisms of kidney injury

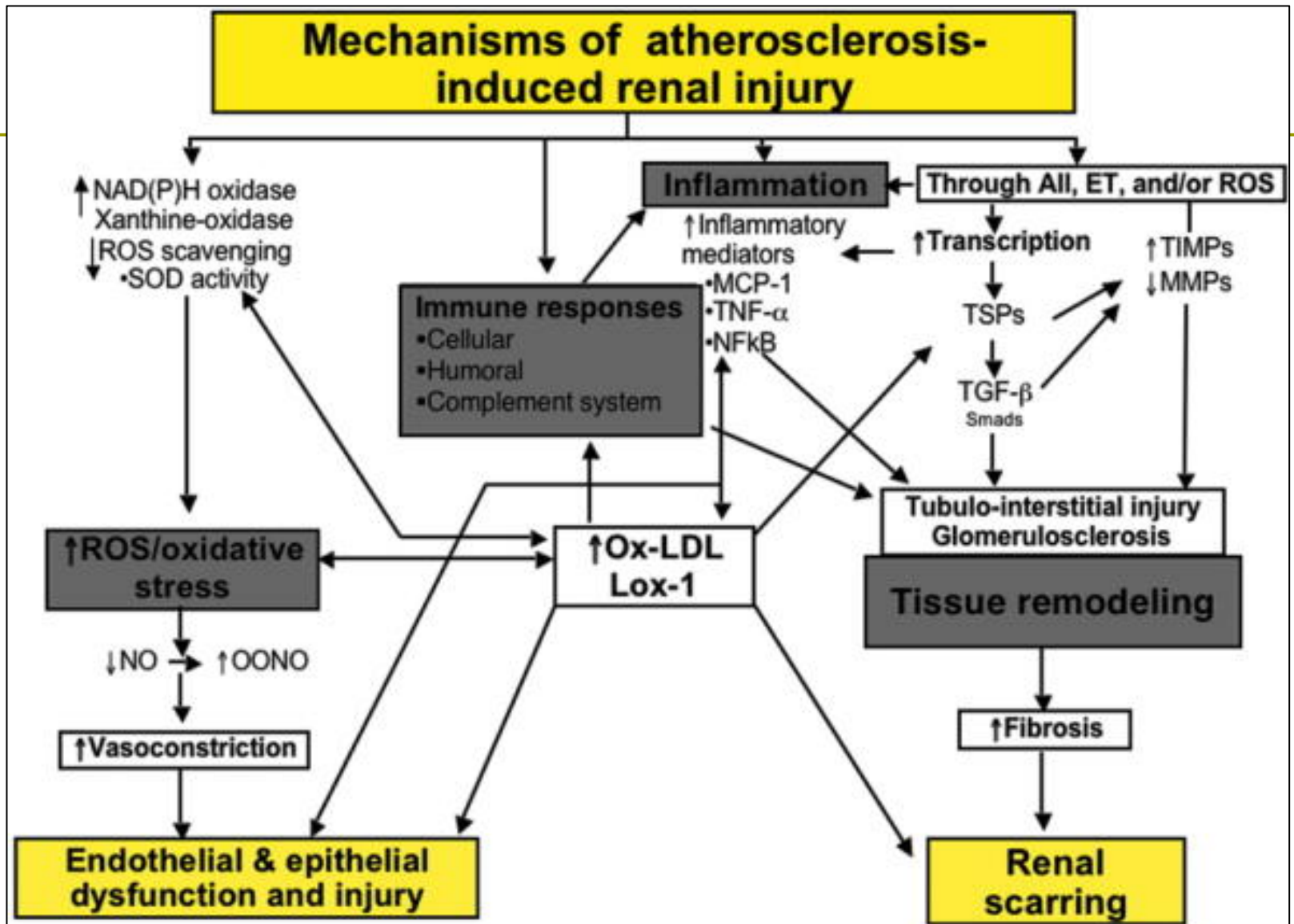
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- ❑ The decrease in renal perfusion and function does not correlate with the angiographic degree of stenosis
 - ❑ The decrease in renal perfusion in patients with atherosclerotic RAS exceeds that incurred in age- and treatment-matched patients with fibromuscular dysplasia with a similar degree of stenosis

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- Endothelial injury
 - Reduced bioavailability of the vasodilator nitric oxide
 - Increased activity of vasoconstrictors

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- Renal microvessels are susceptible to noxious insults including
 - Ischemia
 - low shear stress
 - Oxidized low-density lipoprotein (ox-LDL)

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- Endothelial dysfunction is accompanied by increased generation of reactive oxygen species and oxidative stress which causes
 - Increased renal vascular tone
 - Increased sensitivity to vasoconstrictors
 - Endothelial dysfunction

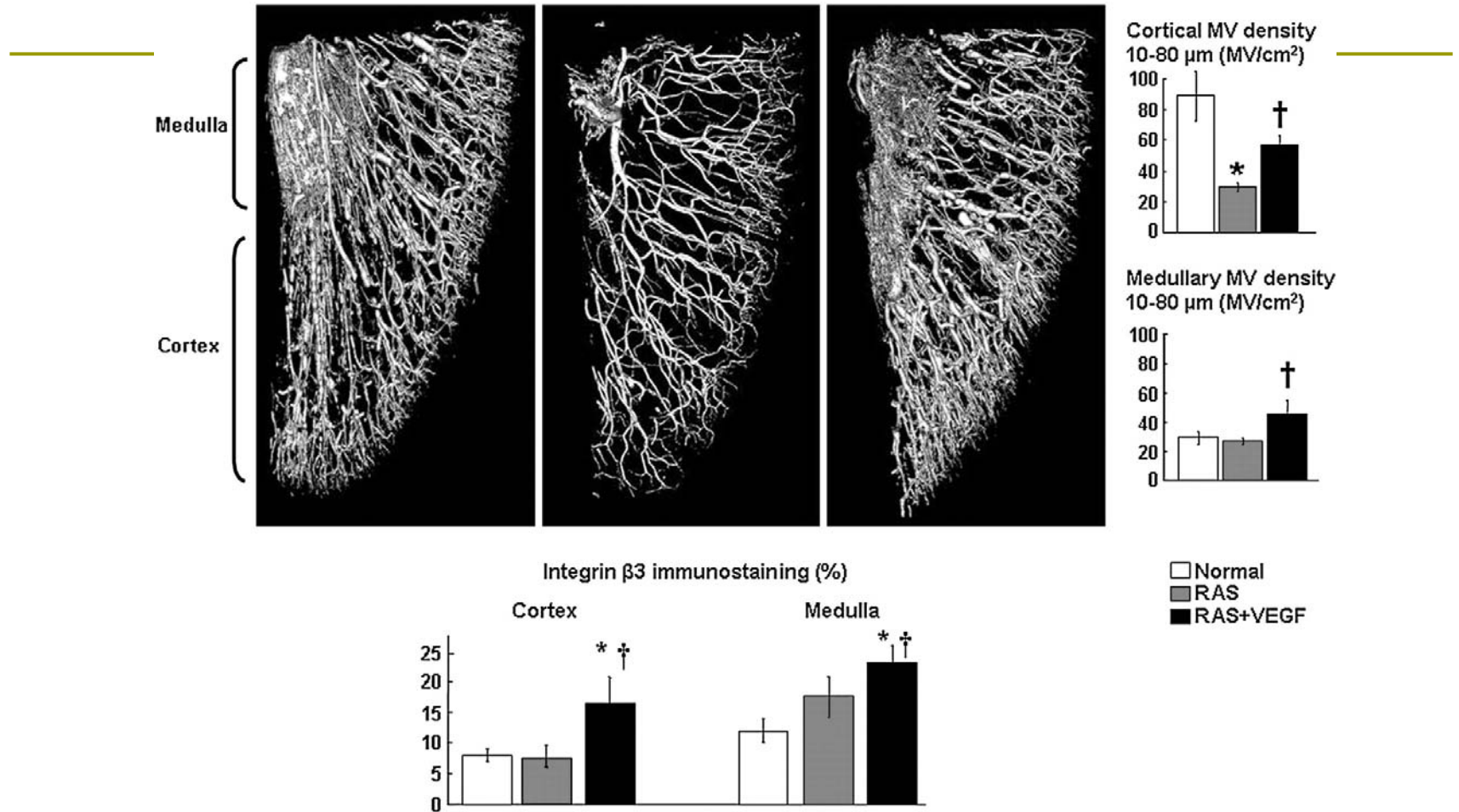
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- ❑ ROS decreases bioavailability of nitric oxide and results in formation of the pro-oxidant peroxynitrite
 - ❑ Which allows intrarenal vasopressors like angiotensin II and endothelin-1 to predominate



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- RAS causes renal injury partly via microvascular endothelial dysfunction and damage
 - VEGF is crucial for preservation of microvasculature and promotes vascular proliferation and endothelial repair
 - Microvascular rarefaction is associated with decreased VEGF in the kidney exposed to chronic RAS, accompanied by deteriorated renal function and fibrosis

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- Unilateral RAS was induced in 16 pigs
 - In eight, VEGF (0.05 micrograms/kg) was infused intra-renal at the onset of RAS
 - After 6 weeks, single-kidney haemodynamics and function were assessed
 - Pre-emptive administration of VEGF preserved MV architecture, attenuated fibrosis and normalized RBF and GFR

Representative 3D tomographic images of the kidney and quantification of microvascular density of the renal cortex and medulla (top); quantification of renal expression of integrin {beta}3 in Normal, RAS and RAS treated with intra-renal VEGF (RAS + VEGF) kidneys (bottom)



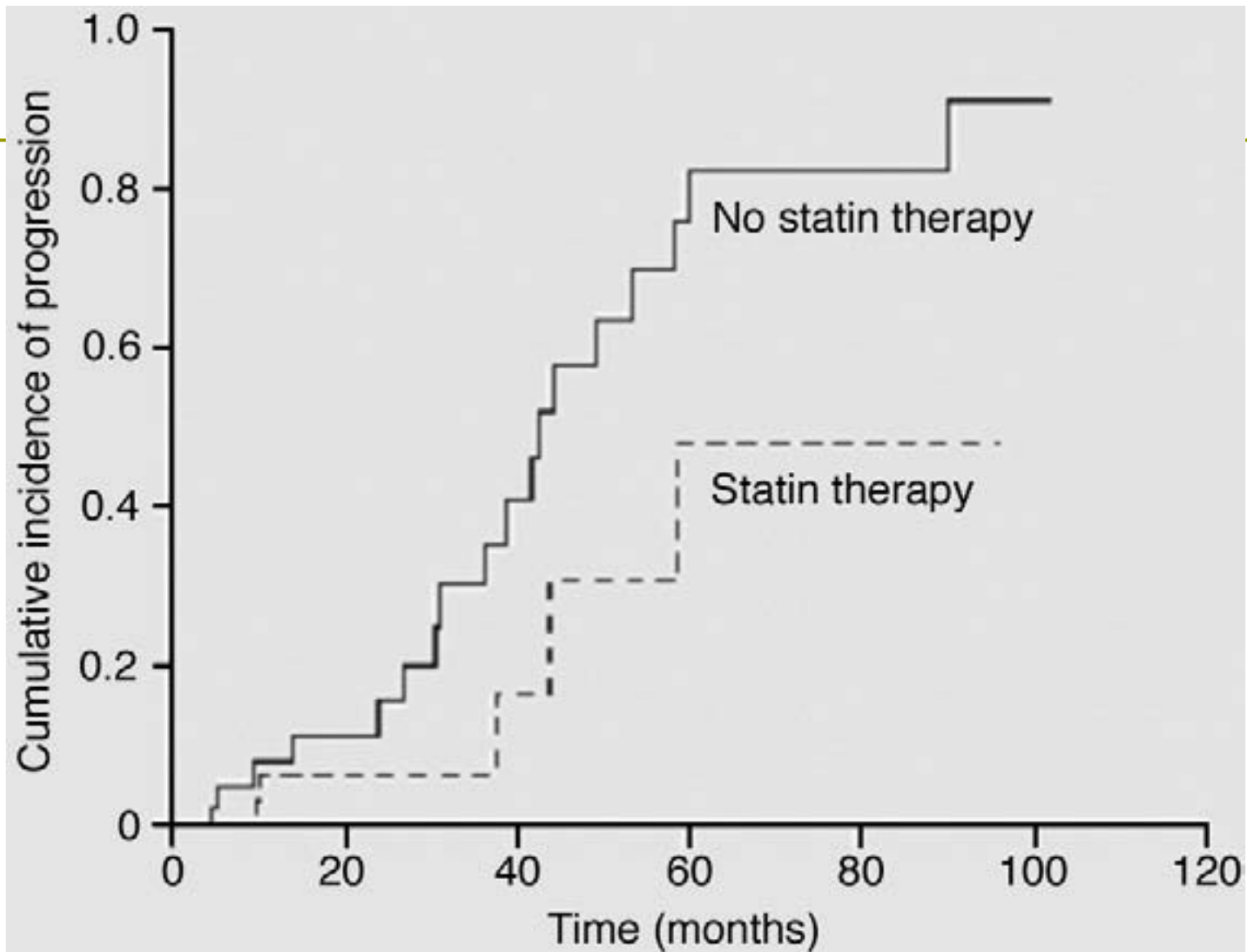
Iliescu, R. et al. Nephrol. Dial. Transplant. 2009

Management



Medical management

- Because the renin–angiotensin–aldosterone system is often activated, a regimen including an inhibitor of this system is recommended in most patients
- Renal failure secondary to a RAAS inhibitor is only seen in some patients with bilateral severe stenosis, high-grade stenosis in one kidney, or advanced chronic kidney disease
- Recent data from a large cohort of patients with RAS suggested a reduced risk of death among patients treated with an ACE inhibitor



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- ❑ Surgical revascularization can result in durable relief of renal-artery stenosis however mortality with the procedure can reach up to 10%
 - ❑ Comparison between balloon angioplasty and surgery shows that both have similar effects on renal function and blood pressure

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- ❑ There are high rates of improvement in blood pressure with angioplasty among patients with fibromuscular dysplasia
 - ❑ Predictors of a favorable outcome of angioplasty include:
 - An age younger than 40 years at diagnosis
 - A duration of hypertension of less than 5 years
 - A systolic blood pressure of less than 160 mm

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- A meta analysis of three trials involving a total of 210 patients with RAS and poorly controlled HTN showed that compared with medical therapy pts who underwent angioplasty had:
 - Better BP control (7 mm systolic and 3 mm diastolic)
 - Similar kidney function
 - Used fewer antihypertensive medications
 - Fewer major cardiovascular and renovascular complications



STAR trial

Eligibility criteria

- ❑ Impaired renal function defined as a creatinine clearance less than 80 mL/min
- ❑ Ostial ARAS defined as a reduction in the luminal diameter of the renal artery of 50% or more within 1 cm of the aortic wall in the presence of atherosclerotic changes in the aorta
- ❑ Have controlled blood pressure

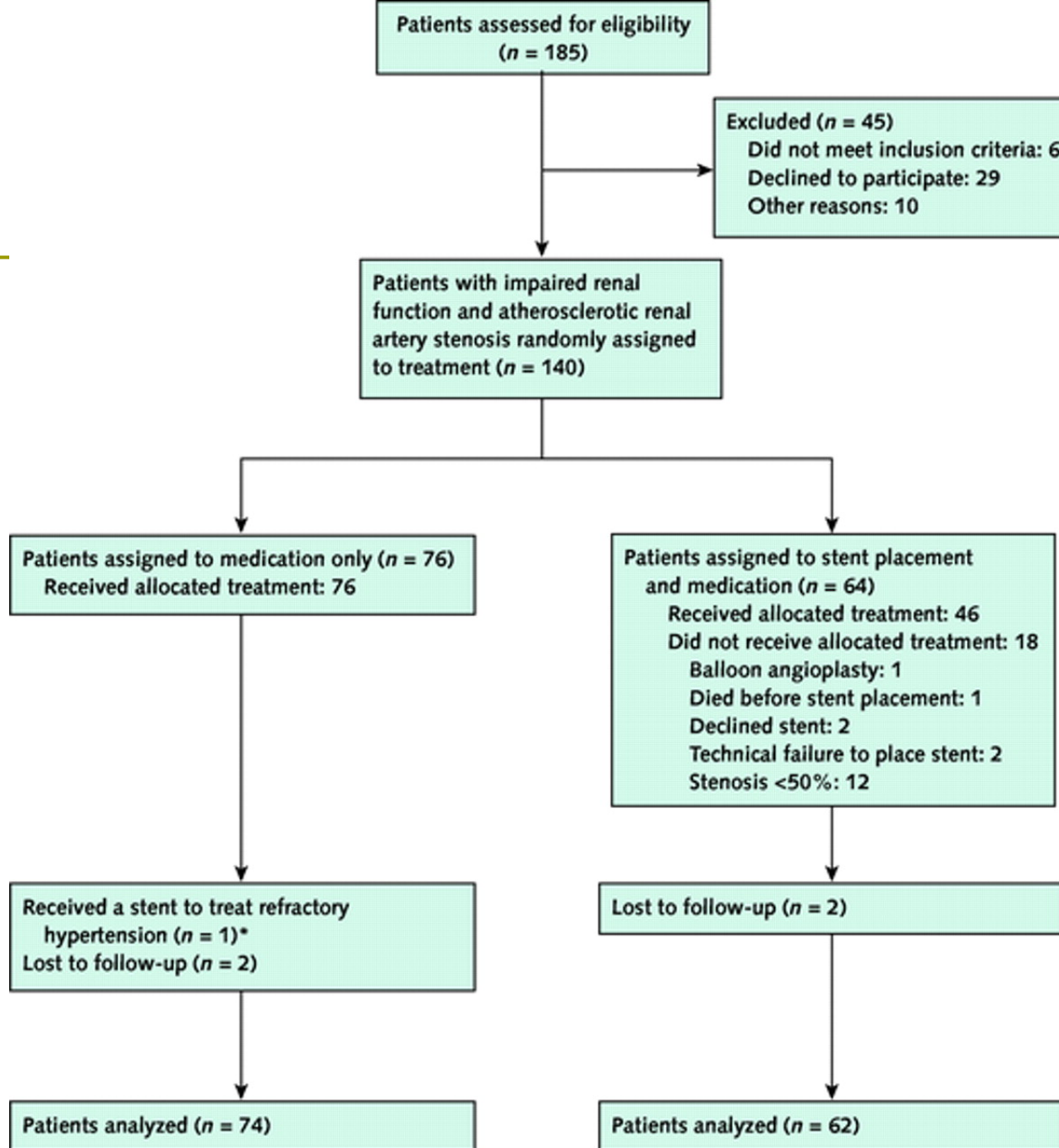


Table 1. Participant Characteristics at Baseline

Characteristic	Medication Group (n = 76)	Stent Group (n = 64)
Mean age (SD), y	67 (9)	66 (8)
Men, n (%)	45 (59)	43 (67)
Vascular history, n (%)		
Any vascular disease	59 (78)	54 (84)
Diabetes mellitus	18 (31)	16 (30)
Cerebrovascular disease	18 (31)	15 (28)
Heart failure	7 (12)	5 (9)
Abdominal aortic aneurysm	9 (15)	7 (13)
Peripheral arterial disease	30 (51)	26 (48)
Coronary artery disease	32 (54)	23 (43)
Current or past smoking	52 (68)	46 (72)
Current smoking	15 (20)	20 (31)
Renal function		
Mean serum creatinine level (SD)		
μmol/L	145 (51)	154 (60)
mg/dL	1.6 (0.58)	1.7 (0.68)
Mean estimated creatinine clearance (SD), mL/min per 1.73 m ²	46 (16)	45 (15)
Blood pressure		
History of hypertension, n (%)	73 (96)	63 (98)
Mean systolic blood pressure (SD), mm Hg	163 (26)	160 (25)
Mean diastolic blood pressure (SD), mm Hg	82 (12)	83 (13)
Antihypertensive drugs		
Mean number of drug categories (SD)	2.9 (1.0)	2.8 (1.0)
Treatment, n (%)		
ACE inhibitors	23 (30)	21 (33)
Angiotensin II-receptor antagonists	18 (24)	17 (27)
Laboratory data		
Mean total cholesterol level (SD)		
mmol/L	5.1 (1.0)	4.9 (1.2)
mg/dL	197 (38)	189 (46)
Mean HDL cholesterol level (SD)		
mmol/L	1.2 (0.4)	1.2 (0.4)
mg/dL	46 (15)	46 (15)
Mean LDL cholesterol level (SD)		
mmol/L	3.1 (0.9)	2.8 (1.3)
mg/dL	119 (35)	108 (50)
Mean triglyceride level (SD)		
mmol/L	1.8 (1.2)	2.2 (1.6)
mg/dL	159 (106)	195 (142)
Mean glucose level (SD)		
mmol/L	6.2 (2.0)	5.9 (1.6)
mg/dL	112 (36)	106 (29)
Median proteinuria (IQR), g/d	0.14 (0.08–0.36)	0.19 (0.1–0.5)
Previous renal artery intervention, n (%)	8 (11)	7 (11)
Balloon angioplasty, n (%)	7 (9)	6 (9)
Stent, n (%)	1 (1)	1 (2)
Test used to evaluate stenosis, n (%)		
Computed tomographic angiography	24 (32)	23 (36)
Magnetic resonance angiography	39 (51)	35 (55)
Angiography	13 (17)	6 (9)
Type of ostial stenosis, n (%)		
Unilateral	41 (54)	32 (50)
Bilateral	35 (46)	32 (50)
Occlusion or shrunken kidney	11 (31)	14 (44)
Single kidney	3 (8)	1 (3)
Degree of stenosis of the most affected kidney		
50%–70%	24 (32)	22 (34)
70%–90%	35 (46)	20 (31)
>90%	17 (22)	22 (34)

ACE = angiotensin-converting enzyme; HDL = high-density lipoprotein; IQR = interquartile range; LDL = low-density lipoprotein.

Table 2. Primary and Secondary End Points

End Point	Medication Group (n = 74)*	Stent Group (n = 62)*	Crude Hazard Ratio (95% CI)†
Primary end point, n (%)‡			
Unilateral or bilateral stenosis	16 (22)	10 (16)	0.73 (0.33–1.61)
Unilateral stenosis only	8 (20)	3 (9)	0.48 (0.13–1.81)
Bilateral stenosis only	8 (23)	7 (22)	0.95 (0.34–2.61)
Secondary end points, n (%)			
Therapy-refractory hypertension	3 (4)	0	–
Malignant hypertension	0	0	–
Pulmonary edema	1 (1)	0	–
Cardiovascular morbidity			
Heart failure	3 (4)	1 (2)	0.39 (0.04–3.71)
Coronary artery disease	3 (4)	3 (5)	1.16 (0.23–5.73)
Peripheral arterial disease	7 (9)	4 (6)	0.67 (0.20–2.28)
Cerebrovascular disease	1 (1)	0	–
Abdominal aortic aneurysm	0	0	–
All-cause mortality			
Overall deaths	6 (8)	5 (8)	0.99 (0.30–3.24)
Cardiovascular mortality	4 (5)	2 (3)	0.59 (0.11–3.25)
Periprocedural mortality§	0	2 (3)	–
Primary end point or death, n (%)	22 (30)	15 (24)	0.81 (0.42–1.56)

* 2 patients in each group were lost to follow-up at 2 years.

† The medication group is the reference group.

‡ The primary end point was a $\geq 20\%$ decrease in estimated creatinine clearance compared with baseline. In the stent group, the primary end point was reached if the $\geq 20\%$ reduction in creatinine clearance persisted 1 month after re-intervention.

§ Death within 30 days after start of treatment.

Complications

- ❑ 2 deaths secondary to procedure-related causes
- ❑ Groin infection requiring surgical reconstruction with pt subsequently developing multi organ failure and dying 6 months after the procedure
- ❑ 2 pts developed false renal artery aneurysm
- ❑ 5 pts sustained injury to the kidney or renal artery



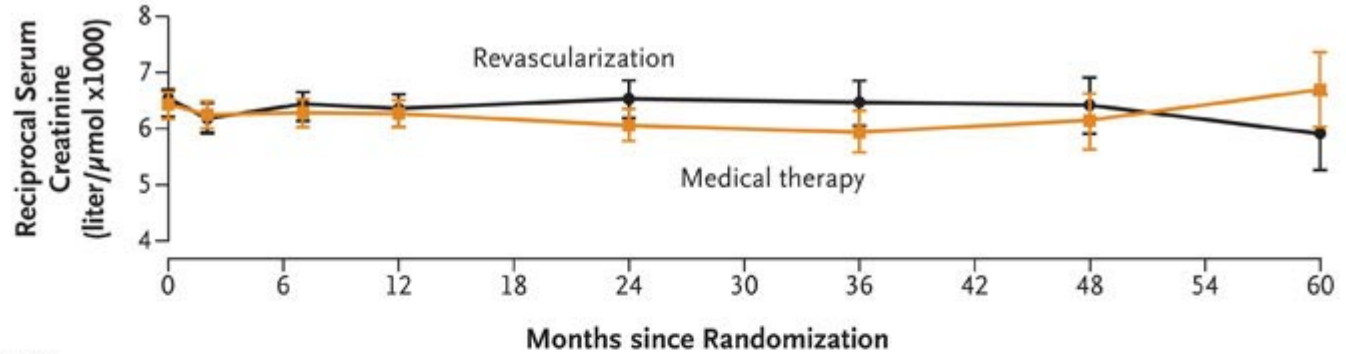
ASTRAL trial

Table 1. Baseline Characteristics of the Patients.*

Variable	Revascularization (N = 403)	Medical Therapy (N = 403)	P Value
Demographic			
Mean age (range) — yr	70 (42–86)	71 (43–88)	0.75
Male sex — no. (%)	254 (63)	253 (63)	0.94
Clinical			
Smoking status — no./total no. (%)			
Current smoker	77/387 (20)	85/391 (22)	0.53
Former smoker	199/387 (51)	216/391 (55)	0.29
Coexisting conditions — no./total no. (%)			
Diabetes	121/387 (31)	115/391 (29)	0.57
Coronary heart disease	192/387 (50)	189/391 (48)	0.22
Peripheral vascular disease	158/387 (41)	157/391 (40)	0.79
Stroke	69/387 (18)	75/391 (19)	0.42
Need for dialysis	0	1/391 (<1)	0.81
Renal function			
Serum creatinine			
Mean (range) — $\mu\text{mol/liter}$	179 (66–551)	178 (64–750)	0.85
Level — no. (%)			
<150 $\mu\text{mol/liter}$	163 (40)	162 (40)	0.99
150–300 $\mu\text{mol/liter}$	212 (53)	212 (53)	
>300 $\mu\text{mol/liter}$	28 (7)	29 (7)	
Rapid increase†	48 (12)	49 (12)	0.91
Estimated glomerular filtration rate			
Mean (range) — ml/min	40.3 (5.4–124.5)	39.8 (7.1–121.7)	0.66
Level — no. (%)			
<25 ml/min	89 (22)	89 (22)	1.00
25–50 ml/min	213 (53)	213 (53)	
>50 ml/min	101 (25)	101 (25)	
Urinary protein			
Mean (range) — g/day‡	0.55 (0–4.77)	0.72 (0–7.7)	0.18
Related laboratory measures			
Mean blood pressure (range) — mm Hg			
Systolic	149 (87–270)	152 (90–241)	0.07
Diastolic	76 (45–120)	76 (46–130)	0.63
Mean total cholesterol (range) — mmol/liter§	4.7 (0.1–14.8)	4.7 (1.9–9.6)	0.79
Renal physiology			
Stenosis¶			
Mean (range) — %	76 (40–100)	75 (20–99)	0.29
Severity — no. (%)			
<50%	2 (<1)	4 (1)	0.68
50–70%	159 (39)	164 (41)	
>70%	242 (60)	235 (58)	
Mean length of kidney (range) — cm	9.7 (6–14)	9.8 (6–20)**	0.44
Use of concomitant medication			
Antihypertensive drug — no./total no. (%)			
Any	373/384 (97)	383/388 (99)	0.12
Diuretic	261/373 (70)	257/383 (67)	0.40
Calcium-channel blocker	227/373 (61)	259/383 (68)	0.05
Beta-blocker	172/373 (46)	200/383 (52)	0.09
ACE inhibitor or ARB	174/373 (47)	146/383 (38)	0.02
Alpha-blocker	147/373 (39)	141/383 (37)	0.46
Mean no. of antihypertensive drugs in class (range)	2.79 (1–6)	2.80 (1–6)	0.86
Antiplatelet drug — no./total no. (%)			
Any	289/381 (76)	298/383 (78)	0.52
Aspirin	263/289 (91)	277/298 (93)	0.38
Cholesterol-lowering drug — no./total no. (%)			
Any	304/381 (80)	312/389 (80)	0.89
Statin	293/304 (96)	296/312 (95)	0.36
Warfarin — no./total no. (%)	42/380 (11)	42/385 (11)	0.95

* ACE denotes angiotensin-converting enzyme, and ARB angiotensin-receptor blocker. To convert the values for creati-

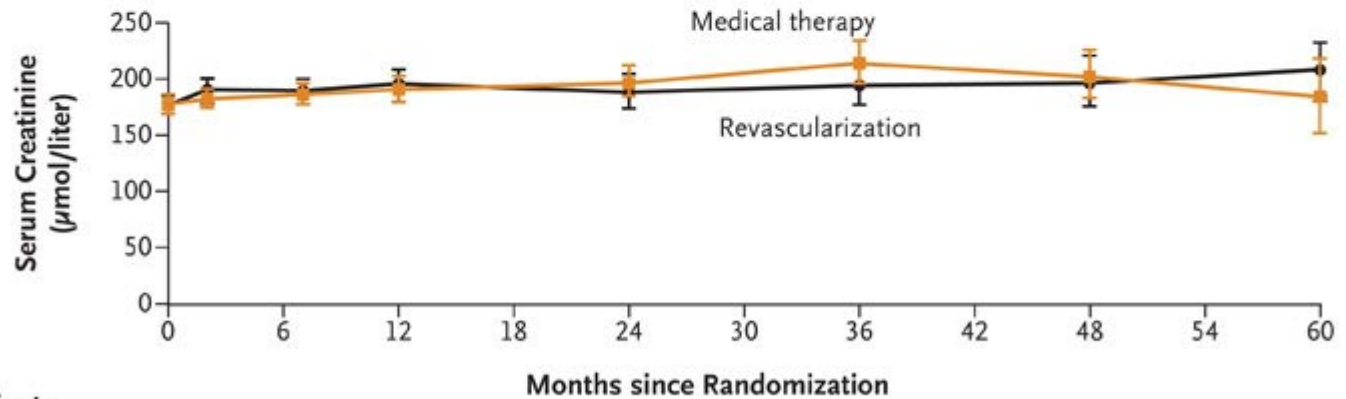
A Reciprocal of Serum Creatinine



No. of Patients

Revascularization	403	349	336	329	263	191	127	72
Medical therapy	403	363	347	343	272	183	119	61

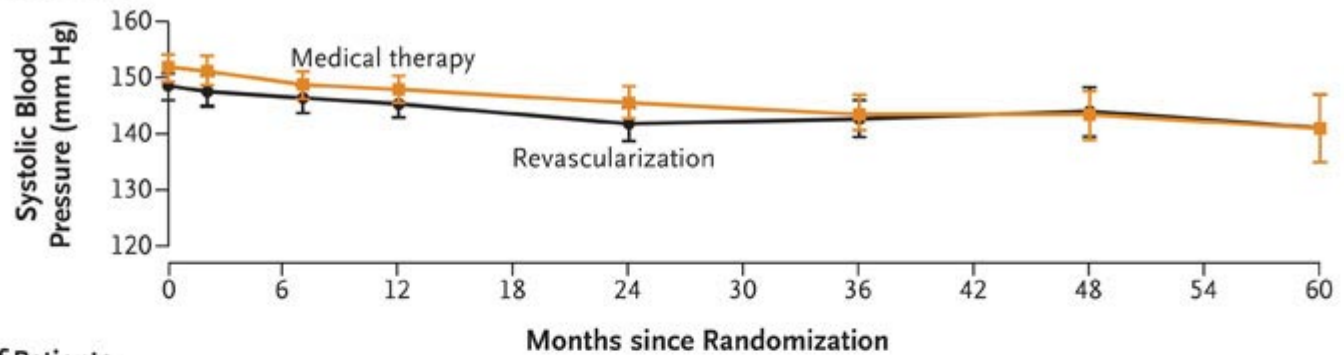
B Serum Creatinine



No. of Patients

Revascularization	403	349	336	329	263	191	127	72
Medical therapy	403	363	347	343	272	183	119	61

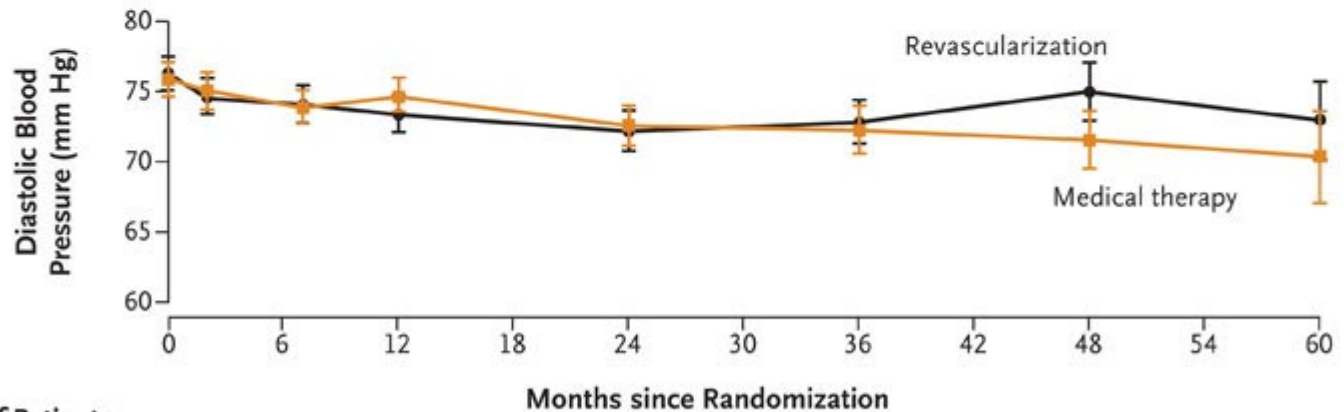
A Systolic Blood Pressure



Number of Patients

Revascularization	385	346	332	321	257	197	125	71
Medical therapy	388	361	350	336	264	178	124	62

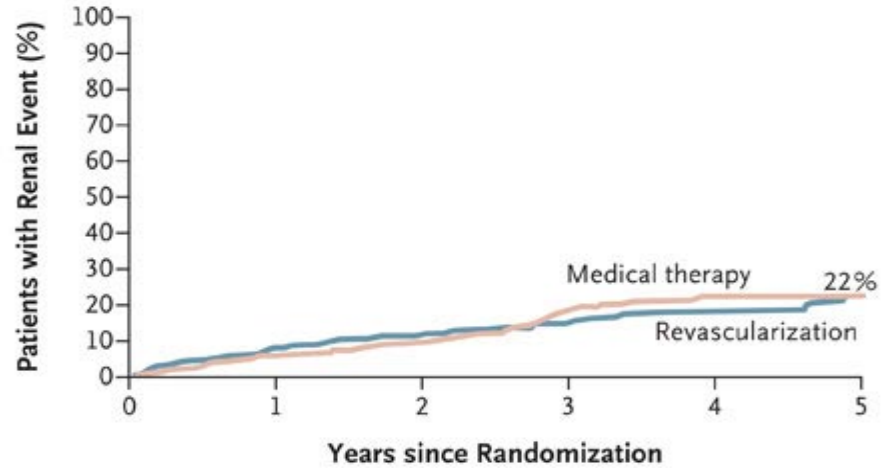
B Diastolic Blood Pressure



Number of Patients

Revascularization	384	344	330	320	256	197	125	70
Medical therapy	388	361	349	335	262	178	123	63

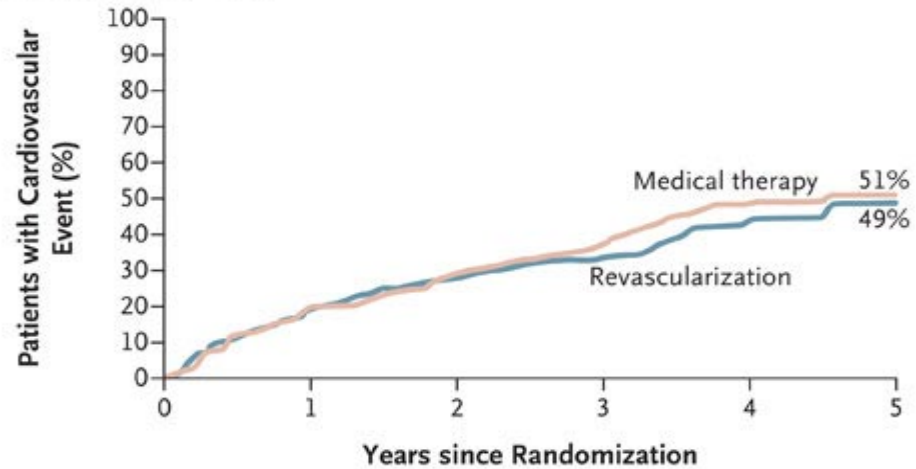
A First Renal Event



No. at Risk

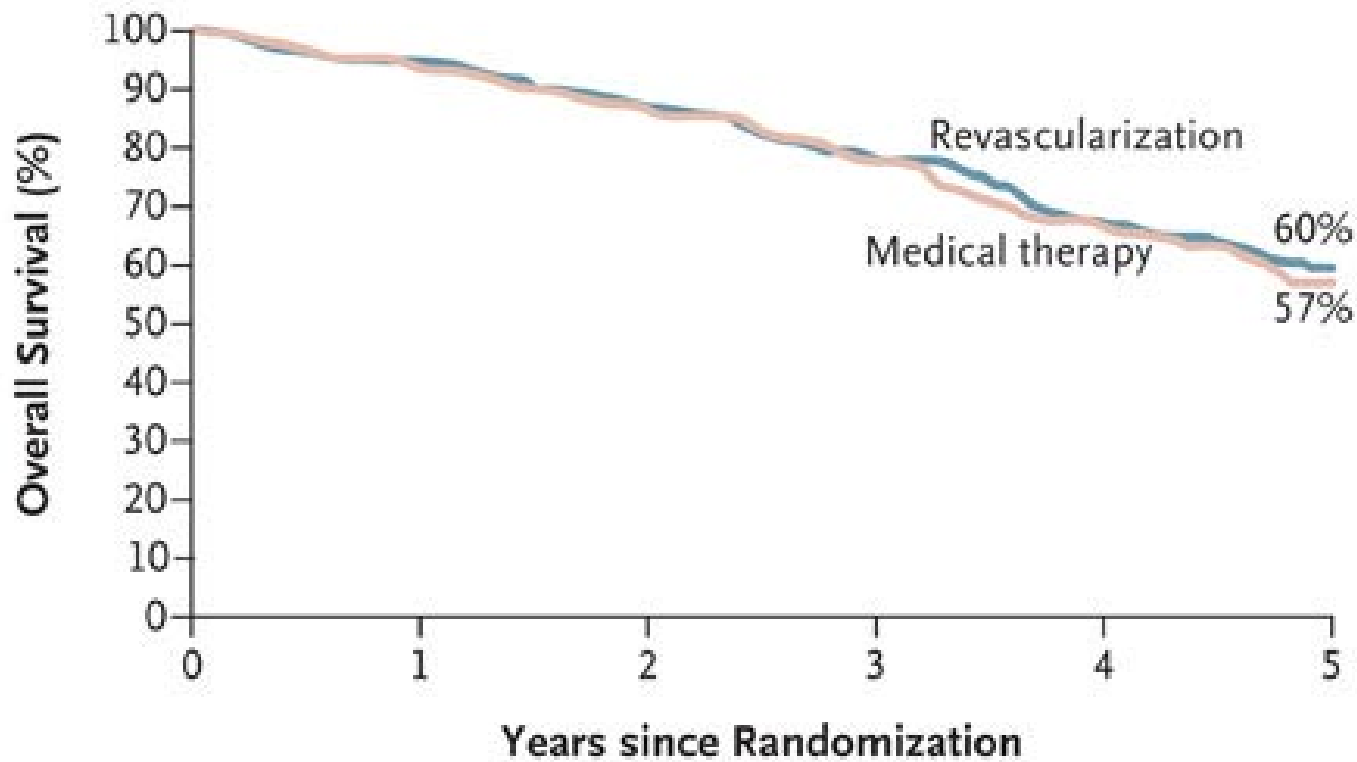
Revascularization	403	315	236	157	99	39
Medical therapy	403	319	233	145	84	37

B First Cardiovascular Event



No. at Risk

Revascularization	403	278	200	133	77	33
Medical therapy	403	286	194	118	61	27



No. at Risk

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

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- There were no significant differences in the primary outcome in any of the subgroups defined according to:
 - the serum creatinine level
 - estimated glomerular filtration rate
 - severity of renal-artery stenosis
 - kidney length
 - previous rate of progression of renal impairment

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- ❑ 38 periprocedural complications were reported in 31 of the 359 patients (9%) who underwent revascularization
 - ❑ Nineteen of these events (in 17 patients) were considered to be serious complications
 - ❑ 55 (20%) had an adverse event between 24 hours and 1 month after the procedure, 12 events (in 11 patients) were considered to be serious
 - 2 deaths (both from cardiac causes)
 - 4 cases of groin hematoma or hemorrhage requiring hospitalization
 - 5 cases of clinically significant acute kidney injury
 - 1 renal-artery occlusion

Conclusion



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- ❑ Revascularization is performed in 16% of patients with newly diagnosed atherosclerotic renovascular disease in the US
 - ❑ Since endovascular interventions are associated with substantial morbidity, inconvenience, and cost, with little apparent benefit, the widespread use of such procedures should be questioned
 - ❑ There will also be little value in screening asymptomatic patients who have atherosclerosis and chronic renal disease or hypertension for renovascular disease