There Still Are Indications for Renal Artery Stenting After CORAL

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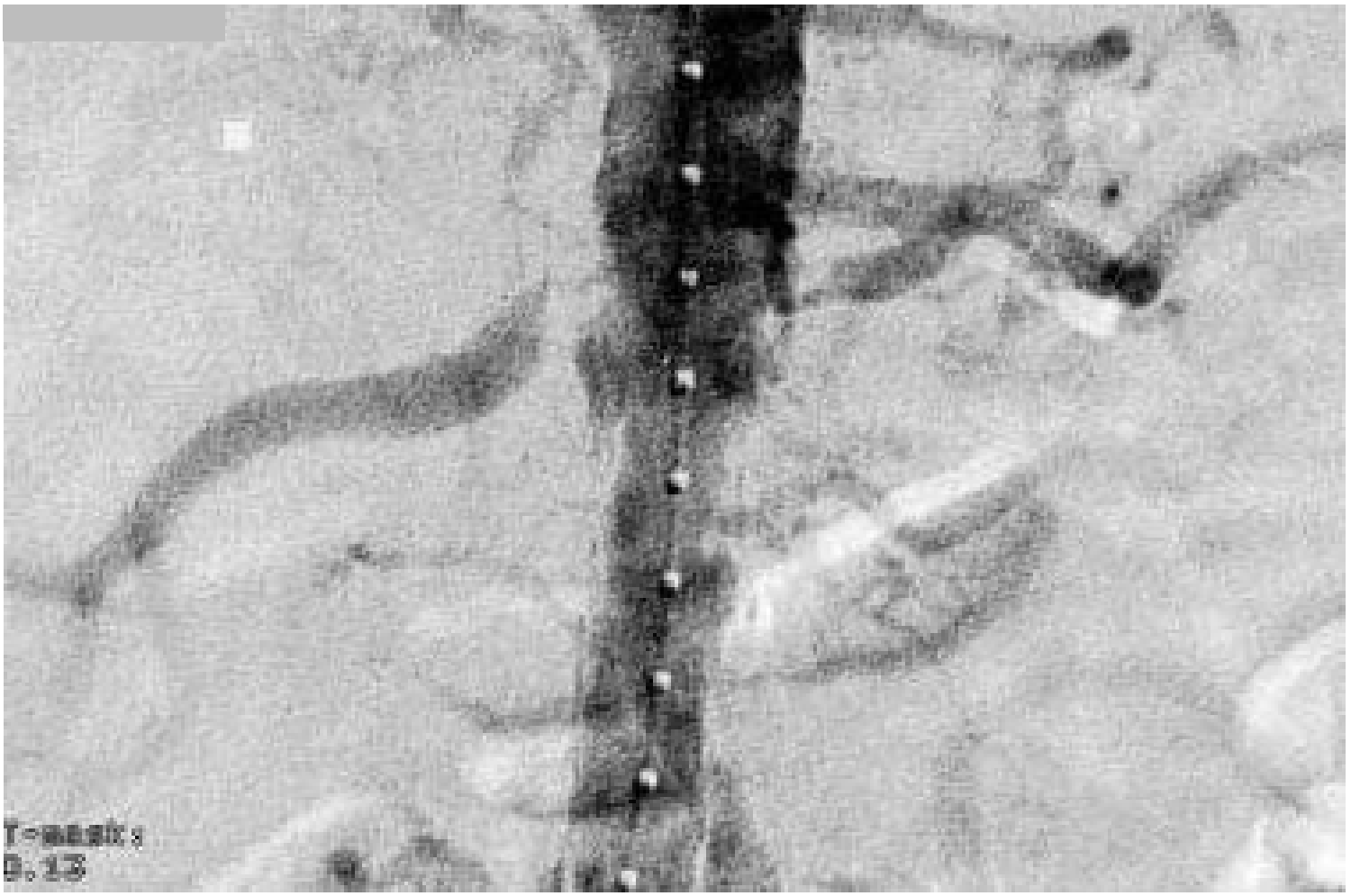
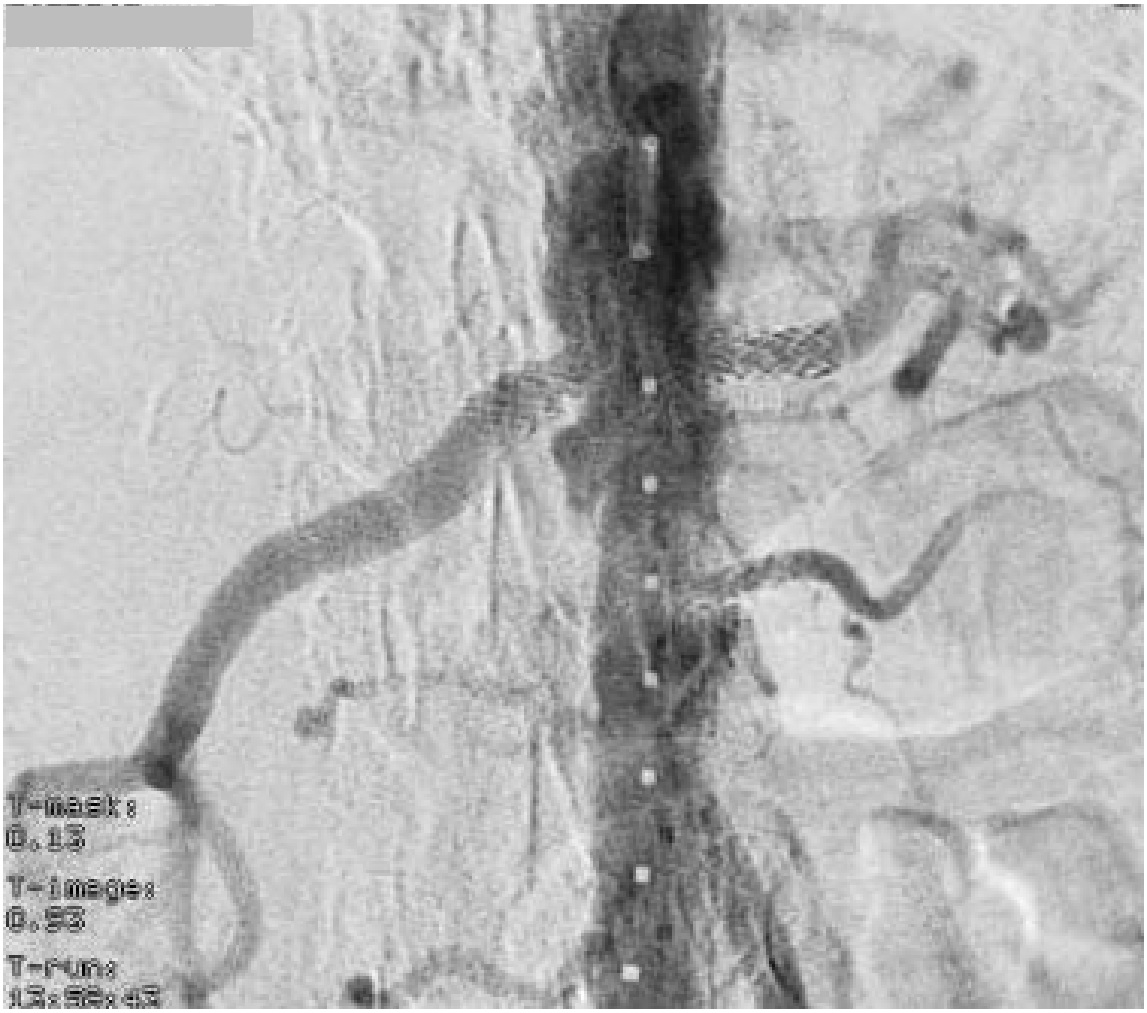
Case Summary

- 73 year old female was transferred from an outside hospital to the Mount Sinai coronary care unit
  - She was in acute pulmonary edema and on an FiO_2 of 50%
  - The blood pressure was 180/104 mmHg on:
    - Furosemide 120 mg BID
    - Metolazone 5 mg daily
    - Atenolol 100 mg daily
    - Hydralazine 100 mg TID
    - Clonidine patch 0.3 mg weekly
    - Isosorbide mononitrate 90 mg daily

Case Summary (contin)

- Despite large doses of diuretics, her urine output over the last several days was 250 cc/24 hours
- The serum creatinine 4 weeks ago was 1.6 mg/dL and on transfer to the CCU it was 3.9 mg/dL
  - She underwent hemodialysis and ultrafiltration
- Four weeks ago she had a nuclear stress test that was negative for ischemia and an echocardiogram with LVH, normal systolic LV function and diastolic dysfunction.

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0.13
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Case Summary (contin)

- Post stenting she required no dialysis
- The serum creatinine was 1.2 mg/dL four days after renal artery stent implantation
- The blood pressure was 130/70 mmHg on:
  - HCTZ 25 mg daily
  - Lisinopril 20 mg BID
  - Atenolol 100 mg daily
- She returned in 2 weeks for the first surveillance duplex ultrasound which was normal

Hospital Practice

RECURRENT PULMONARY OEDEMA IN HYPERTENSION DUE TO BILATERAL RENAL ARTERY STENOSIS: TREATMENT BY ANGIOPLASTY OR SURGICAL REVASCULARISATION

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Summary 11 patients with atheromatous renovascular hypertension had a history of multiple episodes of pulmonary oedema. 7 had stenosis of both renal arteries, 2 had stenosis of the artery to a solitary kidney, and 2 had unilateral stenosis with an intact contralateral kidney. Successful revascularisation (by angioplasty in 8, and surgery in 3) improved blood pressure and renal function, and virtually eliminated pulmonary oedema. In a second series of 55 consecutive patients with azotaemia and renovascular hypertension, pulmonary oedema occurred in 13 (23%). Blood pressure and renal function were not significant predictors of pulmonary oedema, but coronary heart disease and bilateral (vs unilateral) renal artery stenosis were. Bilateral renal artery stenosis may be a specific and treatable predisposing factor to pulmonary oedema in azotaemic hypertensive patients.

Renal Artery Stenting for Control of Congestive Heart Failure

- 18 patients had bilateral renal artery stenosis
  - 12 (66.6%) underwent bilateral stenting
- 21 patients had renal artery stenosis to a solitary functioning kidney
  - All of these patients underwent unilateral stenting.
- Renal artery angioplasty and stenting was technically successful in all patients

Gray BH, Olin JW, Childs MB, Bacharach JM, Sullivan T. Renal artery stenting to control congestive heart failure. Vascular Medicine 2002;7:275-9,.

Effects of Renal Artery Stenting on Renal Function

Baseline Serum Creatinine (mg/dl)	N	Improved	Unchanged	Worse
1.1-1.9	9	2	5	2
2.0-2.9	12	7	3	2
3.0-3.9	8	5	2	1
≥4.0	10	6	0	4
Total	39	20 (51.4%)	10 (25.6%)	9 (23%)*
*Three patients required dialysis				

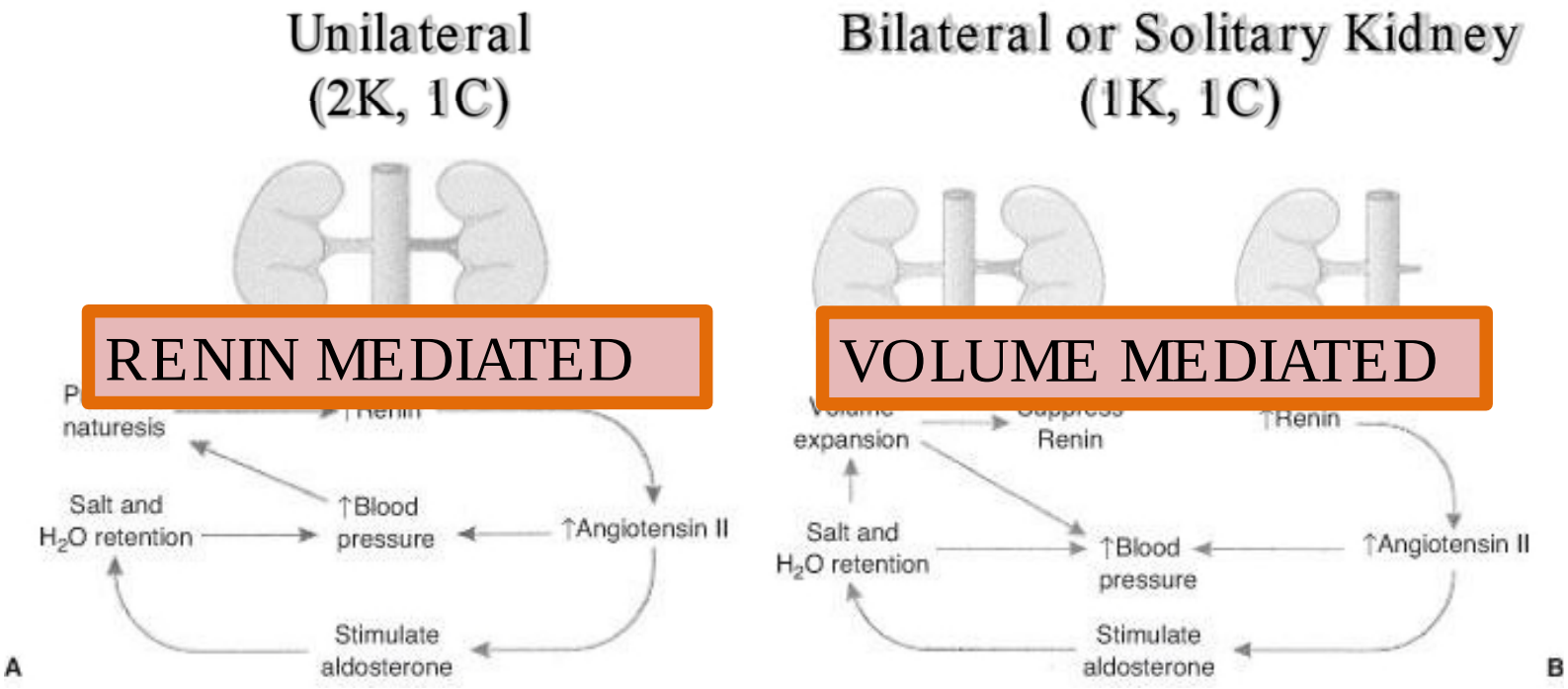
Gray BH, Olin JW, Childs MB, Bacharach JM, Sullivan T. Renal artery stenting to control congestive heart failure. Vascular Medicine 2002;7:275-9,.

Effects of Renal Artery Stenting on Control of Congestive Heart Failure

Hospitalizations for CHF	Before Stenting N (%)	After Stenting N (%)
0	---	30 (76.9)
1	13 (33.3)	6 (15.4)
2	13 (33.9)	1 (2.6)
3	6 (15.4)	---
4	3 (7.7)	---
5	2 (5.1)	---
6	2 (5.1)	---

Mean Follow Up 21.5 Months

Pathophysiology of Renovascular Hypertension

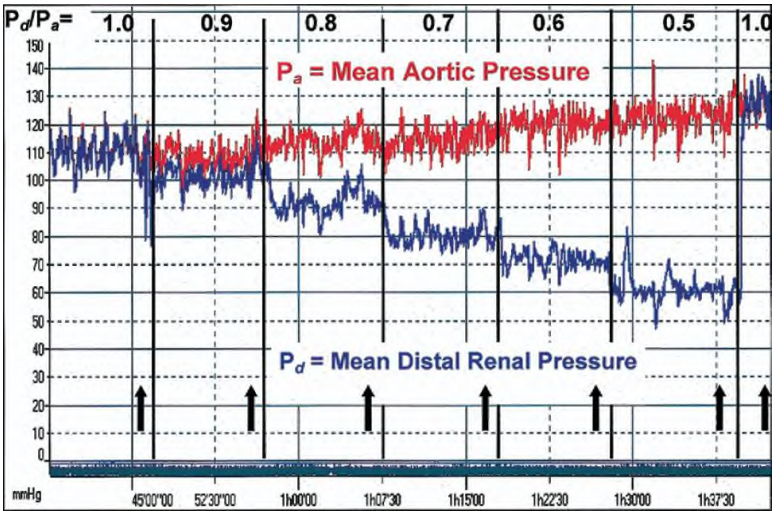


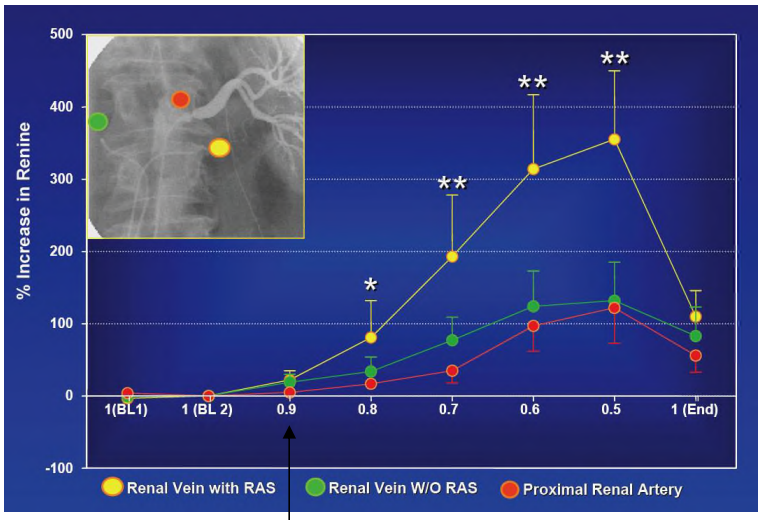
Olin JW. Renal Artery Disease. In Textbook of Cardiovascular Medicine, ED Topol EJ, 2006.

Pressure Gradient and Renin Release.

When distal pressure falls 10-20% below aortic pressures
There is a peak systolic gradient of 15-25 mmHg which
Corresponds to a cross sectional area reduction of 70-80%

Pa/ Pd ratio reflects gradient from aorta to renal artery.





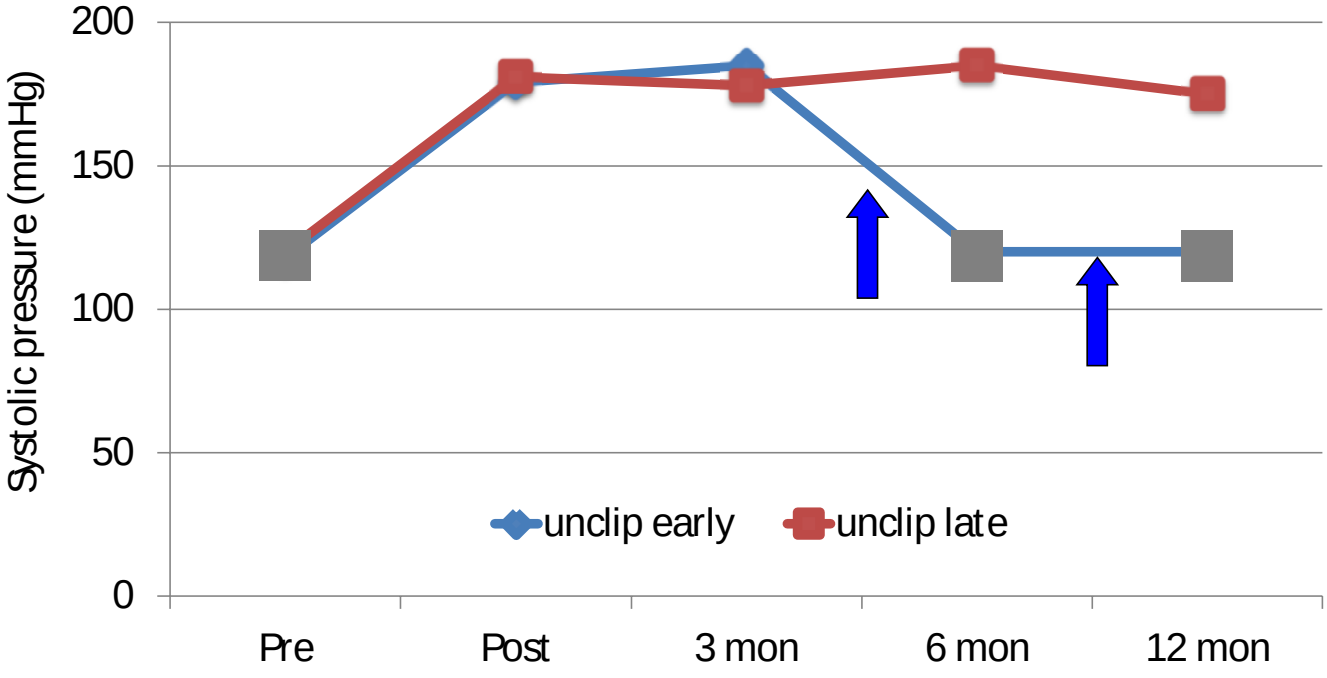
De Bruyne, B. et al. J Am Coll Cardiol 48, 1851-5 (2006).

Pa/ Pd = 0.9 is threshold for renin production.
Renin release proportional to gradient.

Why Do Some Patients Not Have BP Improvement After Stenting?

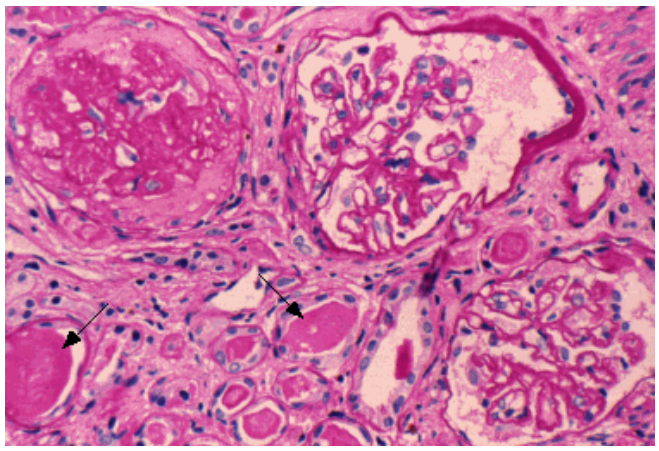
- The blood pressure is not mediated by the renal artery disease
  - Stenosis not hemodynamically significant
    - » Star, Astral, Coral
  - The patient has primary (essential) hypertension and renal artery stenosis, not renovascular hypertension.
- There is so much parenchymal disease that it does not matter what happens to the proximal renal artery

Experimental RAS: Effect on BP of Unclipping

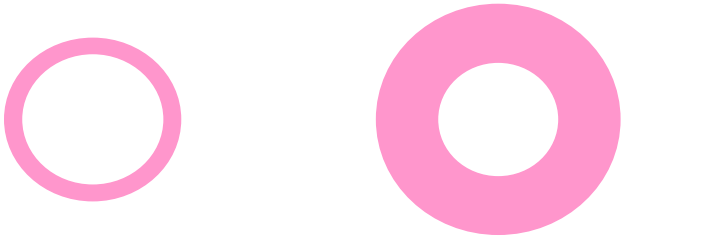


Factors that Sustain Hypertension after Anatomic Correction

- Damage to contralateral kidney



- Vascular remodeling

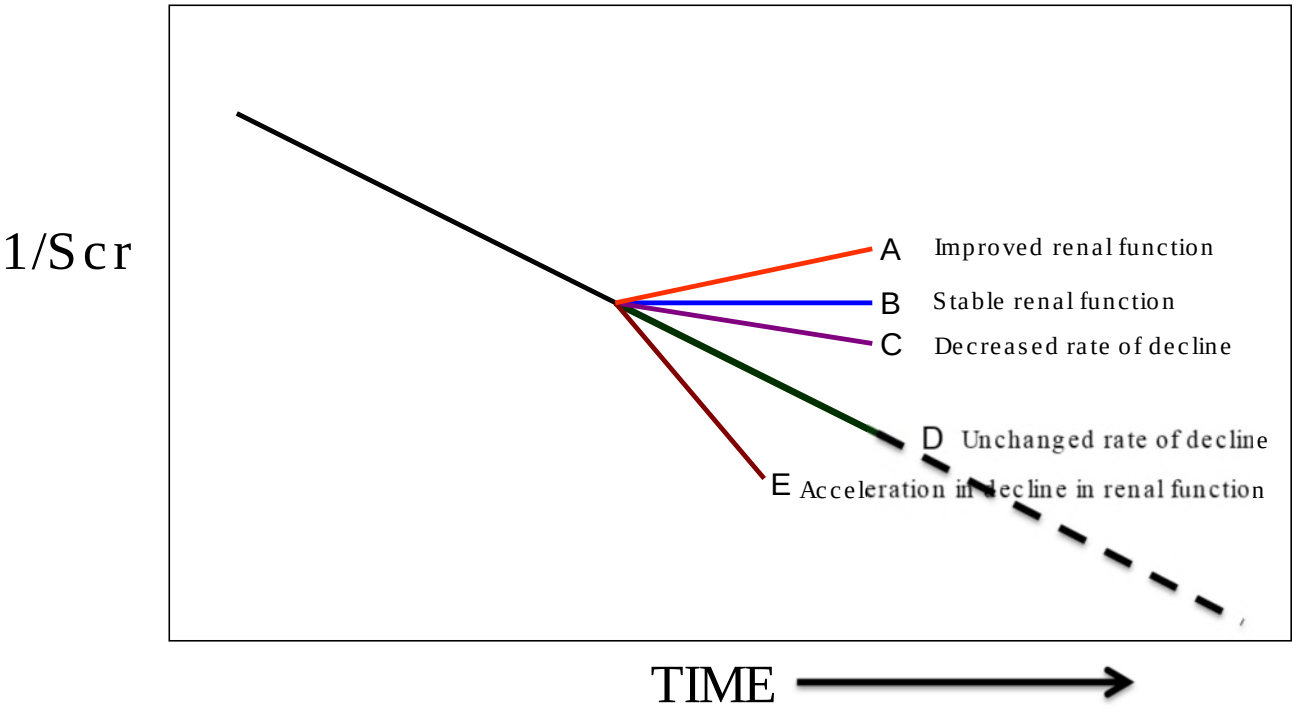


Why Renal Function Does Not Improve; Or Why it Worsens

- Look at STAR, ASTRAL
  - Primary endpoint renal function yet many had unilateral disease, or stenosis less than 70%, and some less than 50%
- The renal function declined slowly over a period of years…as opposed to a more rapid decline over 6 months
- Atheroembolic renal failure

Possible Renal Function Outcomes After Stenting

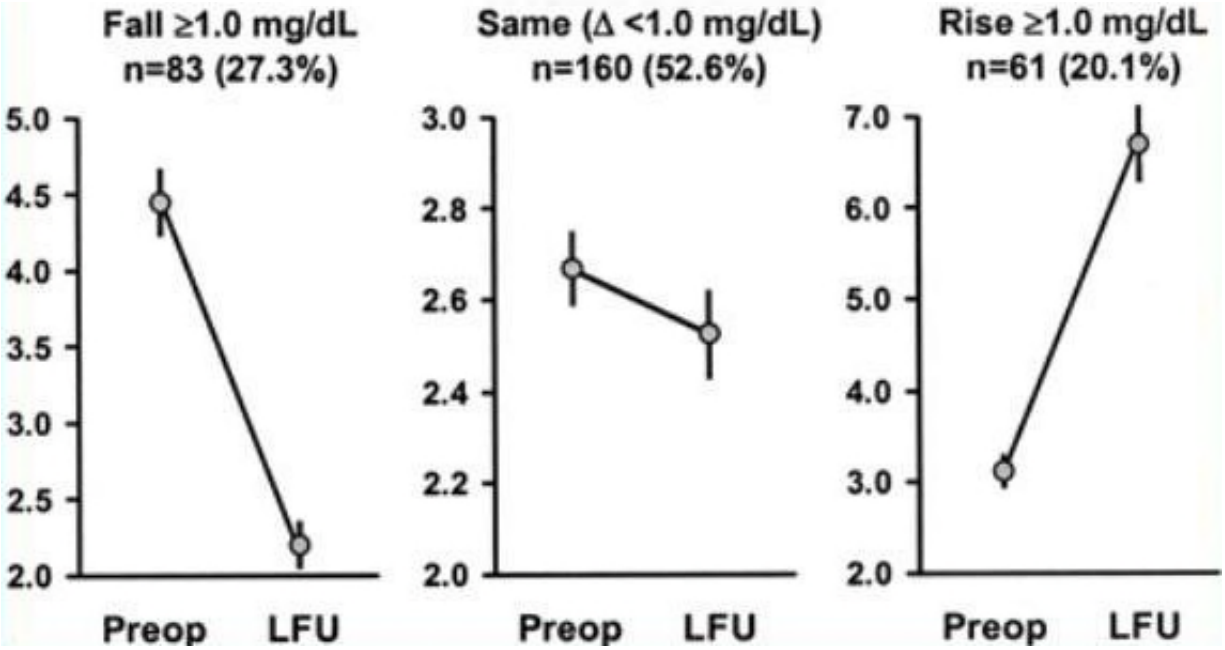
Slope of the reciprocal of the serum creatinine became positive in 18 (72%) patients and less negative in the remaining 7 (28%) patients.



Watson PS et. Al. Circulation 2000;102:1671-1677.

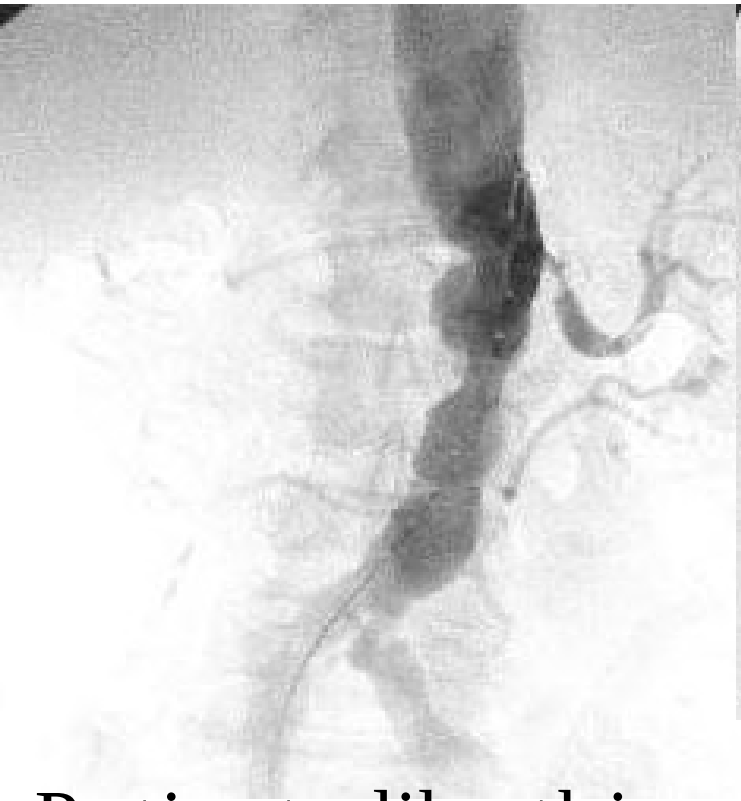
304 Azotemic Patients (Scr>2.0) Undergoing Surgical Revasularization

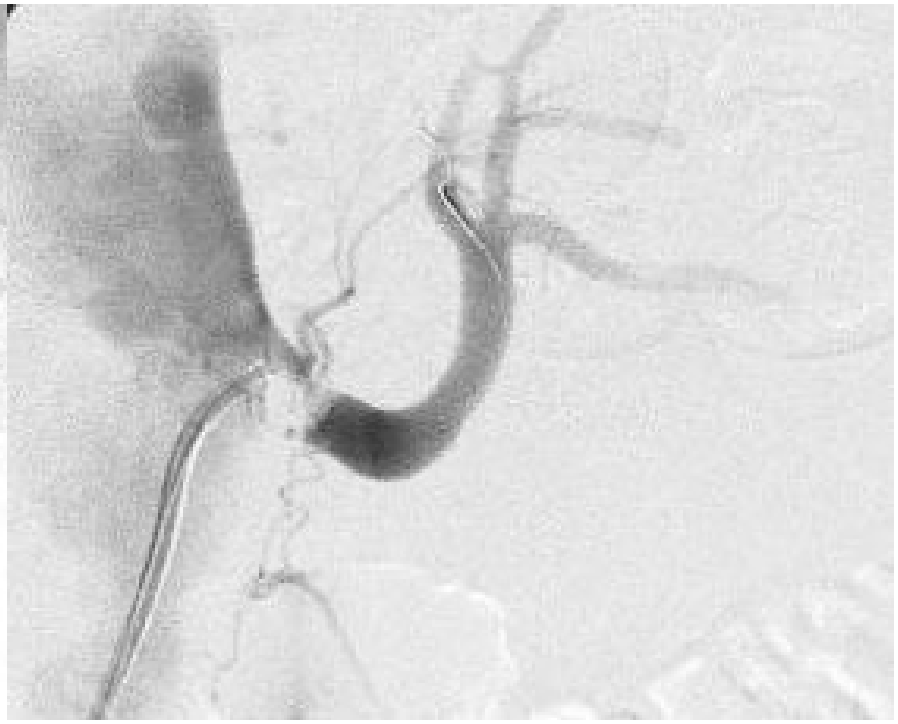
Mean Follow-up 3 Years



Textor S. J Am Soc Nephrol 2004;15:1974-82.

Atherosclerotic Renal Artery Stenosis





Patients like this were never entered into any of the clinical trials

EDITORIAL

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Stenting for atherosclerotic renal artery stenosis: One poorly designed trial after another

We Contend that the randomized trials published so far are seriously flawed

Cleveland Clinic J Med 2010;77:164

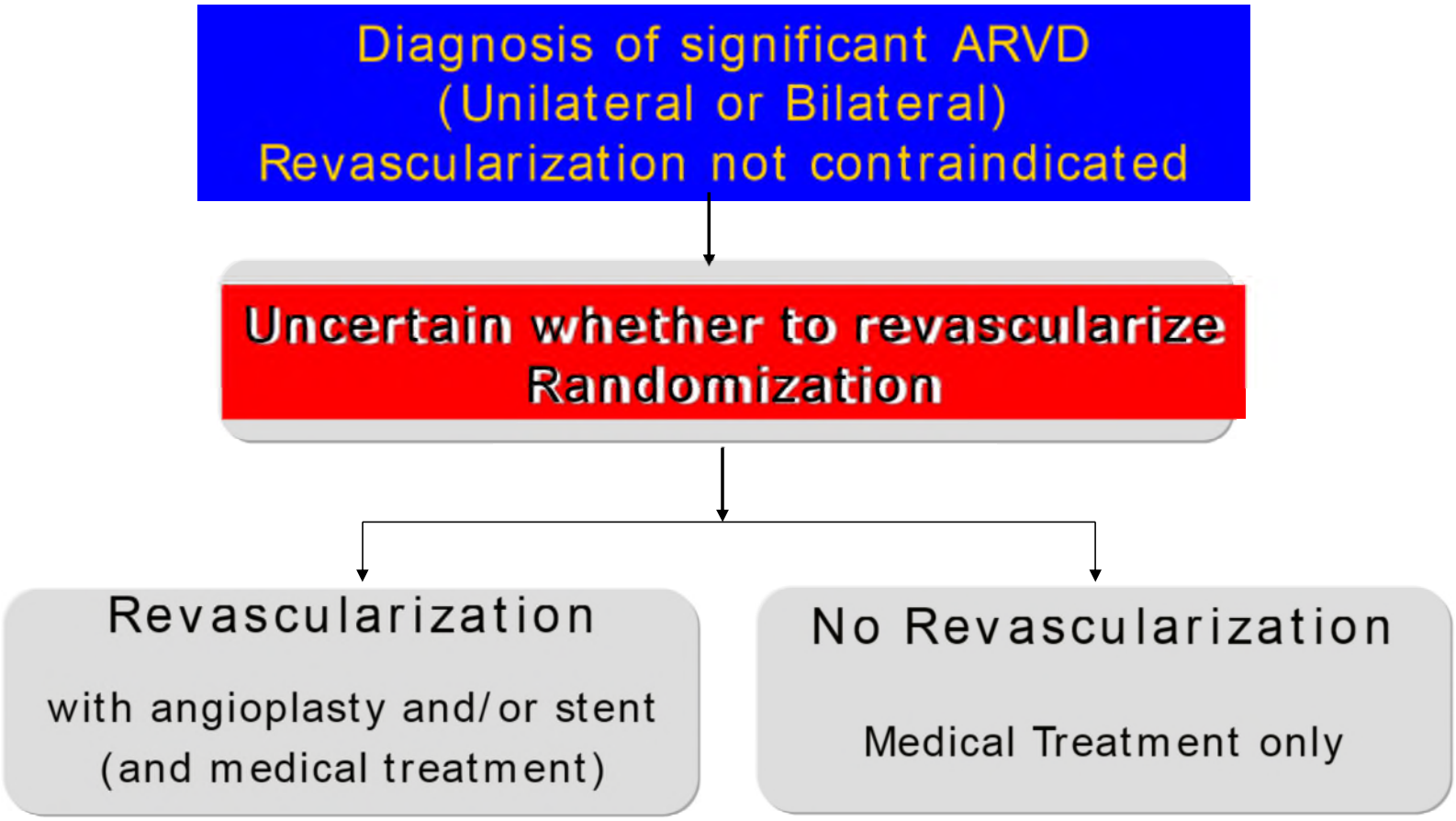
Randomized Trials of Renal Artery Intervention vs. Medical Therapy

- DRASTIC: N Engl J Med 2000;342;1007-14
  - Poorly Designed
- STAR: Ann Intern Med 2009;150;840-48
  - Poorly Designed
- ASTRAL: N Engl J Med 2009;361:1953-62
  - Poorly Designed
- CORAL: N Engl J Med 2014;370:13-22.

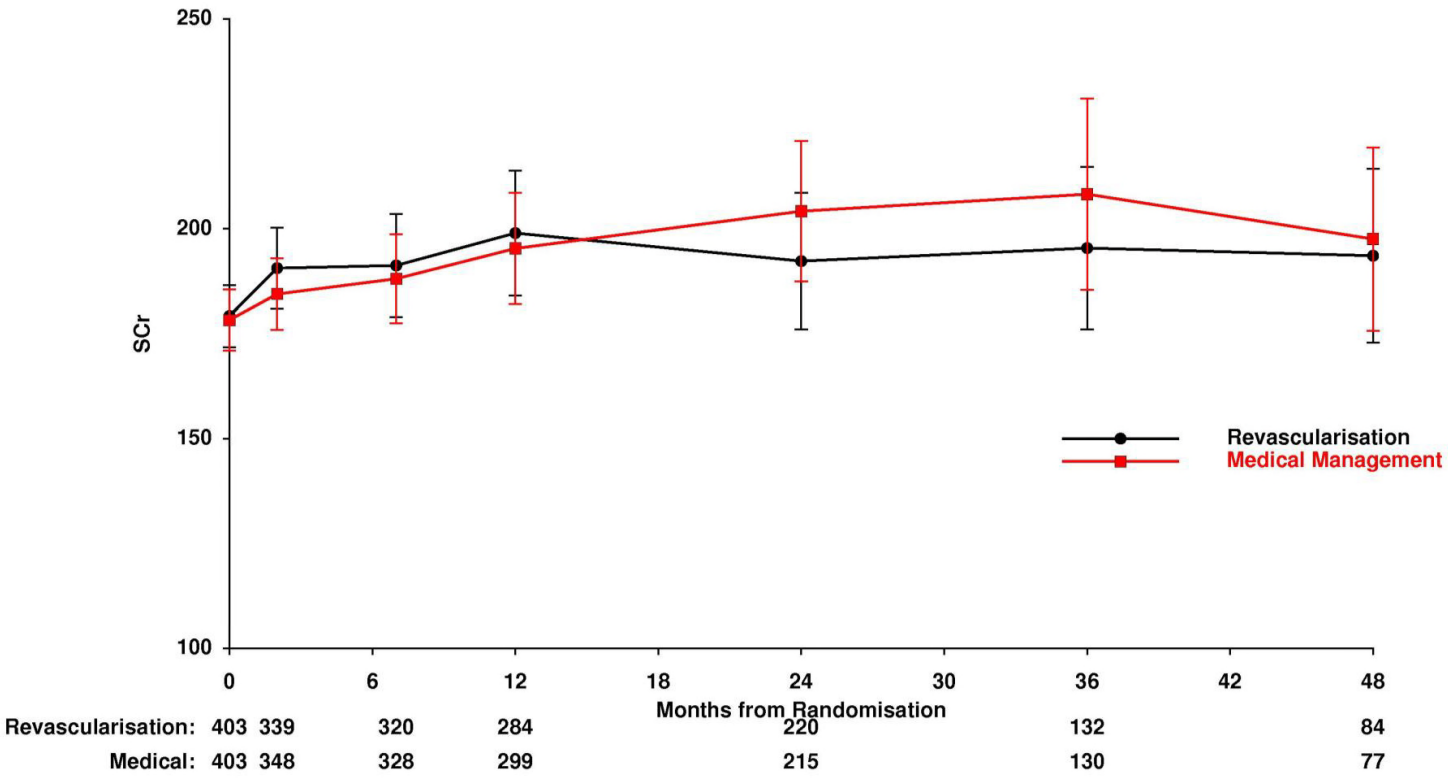
ASTRAL

- The ASTRAL Investigators. Revascularization Versus Medical Therapy for Renal Artery Stensois. N Engl J Med 2009;361:1953-62.
- Results:
  - "We found substantial risks but no evidence of a worthwhile clinical benefit from revascularization in patients with atherosclerotic renovascular disease."

Angioplasty and STent for Renal Artery Lesions (ASTRAL trial)



PLOT OF SCr OVER TIME



Astral's Fatal Flaws:

1. Selection Bias: If the investigator knew what to do, the patient was not randomized.
2. Primary endpoint renal function when:

   --Renal function was normal in 25% and nearly normal in another 15%

   --Many patients had unilateral disease
3. There was no core laboratory to adjudicate the imaging studies. This leads to overestimation of the degree of stenosis.
4. Patients in trial had mild disease overall: 40% had 50-70% stenosis and in fact many probably had less than 50%. For the most part ASTRAL included patients with mild to moderate disease, often unilateral.
5. Adverse event rate much higher than in other clinical trials.
   - The major adverse event rate in the first 24 hours was 9%, whereas the usual rate is 2% or less.
6. Trial centers were not high volume centers:

   --42% of centers recruited 1-5 patients over 7 years and 61% of centers recruited 9 or fewer patients.

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Our institution was one of the centres recruiting for ASTRAL; over the entire period, 14 of the 35 recruited patients were randomized to undergo revascularization as part of the trial's protocol. However, over the same period, there were substantially more patients undergoing renal revascularization outside of the trial. As patients were being enrolled into ASTRAL only if there was uncertainty as to the best course of action, presumably, for all the other patients intervention was deemed to be likely beneficial despite the lack of evidence.

Kalra P. Catheterization and Cardiovascular Interventions 75:1–10 (2010)

A Randomized Multicenter Clinical Trial of Renal Artery Stenting in Preventing Cardiovascular and Renal Events: Results of the CORAL Study

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., M.Sc., 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.,

on behalf of the CORAL Investigators

NIH National Heart, Lung, and Blood Institute

Inclusion Criteria

Clinical Syndrome:

- Hypertension ≥2 anti-hypertensive medications, OR
- Renal dysfunction defined as Stage 3 or greater CKD

-AND-

Atherosclerotic Renal Artery Stenosis:

- Angiographic: ≥ 60% and < 100%, OR
- Duplex: systolic velocity of >300 cm/sec, OR
- Core lab approved MRA, OR
- Core lab approved CTA

Primary Endpoint

- **Composite of major cardiovascular or renal events:**
  - Cardiovascular or Renal Death
  - Stroke
  - Myocardial Infarction
  - Heart Failure Hospitalization
  - Progressive Renal Insufficiency
  - Permanent Renal Replacement Therapy

C. Cooper, AHA 2013

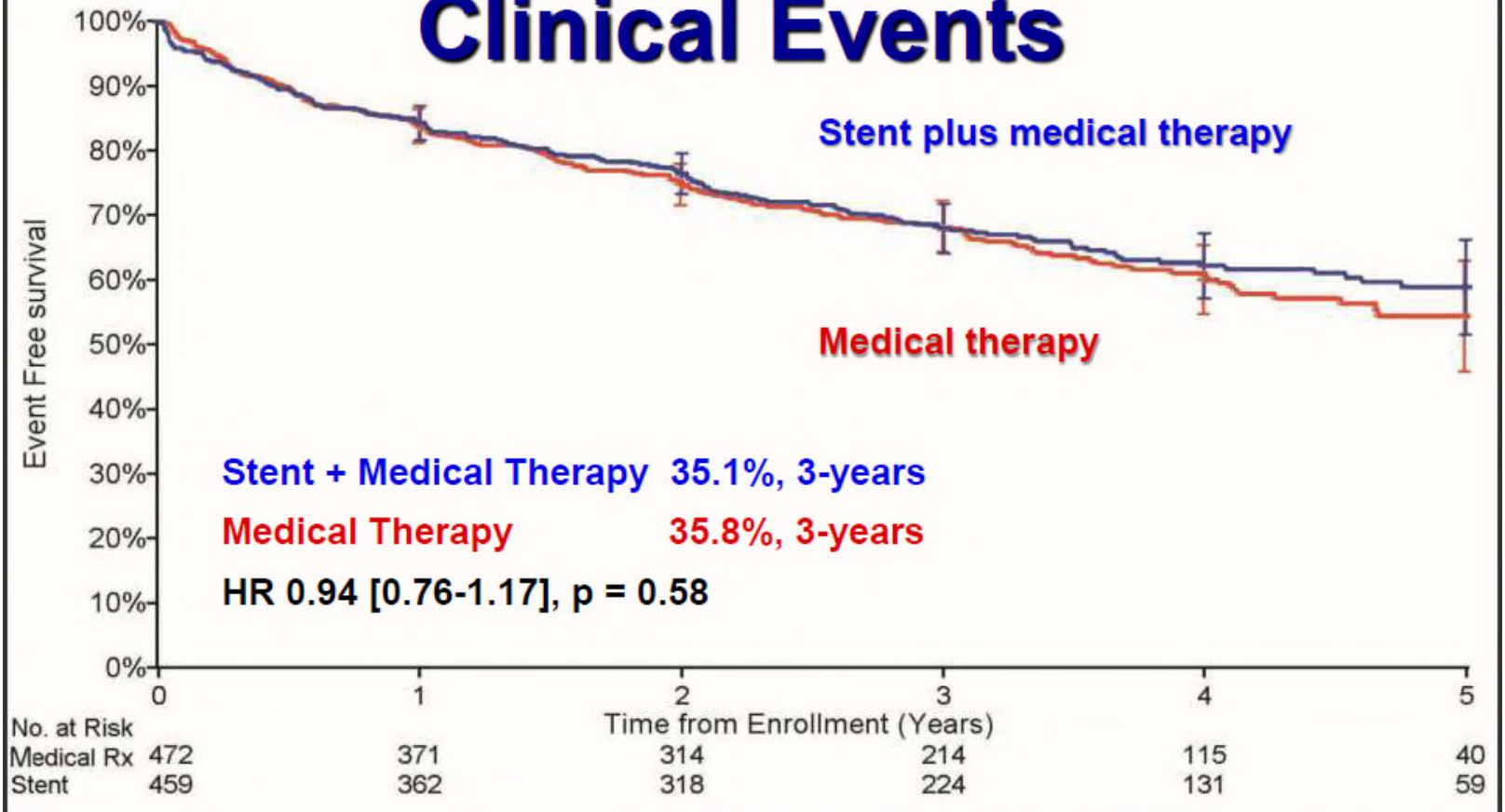
NIH National Heart, Lung, and Blood Institute

Baseline Characteristics

Baseline Characteristics of the Study Population According to Treatment Group		
Characteristic	Stent + Medical N = 459	Medical N = 472
Age *(years)*	69.3 ± 9.4	69.0 ± 9.0
Male gender *(%)*	51.0	48.9
White race *(%)*	91.5	90.9
Black race *(%)*	7.0	7.0
Body mass index *(kg/m^2)*	28.2 ± 5.3	28.7 ± 5.7
Systolic blood pressure *(mmHg)*	149 ± 23.2	150.4 ± 23.0
Estimate GFR *(ml/minute)*	58.0 ± 23.4	57.4 ± 21.7
Medical history and risk factors *(%)*		
Diabetes	32.4	34.3
Prior myocardial infarction	26.5	30.2
History of heart failure	12.0	15.1
Smoking in past year	28.0	32.2
Angiography		
% stenosis *(core lab)*	67.3 ± 11.4	66.9 ± 11.9
% stenosis *(investigator)*	72.5 ± 14.6	74.3 ± 13.1
Global ischemia *(%)*	20.0	16.2
Bilateral disease *(%)*	22.0	18.1

Results: Primary Endpoint

Clinical Events



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Conclusion

- Renal artery stenting did not confer a benefit to the prevention of clinical events when added to comprehensive, multi-factorial medical therapy in people with atherosclerotic renal artery stenosis and hypertension or chronic kidney disease.

Now available at: **www.NEJM.org**

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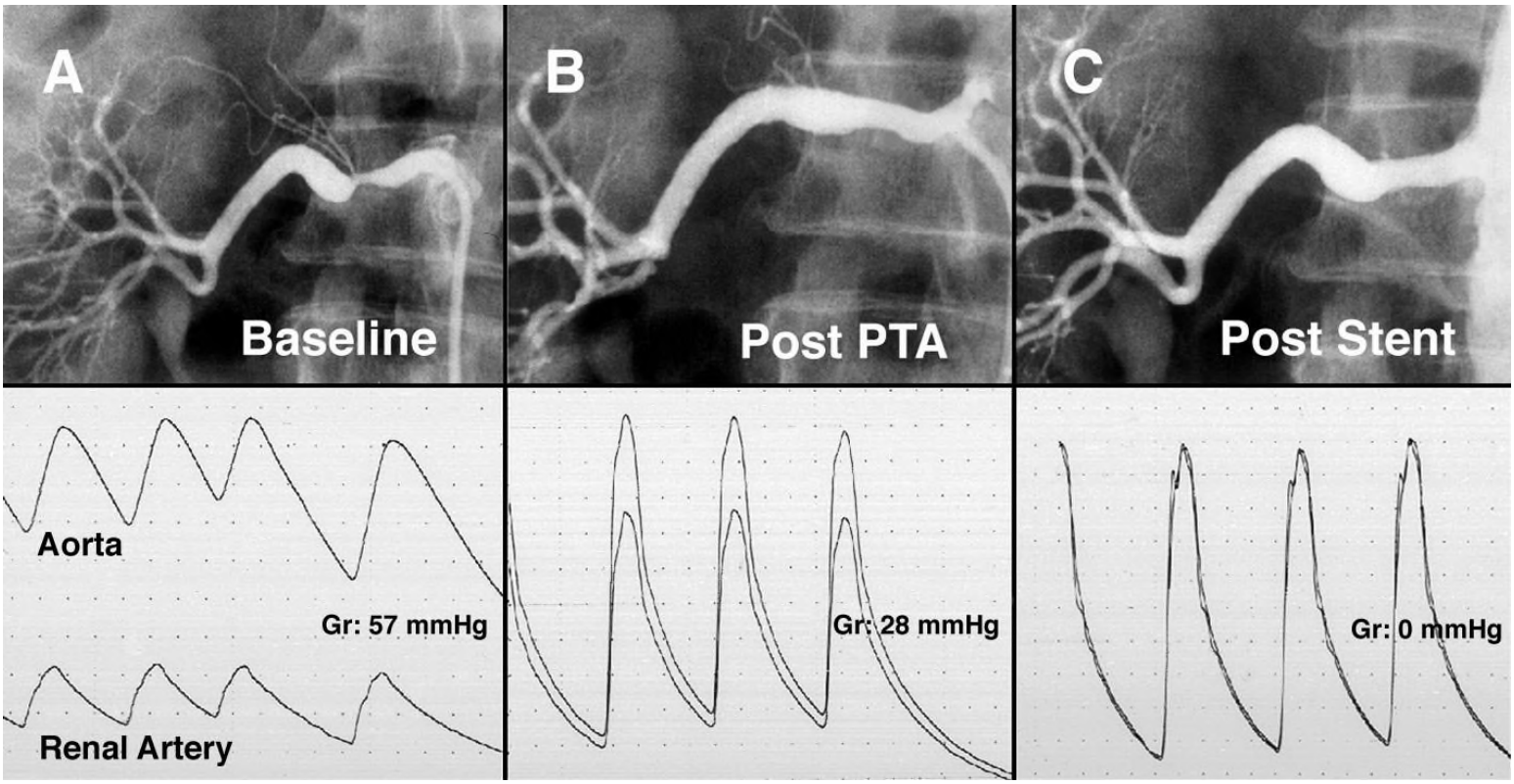
CORAL

- This was a very well designed trial initially.
- Same flaws as Astral: moderate disease, what they call global ischemia is not global ischemia
- Because of difficult recruiting, there were many protocol changes during the course of the trial which lessened its impact:
  - Use of distal protection
  - Use of pressure gradients
    - Some investigators could not do pressure gradients; why were they in the trial?

Translesional Pressure Gradients



White CJ, Olin JW. Nat Clin Practice CV Medicine 2009;6:176-190.

Parachute use to prevent death and major trauma related to gravitational challenge: systematic review of randomised controlled trials

Gordon C S Smith, Jill P Pell

BMJ VOLUME 327 20–27 DECEMBER 2003

Abstract

Objectives To determine whether parachutes are effective in preventing major trauma related to gravitational challenge.

Design Systematic review of randomised controlled trials.

Data sources: Medline, Web of Science, Embase, and the Cochrane Library databases; appropriate internet sites and citation lists.

Study selection: Studies showing the effects of using a parachute during free fall.

Main outcome measure Death or major trauma, defined as an injury severity score > 15.

Results We were unable to identify any randomised controlled trials of parachute intervention.

Conclusions As with many interventions intended to prevent ill health, the effectiveness of parachutes has not been subjected to rigorous evaluation by using randomised controlled trials. Advocates of evidence based medicine have criticised the adoption of interventions evaluated by using only observational data. We think that everyone might benefit if the most radical protagonists of evidence based medicine organised and participated in a double blind, randomised, placebo controlled, crossover trial of the parachute.

Parachutes reduce the risk of injury after gravitational challenge, but their effectiveness has not been proved with randomised controlled trials

What is already known about this topic

Parachutes are widely used to prevent death and major injury after gravitational challenge

Parachute use is associated with adverse effects due to failure of the intervention and iatrogenic injury

Studies of free fall do not show 100% mortality

What this study adds

No randomised controlled trials of parachute use have been undertaken

The basis for parachute use is purely observational, and its apparent efficacy could potentially be explained by a "healthy cohort" effect

Individuals who insist that all interventions need to be validated by a randomised controlled trial need to come down to earth with a bump

What is the Best Predictor of Benefit with Renal Artery Stenting?

Carefully selecting your patients according to ACC/AHA Practice Guidelines

Is Renal Artery Stenting Dead?

NO!

- Resistant hypertension:
  - Failure to adequately control blood pressure with a good 3 drug antihypertensive regimen (one drug being a diuretic)
- Preservation of renal function
  - High grade bilateral disease or equivalent and rapid decline in renal function
  - Severe bilateral disease or equivalent and chronic kidney disease and no other explanation
  - Azotemia after ACE-I or ARB and severe bilateral disease or equivalent
  - Dialysis dependent and severe bilateral disease or equivalent
- CHF or "flash" pulmonary edema in patients without active coronary ischemia and jeopardy of entire renal mass

Hirsch AT et. A. J Am Coll Cardiol 2006;47:1239-1312.