TCTAP
Seoul, Korea
April 24, 2012

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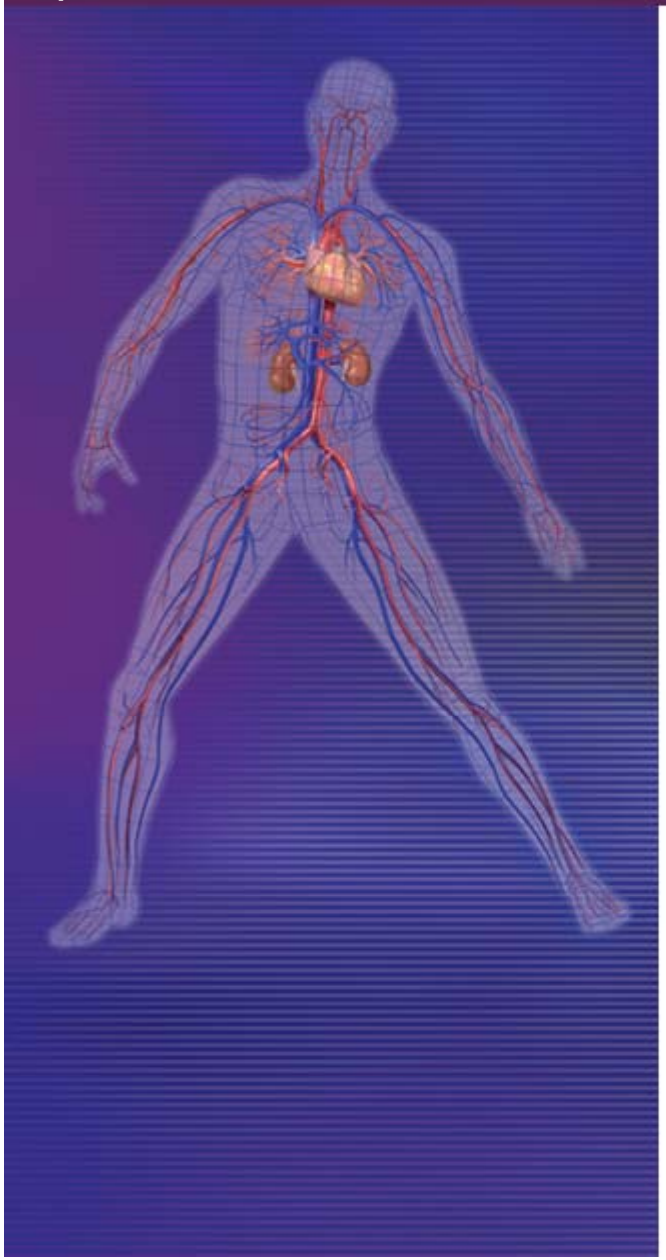

Management of Renal Artery Stenosis
Is Intervention Dead?

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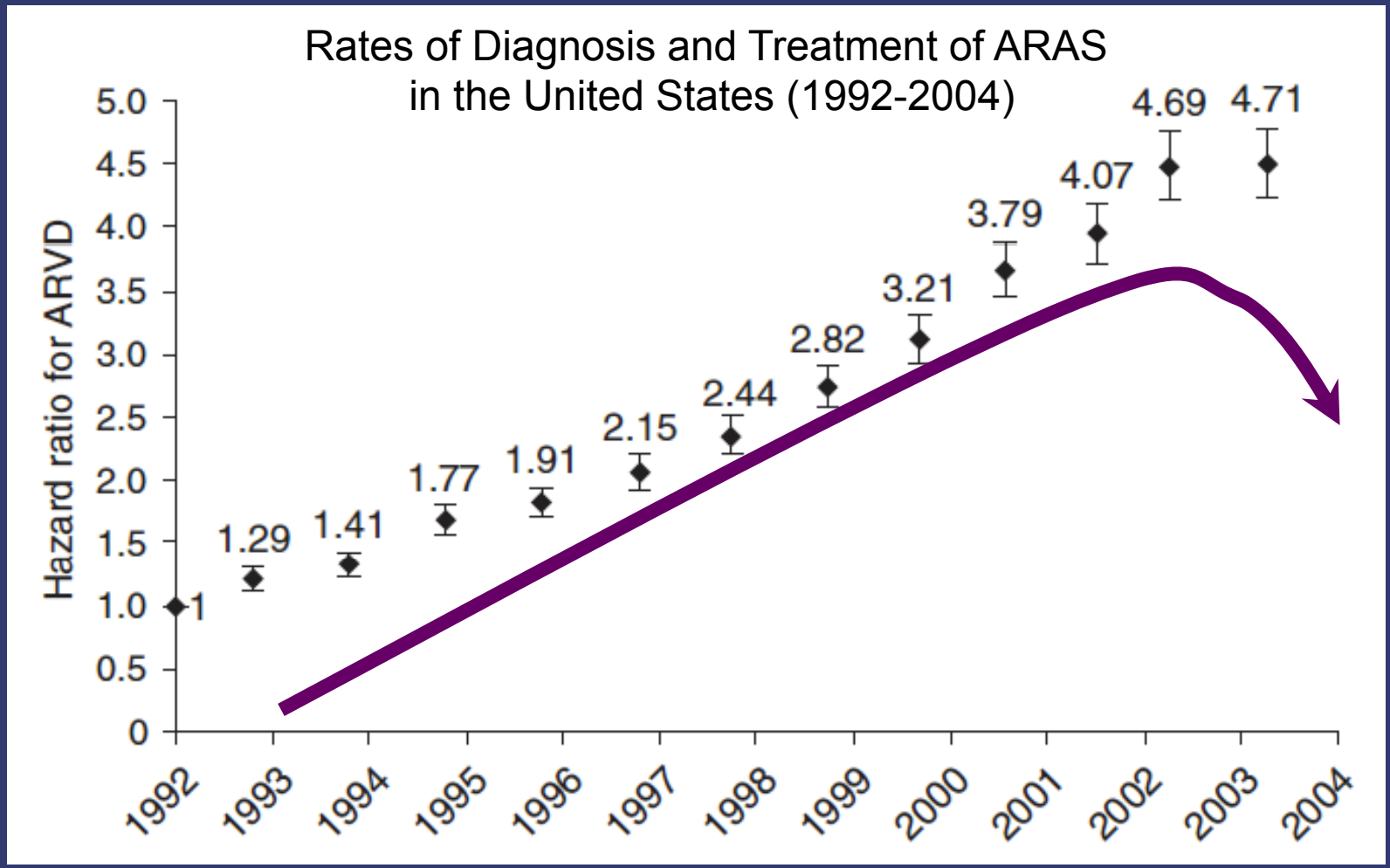
VASCULAR CENTER

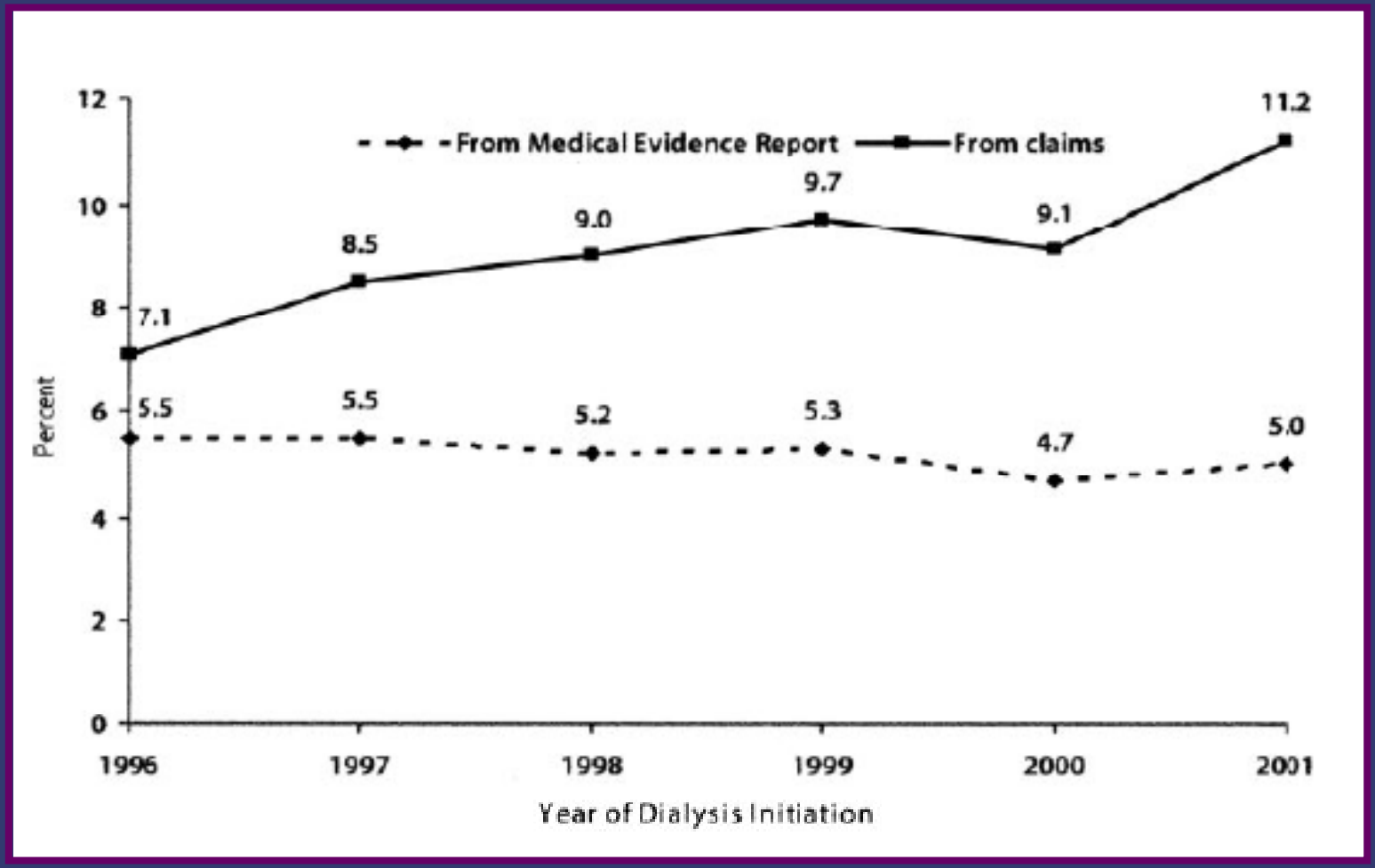
Michael R. Jaff, DO
Conflicts of Interest

- **Consultant**
  - Abbott Vascular (non-compensated)
  - Becker Venture Services Group
  - Bluegrass Vascular Therapies
  - Cordis Corporation(non-compensated)
  - Covidien (non-compensated)
  - Hansen Medical
  - Medtronic (non-compensated)
  - Micell, Incorporated
  - Primacea
  - Trivascular, Inc.
  - Vortex
- **Equity**
  - Access Closure, Inc
  - Embolitech, Inc
  - Hotspur, Inc
  - Icon Interventional, Inc
  - I.C.Sciences, Inc
  - Janacare, Inc
  - Northwind Medical, Inc.
  - PQ Bypass, Inc
  - Primacea
  - Sadra Medical
  - TMI/Trireme, Inc
  - Vascular Therapies, Inc
- **Board Member**
  - VIVA Physicians (Not For Profit 501(c) 3 Organization)
    - www.vivapvd.com

What DO We Know?



Atherosclerotic Renovascular Disease in Older US Patients Starting Dialysis, 1996 to 2001



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Circulation 2007;115:50-58

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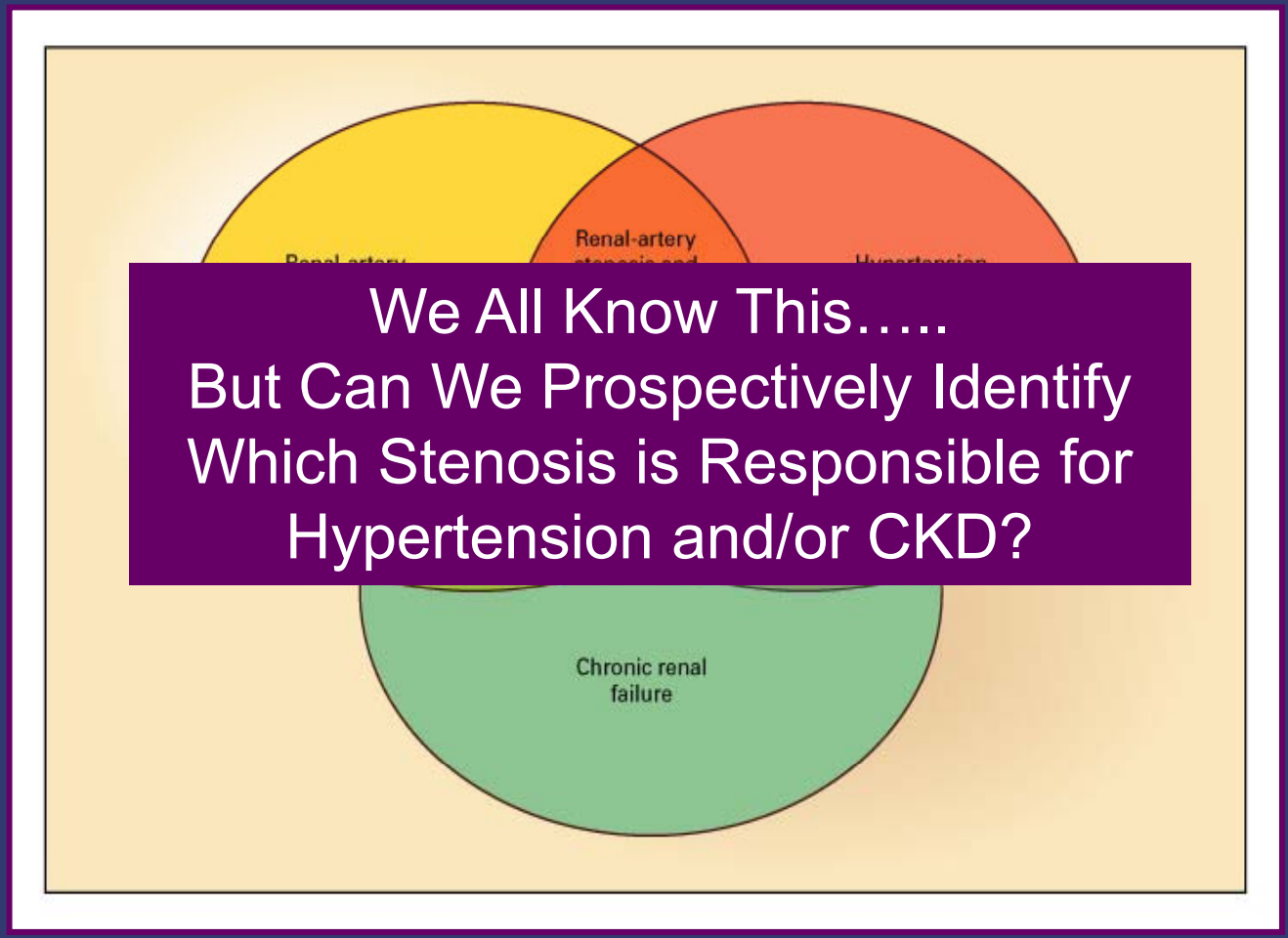
Relation Between Renal-Artery Stenosis, Hypertension and Chronic Renal Failure



We All Know This…..
But Can We Prospectively Identify Which Stenosis is Responsible for Hypertension and/or CKD?

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Safian et al. N Engl J Med 2001;344:410.

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Clinical Consequence of Atherosclerotic Renal Artery Stenosis

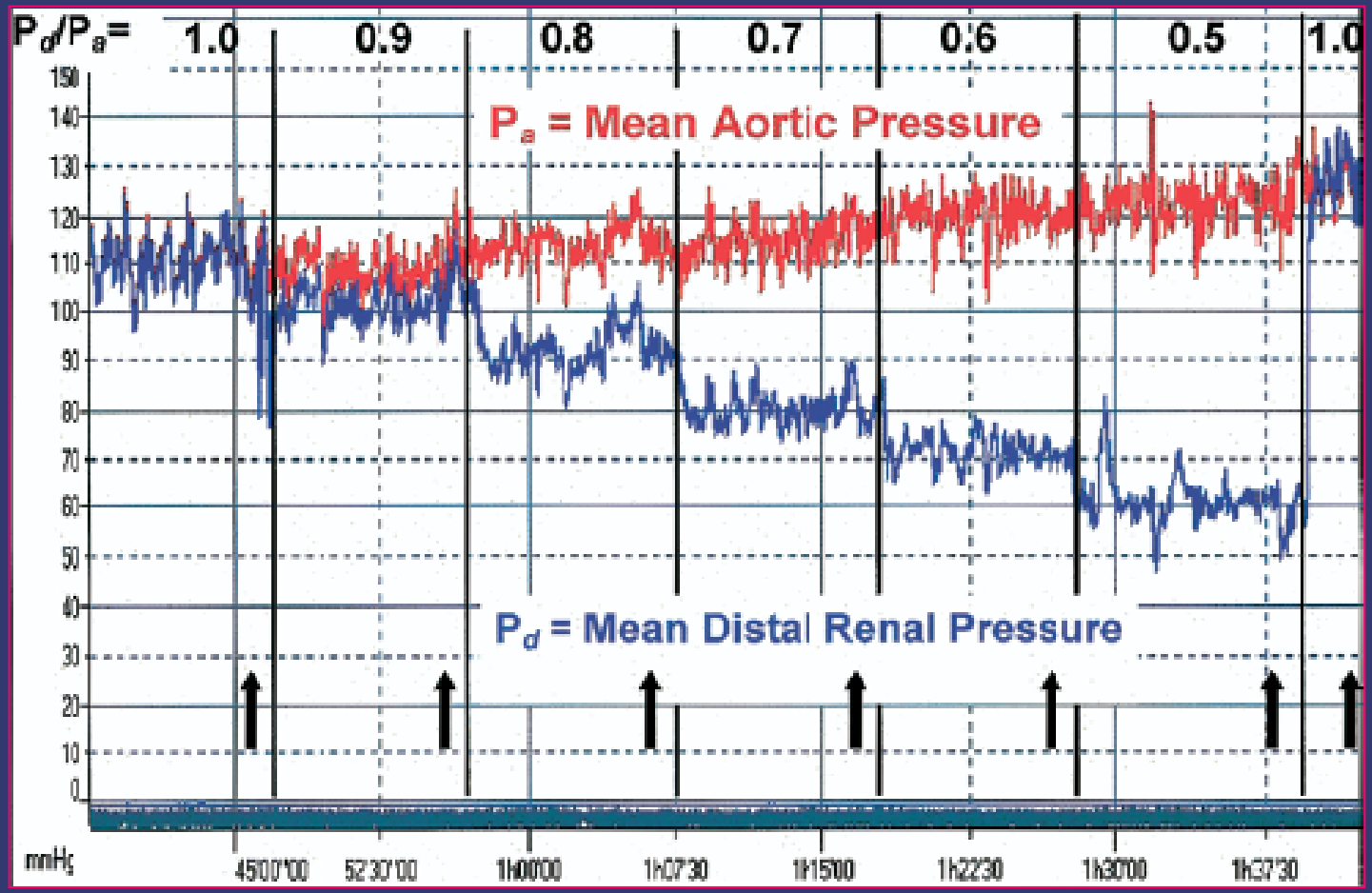
- **Cardiovascular**
  - Angina Pectoris
  - 'Flash' Pulmonary Edema
  - Myocardial Infarction
  - Left Ventricular H
  - Stroke
  - Aortic
- **Renal**
  - Chronic R nsufficiency
  - End-Stage Renal Disease

Do You Think This Patient with Recurrent "Flash" Pulmonary Edema Would Benefit from Right Renal Artery Stent?

Why Don’t We Know Who To Treat and When?

- The data is
  - prospectiv
  - mized
- The indust
  - approval, a
  - igned to gain
  - science
- Endpoints
- There are
  - al data
- Are we ab
  - Predict
  - Make th

How To Know When Renal Artery Stenosis is Really Significant?



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J Am Coll Cardiol 2006;48:1851-5

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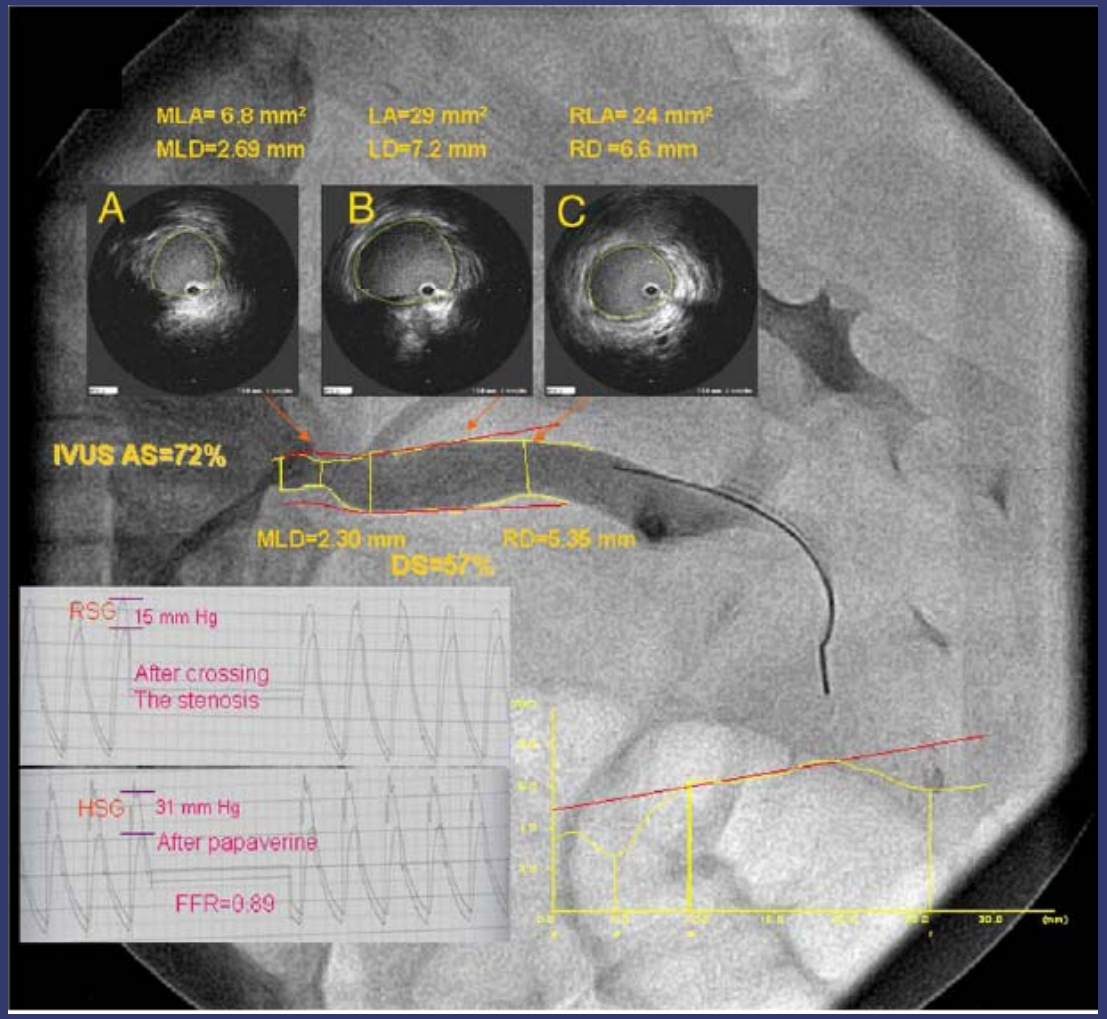
What About Translesional Pressure Gradients?



J Am Coll Cardiol 2009;53:2363-71

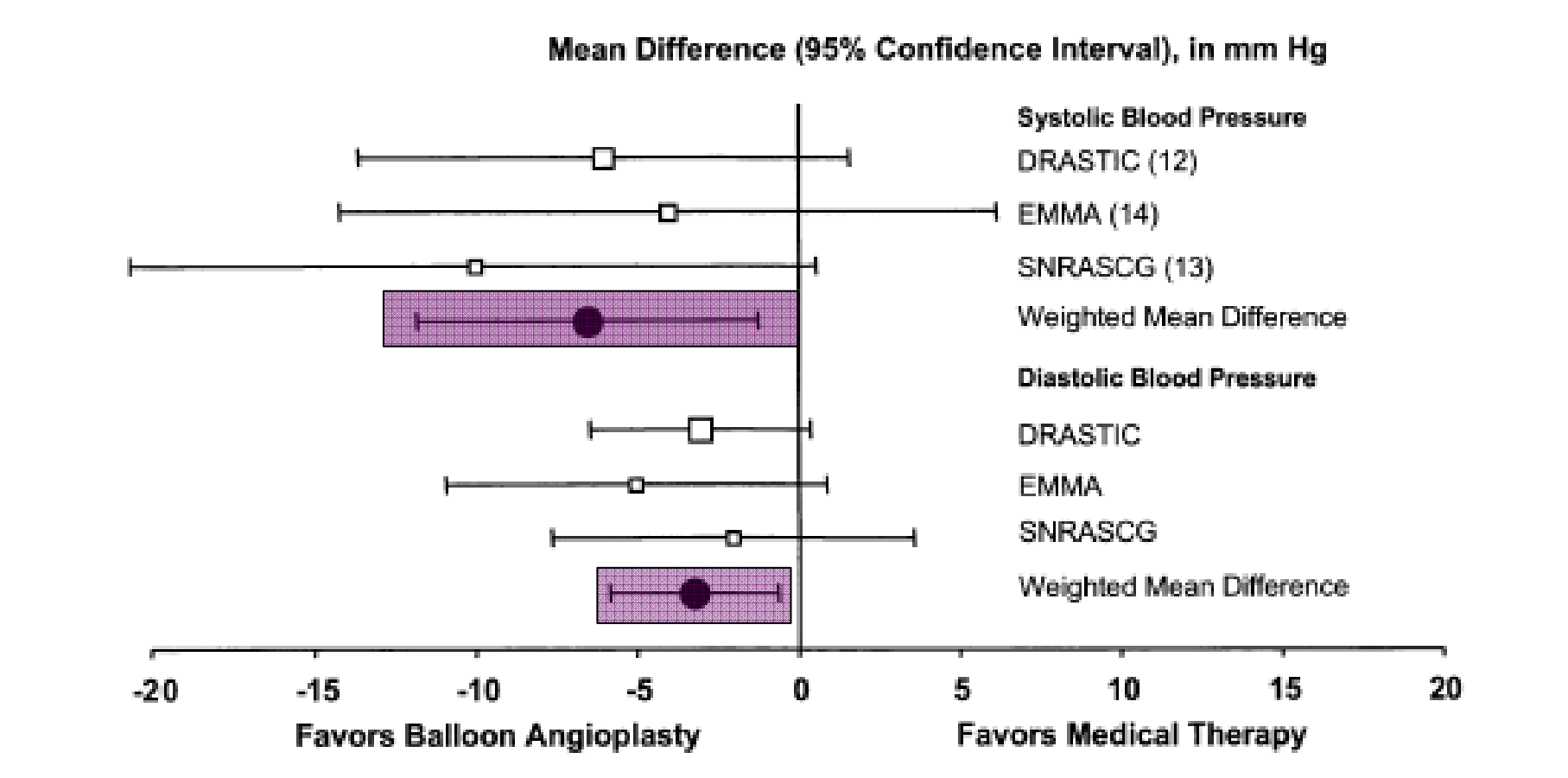
Hyperemic Systolic Gradients

Predictors	Odds Ratio	95% Confidence Interval	p Value
HSG, mm Hg	1.12	1.05–1.19	0.0001
IVUS MLA, mm^2	0.78	0.68–0.89	0.0003
IVUS area stenosis, %	1.04	1.02–1.07	0.0005
IVUS MLD, mm	0.62	0.12–0.57	0.0008
HMG, mm Hg	1.22	1.06–1.41	0.0045
RSG, mm Hg	1.09	1.02–1.17	0.0068
MLD by quantitative renal angiography, mm	0.39	0.17–0.92	0.03
Diameter stenosis by quantitative renal angiography, %	1.02	0.95–1.09	0.48
Baseline systolic blood pressure, mm Hg	1.01	0.97–1.05	0.49
Baseline diastolic blood pressure, mm Hg	0.97	0.93–1.01	0.11
Baseline mean blood pressure, mm Hg	0.98	0.93–1.02	0.40

HSG ≥21 mmHg Sens 82%/Spec 84%/Accuracy 84%

J Am Coll Cardiol 2009;53:2363-71

Meta-Analysis: PTRA vs Medicine in Hypertension and RAS



Am J Med 2003;114:44-50

Revascularization versus Medical Therapy for Renal-Artery Stenosis

The ASTRAL Investigators*

- Multicenter prospective randomized trial of endovascular renal intervention vs optimal medical therapy
- Primary Endpoint:

In a randomized, unblinded trial, we assigned 806 patients with atherosclerotic renovascular disease either to undergo revascularization in addition to receiving medical therapy or to receive medical therapy alone. The primary outcome was renal function, as measured by the reciprocal of the serum creatinine level (a measure that has a linear relationship with creatinine clearance). Secondary outcomes were blood pressure, the time to renal and major cardiovascular events, and mortality. The median follow-up was 34 months.

N Engl J Med 2010;361:1953-62

Revascularization versus Medical Therapy for Renal-Artery Stenosis

The ASTRAL Investigators*

Variable	Revascularization (N = 403)	Medical Therapy (N = 403)	P Value
Demographic			
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)	

Revascularization versus Medical Therapy for Renal-Artery Stenosis

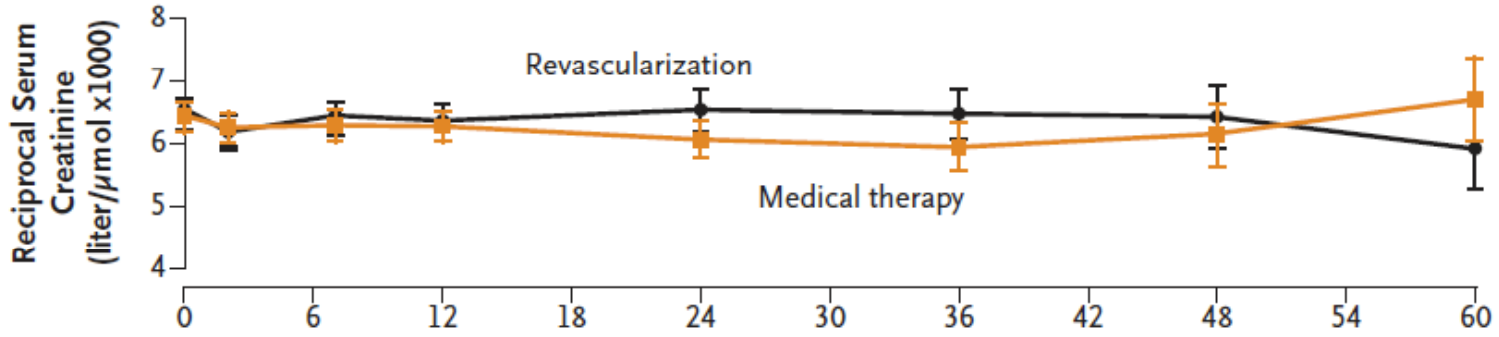
The ASTRAL Investigators*

Variable	Revascularization (N = 403)	Medical Therapy (N = 403)	P Value
Demographic			
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)	

Revascularization versus Medical Therapy for Renal-Artery Stenosis

The ASTRAL Investigators*

Primary Endpoint



No. of Patients								
Revascularization	403	349	336	329	263	191	127	72
Medical therapy	403	363	347	343	272	183	119	61

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N Engl J Med 2010;361:1953-62

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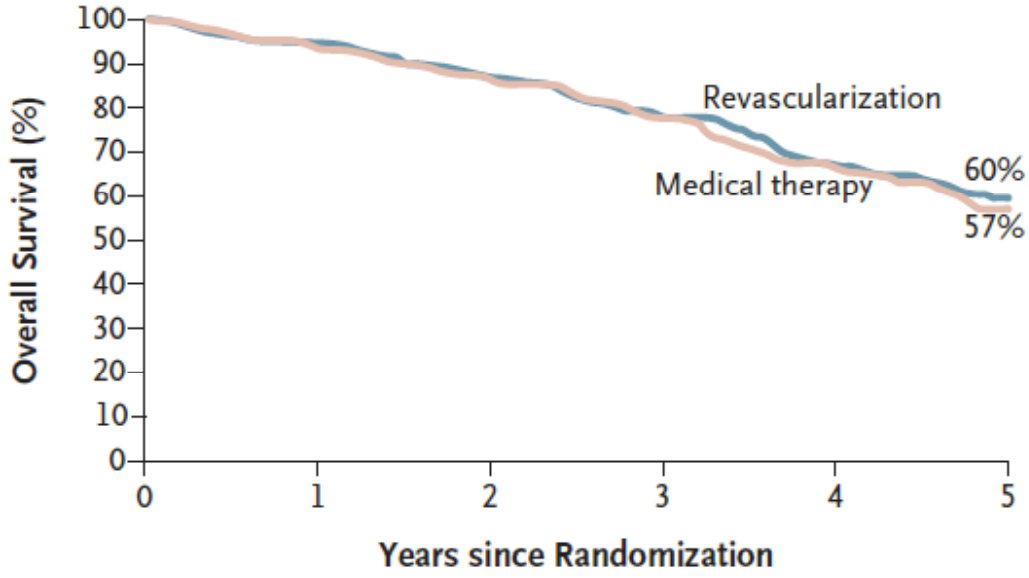
Revascularization versus Medical Therapy for Renal-Artery Stenosis

Overall Survival



No. at Risk						
Revascularization	403	337	257	178	109	46
Medical therapy	403	332	248	165	96	40

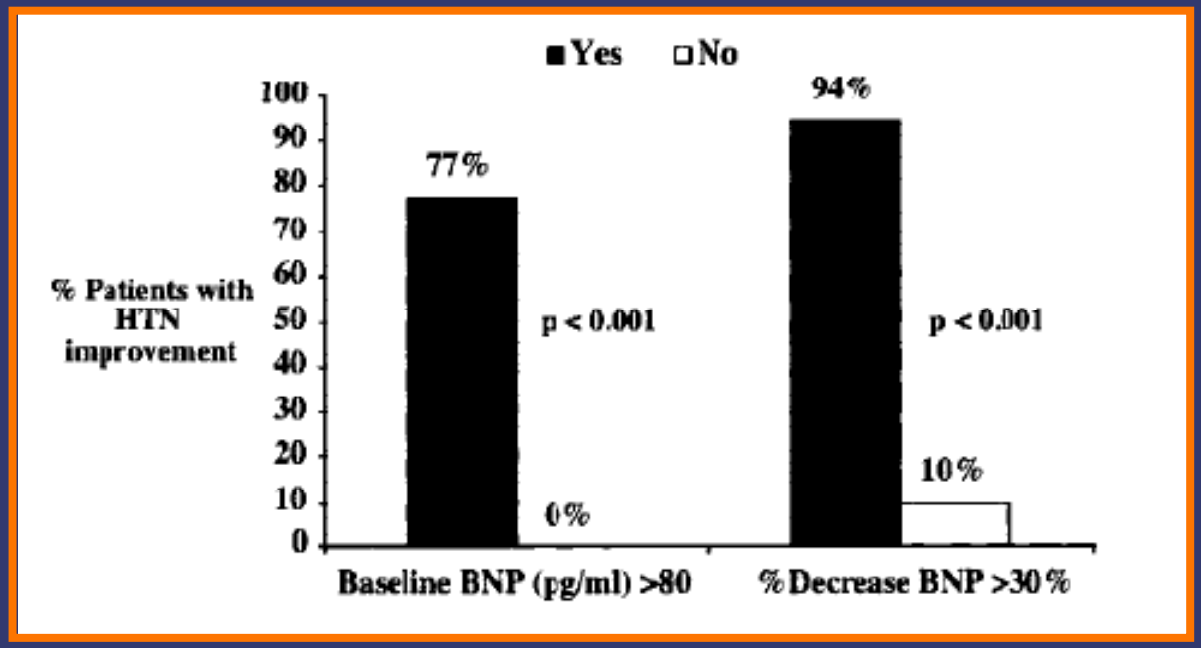
BNP Levels and Improvement in HTN with Renal Artery Stenting

- 27 patients with refractory HTN and significant RAS had Brain Natriuretic Peptide (BNP) levels measured pre- and post-RA Stenting
  - Mean baseline SBP 173 ± 19 mmHg
  - Mean baseline DBP 89 ± 13 mmHg
  - Mean number of anti-hypertensive agents per patient 3.8 ± 0.8

Circulation 2005;111:328-33

BNP Levels and Improvement in HTN with Renal Artery Stenting

Baseline BNP Levels >80 *All* Responded



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Circulation 2005;111:328-33

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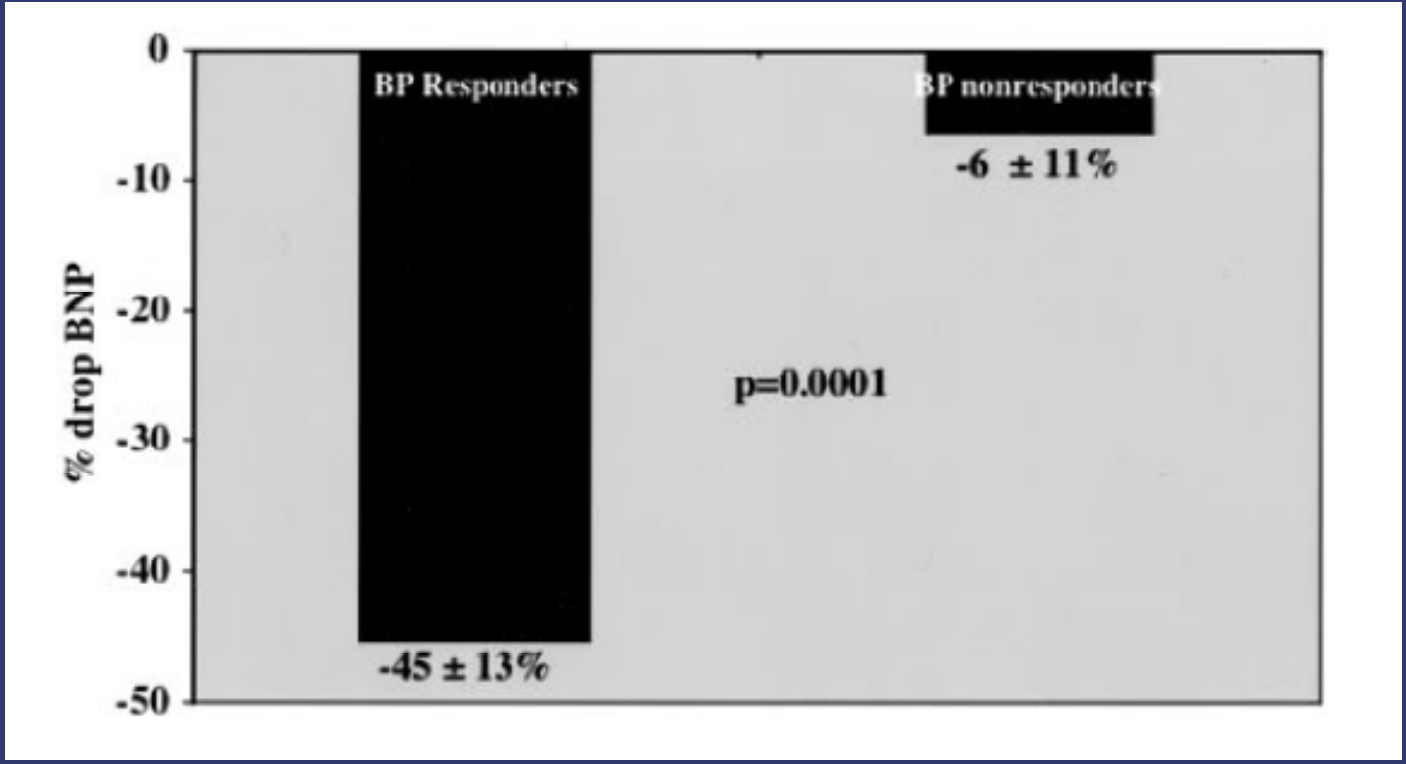
BNP Levels and Improvement in HTN with Renal Artery Stenting



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Circulation 2005;111:328-33

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Herculink Elite Cobalt Chromium Renal Stent Trial to Demonstrate Efficacy and Safety (HERCULES)

OBJECTIVE

Evaluate the safety and effectiveness of RX Herculink Elite Renal Stent System in the treatment of suboptimal post-procedural PTA of atherosclerotic de *novo* or restenotic RAS in patients with uncontrolled hypertension

202 patients at 37 US sites treated from August 2007 to October 2009

PRIMARY ENDPOINT:
9M Restenosis Rate (Performance Goal 28.6%)

Clinical, lab and DUS follow-up at 1, 6, 9,12 mos, 2Y and 3Y

BNP measurement at baseline, 24 hrs and 1 month

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Catheter Cardiovasc Intervent 2012.

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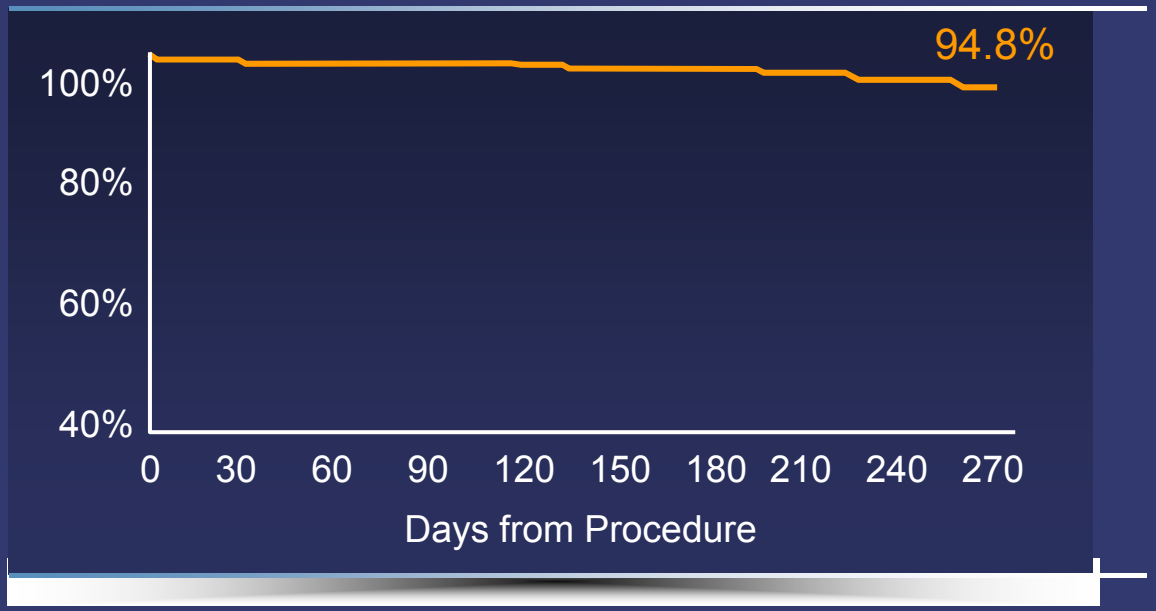
Key Safety Endpoint

Freedom from Death, Ipsilateral Nephrectomy and Embolic Events Resulting in Kidney Damage Through 30 days and Clinically Driven TLR through 270 days



Days from Procedure	[0, 30]	[30, 180]	[180, 270]
Subjects at Risk	202	198	191
Number of Events	3	2	5
Event Free (%)	98.5%	97.5%	94.8%

Catheter Cardiovasc Intervent 2012.

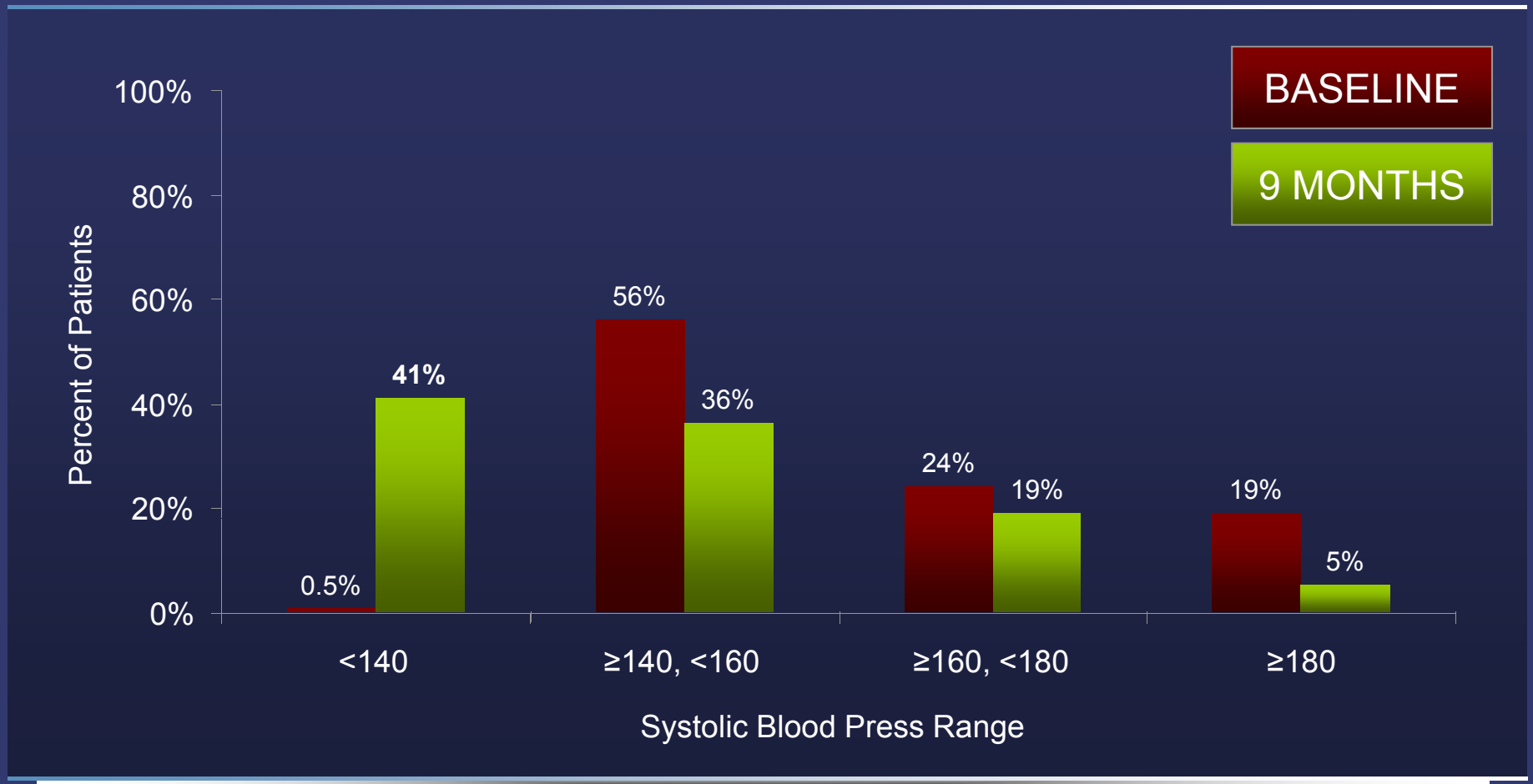
Blood Pressure and Medications

	Baseline	1 Month	9 Months	p-value
SBP (mmHg)	162 ± 18	145 ± 21	145 ± 21	<0.0001[a]
DBP (mmHg)	78 ± 12	76 ± 11	75 ± 12	0.05[a]
eGFR (mL/min per 1.73m^2)	58 ± 21	59 ± 21	57 ± 23	0.38[a]
≥ 3 anti-hypertensive meds	70%	68%	66%	0.61[b]
% ACEI or ARB	76%	76%	76%	0.99[b]
% Diuretics	65%	63%	60%	0.60[b]

Catheter Cardiovasc Intervent 2012.

[a] p-value compares baseline to 9 months; [b] p-value compares baseline, 1 month and 9 months.

SBP Reduction in 77.5% of Patients at 9 Months



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Change in SBP at 9 Months by ≥ 1 Category

	Improved by ≥ 1 Category	Decrease in SBP (mmHg)	9-Month SBP (mmHg)
≥ 180 mmHg* Mean SBP 194 ± 12 (n=39)	94%	48	146 ± 21
≥ 160, < 180 mmHg** Mean SBP 167 ± 6 (n=49)	71%	31	136 ± 13
≥ 140, < 160 mmHg*** Mean SBP 150 ± 5 (n=113)	44%	23	127 ± 9

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Catheter Cardiovasc Intervent 2012.

* Unknown (n=3)
** Unknown (n=7)
*** Unknown (n=18)

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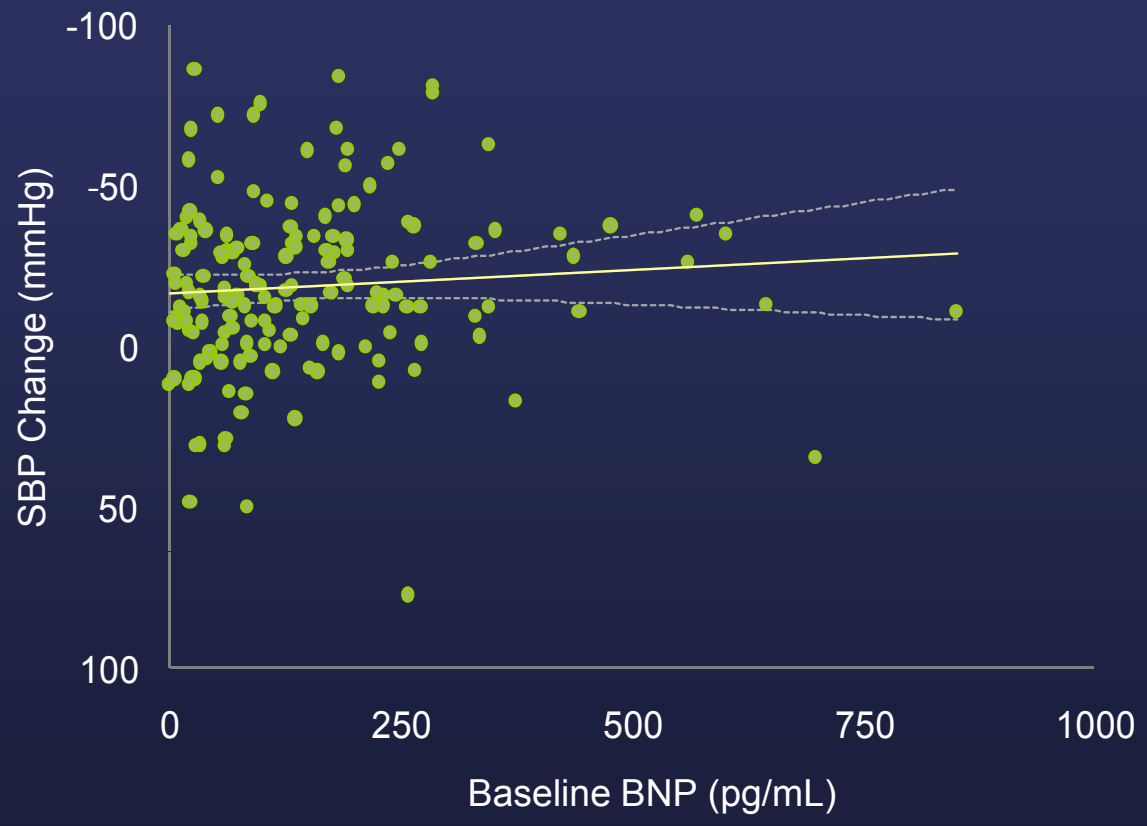
No Evidence of Correlation Between Baseline BNP and SBP Change

Correlation:
Pearson r = -0.076
R-square = 0.006

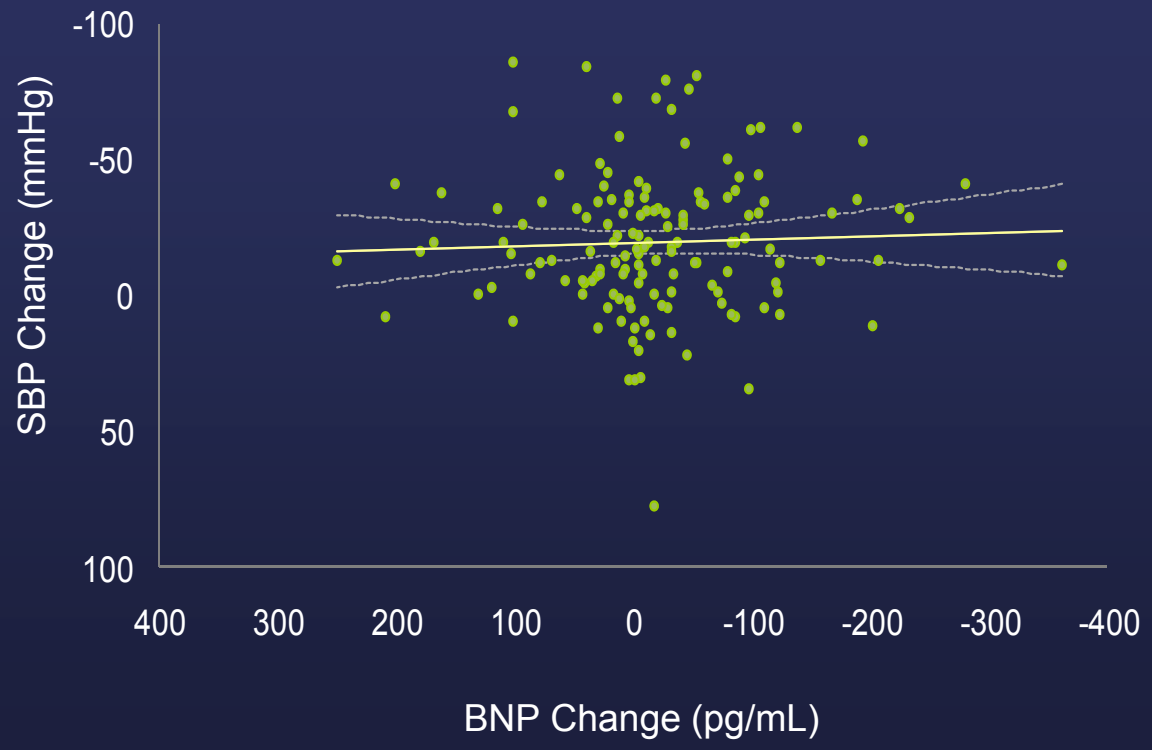
Linear Regression:
p = 0.33



No Evidence of Correlation Between BNP Change and SBP Change

Correlation:
Pearson r = 0.044
R-square = 0.002

Linear Regression:
p = 0.60



9 Month Patency

	(N=202 patients / 241 lesions)
Primary Patency	88.0%
Primary Assisted Patency	95.2%

The CORAL Trial

Stent revascularization for the prevention of cardiovascular and renal events among patients with renal artery [redacted]nsion: Rationale and design of the CORAL trial

Enrollment Completed!!!

Christopher J. Cooper, MD,[a] Timothy P. Murphy, MD,[b] Alan Matsumoto, MD,[c] Michael Steffes, MD,[d] David J. Cohen, MD,[e] Michael Jaff, DO,[f] Richard Kuntz, MD,[g] Kenneth Jamerson, MD,[h] Diane Reid, MD,[i] Kenneth Rosenfield, MD,[f] John Rundback, MD,[j] Ralph D'Agostino, MD,[k] William Henrich, MD,[l] and Lance Dworkin, MD[b] *Toledo, OH; Providence, RI; Charlottesville, VA; Minneapolis, MN; Boston, MA; Ann Arbor, MI; Bethesda and Baltimore MD; and Teaneck, NJ*

OMT + Stent vs OMT Alone

CORAL Primary Composite Endpoint

- Event-free survival from CV and renal adverse events
  - CV or renal death
  - Stroke
  - MI
  - Hospitalization for CHF
  - Progressive renal insufficiency
  - Renal replacement therapy

Renal Artery Intervention is *NOT* Dead

- ***Choose patients wisely….***
- Must provide a reasonable trial of optimal antihypertensive therapy first…
- Must have a high degree of evidence that
  - Blood pressure truly cannot be controlled with reasonable antihypertensive medications
  - Chronic kidney disease is likely to be due to renal ischemia
  - Recurrent pulmonary edema is not due to myocardial ischemia