Most Important Trials in Vascular Medicine & Intervention

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Disclosures

- PERT Consortium (501c3): Board of Directors
- AHA: Writing Committee Chair
- BEST-CLI trial: Independent Medical Reviewer
- St. Jude: Research Funds to the Institution
- Recor Medical: Research Funds to the Institution
- Astra Zeneca: Advisory Board

CREST

CREST Study Design

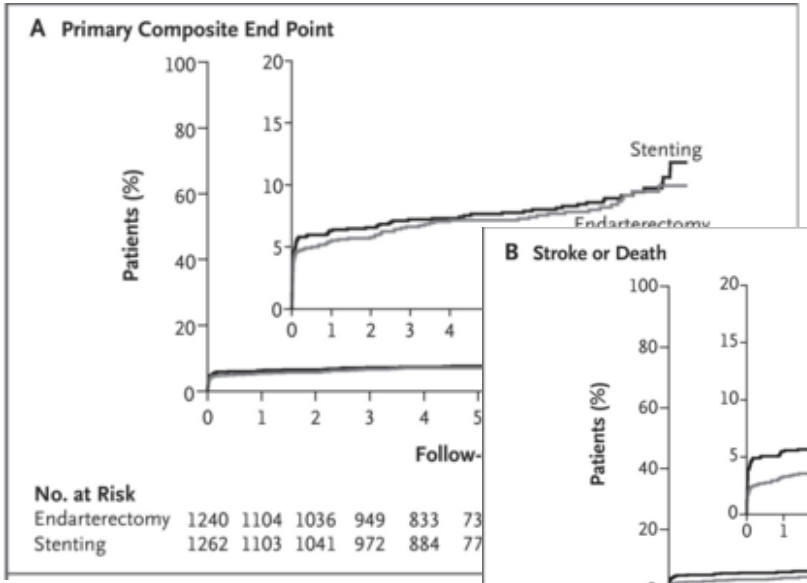
- **CAS vs. CEA in symptomatic and asymptomatic stenosis**
- **108 US and 9 Canadian sites**
- **2300 patients enrolled over a decade**

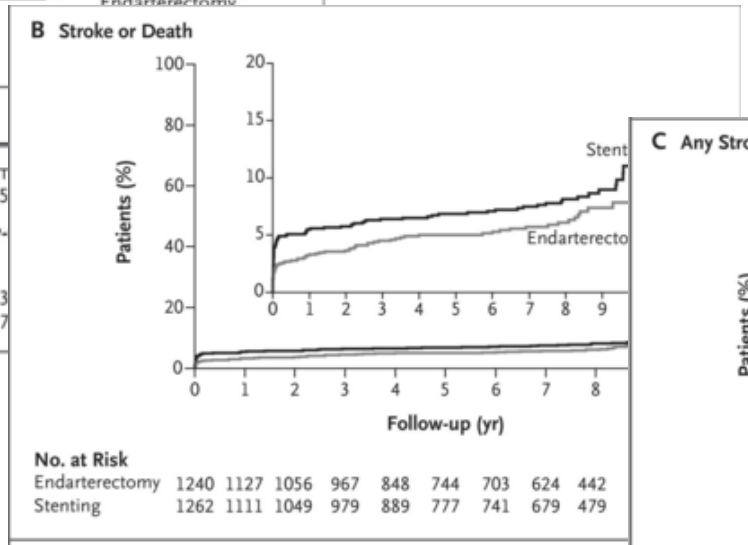
CREST- Death, Stroke and MI within 30 Days

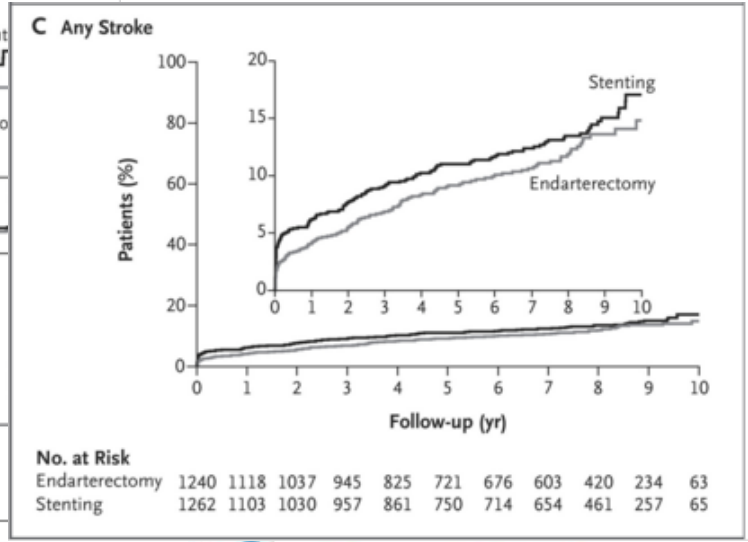
	CAS N = 1,131	CEA N = 1,176	Difference	Unadjusted p-value*
All death, stroke, or MI	5.8% (65)	5.1% (60)	0.7%	0.5200
Death	0.53% (6)	0.26% (3)	0.27%	0.3335
Any stroke	4.1% (46)	1.9% (22)	2.2%	0.0019
Major stroke	0.9% (10)	0.4% (5)	0.5%	0.2005
Minor stroke	3.2% (36)	1.5% (18)	1.7%	0.0088
MI	2.0% (22)	3.4% (40)	-1.5%	0.0387

* Fisher's exact p-values were not adjusted for multiple comparisons; p-values for descriptive purposes only

CREST 10 year Results







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Brott et al, NEJM 2016

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CAS vs. CEA - All Relevant Outcomes in RCTs

TABLE 3 Absolute Risk Metrics of Outcomes of Major Interest

Outcome of Interest	Number of Events/Patients (Absolute Event Rate, %)		NNT/NNH for CAS	p Value
	CAS Group	CEA Group		
Aggregate efficacy/safety outcome*	295/3,636 (8.1)	218/2,890 (7.5)	–	0.14
Periprocedural any stroke + nonperiprocedural ipsilateral stroke	275/3,636 (7.6)	161/2,890 (5.6)	50 (NNH)	<0.001
Periprocedural any stroke	169/3,636 (4.6)	73/2,890 (2.5)	47 (NNH)	<0.001
Periprocedural minor stroke	124/3,636 (3.4)	44/2,890 (1.5)	52 (NNH)	<0.001
Periprocedural death	26/3,636 (0.7)	16/2,890 (0.5)	–	0.48
Periprocedural MI	24/3,636 (0.6)	48/2,890 (1.6)	99 (NNT)	0.002
Periprocedural CN palsy	9/3,636 (0.2)	135/2,890 (4.7)	22 (NNT)	<0.00
Periprocedural neurological injury	178/3,636 (4.9)	208/2,890 (7.2)	43 (NNT)	0.02
Periprocedural neck hematoma	20/3,469 (0.6)	53/2,723 (1.9)	73 (NNT)	<0.001
Composite periprocedural safety outcome†	224/3,636 (6.2)	263/2,890 (9.1)	34 (NNT)	0.008
Long-term stroke in any territory (includes periprocedural stroke)	305/3,636 (8.4)	200/2,890 (6.9)	68 (NNH)	<0.001
Long-term death	429/3,636 (11.8)	357/2,890 (12.3)	–	0.18

*Aggregate efficacy safety outcome is the composite of death, stroke, MI during periprocedural period, and ipsilateral stroke during long-term follow-up. †Composite periprocedural safety outcome is the composite of death, stroke, MI, or cranial nerve palsy during the periprocedural period.

CAS = carotid artery stenting; CEA = carotid endarterectomy; CN = cranial nerve, MI = myocardial infarction; NNH = number needed to harm; NNT = number needed to treat.

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Sardar et al, JACC 2017

30-Day Tradeoffs (Long-Term Equivalence)

PEITHO

Pulmonary Embolism Thrombolysis Trial (PEITHO)

PE-related early MORTALITY RISK		RISK MARKERS: CLINICAL (Shock or hypotension)	RISK MARKERS: RV Dysfunction	RISK MARKERS: Myocardial injury	Potential treatment implications
HIGH > 15%		+	(+)*	(+)*	Thrombolysis or Embolectomy
NON HIGH	Intermediate 3 - 15%	–	+	+	Hospital Admission
			+	–	
			–	+	
	Low <1%	–	–	–	Early discharge or home treatment

Meyer et al. , NEJM 2014

PEITHO- Primary Endpoint

- Death or hemodynamic collapse (7 days)
  - Need for CPR
  - Systolic BP <90 mm Hg or drop of >40 mm Hg for >15 min with end-organ hypoperfusion
  - Need for pressors

PEITHO- Baseline Characteristics

	Tenecteplase (n=506)	Placebo (n=499)
Age (y,) mean±SD	66.5±14.7	65.8±15.9
Age (y), median (Q1-Q3)	70.0 (57.0-78.0)	70.0 (58.0-78.0)
Sex (female/male)	264/242	268/231
Weight (kg), mean±SD	82.5±17.9	82.6±18.2
Systolic blood pressure (mm Hg), mean±SD	130.8±18.3	131.3±18.5
Diastolic blood pressure (mm Hg), mean±SD	78.6±12.6	79.2±12.1
Heart rate (beats per min), mean±SD	94.5±17.1	92.3±16.7
Respiratory rate (resp per min), mean±SD	21.8±5.8	21.6±5.7
Chronic obstructive pulmonary disease (%)	26 (5.1)	34 (6.8)
Chronic heart failure (%)	21 (4.2)	26 (5.2)
Previous VTE (%)	126 (24.9)	147 (29.5)
Known malignant tumor (%)	41 (8.1)	32 (6.4)
Surgery or trauma in previous 30 days (%)	31 (6.1)	27 (5.4)

PEITHO:Efficacy Endpoints

	Tenecteplase (n=506)		Placebo (n=499)		*P* value
	n	(%)	n	(%)	
All-cause mortality within 7 days	**6**	**(1.2)**	**9**	**(1.8)**	**0.43**
Hemodynamic collapse within 7 days	**8**	**(1.6)**	**25**	**(5.0)**	**0.002**
Need for CPR	1		5		
Hypotension / blood pressure drop	8		18		
Catecholamines	3		14		
Resulted in death	1		6		

N Engl J Med 2014;370:1402-11

Safety Concerns with Thrombolysis

	Tenecteplase (n=506)		Placebo (n=499)		*P* value
	n	(%)	n	(%)	
Non-intracranial major bleeding	**32**	**(6.3)**	**6**	**(1.5)**	**<0.001**
Severe	16		2		
Moderate	16		4		

	Tenecteplase (n=506)		Placebo (n=499)		*P* value
	n	(%)	n	(%)	
All strokes by day 7	**12**	**(2.4)**	**1**	**(0.2)**	**0.003**
Hemorrhagic	10		1		
Ischemic	2		0		
Serious adverse events (SAE)	**29**	**(5.7)**	**39**	**(7.8)**	**0.19**

N Engl J Med 2014;370:1402-11

Thrombolysis for Pulmonary Embolism and Risk of All-Cause Mortality, Major Bleeding, and Intracranial Hemorrhage
A Meta-analysis

Figure 2. Odds of Mortality in Patients With Pulmonary Embolism Treated With Thrombolytic Therapy vs Anticoagulation

Source	Thrombolytics		Anticoagulants		OR (95% CI)
	No. of Events	No. of Patients	No. of Events	No. of Patients	
UPETSG,[31] 1970	6	82	7	78	0.80 (0.26-2.49)
Tibbutt et al,[28] 1974	0	13	1	17	0.17 (0.00-8.94)
Ly et al,[25] 1978	1	14	2	11	0.37 (0.03-3.96)
Marini et al,[26] 1988	0	20	0	10	Not estimable
Levine et al,[22] 1990	1	33	0	25	5.80 (0.11-303.49)
PIOPED,[27] 1990	1	9	0	4	4.24 (0.06-296.20)
Dalla-Volta et al,[23] 1992	2	20	1	16	1.61 (0.15-16.82)
Goldhaber et al,[2] 1993	0	46	2	55	0.16 (0.01-2.57)
Jerges-Sanchez et al,[24] 1995	0	4	4	4	0.03 (0.00-0.40)
Konstantinides et al,[3] 2002	4	118	3	138	1.58 (0.35-7.09)
TIPES,[29] 2010	0	28	1	30	0.14 (0.00-7.31)
Fasullo et al,[11] 2011	0	37	6	35	0.11 (0.02-0.58)
MOPETT,[10] 2012	1	61	3	60	0.35 (0.05-2.57)
ULTIMA,[30] 2013	0	30	1	29	0.13 (0.00-6.59)
TOPCOAT,[9] 2014	1	40	1	43	1.08 (0.07-17.53)
PEITHO,[8] 2014	6	506	9	499	0.66 (0.24-1.82)
Total	23	1061	41	1054	0.53 (0.32-0.88)

Heterogeneity: $\chi^2_{14} = 16.51$; $P = .28$; $I^2 = 15\%$
Overall effect: $z = 2.45$; $P = .01$

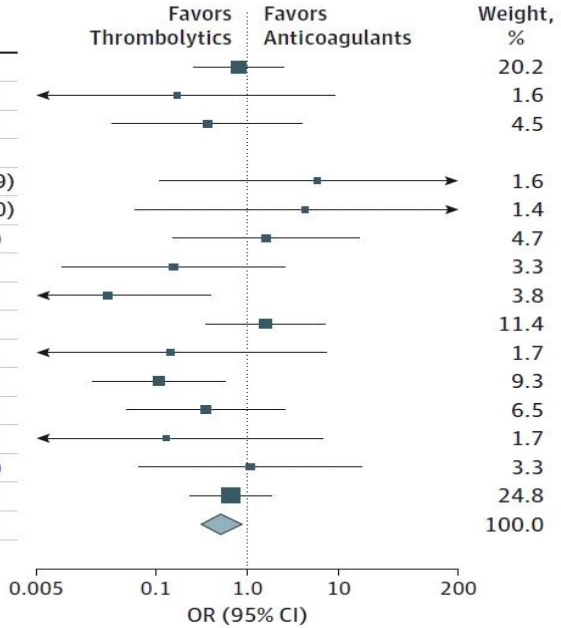


Table 2. Absolute Risk Metrics of Outcomes of Major Interest

Outcome of Interest (No. of Studies Reporting)	No. of Events/No. of Patients, Absolute Event Rate (%)		No. Needed to Treat or Harm	*P* Value
	Thrombolytic Group	Anticoagulant Group		
All-cause mortality (16)	23/1061 (2.17)	41/1054 (3.89)	NNT = 59	.01
Major bleeding (16)[a]	98/1061 (9.24)	36/1054 (3.42)	NNH = 18	<.001
ICH (15)	15/1024 (1.46)	2/1019 (0.19)	NNH = 78	.002
Recurrent PE (15)	12/1024 (1.17)	31/1019 (3.04)	NNT = 54	.003
Age >65 y				
All-cause mortality (5)	14/673 (2.08)	24/658 (3.65)	NNT = 64	.07
Intermediate-risk PE				
All-cause mortality (8)	12/866 (1.39)	26/889 (2.92)	NNT = 65	.03
Major bleeding (8)[a]	67/866 (7.74)	20/889 (2.25)	NNH = 18	<.001

Net clinical benefit 0.81% (0.65%-1.01%)
Net clinical benefit for intermediate risk-PE 0.62% (0.57%-0.67%)

Major Lessons

1) You are more likely to feel better sooner

2) The cost of this is a higher risk of bleeding and a small but real risk of ICH

3) We cannot promise you that this will make you live longer or prevent the development of long-term dyspnea or pulmonary hypertension from your PE

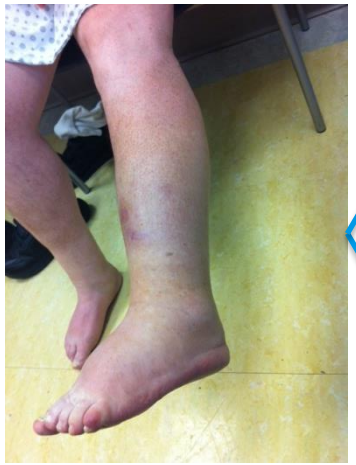
ATTRACT

Acute Venous Thrombosis: Thrombus Removal with Adjunctive Catheter-Directed Thrombolysis

- ✓ **Prospective, randomized, single blinded phase 3 clinical trial**
- ✓ **Multicenter**
- ✓ **Large sample size (692 patients!)**
- ✓ **Modern techniques (single session PCDT, short infusion times if necessary)**
- ✓ **Primary outcome – the post-thrombotic syndrome at 2 years (using standard assessments)**
- ✓ **Sponsored by the NIH**

ATTRACT study design

Vedantham, et al.
NEJM2017



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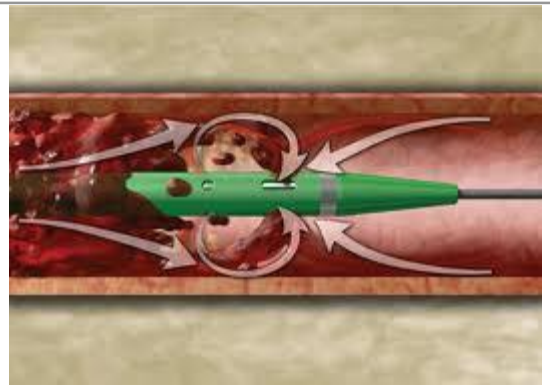
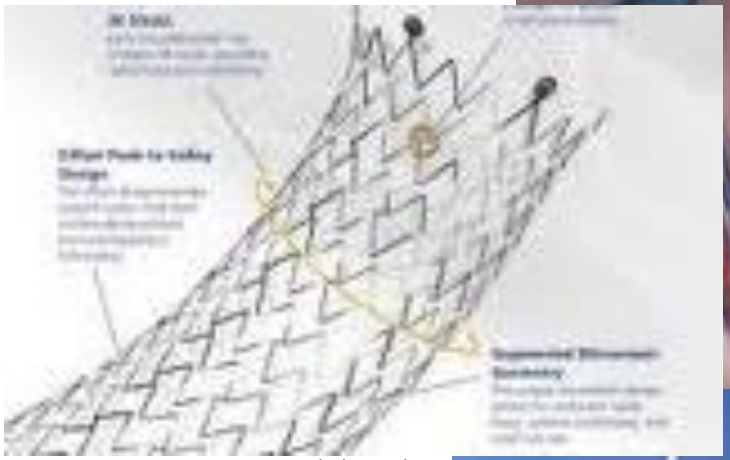
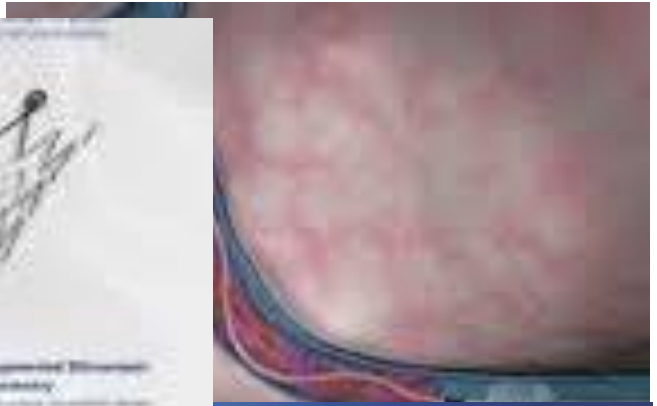
10d, 30d, 6mo, 1 yr, 18 mo, 24 mo follow ups

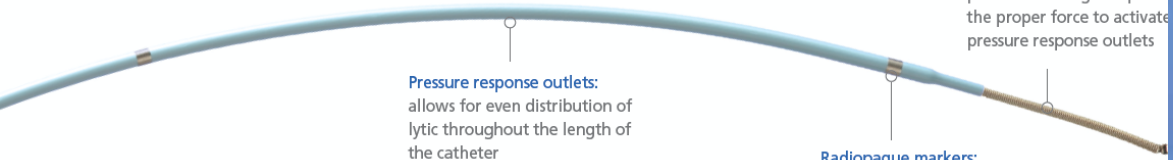
Courtesy: A Sista & S Vedantham

ATTRACT Treatment Tools









Overall Study Outcomes

Short-Term Effects of PCDT

Vedantham, et al.
NEJM 2017

Outcome	PCDT (n=336)	No-PCDT (n=355)	P Value
Major Bleeding (10 days)	1.7%	0.3%	0.049
Any Bleeding (10 days)	4.5%	1.7%	0.033
Leg Pain (10d)	-1.62	- 1.29	0.019
Leg Pain (30d)	-2.17	- 1.83	0.026
Leg Swelling (10d)	-0.26	+0.27	0.024
Leg Swelling (30d)	-0.74	-0.28	0.051

Long-Term Effects of PCDT

Vedantham, et al.
NEJM 2017

Outcome (24 months)	PCDT (n=336)	No-PCDT (n=355)	P Value
Any PTS	**46.7%**	**48.2%**	**0.56**
Recurrent VTE	12.5%	8.5%	0.087
Generic QOL (SF-36 PCS)	11.18	10.06	0.37
Venous QOL (VEINES)	27.67	23.47	0.08
Moderate or severe PTS	17.9%	23.7%	0.035
MS-PTS: IFDVT	18.4%	28.2%	
MS-PTS: FPDVT	17.1%	18.1%	

Who Should You Consider for CDT?

- **Door is almost closed on CDT for femoral vein DVT**

1) You will feel better faster

2) There is a small chance that this will have long term benefits in your overall leg swelling

3) There is a small chance of major bleeding or bleeding in the brain with the procedure

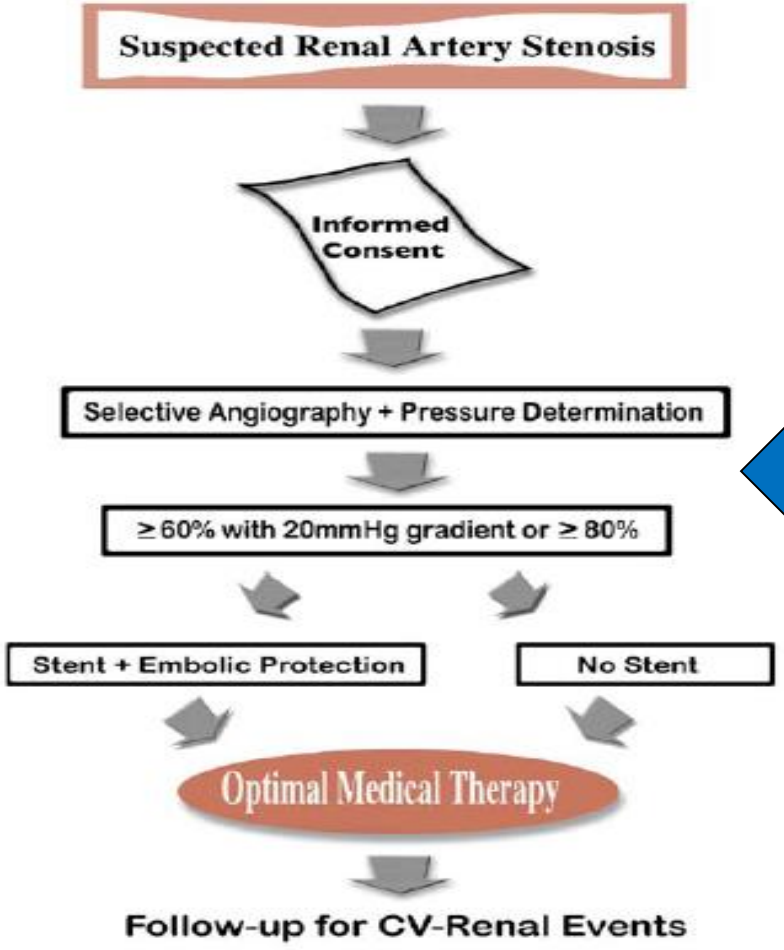
CORAL

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*



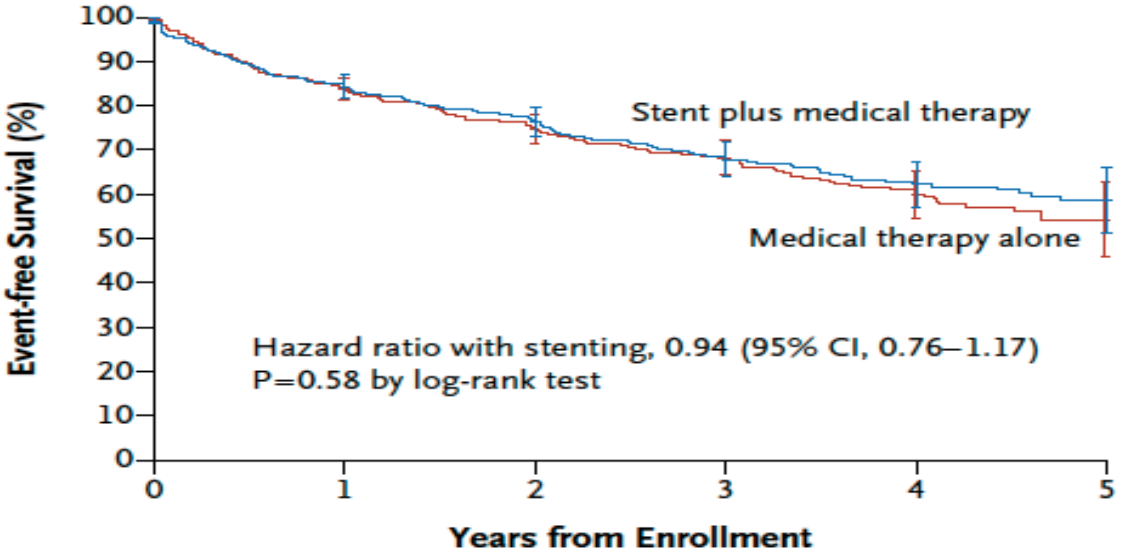
No pressures after first 25% of trial

Cooper et al, NEJM 2014

CORAL Trial

- **947 patients with atherosclerotic renal artery stenosis and systolic hypertension or chronic kidney disease**
  - Randomized to OMT & stenting vs. OMT alone

- **Endpoints**
  - Adverse cardiovascular and renal events
    - Death from CV/renal causes, MI, stroke, RRT, progressive renal failure



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

Figure 2. Kaplan–Meier Curves for the Primary Outcome.

Survival curves are truncated at 5 years owing to instability of the curves because few participants remained in the study after 5 years.

Coral Trial

- **Median follow up 43 months**
- **No significant difference in the primary end point (35.1% (stent) vs 35.8% (medical therapy))**
- **Systolic blood pressure declined in medical therapy (15.6 ± 25.8 mmHg) and stent group (16.6 ± 21.2 mmHg)**

STENOSIS CHARACTERISTICS	Randomized Stent Pts (N=459 Patients	
Minimal lumen diameter (mm)	1.80±0.74 (n=555)	Range 0.00-5.45
Reference lumen diameter (mm)	6.19±15.90	
% Stenosis	**67.41±11.33**	**Range 20.80-100.00**
# of stenosis > 80%	**16.3% (74/453)**	
Lesion length (mm)	9.48±4.10	Range 0.00-35.45
Lesion appearance		[95% CI]
Calcified	49.5% (275/556)	[45.2%, 53.7%]
Concentric	42.6% (237/556)	[38.5%, 46.9%]
Eccentric	57.7% (321/556)	[53.5%, 61.9%]
Smooth	58.8% (327/556)	[54.6%, 62.9%]
Ulcerated	38.7% (215/556)	[34.6%, 42.9%]
Pressure Gradients		
Peak Systolic (mmHg) n=133	48.83±28.68	Range 0.00-139.00
Mean Pressure (mmHg) n=122	23.86±16.66	Range 1.00-76.00
Diastolic (mmHg) n=115	11.18±12.38	Range 0.00-63.00

Take-Away Points

- **Maximize medical management for moderate renal artery stenosis**
- **Only consider stenting in patients truly failing medical management with refractory symptoms**
- **Verify that stenosis is severe and kidney is viable**
  - High US velocity or Invasive Pressure Gradient
  - Preserved kidney size and preserved renal function

SPYRAL – HTN OFF MED

RDN decreased ABP @ 3 months

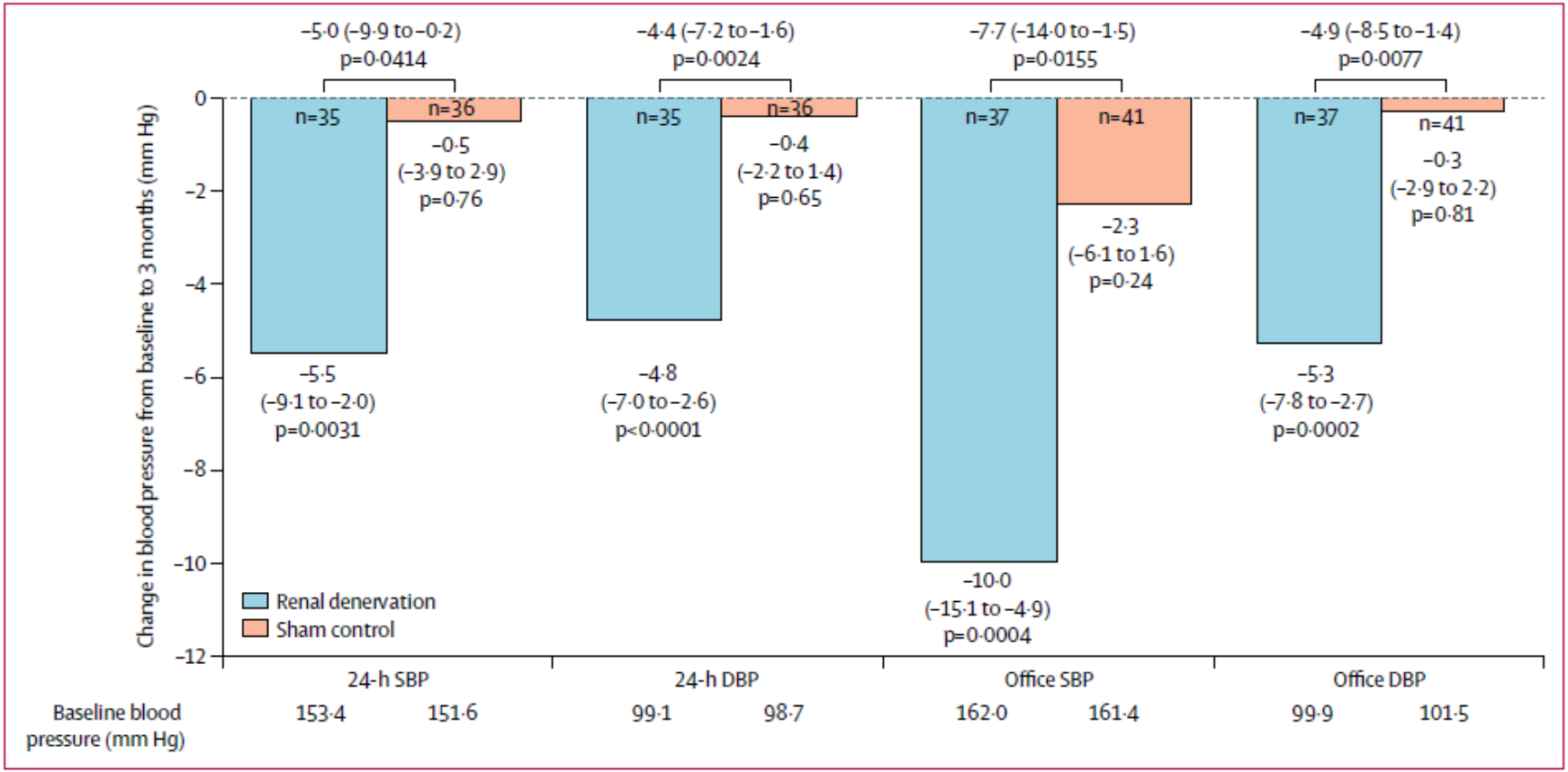
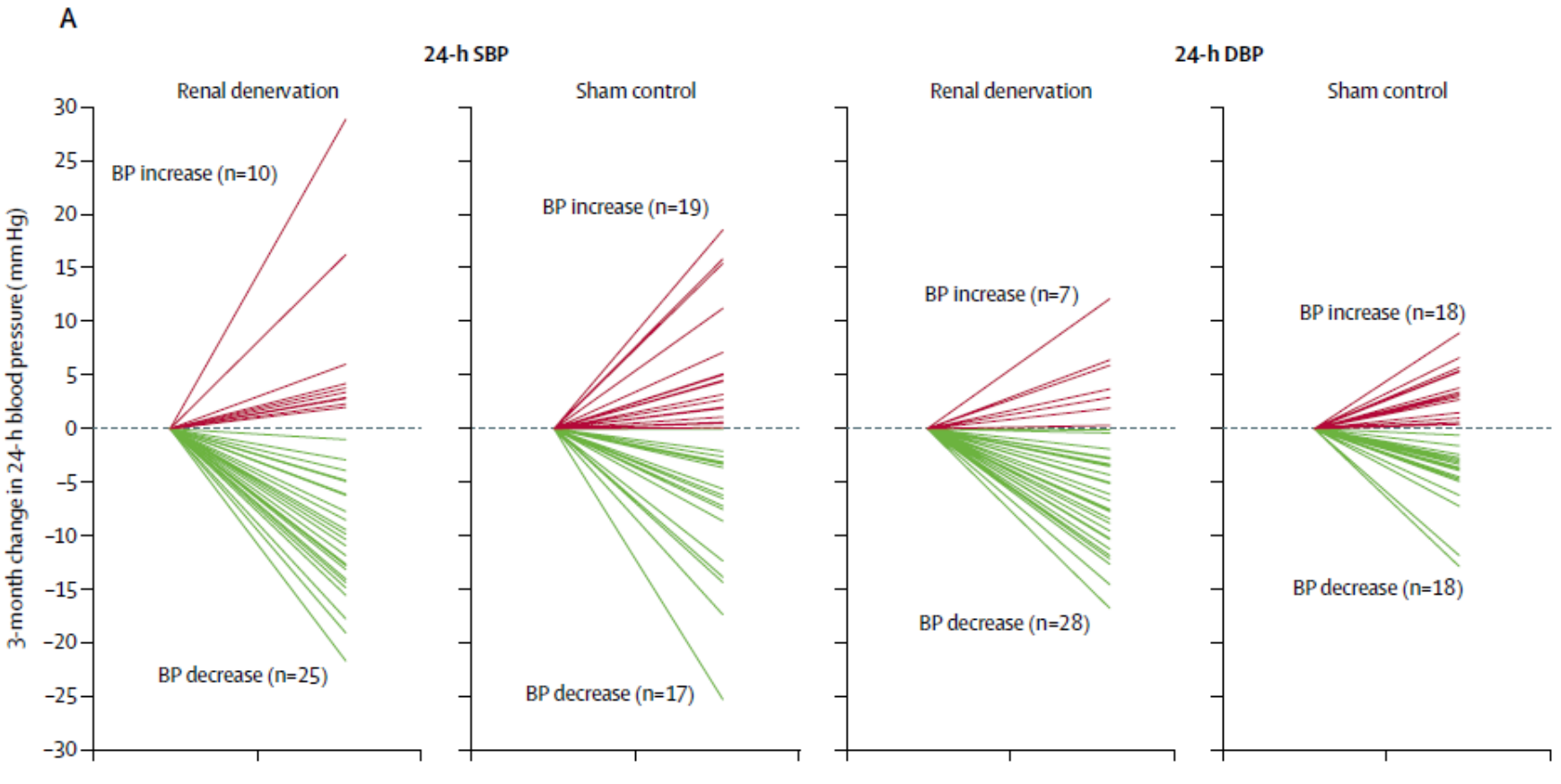


Figure 3: Changes at 3 months in office and ambulatory SBP and DBP for renal denervation and sham control groups

Townsend et al, Lancet, 2017

Individual Patient Data



Other Important Trials

- LEVANT 2 (DEB for SFA PAD)
- ZILVER – PTX (DES for SFA PAD, 5 year results complete)
- PREPIC 2 (IVC Filter for PE with LE DVT)
- EVAR 1 (EVAR vs. Open AAA repair, 15 year follow-up complete)
- Coming Up: BEST-CLI (Open vs Endo First for CLI)