Lessons from Clinical Trials 2009: Lessons and Future Perspectives

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Presenter Disclosure Information

Name: Dierk Scheinert MD

Within the last 12 months, the presenter or their spouse/partner have had a financial interest/arrangement or affiliation with the organizations listed below.

Company	*Relationship*
Abbott	*Advisory Board*
Boston Scientific	*Advisory Board*
Cordis	*Advisory Board*
Novostent	*Advisory Board*
Angioslide	*Advisory Board*
Gardia Medical	*Advisory Board*
Revascular Therapeutics	*Advisory Board*
Minnow Medical	*Consultant*
Lutonix	*Consultant*
Atheromed	*Consultant*
Angioscore	*Consultant*
Cook Medical	*Consultant*
Invatec	*Consultant*
Ev3	*Consultant*
Pathway Medical	*Consultant*
IDEV Techn.	*Stockholder*
CSI	*Stockholder*

Carotid Artery Revascularization

New Data from two RCT:

- ICSS
- CREST

The Discussion continues !

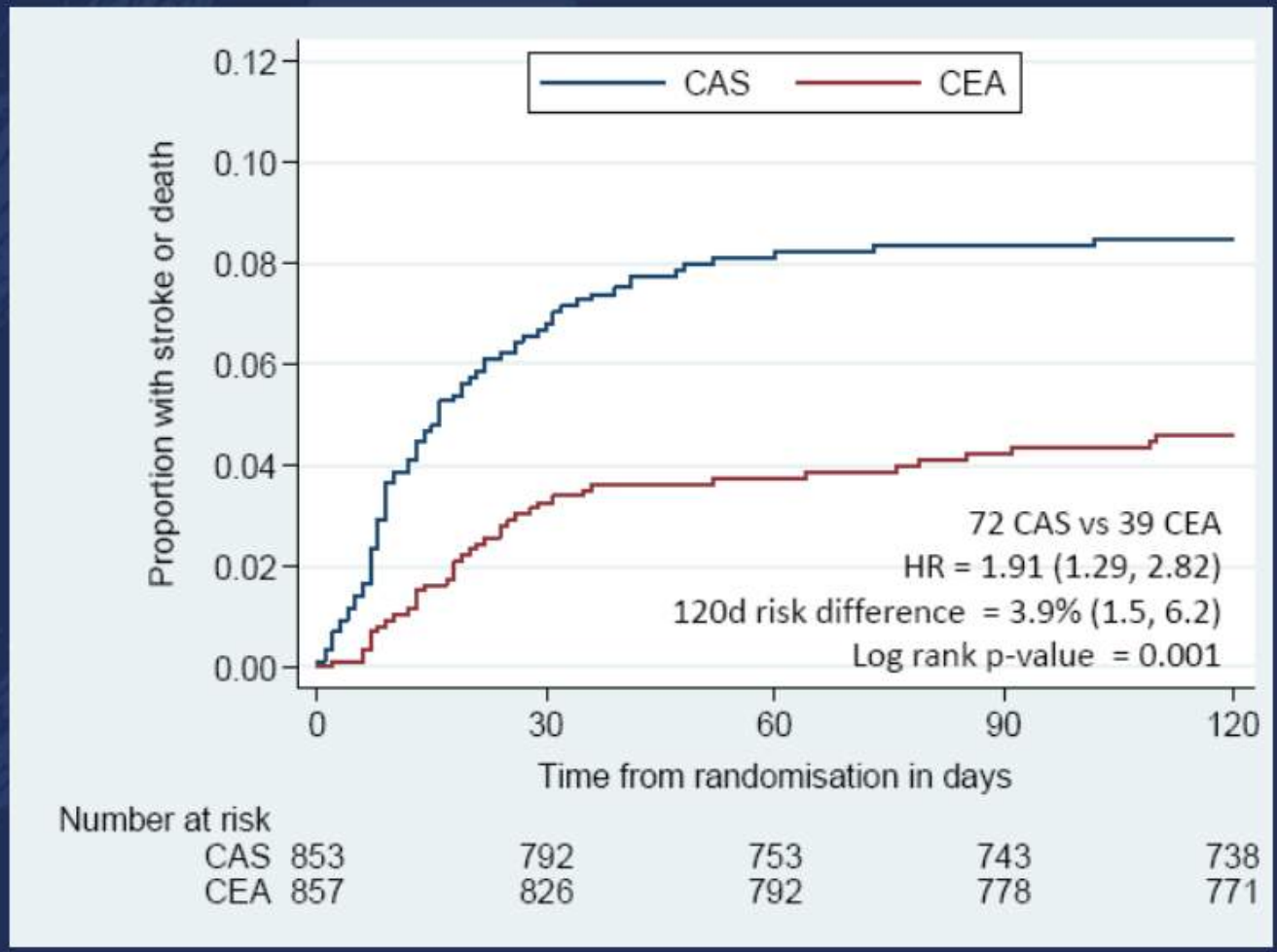
ICSS- STUDY

- 1713 patients randomized 1:1 CAS vs. CEA
- Major Inclusion Criteria:
  - sympt. Stenosis >50%

- Primary Endpoint:
  - Composite of Death, Stroke, MI @ 120 days

	CAS	CEA	p
Death+ Major Stroke	4.0%	3.2%	ns

ICSS: Death + Stroke + MI



Brown M, 2009

Minimal Endovascular Requirements in the CAS vs. CEA Randomized trials >300 Patients

CAVATAS[41]	Training in neuroradiology and angioplasty (but not necessarily in the carotid artery) required. Tutor-assisted procedures allowed.
SAPPHIRE[40]	Procedures submitted to an executive review committee; CAS periprocedural death or stroke rate had to be <6%. No tutor-assisted procedures allowed.
SPACE[42, 51]	At 25 successful CAS or assistance of a tutor for interventionalists having performed at least 10 CAS.
EVA-3S[43]	≥ 12 CAS cases or ≥ 5 CAS and ≥ 30 cases of endovascular treatment of supra-aortic trunks. Tutor-assisted CAS allowed for centers not fulfilling minimal requirements.
ICSS[44]	A minimum of 50 total stenting procedures, of which at least 10 should be in the carotid artery. Tutor-assisted procedures allowed for interventionalists with insufficient experience.

4/5 trials allowed for minimal expertise of 10 CAS and tutoring

Roffi M et al. EHJ 2009;30:2693-2704

CREST- STUDY

- Major Inclusion Criteria
  - asympt. Stenosis >60% angio, >70 duplex
  - sympt. Stenosis >50% angio, >70% duplex

- Primary Endpoint:
  - Composite of Death, Stroke, MI

	CAS	CEA	p
Periprocedural	5.2%	4.5%	0.38
Up to 4 years	7.2%	6.8%	0.51

CREST- STUDY

Periprocedural Complications:

	CAS	CEA	p
Stroke	4.1%	2.3%	0.01
MI	1.1%	2.3%	0.03

Final publication expected April/ May 2010

Renal Arteries + Hypertension

- Astral Study
- New Concept: Renal Denervation

UK MULTI-CENTRE TRIAL IN ATHEROSCLEROTIC RENOVASCULAR DISEASE

ASTRAL

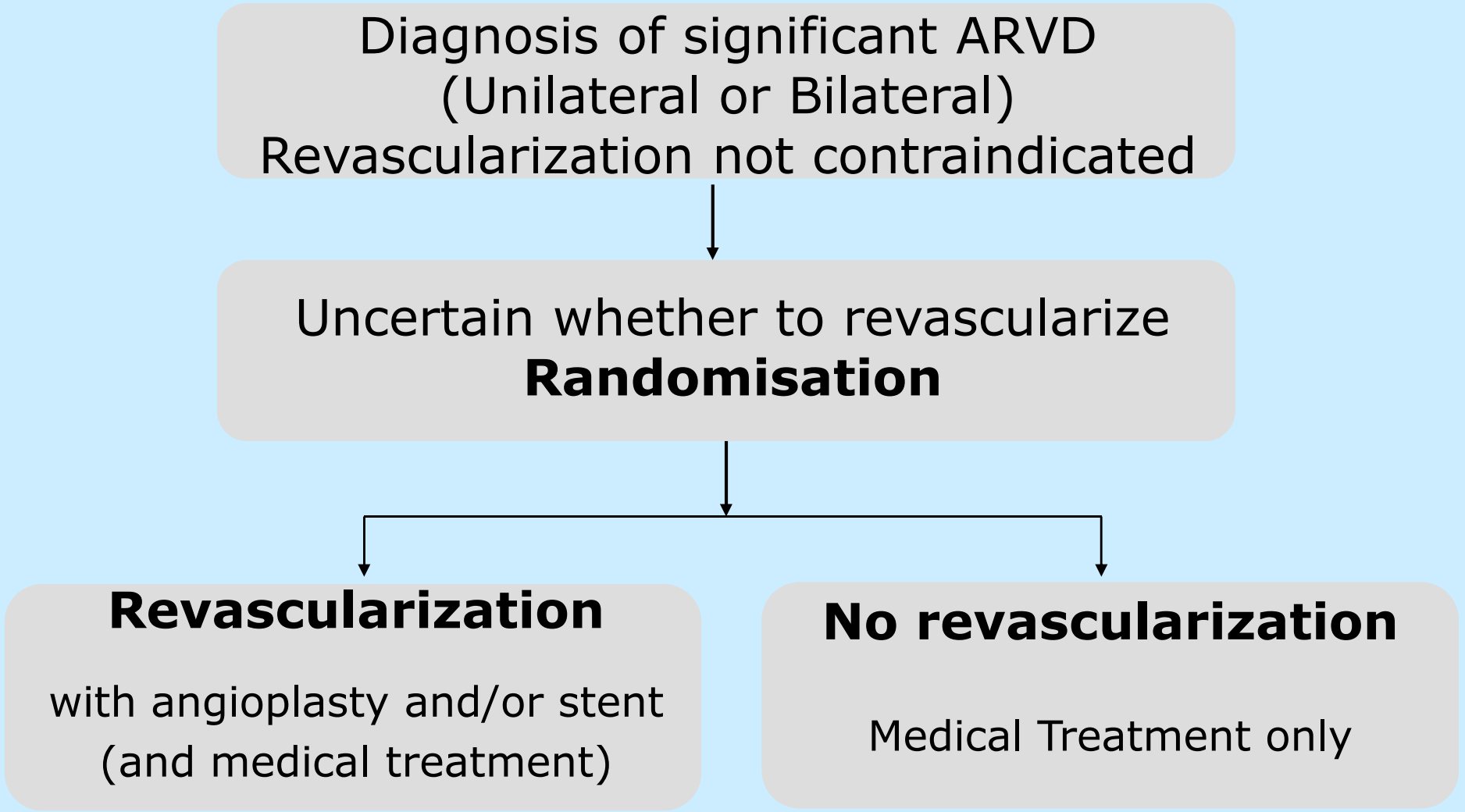
Angioplasty and STent for Renal Artery Lesions

Philip A Kalra

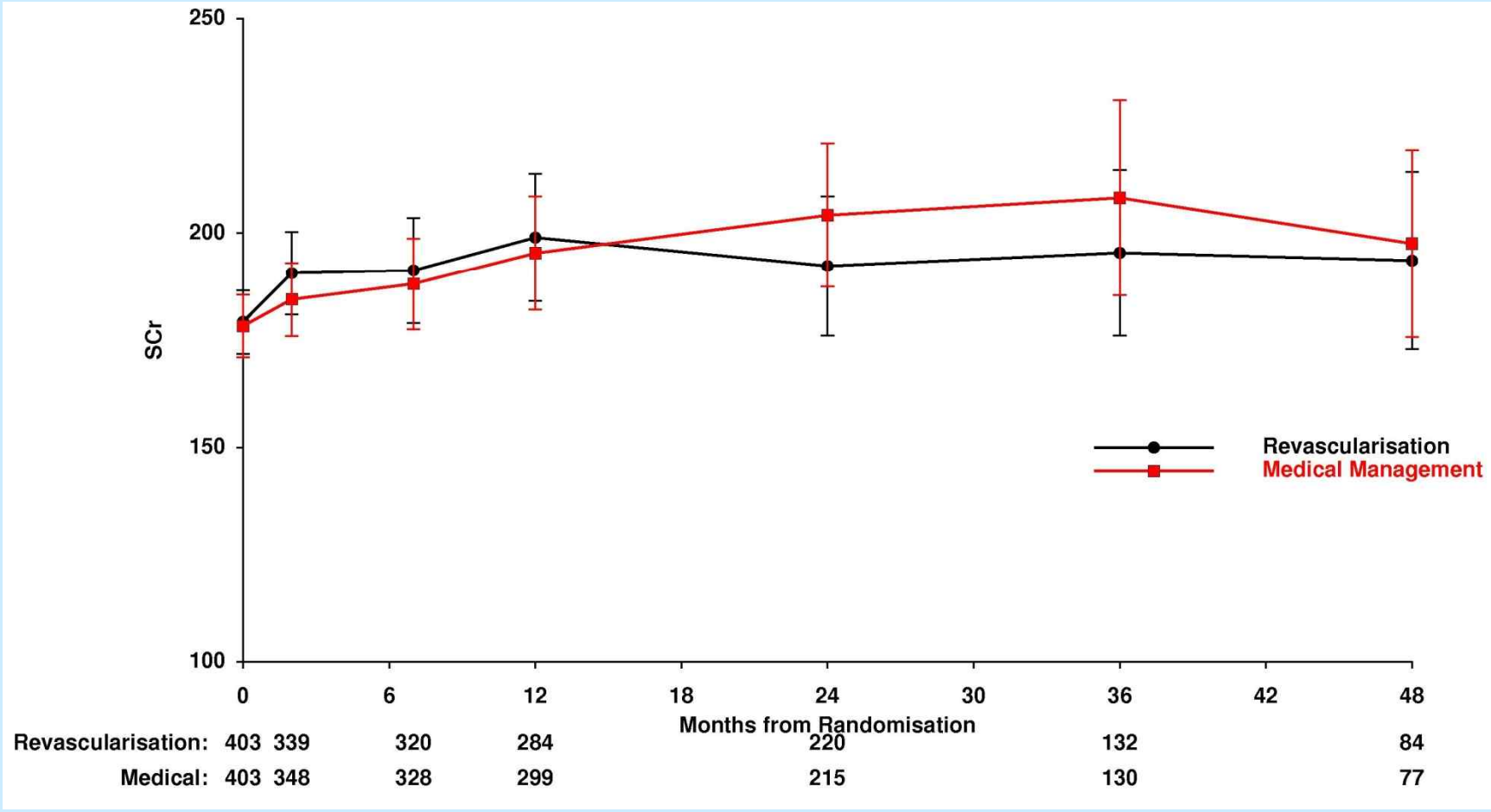
Lead Nephrologist for ASTRAL, Hope Hospital, Salford, UK,

On behalf of the ASTRAL TMC and collaborators

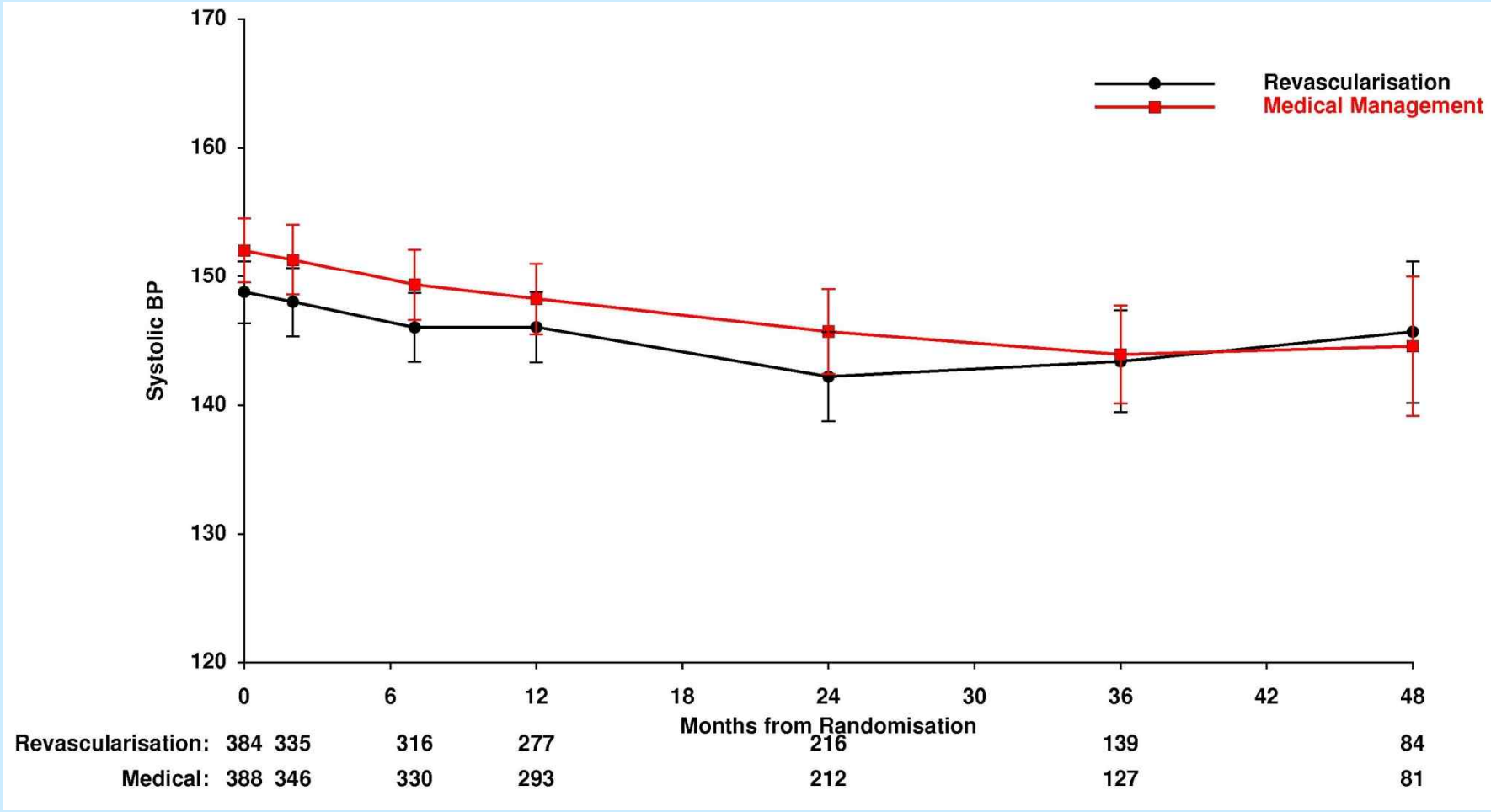
ASTRAL Trial Schema



PLOT OF SCr OVER TIME



PLOT OF SYSTOLIC BP OVER TIME



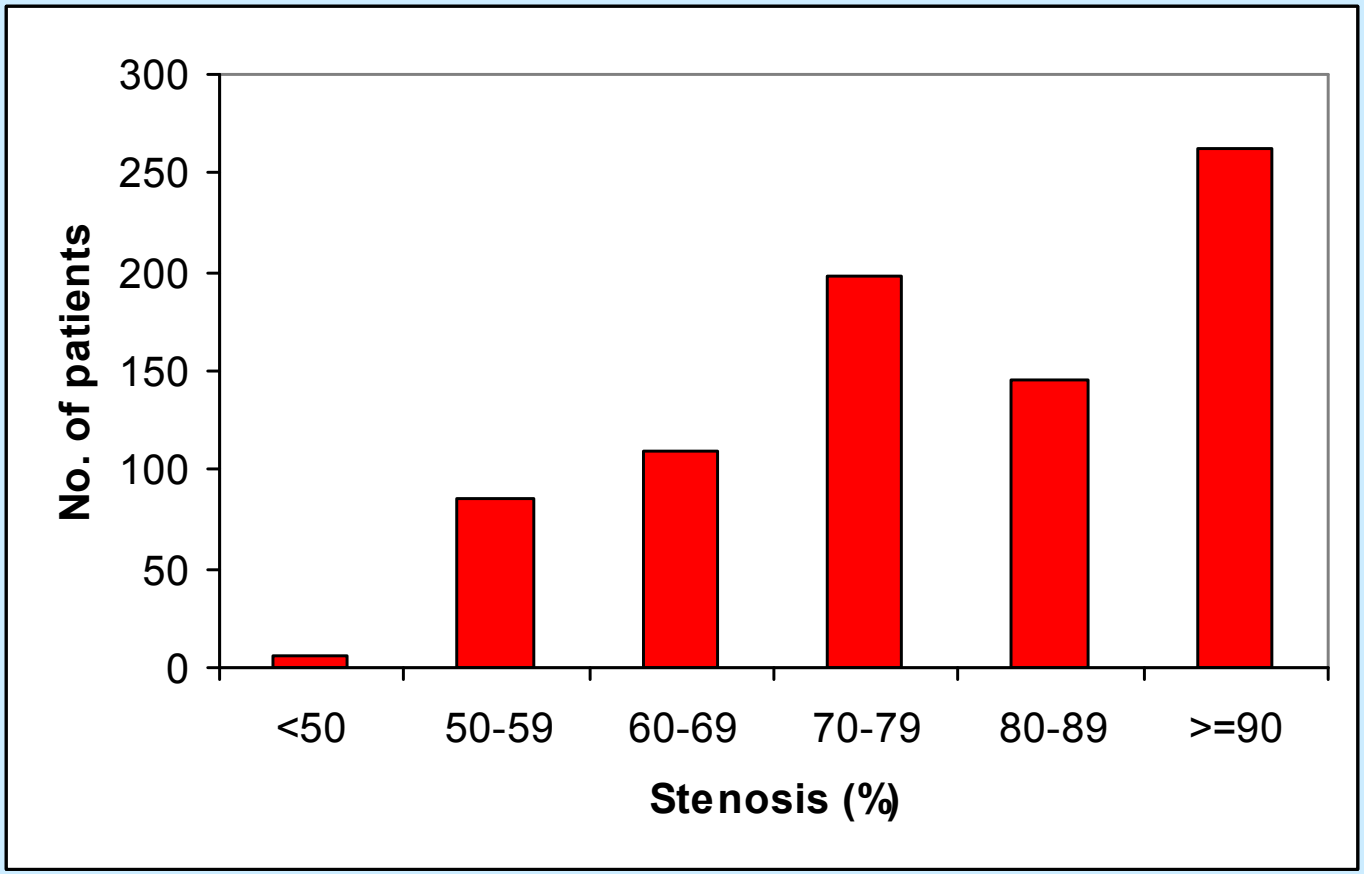
COMPLIANCE WITH RANDOMISED TREATMENT

	N		Revasc. Successful	Attempted but Failed	Not Attempted
Revasc.	403		308 (82%)*	17	44
Medical	403		18 (4.4%)	1	1

*Revascularization forms not yet returned for 34 patients who were randomised to revascularization

PATIENT CHARACTERISTICS – Percent Stenosis

Mean = 76% (Range: 20% – 100%)



ASTRAL Summary (1)

I. Currently no evidence of a benefit for revascularization on renal function in the ARVD patients entered into ASTRAL – **those in whom clinicians 'uncertain' of whether to revascularize**

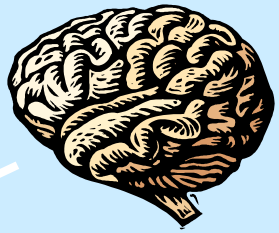
II. …

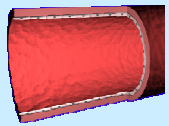
… but maybe there is an advantage for patients with high-grade lesions ??

The Discussion continues !

Renal Sympathetic Afferent Nerve Activity

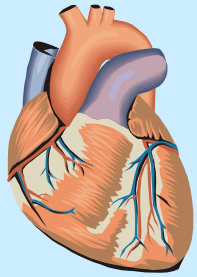
Kidney as the Origin of Central Sympathetic Drive





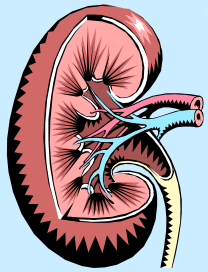
Vasoconstriction
Atherosclerosis

Insulin Resistance



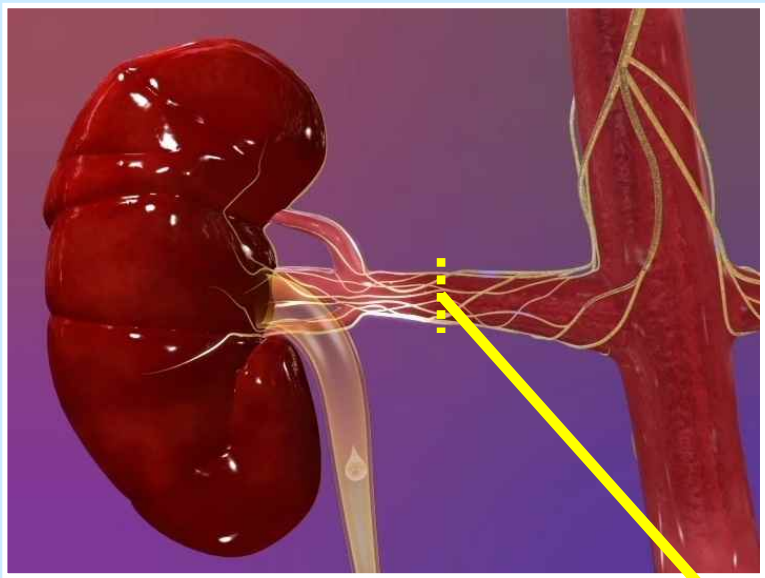
Hypertrophy
Arrhythmia
O_2 Consumption
Heart Failure

Renal Afferent Nerves

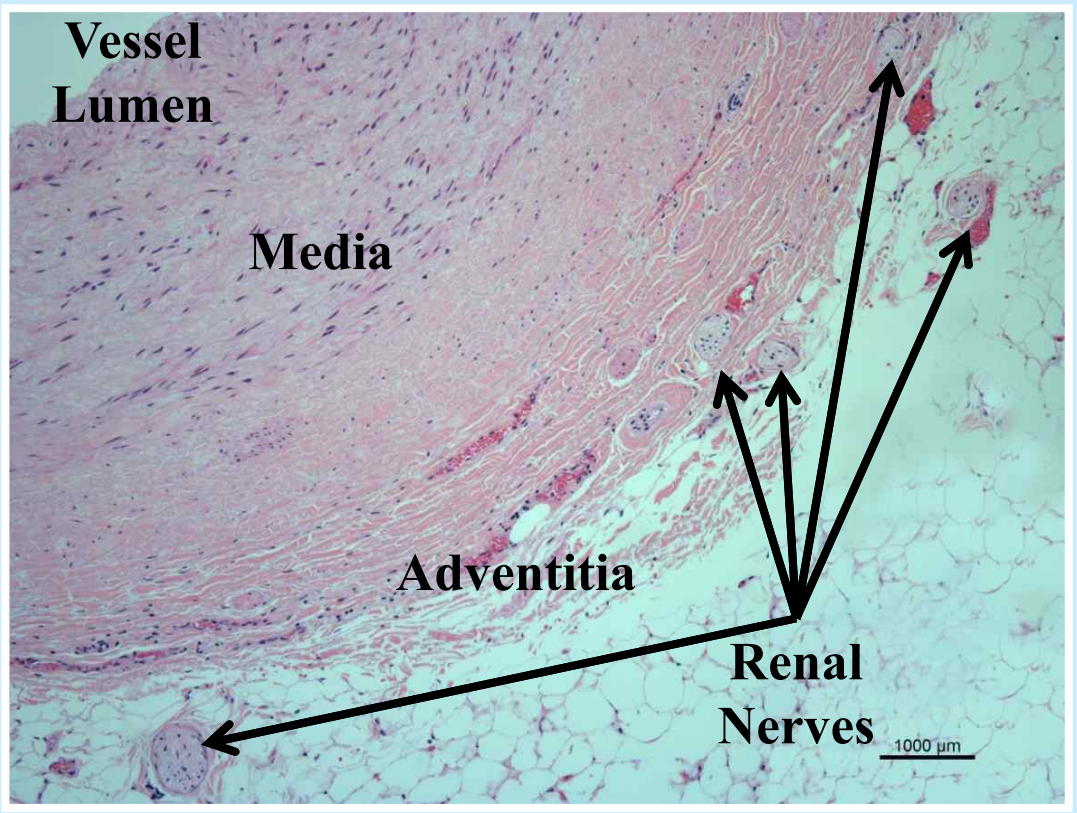


↑ Renin release → ↑ RAAS activation
↑ Sodium retention
↓ Renal Blood Flow

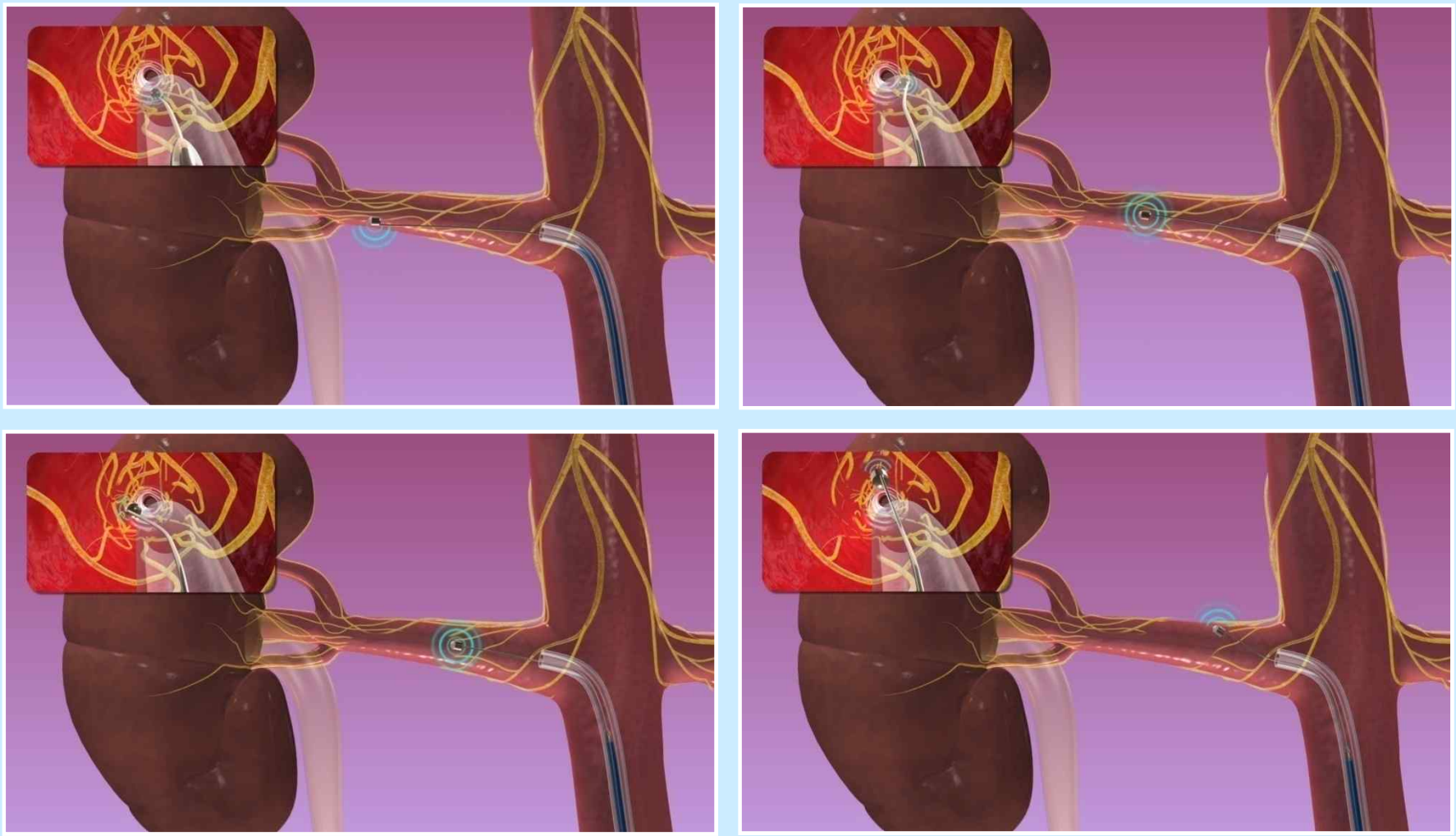
Anatomy of Renal Sympathetic Nerves



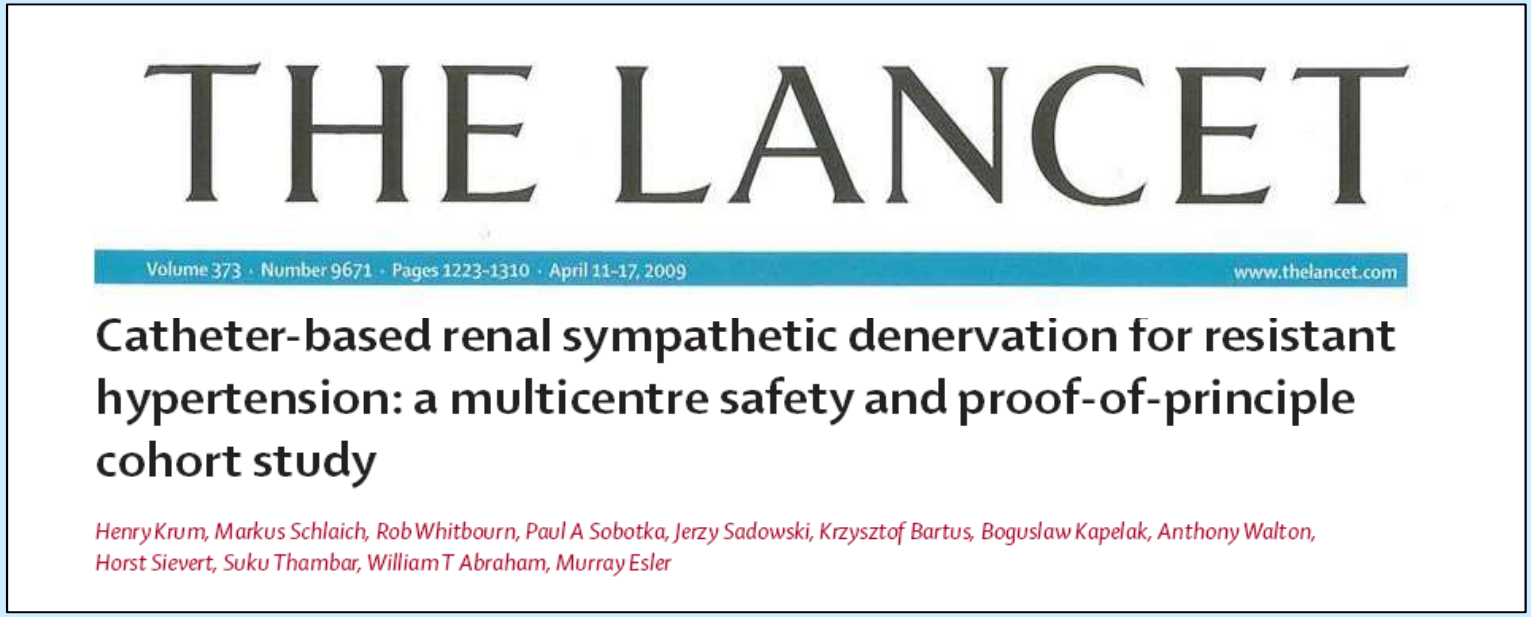
- **Arise from T10-L2**
- **Follow the renal artery to the kidney**
- **Primarily lie within the adventitia**



Renal Denervation by RF-Ablation



In the United States: Caution: Investigational Device. Limited by U.S. law to investigational use.



THE LANCET

Volume 373 · Number 9671 · Pages 1223-1310 · April 11-17, 2009 www.thelancet.com

Catheter-based renal sympathetic denervation for resistant hypertension: a multicentre safety and proof-of-principle cohort study

Henry Krum, Markus Schlaich, Rob Whitbourn, Paul A Sobotka, Jerzy Sadowski, Krzysztof Bartus, Boguslaw Kapelak, Anthony Walton, Horst Sievert, Suku Thambar, William T Abraham, Murray Esler

Study Aims:

To perform a first-in-man 12-month evaluation of the safety and blood pressure-lowering efficacy of percutaneous renal sympathetic denervation in patients with refractory hypertension

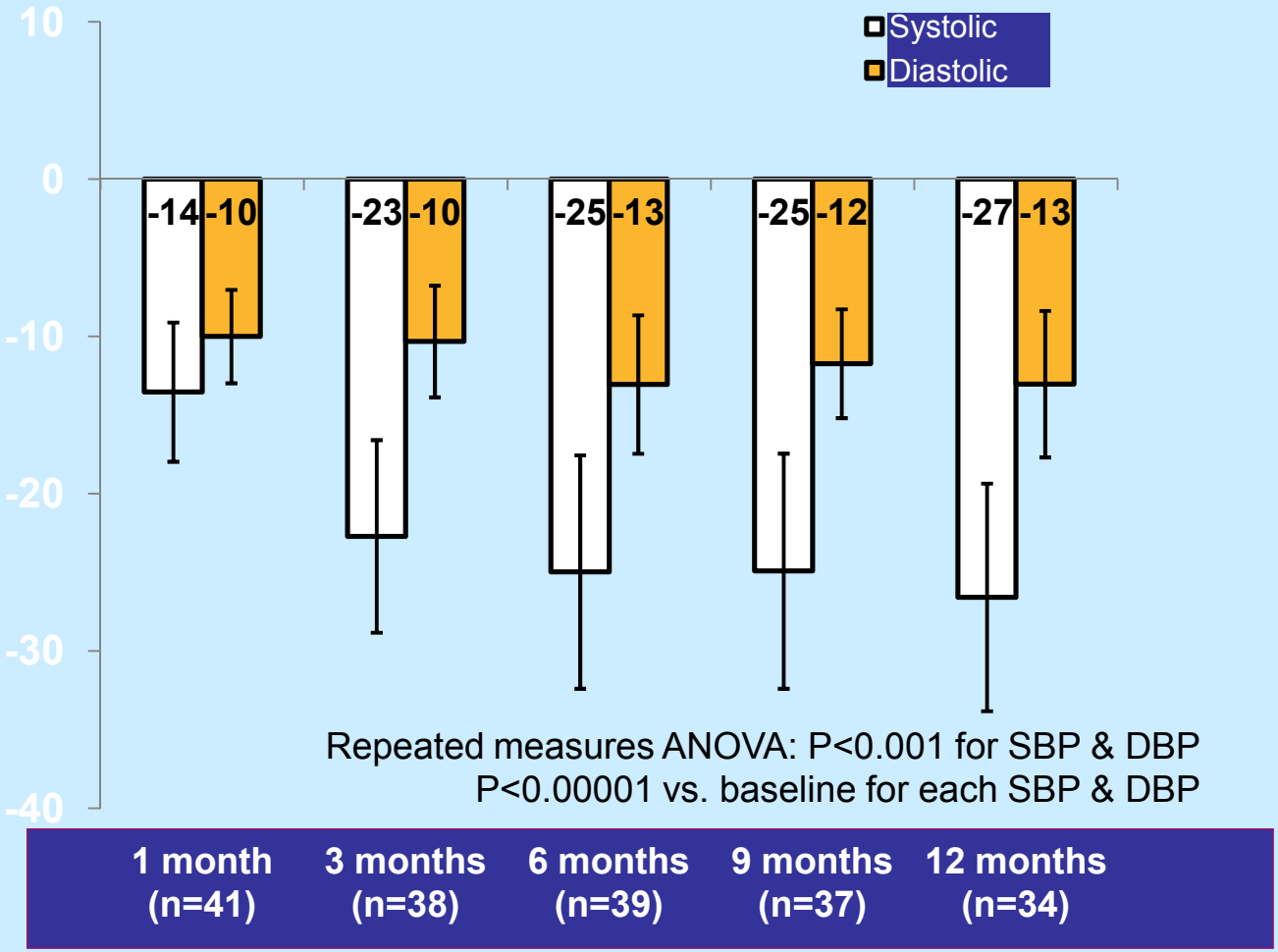
Study Sites:

Melbourne & Newcastle, Australia; Krakow, Poland; & Frankfurt, Germany

Krum et al. *Lancet*. 2009;373(9671):1275-1281

Blood Pressure Response

Originally Reported Cohort (N=45)



91% Responder Rate

Krum et al. TCT 2009

Peripheral Arteries

- VIBRANT-Trial:
  Nitinol Stent vs. Covered Stent for long lesions

- Drug-eluting Stents:
  ZILVER PTX Registry and RCT

- New Concepts:
  SUPERA Registry
  Drug-Eluting Balloons (THUNDER and FEMPAC)

Study Design

- 148 randomized patients enrolled
- TEST GROUP: GORE VIABAHN® Endoprosthesis
  - FDA approved for SFA indication, June 14, 2005
  - Does not include Bioactive Heparin Surface or contoured edge device
  - n = 72
- CONTROL GROUP: Bare Nitinol Stent
  - Commercially available bare nitinol stent as determined by institutional standard of care when treating SFA occlusive disease and were not devices approved for SFA use
  - n = 76

GORE VIBRANT CLINICAL STUDY

Lesion Characteristics: Diffuse and complex

LESION CHARACTERISTICS			
	GORE VIABAHN® Endoprosthesis	Bare Nitinol Stent	p-value
TREATED OCCLUSIONS	59.7%	56.6%	0.74
TARGET LESION LENGTH (cm)			0.87
Mean (Std Dev)	19 (8)	18 (7)	
Median (Range)	20 (8 – 40)	16 (8 – 36)	
LESION CALCIFICATION			0.01
None – Mild	37.5%	57.9%	
Moderate – Severe	62.5%	42.1%	
TIBIAL RUNOFF			0.10
1 Vessel	15.3%	22.4%	
2 Vessel	50.0%	32.9%	
3 Vessel	34.7%	44.7%	

GORE VIBRANT CLINICAL STUDY

One-Year Interim Data

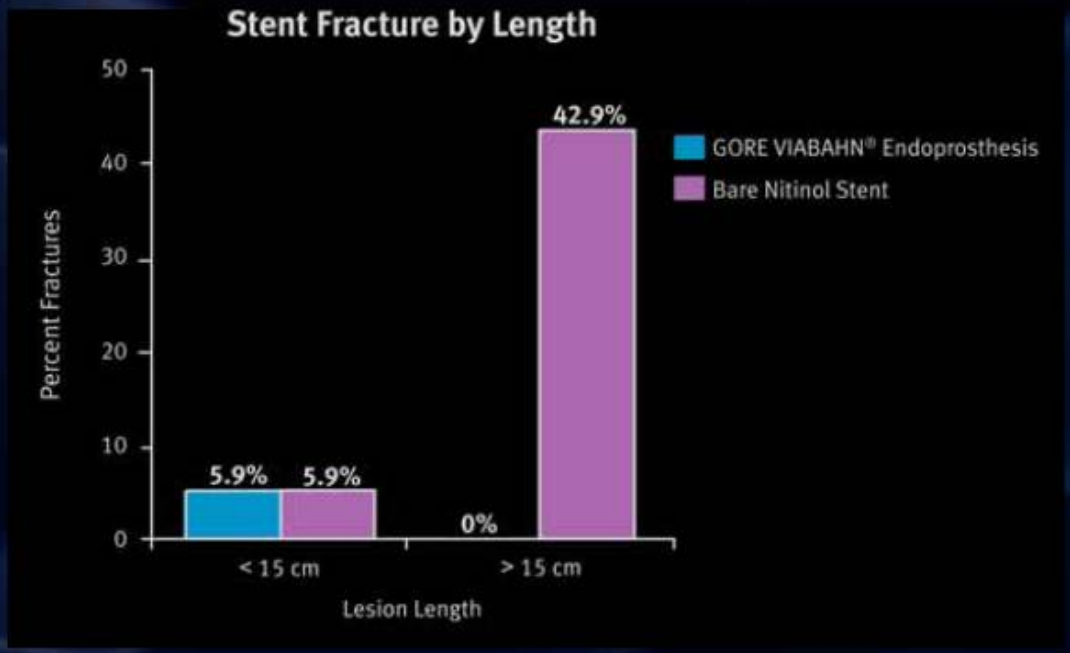
INTERIM ONE-YEAR EFFICACY OUTCOMES			
	GORE VIABAHN® Endoprosthesis	Bare Nitinol Stent	p-value
Technical Success	97%	97%	1.00
Primary Patency (PSVR 2.5)	53%	58%	0.58
Freedom from TLR	73%	69%	0.69
Assisted Primary Patency	84%	91%	0.41
Secondary Patency	93%	98%	0.19

VIBRANT
CLINICAL STUDY

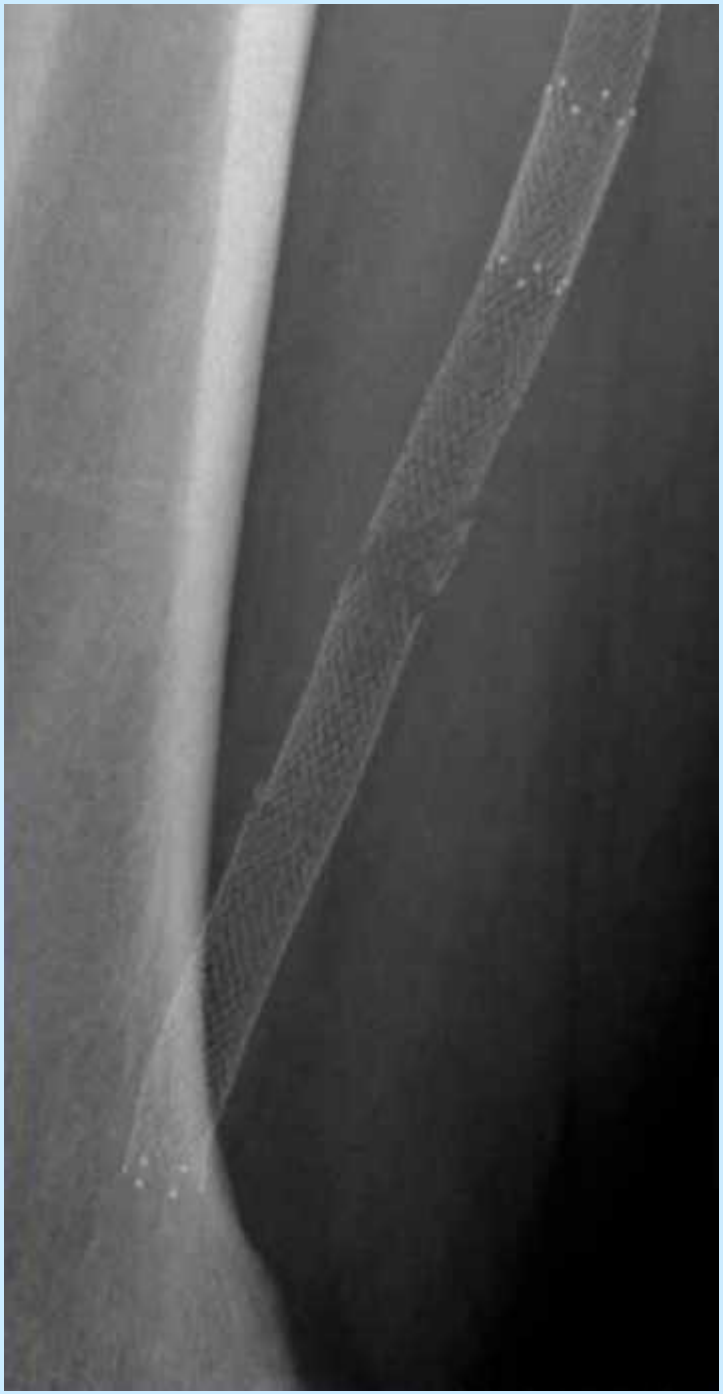
Stent Fracture

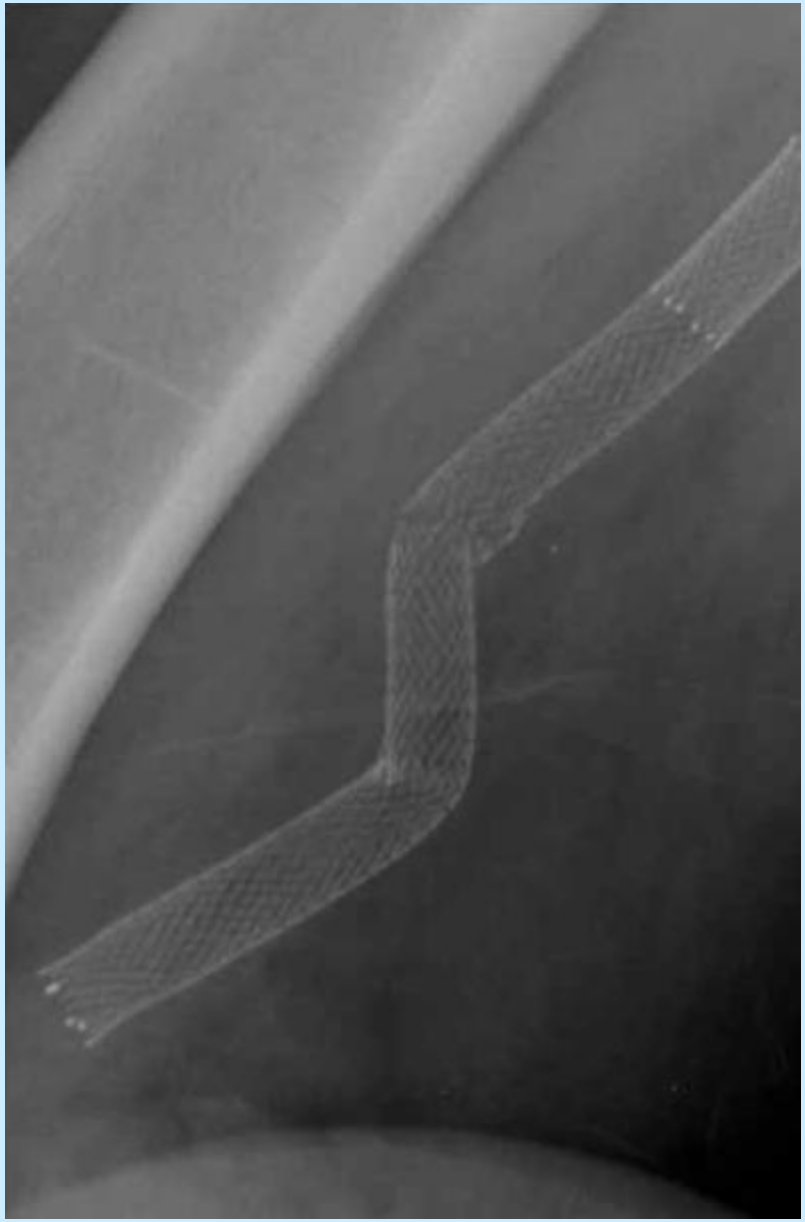
	GORE VIABAHN® Endoprosthesis	Bare Nitinol Stent	p-value
STENT FRACTURE	1/47 (2%)	16/52 (30.8%)	< 0.01
FRACTURE SEVERITY*			
Grade 1	1	7	
Grade 2	0	7	
Grade 3	0	3	
Grade 4	0	2	

* Not mutually exclusive



VIBRANT
CLINICAL STUDY





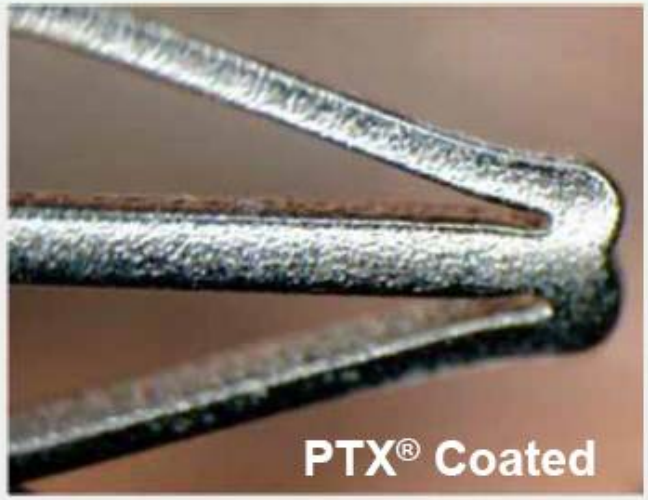
The Zilver-PTX Clinical Trial Program

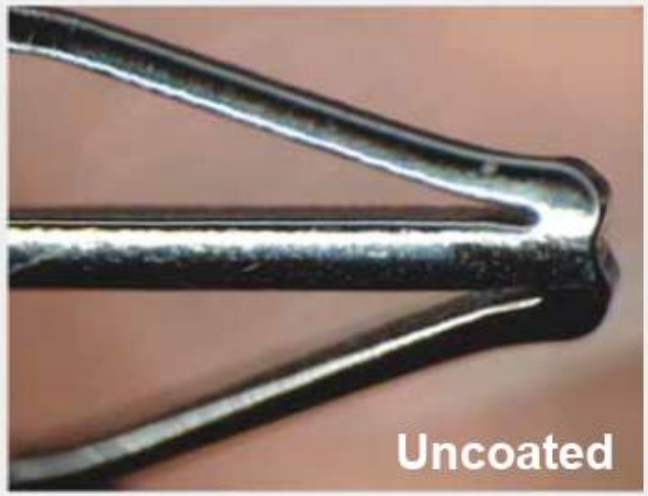
LINC 2010
Wednesday, January 27, 2010

Michael Dake, M.D.
Professor of Cardiothoracic Surgery
Stanford University School of Medicine
Falk Cardiovascular Research Center
Stanford University Medical Center

Zilver® PTX® Drug-Eluting Stent

- CE Marked
- Paclitaxel only
  - No polymer or binder
  - 3 μg/mm^2 dose density
- Zilver® Flex™ Platform





Baseline Angiographic Data

Overall Lesions (n)	818
Lesion Length (cm)	9.9 ± 8.2
Proximal RVD (mm)	5.4 ± 0.9
Distal RVD (mm)	5.2 ± 0.8
MLD in Lesion (mm)	0.8 ± 0.9
% Diameter Stenosis	85 ± 17

Patients	718
Lesions	818
TASC Class*: A	26%
B	29%
C	26%
D	14%
Lesion > 7 cm	47%
Lesion > 15 cm	22%
Total Occlusion	38%
Restenosis (all)	24%
In-stent Restenosis (ISR)	15%

Effectiveness: Freedom from TLR

Freedom from TLR	12 Months (n = 818)	24 Months (n = 427)
	89% (725/818)	82% (351/427)

Target Lesion Revascularization (TLR) defined as:

- Clinically driven re-intervention for ≥ 50% DS within treated segment (including +/- 5 mm)
- Surgical bypass of target vessel

Freedom from TLR

Subgroup	12 Months	24 Months
Overall	89% (n = 818)	82% (n = 427)
De novo (all)	91%	88%
≤ 7 cm Lesions	94%	91%
> 7 cm to 15 cm Lesions	92%	86%
> 15 cm Lesions	84%	80%
TASC C and D*	87%	78%
Occlusions	86%	77%
Restenosis (all)	81%	70%
Restenosis (not ISR)	87%	73%
In-stent Restenosis (ISR)	78%	69%

Freedom from TLR ≠ Patency

*TASC 2000

THUNDER Trial

Design	Prospective, Randomized, 'Blinded,' Multi-Center Drug Coated Balloon vs. Standard Uncoated Balloon
Endpoints	1^0: Late Lumen Loss at 6 months 2^0: Binary restenosis, TLR, etc.
Major Inclusion	SFA/APOP: Occlusion or Stenosis ≥ 70%, ≥ 2cm_ length Rutherford 1-5
Major Exclusion	Distal run-off < 1 artery, PTA directly at promixal SFA origin, known allergy to contrast media/antithrombotics
# Patients	102 Patients : 54 POBA, 48 DCB
Follow-Up	24 Months
Lead Investigator	Gunnar Tepe

Tepe et al., NEJM 2008; 358:689-99

THUNDER: Baseline Characteristics

Characteristic	POBA (n=54)	DCB (n=48)
Age	68	69
Rutherford Stage	3.1	3.4
Lesion Length (mm)	7.4	7.5
SFA ONLY – no popliteal involvement (%)	65	69
Stenosis (%)	91	89
Occlusion (%)	26	27
Treated Lesions (#)	1.6	1.8
De Novo Lesion (%)	70	62

Tepe et al., NEJM 2008; 358:689-99

THUNDER: Outcomes

6 Month Angio	POBA (n=48)	DCB (n=41)	P
Late Lumen Loss , mm	1.7 ± 1.8	0.4 ± 1.2	< 0.001
RVD, mm	4.9 ± 0.6	5.1 ± 0.6	0.05
MLD, mm	2.8 ± 1.9	4.1 ± 1.4	0.001
Binary Restenosis (%)	44	17	0.01

TLR	POBA (n=54)	DCB (n=48)	P
6 Month (%)	37	4	<0.001
12 Month (%)	48	10	<0.001
24 Month (%)	52	15	<0.001

Tepe et al., NEJM 2008; 358:689-99

FemPac Trial

Design	Prospective, Randomized, Multi-Center, 'Blinded Reading' Drug Coated Balloon vs. Conventional Uncoated Balloon
Endpoints	1^0: Late Lumen Loss at 6 months 2^0: Binary restenosis, TLR, etc.
Major Inclusion	SFA/APOP: Occlusion or Stenosis ≥ 70%, Rutherford 1-5
Major Exclusion	Distal run-off < 1 artery, acute symptoms indicating thrombolysis or surgery, allergy to contrast or study meds
# Patients	87 Patients : 42 POBA, 45 DCB
Follow-Up	18-24 Months
Lead Investigator	Michael Werk

Werk et al., CIRC 2008; 118:1358-1365

FemPac: Baseline Characteristics

Characteristic	POBA (n=42)	DCB (n=45)
Age	70.2	67.3
Rutherford Stage	2.9	2.7
Lesion Length (mm)	4.7	4.0
SFA ONLY – no popliteal involvement (%)	81	87
Stenosis (%)	85	85
Occlusion (%)	19	13
De Novo Lesion (%)	67	64

Werk et al., CIRC 2008; 118:1358-1365

FemPac: Outcomes

6 Month Angio	POBA (n=48)	DCB (n=41)	P
Late Lumen Loss , mm	0.8	0.3	0.031
RVD, mm	5.1	5.2	0.62
MLD, mm	2.7	3.6	0.037
Binary Restenosis (%)	47	19	0.035

TLR	POBA (n=54)	DCB (n=48)	P
6 Months (%)	33	7	0.002
18-24 Months (%)	50	13	0.001

Werk et al., CIRC 2008; 118:1358-1365

But: Some DCBs work, others do NOT

Success:

TLR at 2 years					
Indication	Study	Formulation	DCB	POBA	TAXUS
Coronary ISR	Paccocath ISR I & II[1,2]	Paclitaxel + Iopromide	4%	37%	
	PEPCAD II[3*]		6%		15%
SFA	THUNDER[4]		15%	52%	
	FemPac[5]		13%	50%	

[1]Scheller 2006 *NEJM* 355(20):2113-24. [2]Scheller 2008 *Clin Res Cardiol 97(10):773-81*. [3]Unverdorben 2009 *CIRC 119(23):2986-94*; *TLR at 1 years for PEPCAD II; follow-up ongoing but only 12 month data reported. [4]Tepe 2008 *NEJM* 358(7):689-99. [5]Werk 2008 *CIRC* 118:1358-65.

Failure:

TLR at 9 months					
Indication	Study	Study Flaw	DCB	TAXUS	CYPHER
Small Vessel CAD	Piccoleto[6*]	Paclitaxel Alone	32%	10%	
DeNovo CAD	PEPCAD III[7]	DCB w/Pre-crimped stent vs DES	11%		5%

[6]Cortese 2009 PCR Presentation: Paclitaxel-eluting balloon versus paclitaxel-eluting stent in small coronary vessel disease; *TLR at 6 months for Piccoleto. [7]Hamm 2009 AHA resentation: Paclitaxel-eluting PTCA-Balloon in Combination with the Coroflex Blue Stent vs the Sirolimus Coated Cypher Stent in the Treatment of Advanced Coronary Artery Disease

Essential Components of DEB

Active Agent

- Paclitaxel

Additive

- Controls coating integrity and drug loss during transit
- Facilitates tissue uptake: increases exposure, accelerates drug release & transfer to vessel wall
- Necessary to achieve therapeutic drug levels

Active PVD Studies

(as registered with clinicaltrials.gov)

I. SFA Indication

- Advance® 18PTX (Cook)
- LEVANT I (Lutonix)

II. BTK Indication

- INPACT-DEEP (Invatec)
- PICCOLO