Beyond DES: Peripheral Vascular Disease, TAVR, and Hypertension

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NewYork-Presbyterian
The University Hospital of Columbia and Cornell

Presenter Disclosure Information for TCTAP 2011; April 27-29, 2011

Martin B. Leon, M.D.

NON-PAID Consultant:
Abbott, Boston Scientific,
Edwards Lifesciences, Medtronic

Consultant:
Neovasc, Symetis,

Equity Relationship:
Coherex, GDS, Medinol, Mitralign, Sadra

Interventional Opportunities

FUTURE!

Structural Heart Disease

Hypertension

Novel (new) Anti-restenosis Therapy

Out-of-the-box Concepts

Interventional Opportunities

FUTURE!

Structural Heart Disease

STRUCTURAL Heart Disease

What is it?

STRUCTURAL heart disease… "wastebasket" term referring to…

All catheter-based interventional therapies which are not associated with vascular pathology requiring "endoluminal" endovascular treatment.

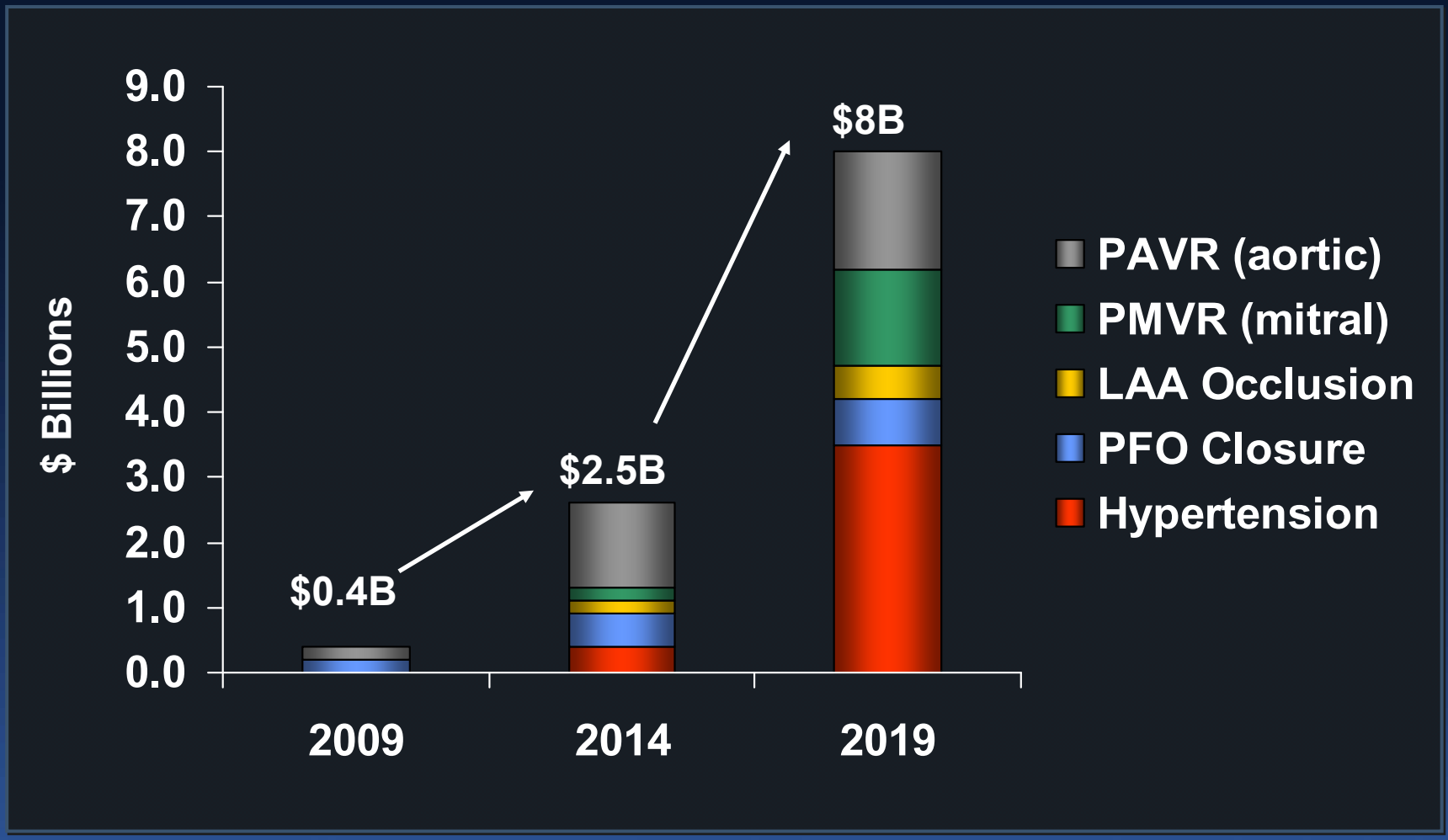
STRUCTURAL Heart Disease

Why the excitement?

- *New patient care treatment alternatives for "common" diseases (e.g. hypertension, migraines)*
- *Completely "additive" to current cath lab procedural activities*
- *Crosses sub-specialty territorial boundaries (e.g. imaging, surgery)*
- *Requires new training and educational initiatives (e.g. simulation)*
- *Extra-ordinary economic market potential!!!*

The Future Growth of IC Markets

Driven by New Segments



Boston Scientific Internal Estimates

Transcatheter Valve Therapy (TVT)

Dr. Alain Cribier

First-in-Man PIONEER

Circulation
JOURNAL OF THE AMERICAN HEART ASSOCIATION
American Heart Association. Learn and Live.

Percutaneous Transcatheter Implantation of an Aortic Valve Prosthesis for Calcific Aortic Stenosis

First Human Case Description

Alain Cribier, MD; Helene Eltchaninoff, MD; Assaf Bash, PhD; Nicolas Borenstein, MD; Christophe Tron, MD; Fabrice Bauer, MD; Genevieve Derumeaux, MD; Frederic Anselme, MD; François Laborde, MD; Martin B. Leon, MD

Conclusions— Nonsurgical implantation of a prosthetic heart valve can be successfully achieved with immediate and midterm hemodynamic and clinical improvement.

April 16, 2002

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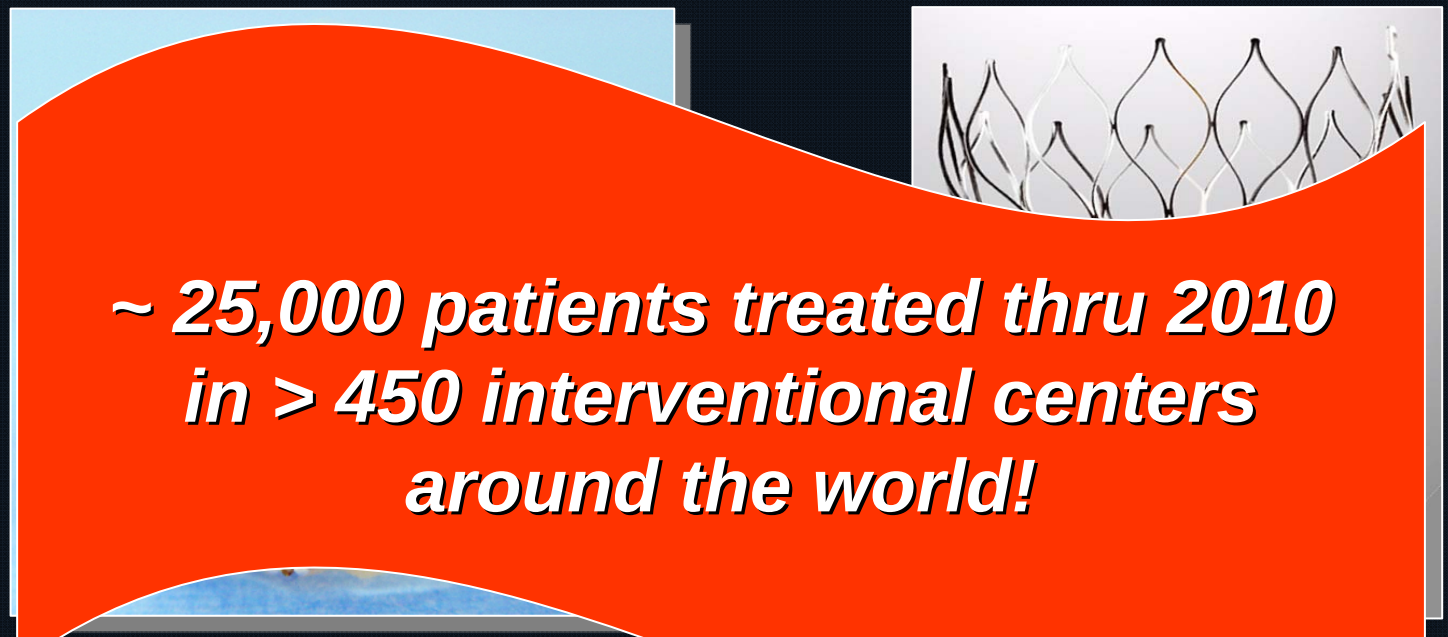
TAVR Technologies

Current Generation Devices



~ 25,000 patients treated thru 2010 in > 450 interventional centers around the world!

Edwards Lifesciences

ative

Published on-line September 22, 2010 @ NEJM.org and print October 21, 2010

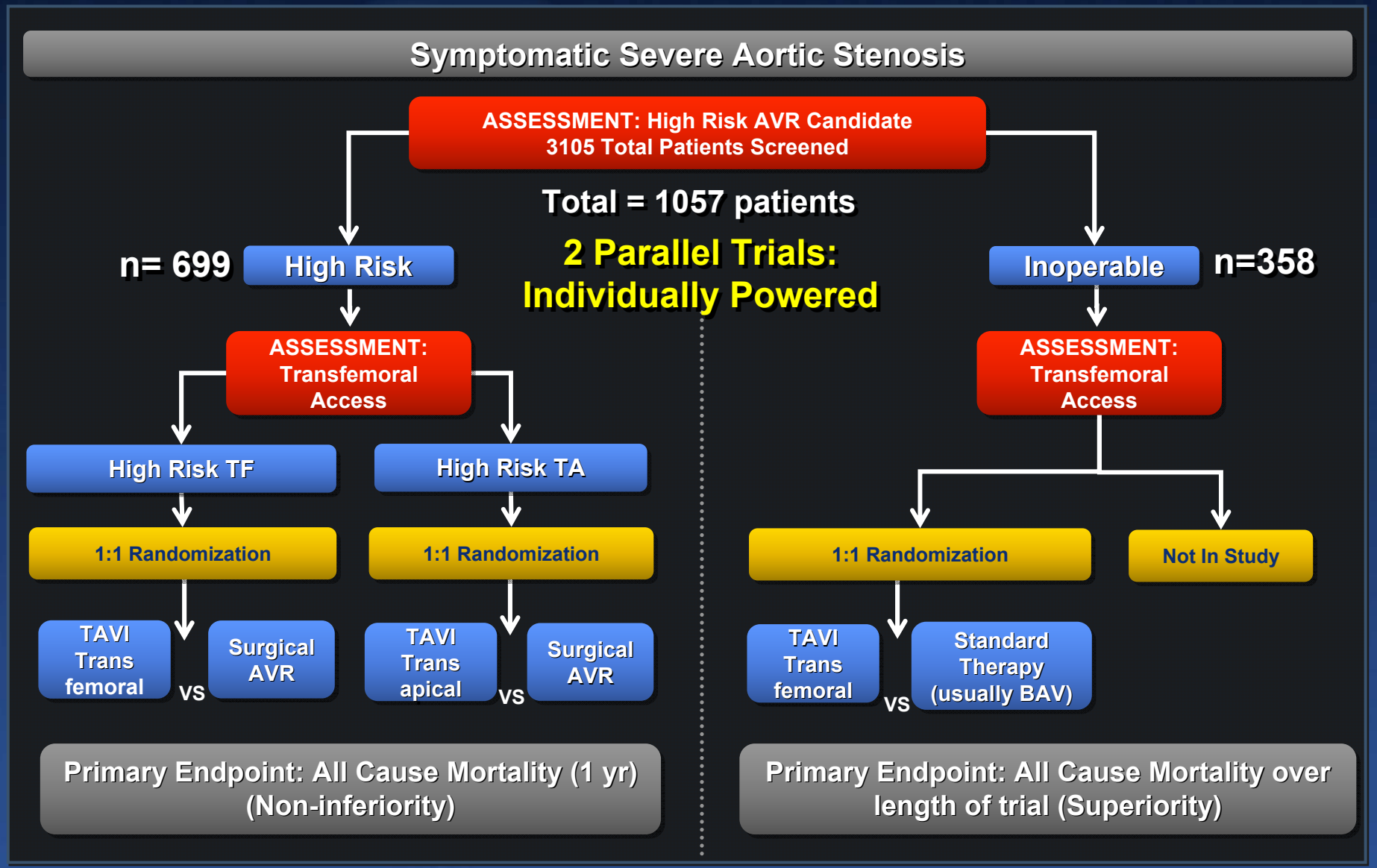
The NEW ENGLAND JOURNAL of MEDICINE

Transcatheter Aortic-Valve Implantation for Aortic Stenosis in Patients Who Cannot Undergo Surgery

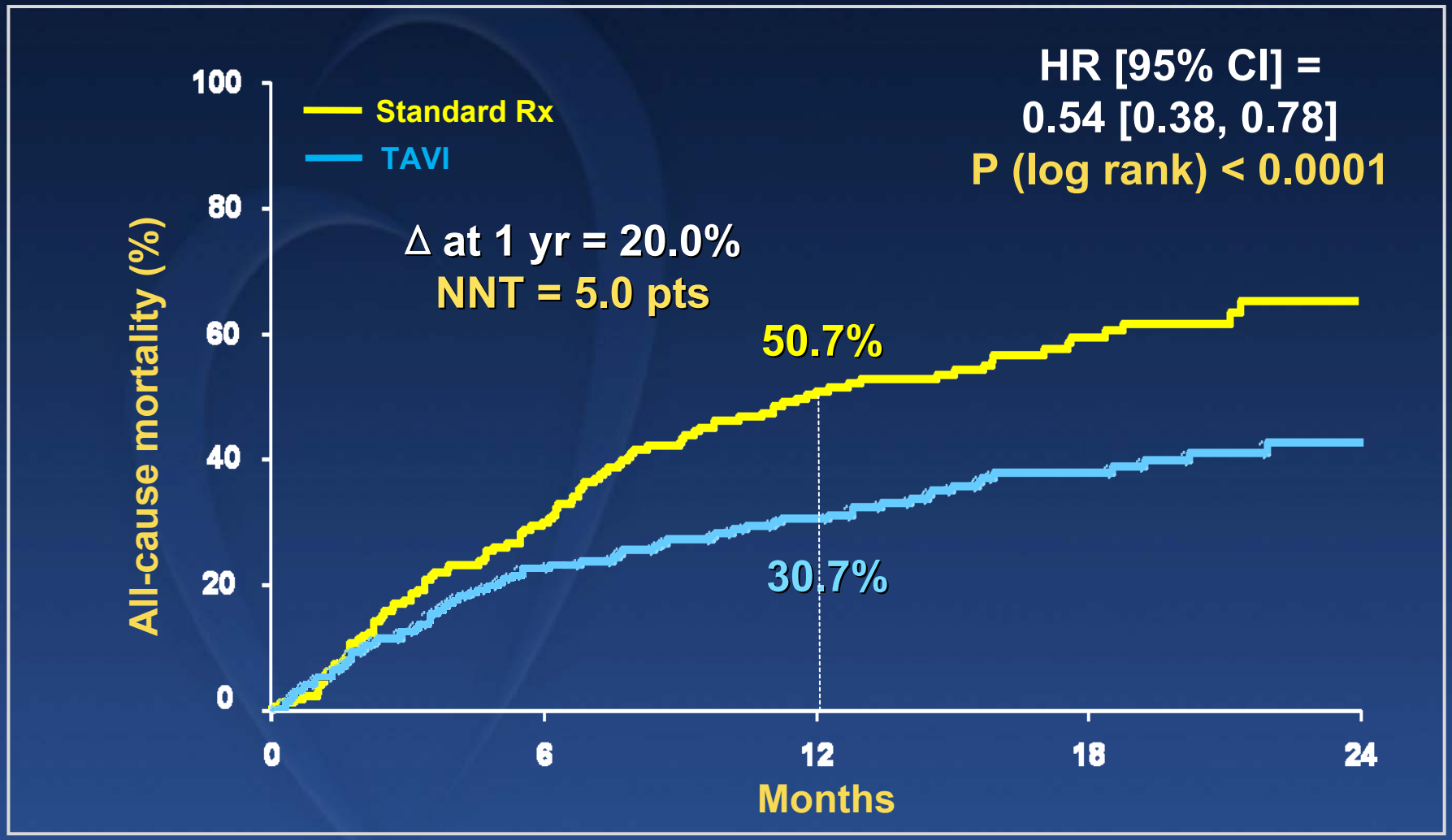
Martin B. Leon, M.D., Craig R. Smith, M.D., Michael Mack, M.D., D. Craig Miller, M.D., Jeffrey W. Moses, M.D., Lars G. Svensson, M.D., Ph.D., E. Murat Tuzcu, M.D., John G. Webb, M.D., Gregory P. Fontana, M.D., Raj R. Makkar, M.D., David L. Brown, M.D., Peter C. Block, M.D., Robert A. Guyton, M.D., Augusto D. Pichard, M.D., Joseph E. Bavaria, M.D., Howard C. Herrmann, M.D., Pamela C. Douglas, M.D., John L. Petersen, M.D., Jodi J. Akin, M.S., William N. Anderson, Ph.D., Duolao Wang, Ph.D., and Stuart Pocock, Ph.D., for the PARTNER Trial Investigators*

On behalf of the Executive Committee, the Investigator Sites, and the courageous patients who participated in the PARTNER trial!

PARTNER Study Design



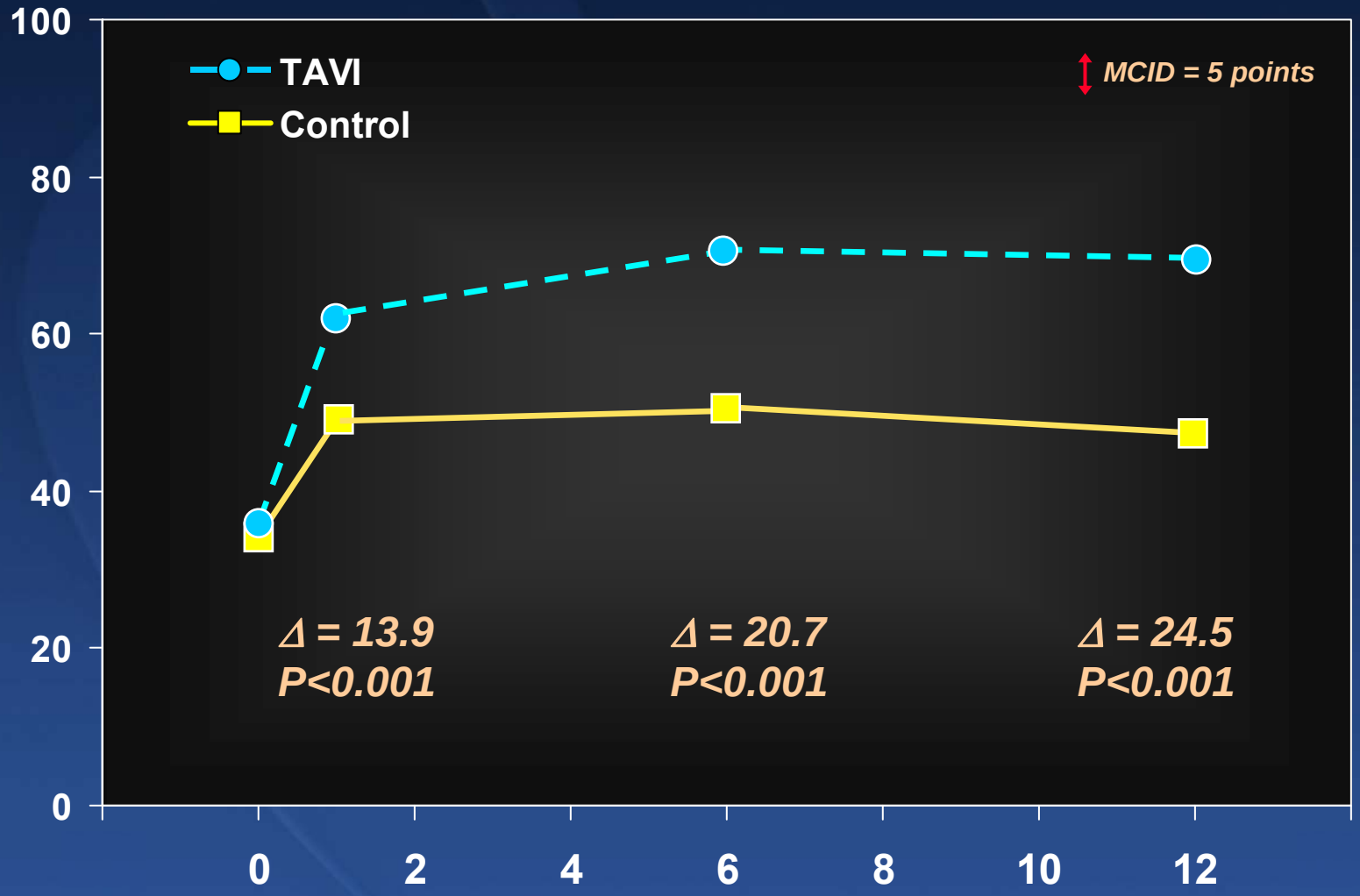
1ry EP: All Cause Mortality



Numbers at Risk					
TAVI	179	138	122	67	26
Standard Rx	179	121	83	41	12

PARTNER: Quality of Life

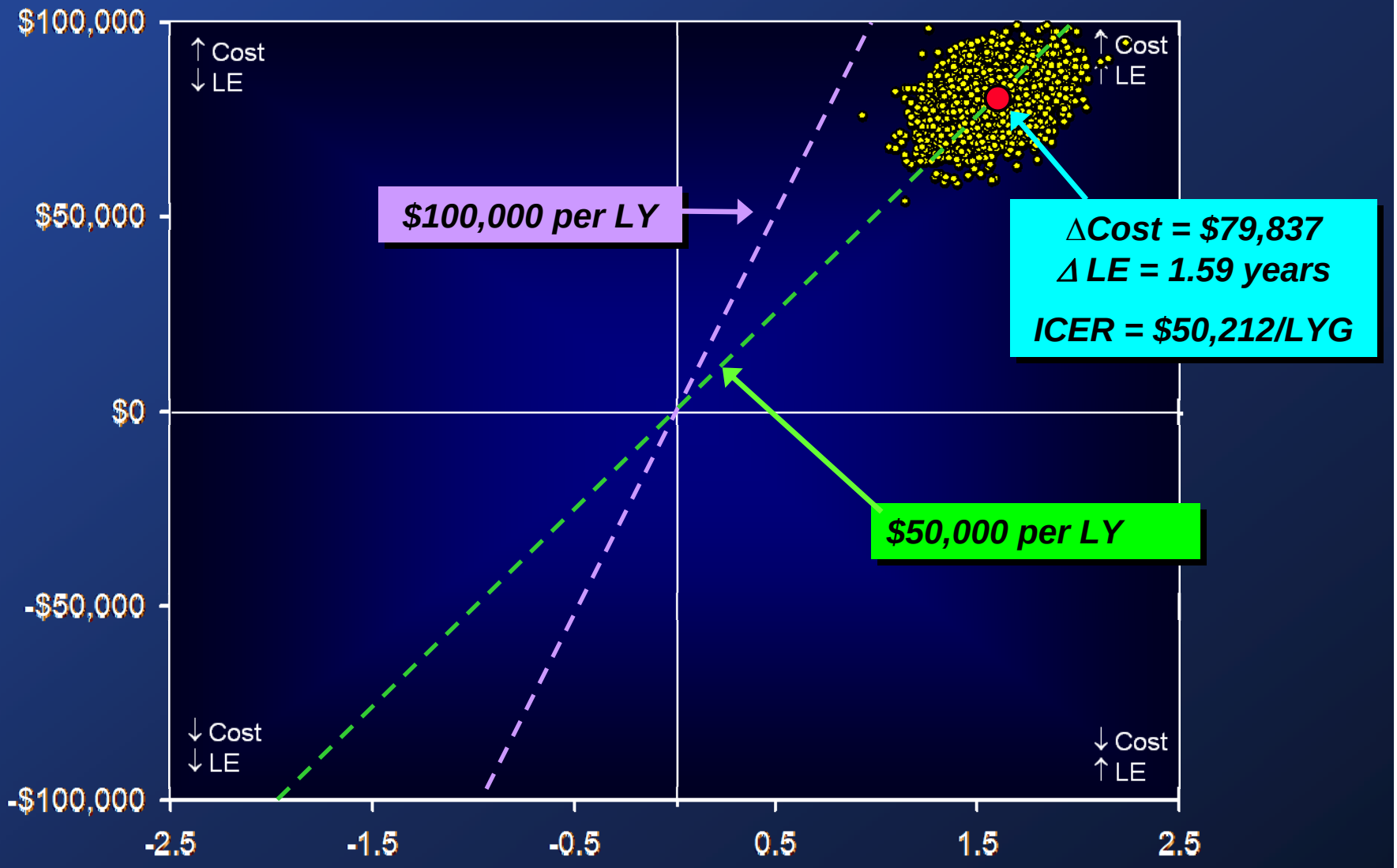
KCCQ Overall Summary



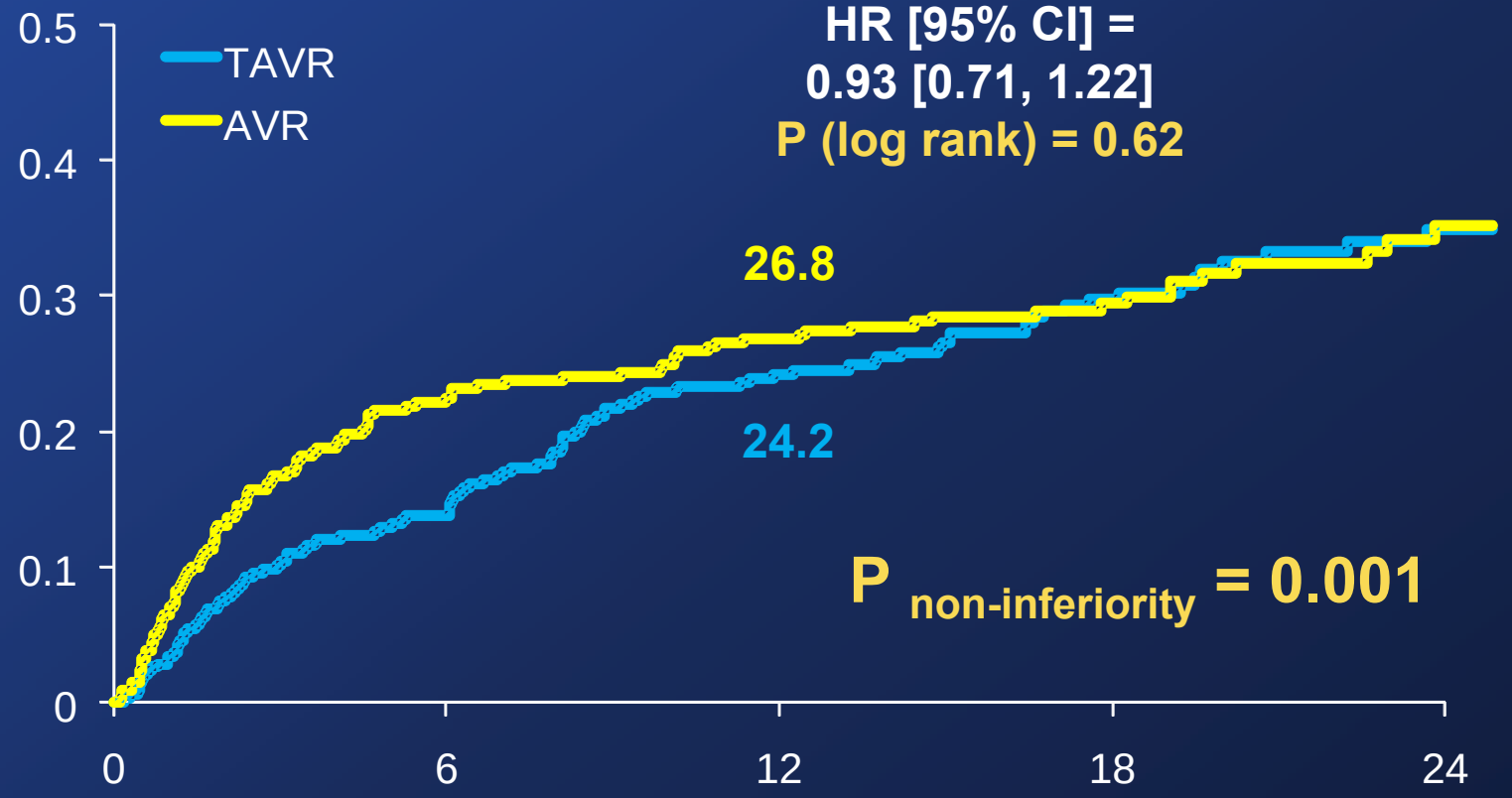
MCID = minimum clinically important differen

Cost-Effectiveness of TAVR vs. Control

Lifetime Results



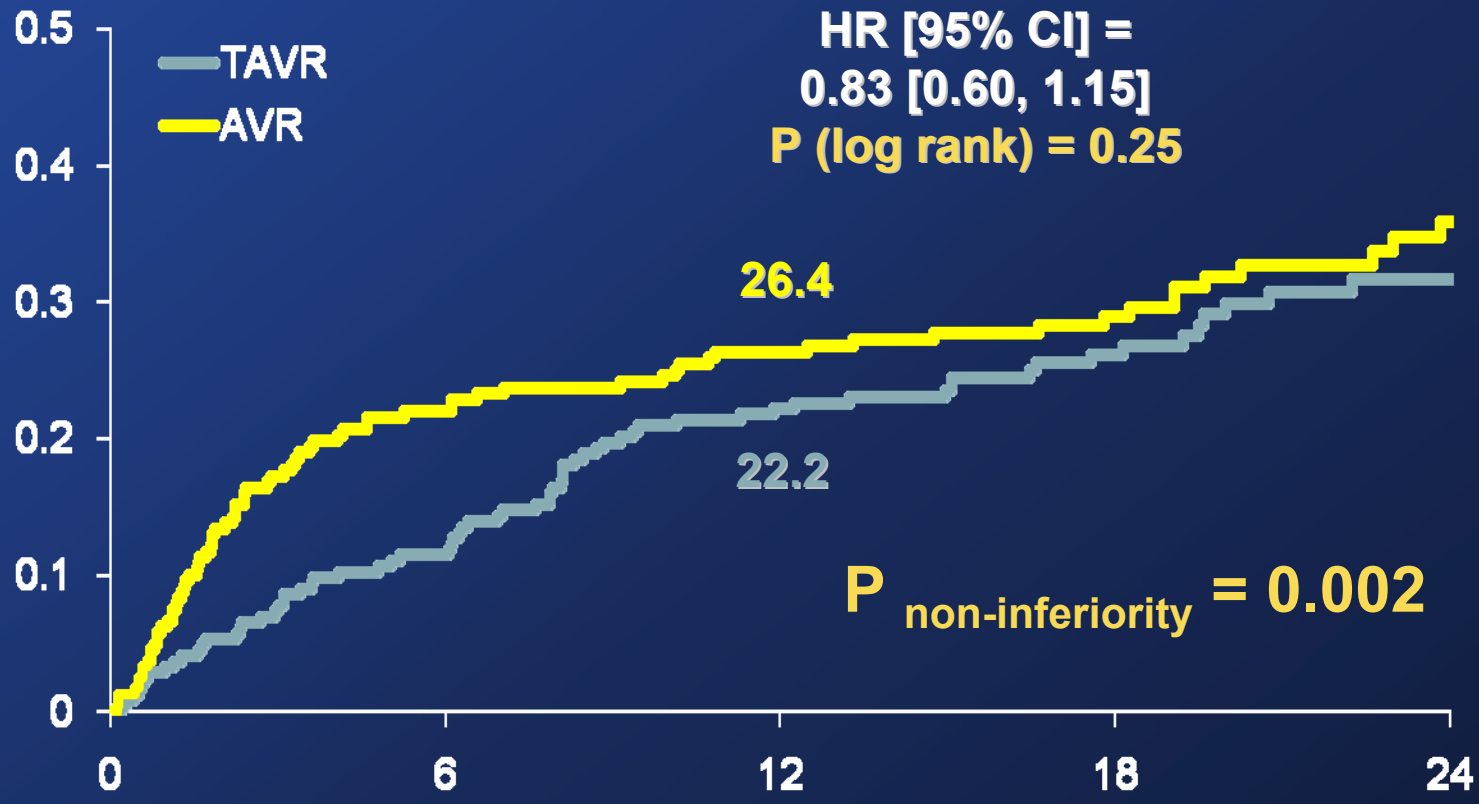
Primary Endpoint:
All-Cause Mortality at 1 Year



No. at Risk

TAVR	348	298	260	147	67
AVR	351	252	236	139	65

All-Cause Mortality
Transfemoral (N=492)



No. at Risk

244	TAVR	188	119	59
248	AVR	168	109	56

Patients Will Always Come First!

Patient #1

92 yo man with critical AS… TAVI at CUMC on 2/8/06… Playing golf in Palm Springs on 3/8/06!!!

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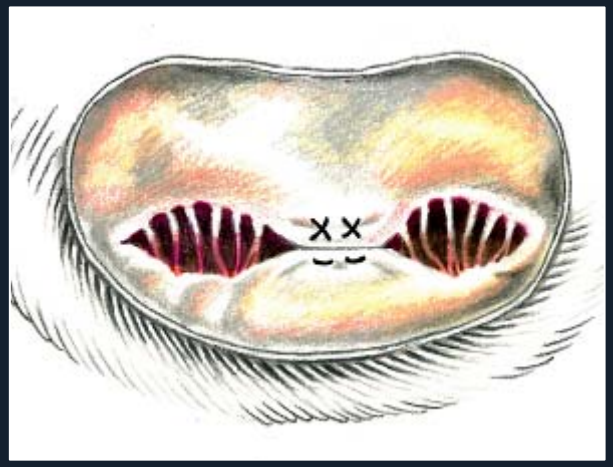
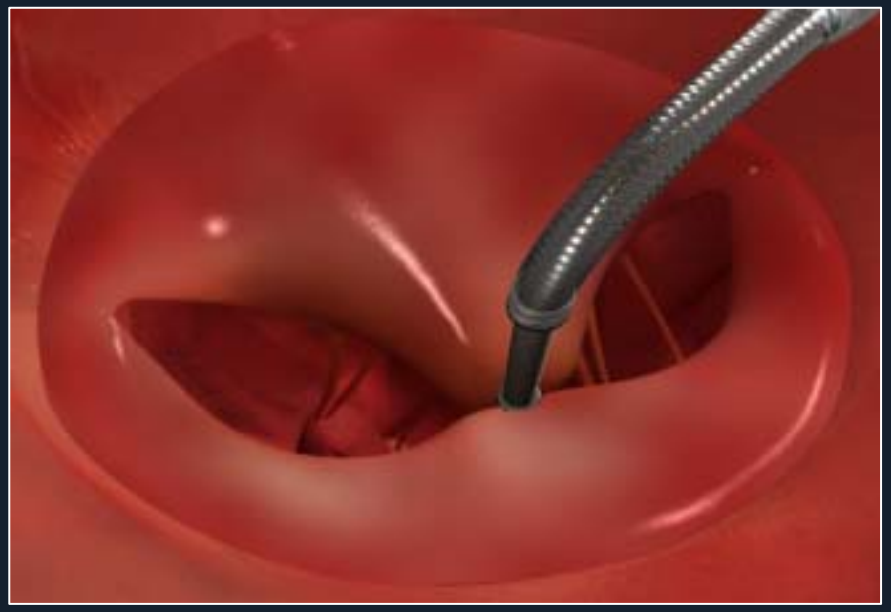
Catheter-Based Mitral Valve Repair
MitraClip® System








Investigational Device only in the US;
Not available for sale in the US

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EVEREST II Randomized Clinical Trial Study Design

279 Patients enrolled at 37 sites

Significant MR (3+-4+)
Specific Anatomical Criteria

↓

Randomized 2:1

↙ ↘

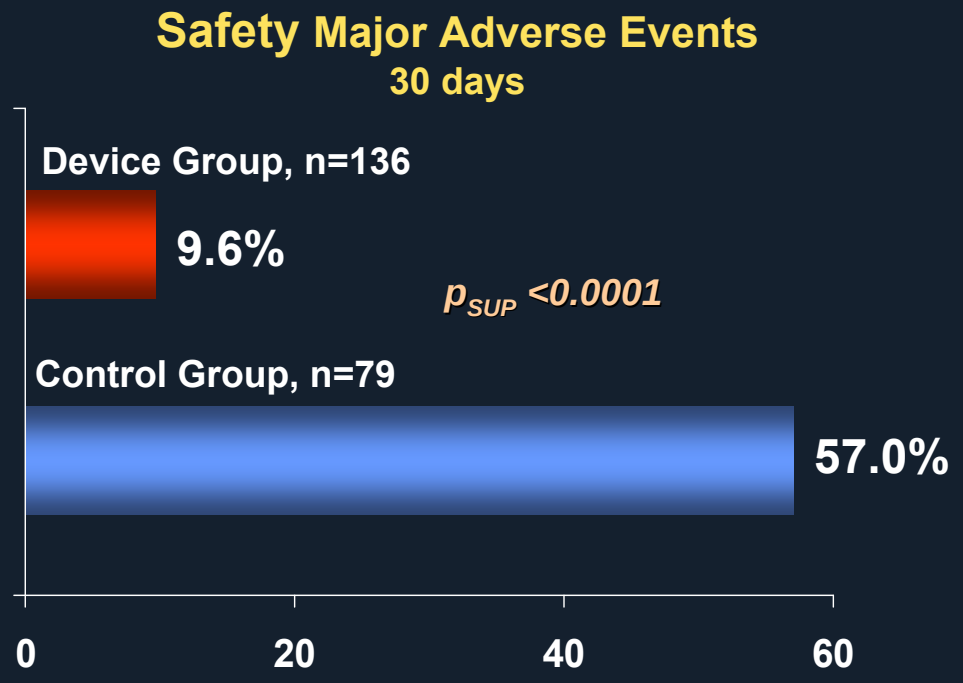
Device Group
MitraClip System
N=184

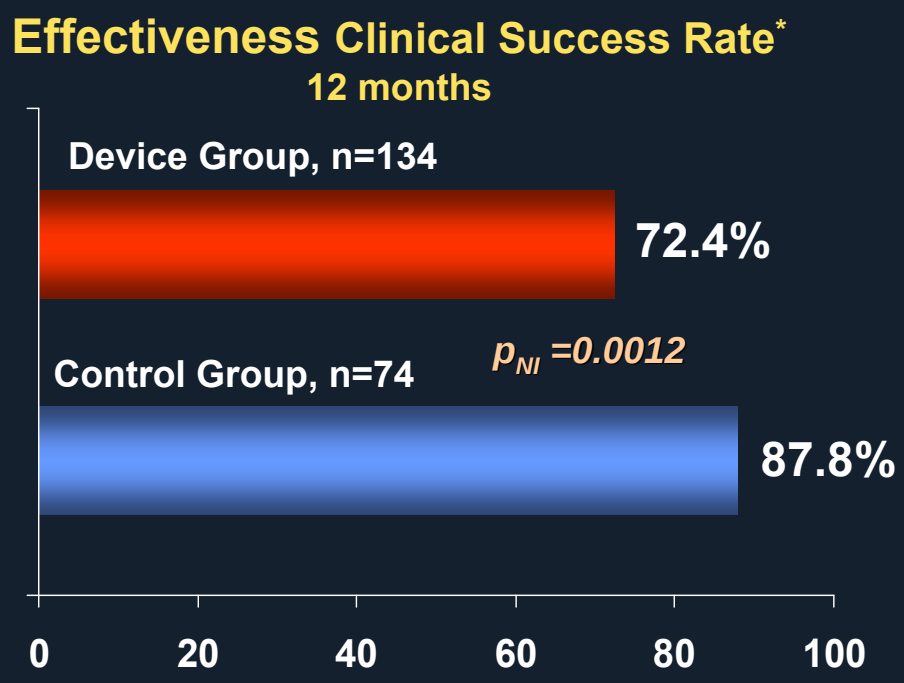
Control Group
Surgical Repair or Replacement
N=95

↓ ↓

Echocardiography Core Lab and Clinical Follow-Up:
Baseline, 30 days, 6 months, 1 year, 18 months, and annually through 5 years

EVEREST II RCT: Primary Endpoints Per Protocol Cohort





Met superiority hypothesis

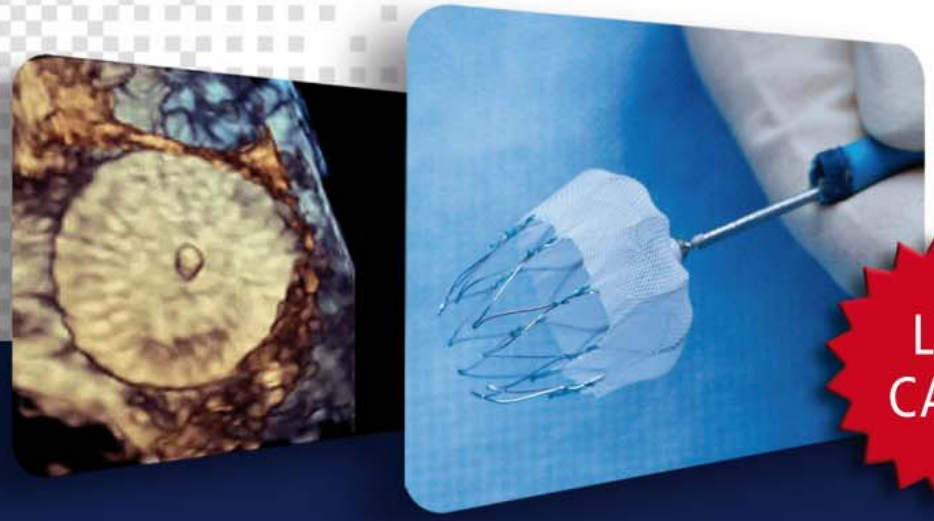
- Pre-specified margin = 6%
- Observed difference = 47.4%
- 97.5% LCB = 34.4%

LCB = lower confidence bound
UCB = upper confidence bound

Met non-inferiority hypothesis

- Pre-specified margin = 31%
- Observed difference = 15.4%
- 95% UCB = 25.4%

* Freedom from the combined outcome of death, MV surgery or re-operation for MV dysfunction, MR >2+ at 12 months



LIVE CASES

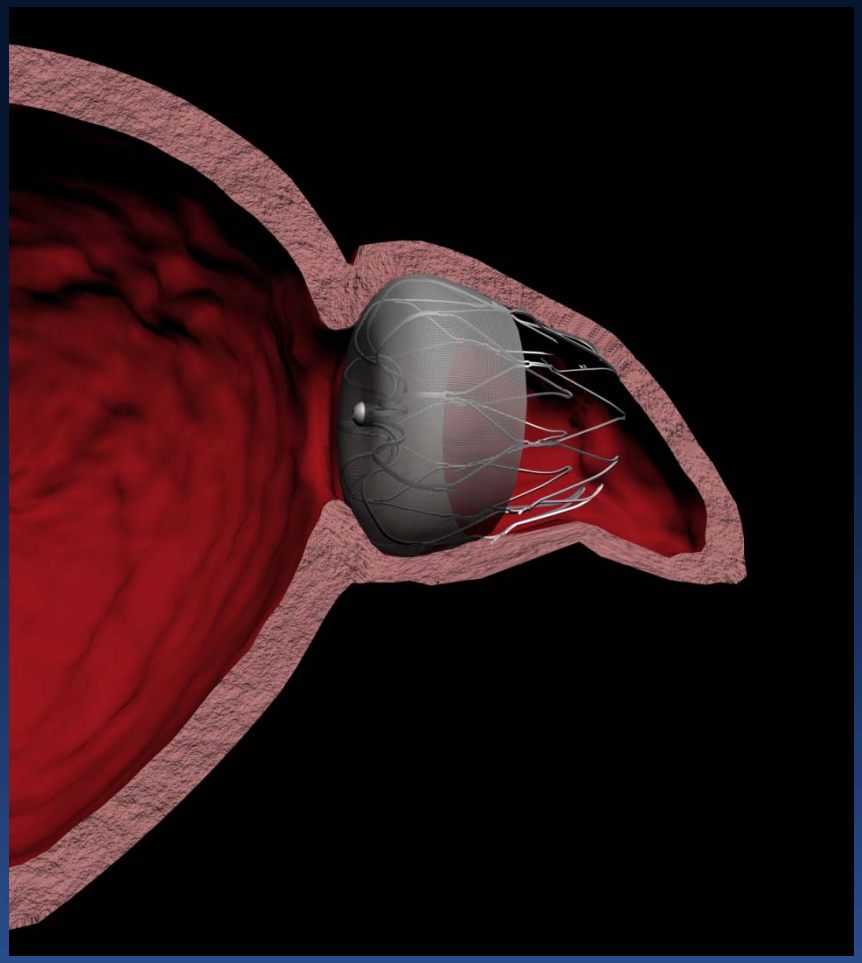
CSI Focus Workshop

November 20, 2010 | Frankfurt, Germany

LAA 2010 – How to Close the Left Atrial Appendage

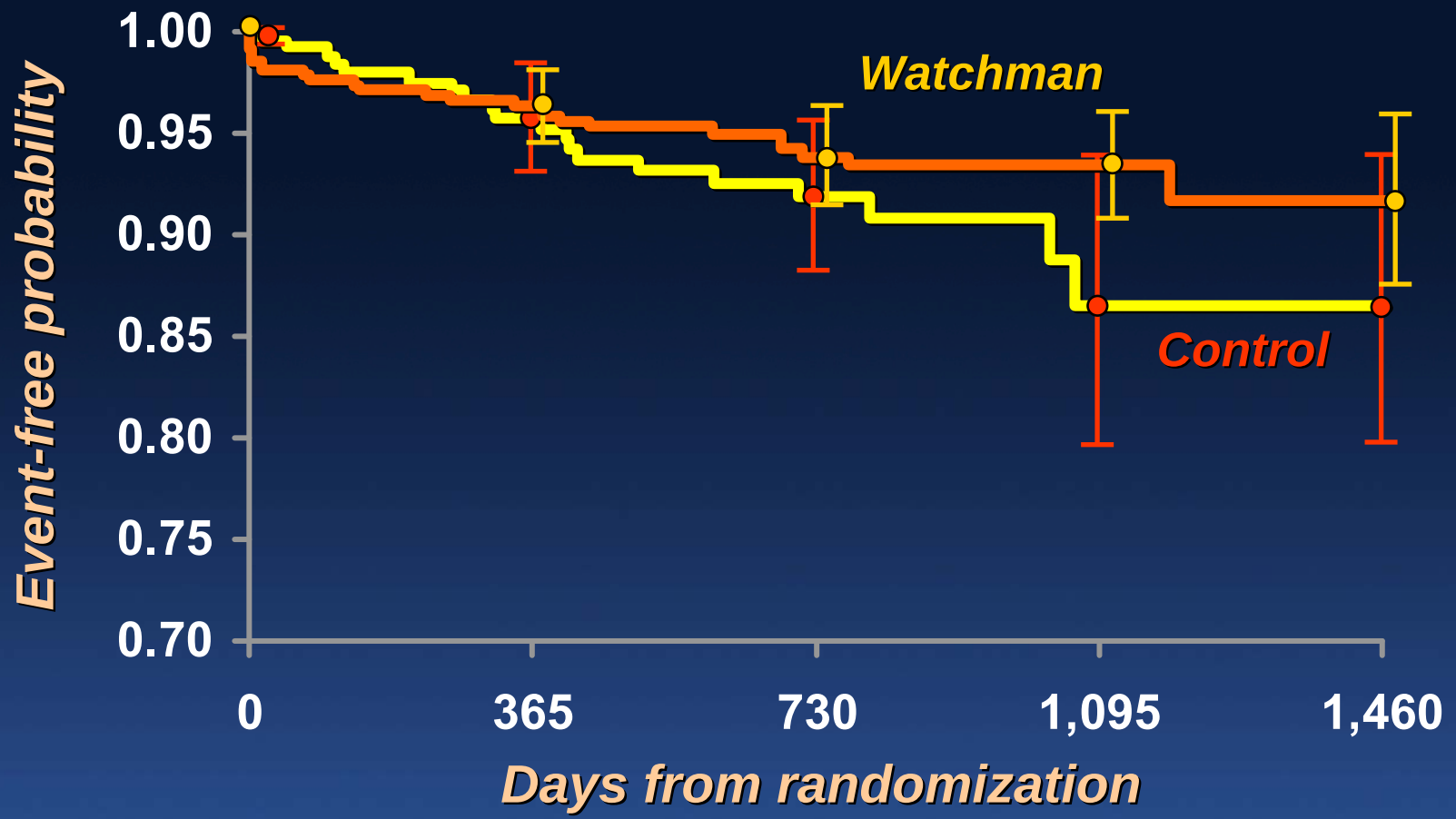
www.csi-congress.org/laa-workshop

WATCHMAN LAA Filter System



- ***Nitinol***
  - Contour shape accommodates most LAA anatomy
  - Barbs engage the LAA tissue
- ***PET Filter***
  - Prevents embolization
  - Reduces the pressure on the peripheral seal until endothelialization has occurred
- ***Available in 4 sizes***

Primary Efficacy Over Time



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Interventional Opportunities

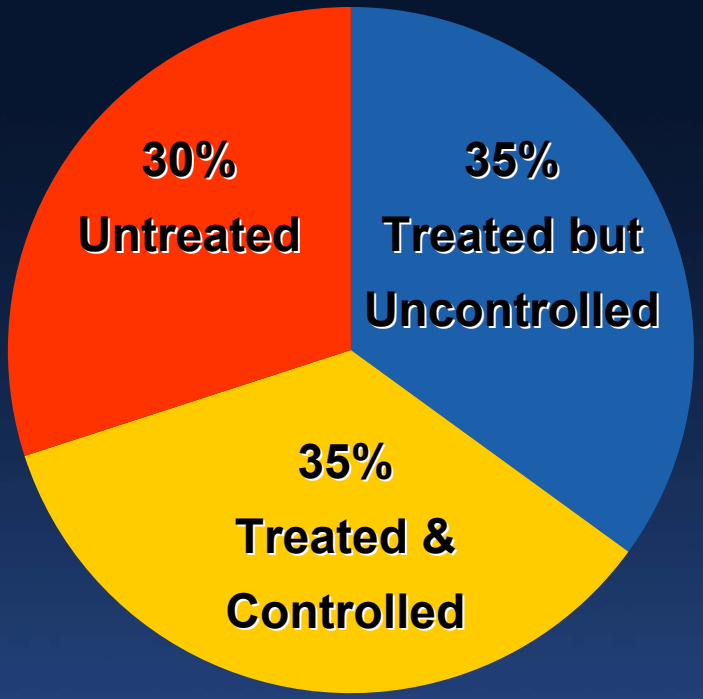
FUTURE!

Structural Heart Disease

Hypertension

Chronic Hypertension

Significant Unmet Clinical Need



Hypertension medications work, but not as well as you may think

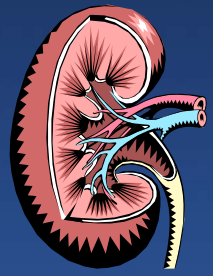
- Astonishing prevalence:
  - Affects 1 in 3 adults
  - 1B people worldwide → 1.6B by 2025
- Single largest contributor to death
- Every 20 mmHG increase in systolic BP doubles 10-year cardiovascular mortality
- Dramatically increases risk of heart attack, stroke, heart failure, kidney failure & insulin resistance
- Only half of all treated hypertensives are controlled to established BP targets
  - Physician Inertia
  - Patient Compliance
  - Resistant HTN

Chobanian AV, Bakris GL, Black HR, et al. Seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. *Hypertension*. 2003;42(6):1206-1252.

Renal Sympathetic Efferent Nerve Activity

Kidney as Recipient of Sympathetic Signals

Renal Efferent Nerves



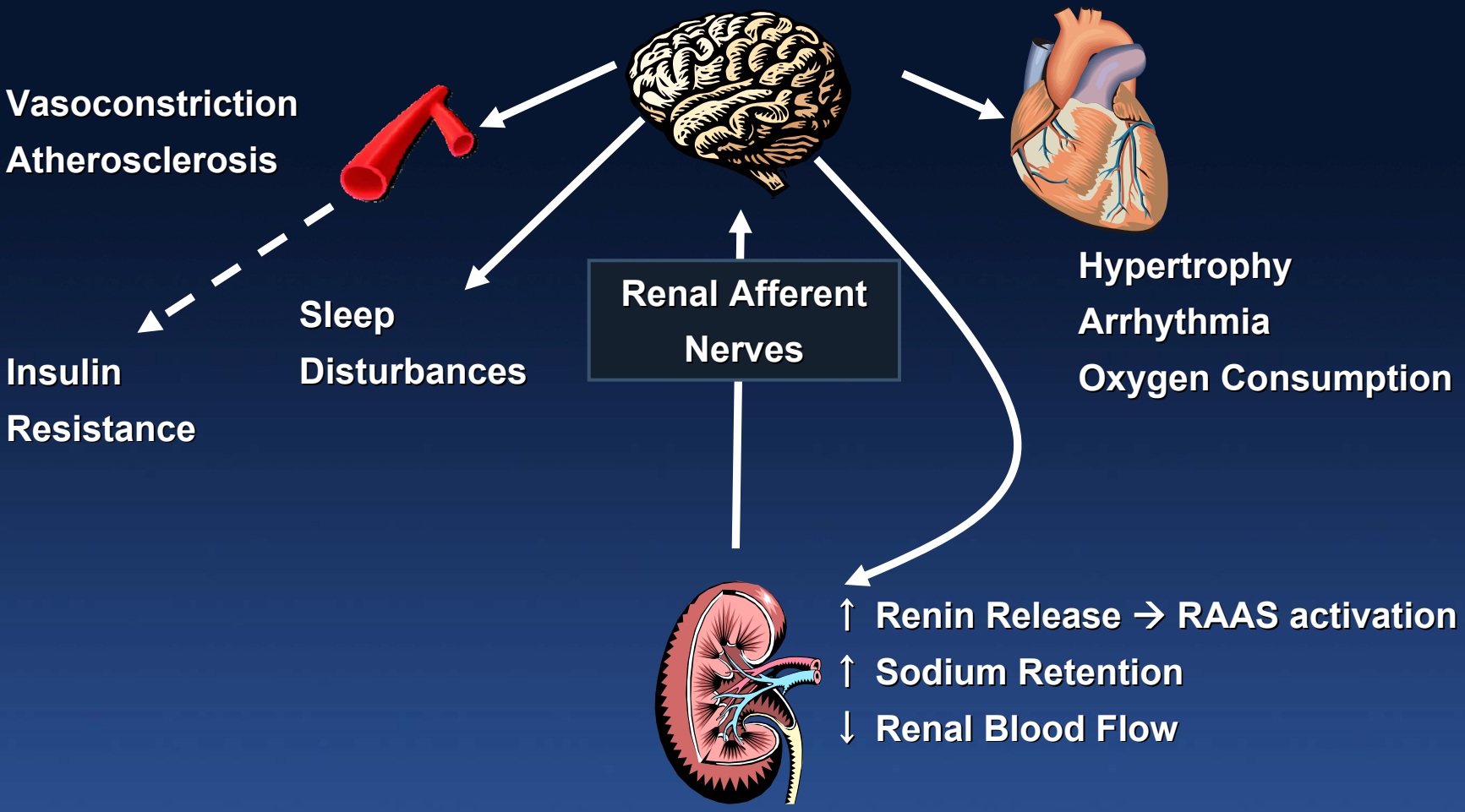
↑ Renin Release → RAAS activation

↑ Sodium Retention

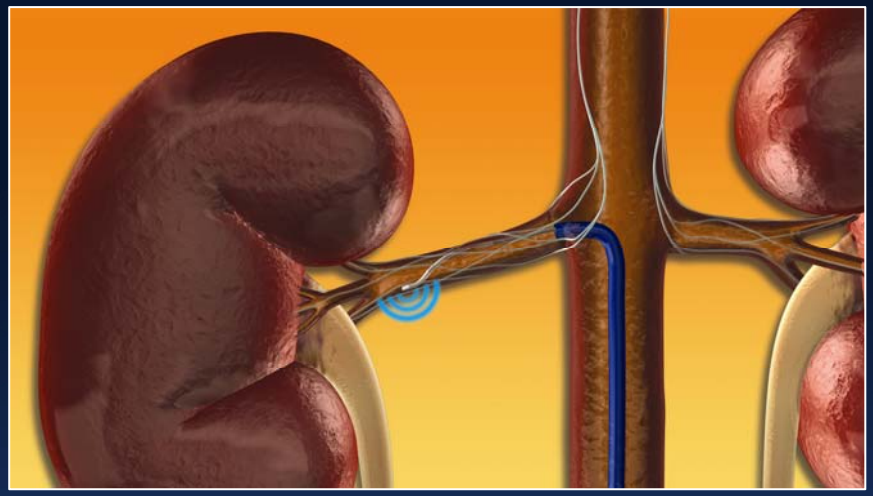
↓ Renal Blood Flow

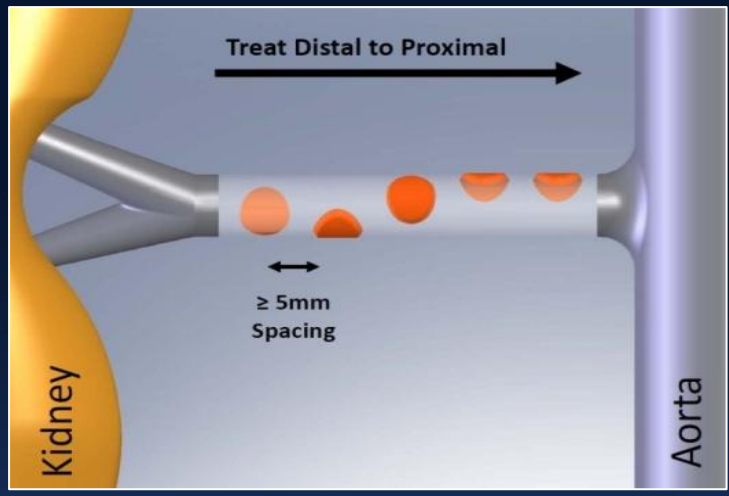
Renal Sympathetic Afferent Nerves

Kidney as Origin of Central Sympathetic Drive

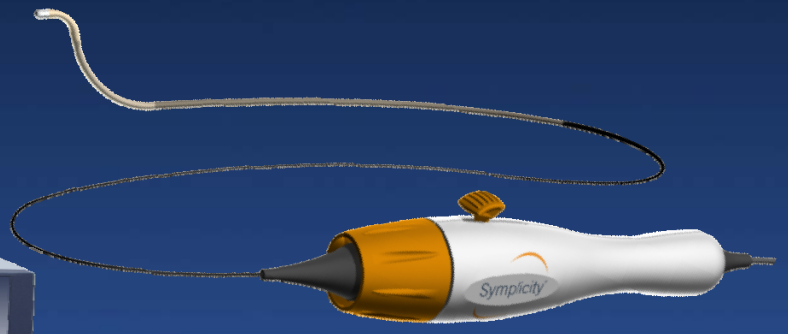


Renal Nerve Anatomy Allows a Catheter-Based Approach





- Standard interventional technique
- 4-6 two-minute treatments per artery
- Proprietary RF Generator
  - Automated
  - Low-power
  - Built-in safety algorithms



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

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Staged Clinical Evaluation

Symplicity HTN-1

First-in-Man ✓

↓

Series of Pilot studies ✓

↓

***Symplicity HTN-2* ✓**
EU/AU Randomized Clinical Trial

↓

USA

Symplicity HTN-3
US Randomized Clinical Trial (upcoming)

EU/AU

Other Areas of Research:
Insulin Resistance, HF/Cardiorenal, Sleep Apnea, More

Symplicity HTN-1


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

Initial Cohort – Reported in the Lancet, 2009:

- **First-in-man, non-randomized**
- **Cohort of 45 patients with resistant HTN (SBP ≥160 mmHg on ≥3 anti-HTN drugs, including a diuretic; eGFR ≥ 45 mL/min)**
- **12-month data**

Expanded Cohort – This Report (Symplicity HTN-1):

- **Expanded cohort of patients (n=153)**
- **24-month follow-up**

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Lancet. 2009;373:1275-1281.
Sievert et al. European Society of Cardiology. 2010.

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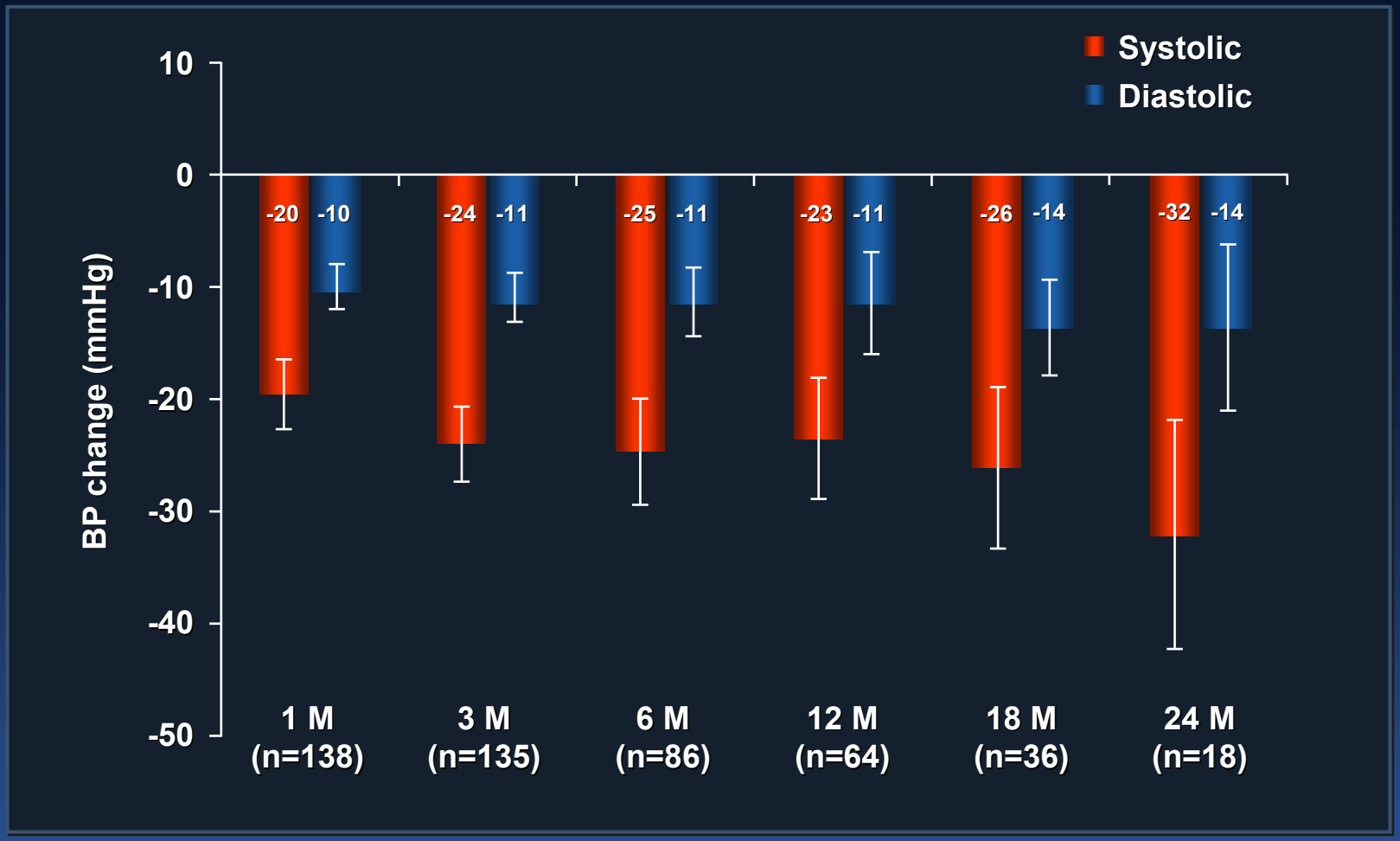
Significant, Sustained BP Reduction



Sievert et al. European Society of Cardiology. 2010.

Symplicity HTN-2


THE LANCET

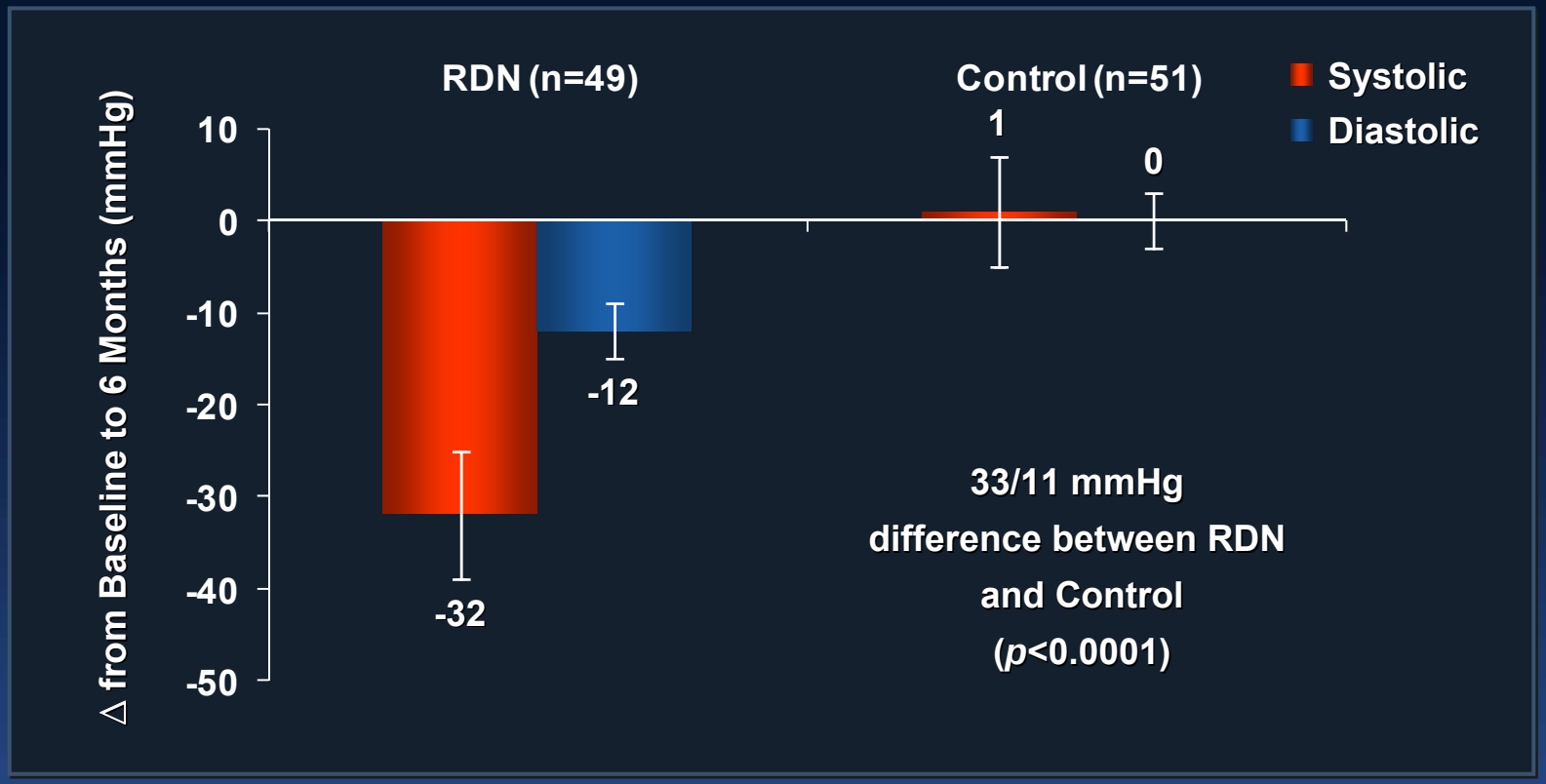
Renal sympathetic denervation in patients with treatment-resistant hypertension (The Symplicity HTN-2 Trial): a randomised controlled trial

*Symplicity HTN-2 Investigators**

- ***PURPOSE***: **To demonstrate the effectiveness of catheter-based renal denervation for reducing blood pressure in patients with uncontrolled hypertension in a prospective, randomized, controlled, clinical trial**
- ***PATIENTS***: **106 patients randomized 1:1 to treatment with renal denervation vs. control**
- ***CLINICAL SITES***: **24 centers in Europe, Australia, & New Zealand (67% were designated hypertension centers of excellence)**

Lancet. 2010;376:1903-1909.
Symplicity HTN-2 Investigators. *Lancet*. 2010;376:1903-1909.

Primary Endpoint: 6-Month Office BP



- 84% of RDN patients had ≥ 10 mmHg reduction in SBP
- 10% of RDN patients had no reduction in SBP

Symplicity HTN-2 Investigators. *Lancet*. 2010;376:1903-1909.

Interventional Opportunities

FUTURE!

Structural Heart Disease

Hypertension

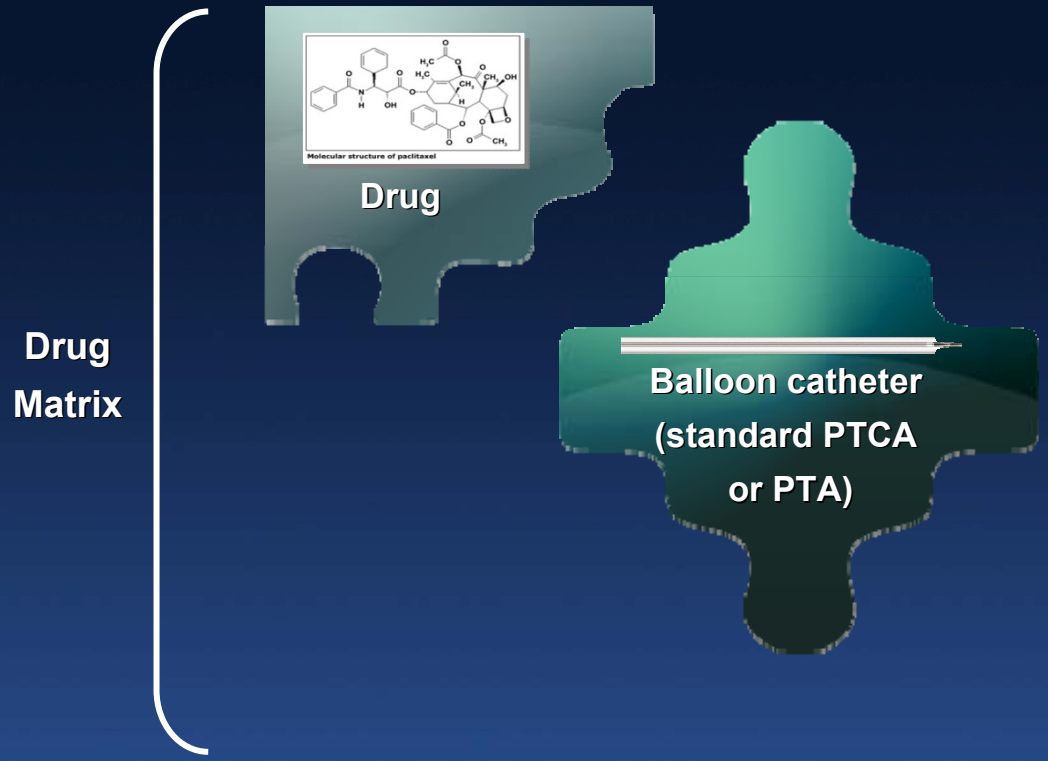
Novel (new) Anti-restenosis Therapy

Rationale for the Clinical Use of DEB for the Prevention of Restenosis

- Shown to be efficacious in reducing restenosis in humans in specific clinical situations (ISR).
- Easy concept, rapid adoption, no learning curve…balloon-based technology.
- Cost-effective strategy…if used alone or with BMS…
- Potential for improved safety: no chronic polymer effects + "shorter" drug exposure = potential for enhanced biocompatibility.
- Complements DES= use in situations where DES problematic or less effective, e.g. ISR, bifurcations, small vessels, diffuse disease.

DEB Technology: How Does It Work?

DEB Components

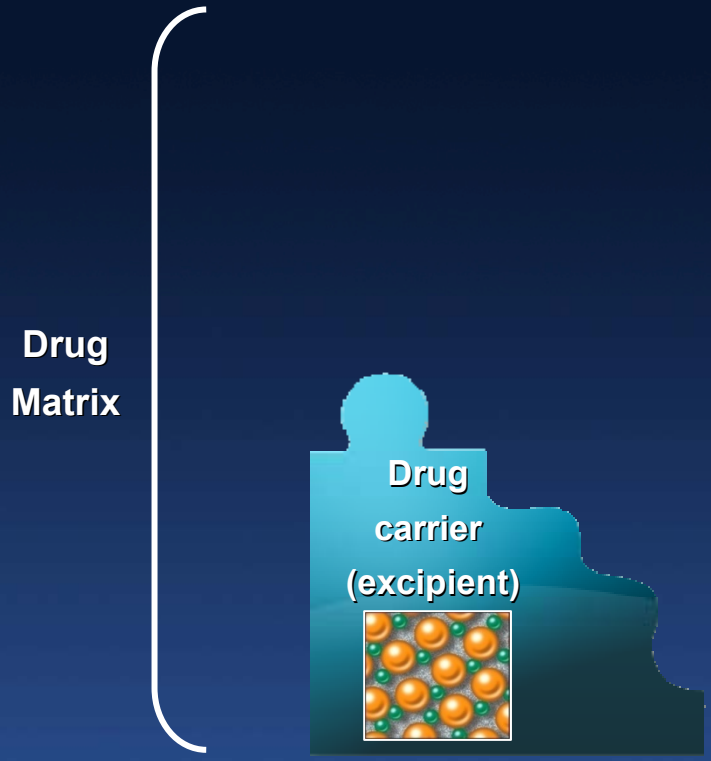


The Drug - Paclitaxel:

- Provides appropriate anti-restenotic drug therapy for an *acute* delivery system such as a DEB
- Facilitates *acute* delivery due to hydrophobicity and tight binding to the microtubule subunit
- Allows for increased potency for *single-shot* therapy
- Limits drug toxicity with DEB delivery

DEB Technology: How Does It Work?

DEB Components

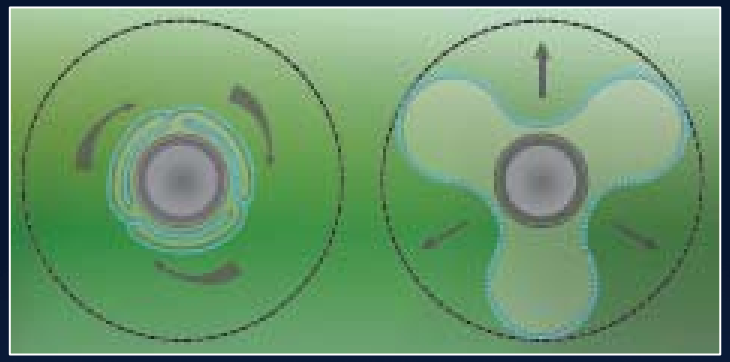


The excipient:

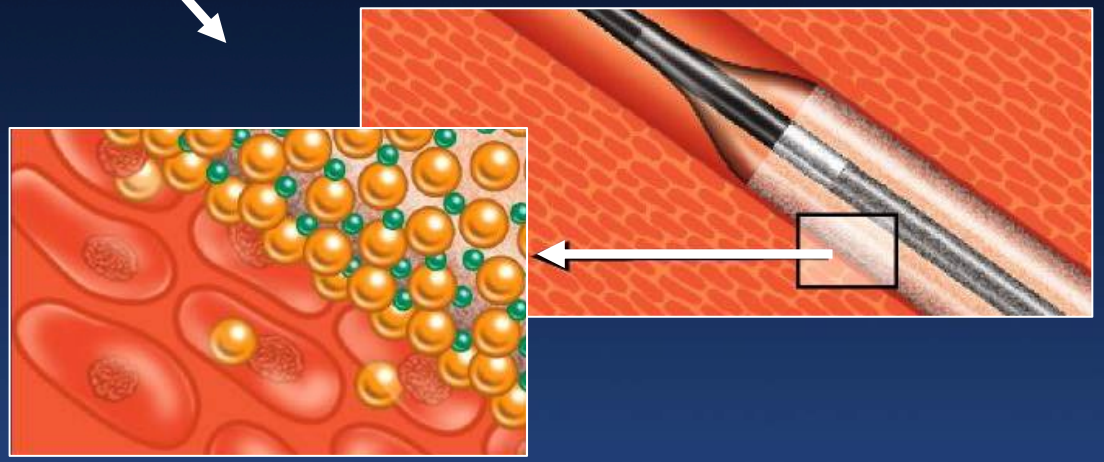
- **Separates paclitaxel molecules to increase drug solubility and balance hydrophobicity**
- **Provides drug transfer time in 30–60 seconds**
- **Remains in the artery post-procedure along with the anti-restenotic drug**

The In.Pact products use urea as an excipient

DEB Drug Transfer



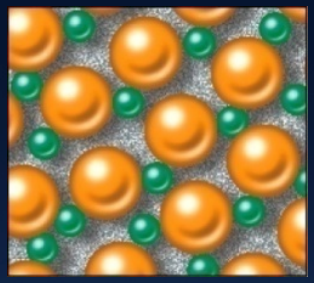
As the balloon unwraps, the drug-excipient coating is fully exposed to the vessel wall



Paclitaxel's hydrophobicity along with the increased solubility conferred by the excipient allows for rapid drug diffusion across the vessel wall

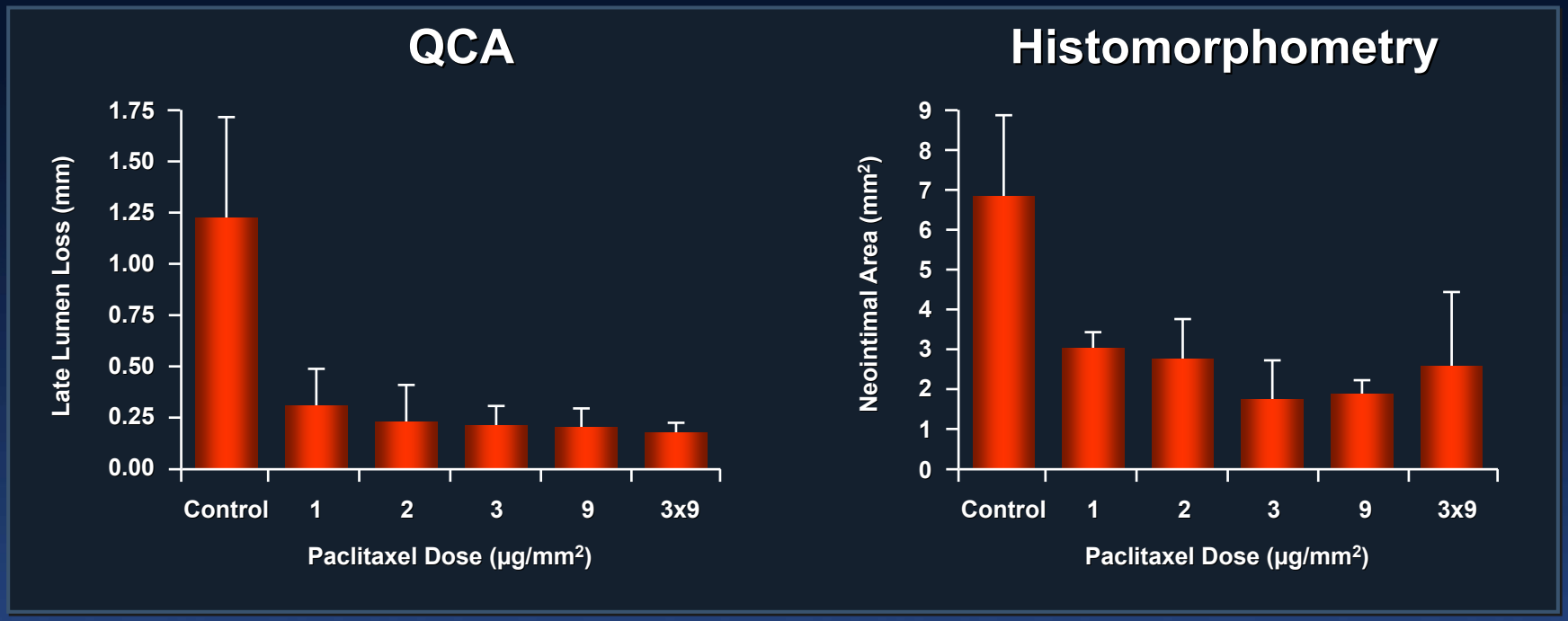
Invatec FreePac™ DEB Technology

- Proprietary hydrophilic coating formulation



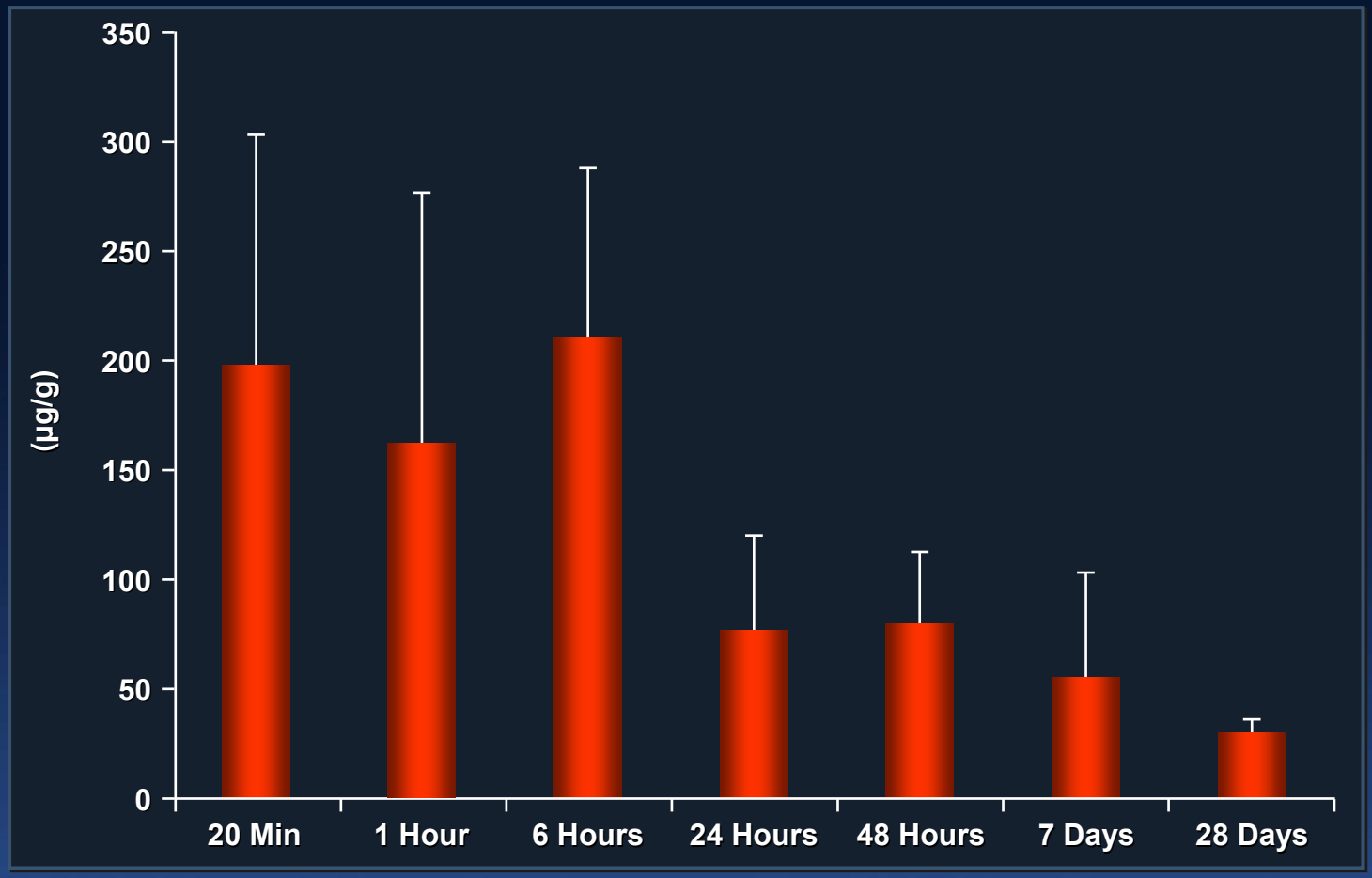
- Paclitaxel (3 µg/mm^2 balloon surface)
- Urea
  - Hydrophilic additive
  - Natural degradation product of protein synthesized in the liver
  - One of the most common substances in human serum (100-500 mg/liter)
  - Low toxicity, no hypersensitivity reactions
- Undisclosed solvents

QCA Lumen Loss and Neointimal Area at 28 Days



- Dose of 3 µg/mm² was determined to be the optimal dose, with significant activity 1 µg/mm²

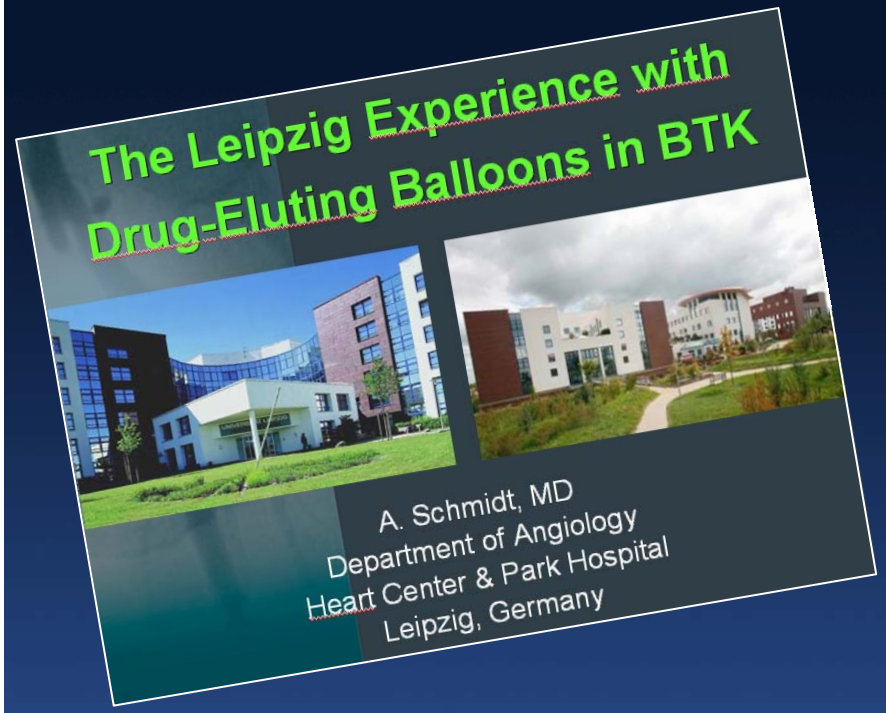
Tissue PK of Paclitaxel Post-treatment



- The majority of paclitaxel is cleared from the media at 24 hours, but retention of therapeutically relevant drug levels in the media are maintained for at least 28 days.

Schnorr B et al. Paclitaxel-coated balloons—survey of preclinical data. *Minerva Cardioangiol*. 2010;58(5):567-582.

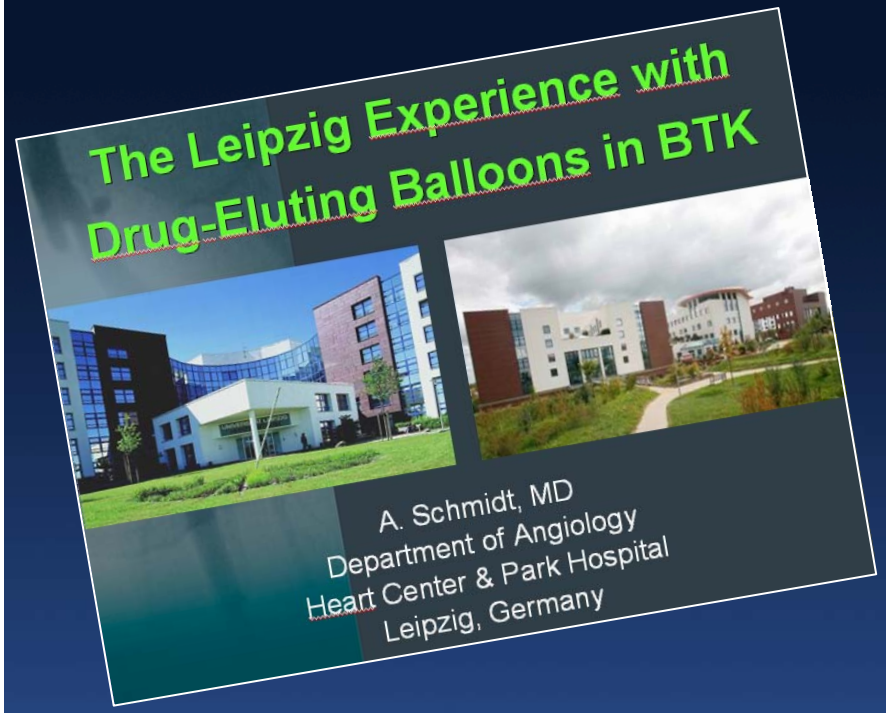
IN.PACT BTK Registry Leipzig (LINC 2010)



- Prospective registry of patients with BTK-lesions
- In.Pact Amphirion paclitaxel-coated balloon
- Angiography after 3 months
- Clinical FU 3, 6 and 12 months
- 102 pts. treated with In.Pact Amphirion
  - 3 months FU available in 64 pts.
  - 2 pts. died
    - 1 cardiac death, 1 major amputation
  - 15 pts. did not come to the 3-months FU

Schmidt A, LINC 2010

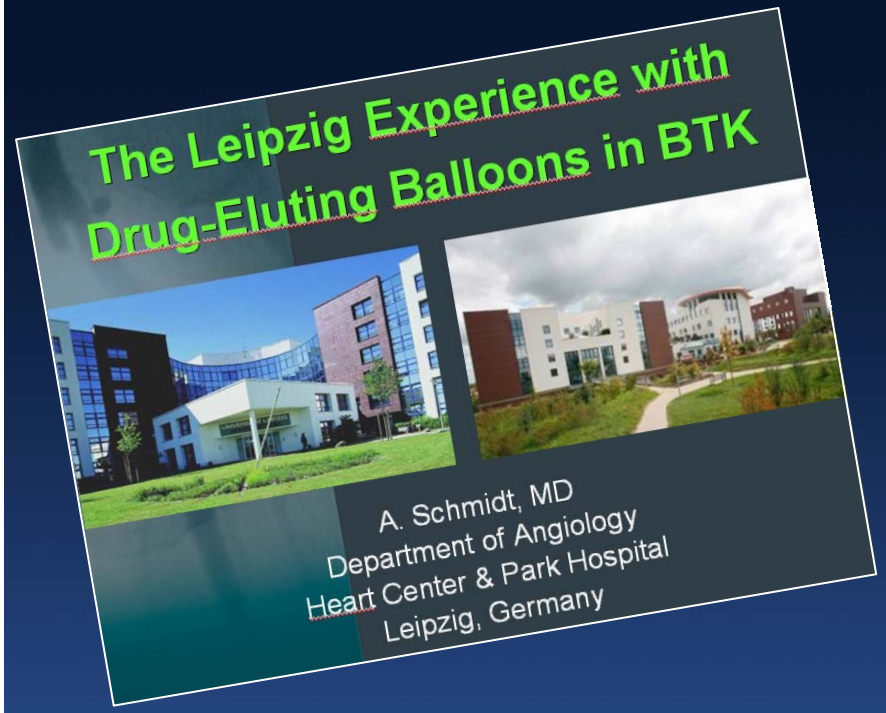
IN.PACT BTK Registry Leipzig (LINC 2010)

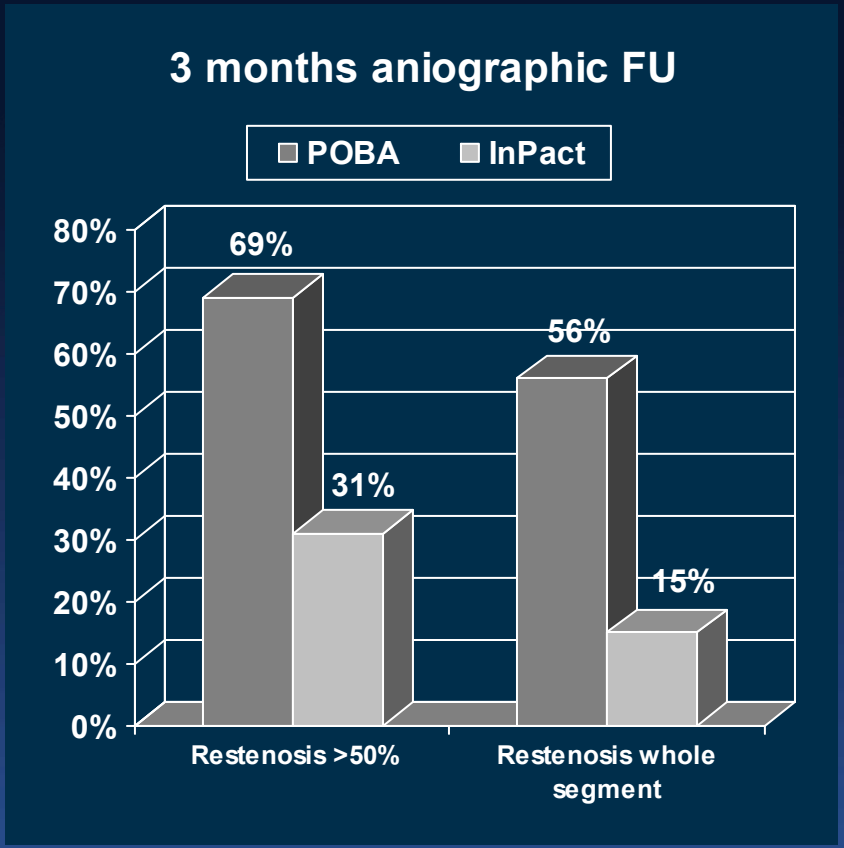


- Angiographic FU in 48 pts
- Diabetes mellitus 41 / 48 (85 %)
- Lesions treated with In.Pact Amphirion
  - De-novo 28 (58 %)
  - Restenosis 15 (31 %)
  - In-stent restenosis 5 (11 %)
  - Mean lesion-length 170 ± 76 mm
  - Total occlusion 28 (58 %)

Schmidt A, LINC 2010

IN.PACT BTK Registry Leipzig (LINC 2010)





Schmidt A, LINC 2010

Interventional Opportunities

FUTURE!

Structural Heart Disease

Hypertension

Novel (new) Anti-restenosis Therapy

Out-of-the-box Concepts

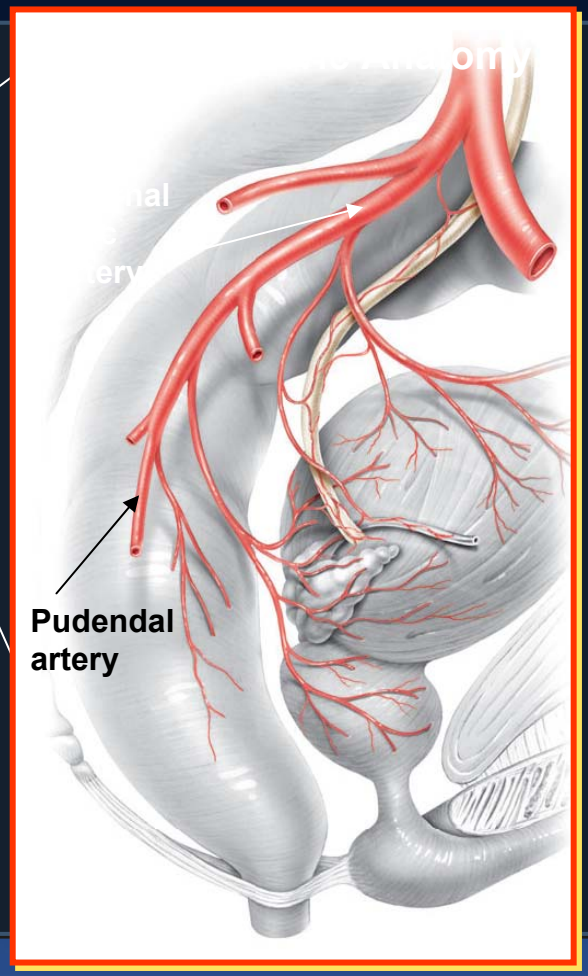
Erectile Dysfunction is Prevalent

- ~25 million men in the United States
- >300 million men worldwide

Laumann et al. JAMA 1999:10:281:537.

Causes of Erectile Dysfunction

- Etiology
  - 80% *Vasculogenic*
  - Traumatic
  - Post-surgical
  - Hormonal
  - Chronic disease- DM, CRI
  - Medication
  - Psychological



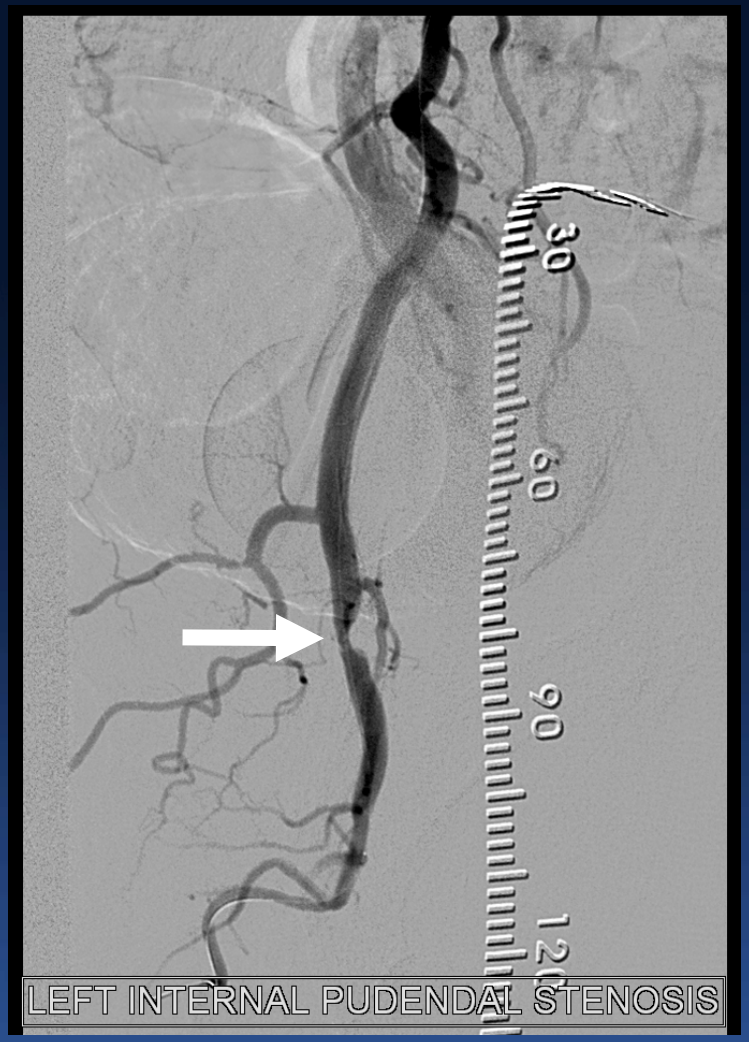
Lue. NEJM 2000;342:1803

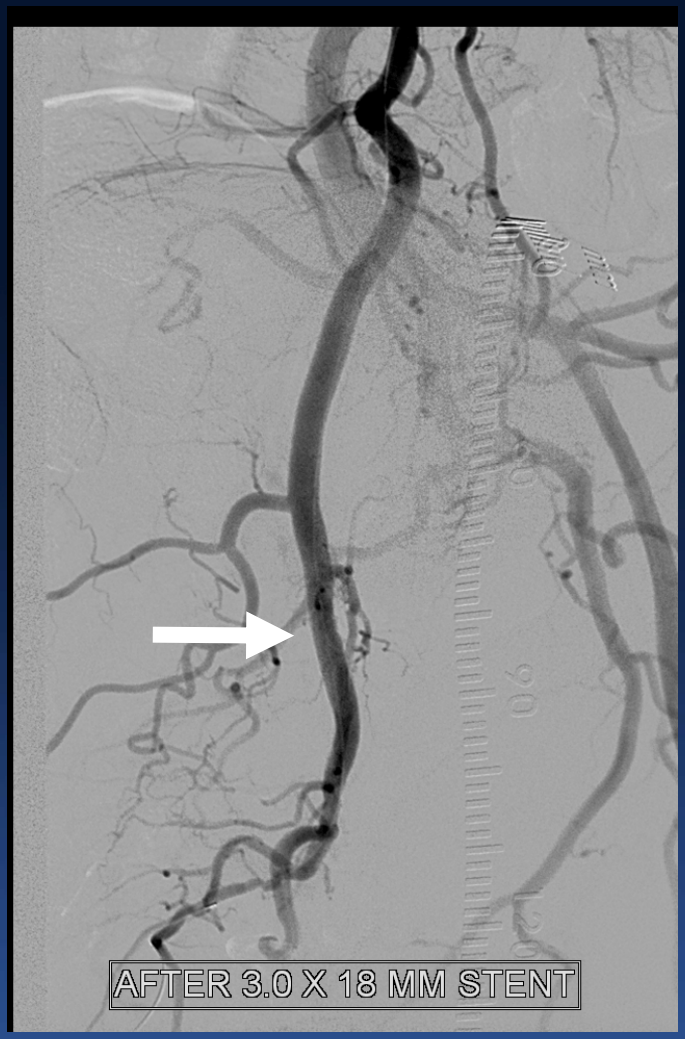
Medtronic ZEN Trial

Zotarolimus-Eluting Peripheral Stent System for the Treatment of Erectile Dysfunction in Males with Suboptimal Response to PDE5 Inhibitors

- Prospective, single arm trial
- Endpoints: 1°Safety, 2°Efficacy
- Enrolling 50 patients,15 U.S. centers

Left Internal Pudendal Stenosis and Rx





CARDIOVASCULAR RESEARCH FOUNDATION
A Passion for Innovation

COLUMBIA UNIVERSITY MEDICAL CENTER
NewYork-Presbyterian
The University Hospital of Columbia and Cornell

Interventional Cardiology 2011

Interventional Heritage

- Over more than three decades, interventional cardiology has evolved in stages, challenging conventional wisdom and overcoming biologic obstacles.
- Innovation combined with a commitment to rigorous scientific principles and a dedicated global collaboration has resulted in a vibrant medical subspecialty.
- BUT, during challenging times, interventional cardiology is at a crossroads – the re-emergence of medical therapy (post-COURAGE) and CABG (post-SYNTAX) coupled with financial pressures threaten to limit future vascular interventional growth.

Interventional Heritage

- **Now is the time to rediscover past success by extending the interventional model to other unmet cardiovascular needs.**
- **The breakthrough emergence of TAVI is the first step as interventional cardiology enters a new phase of striking diversity and creativity.**
- **The interventional community must respond by embracing change and providing the milieu future growth.**

Interventional Opportunities

The *FUTURE!*

There's never been a better time to be an interventional cardiologist!

Interventional Opportunities

The FUTURE!

Our Message:
ADAPT
and
EVOLVE!