# EMERGING TECHNOLOGIES @ I2 SUMMIT

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# EMERGING TECHNOLOGIES @ I2 SUMMIT

- Hypertension management
- Renal sympathetic denervation
- Baroreflex therapy
- Cell Therapy: CD34
- Biodegradable Stents
- Bifurcation Stents
- Imaging:  Chemogram to detect lipid content

# Catheter-Based Renal Sympathetic Denervation in the Management of Resistant Hypertension

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

Centre of Cardiovascular Research & Education in Therapeutics,
Monash University/Alfred Hospital,
Melbourne, Australia

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# Background

- Hypertension is a global public health problem of major magnitude
- Despite the availability of safe and effective pharmacological therapies, only ~50% of patients achieve adequate blood pressure control to guideline targets
- The sympathetic nervous system, in particular renal sympathetic efferent and afferent nerves, is recognized as critical in the hypertension disease process
- Disruption of renal sympathetic nerves has long been considered an attractive therapeutic target for this condition

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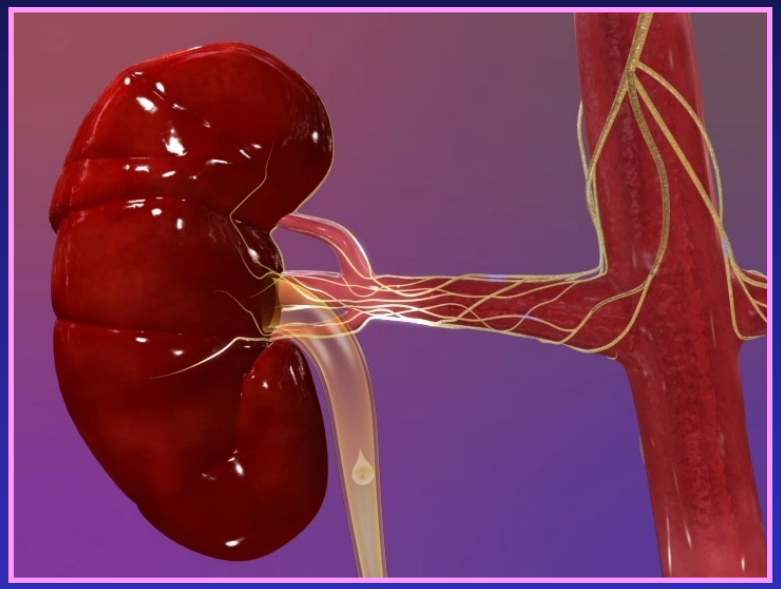
# Anatomical Location of Renal Sympathetic Nerves



- Arise from T10-L1
- Follow the renal artery to the kidney
- Primarily lie within the adventitia

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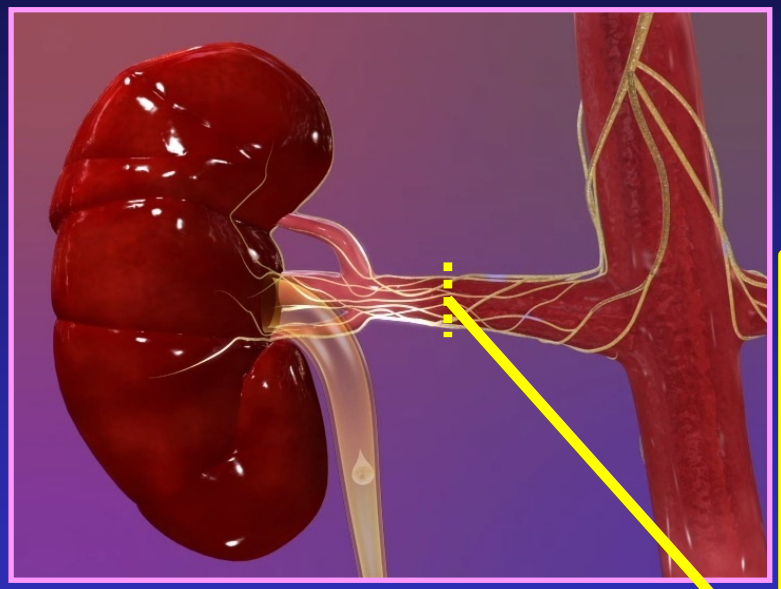
# Anatomical Location of Renal Sympathetic Nerves



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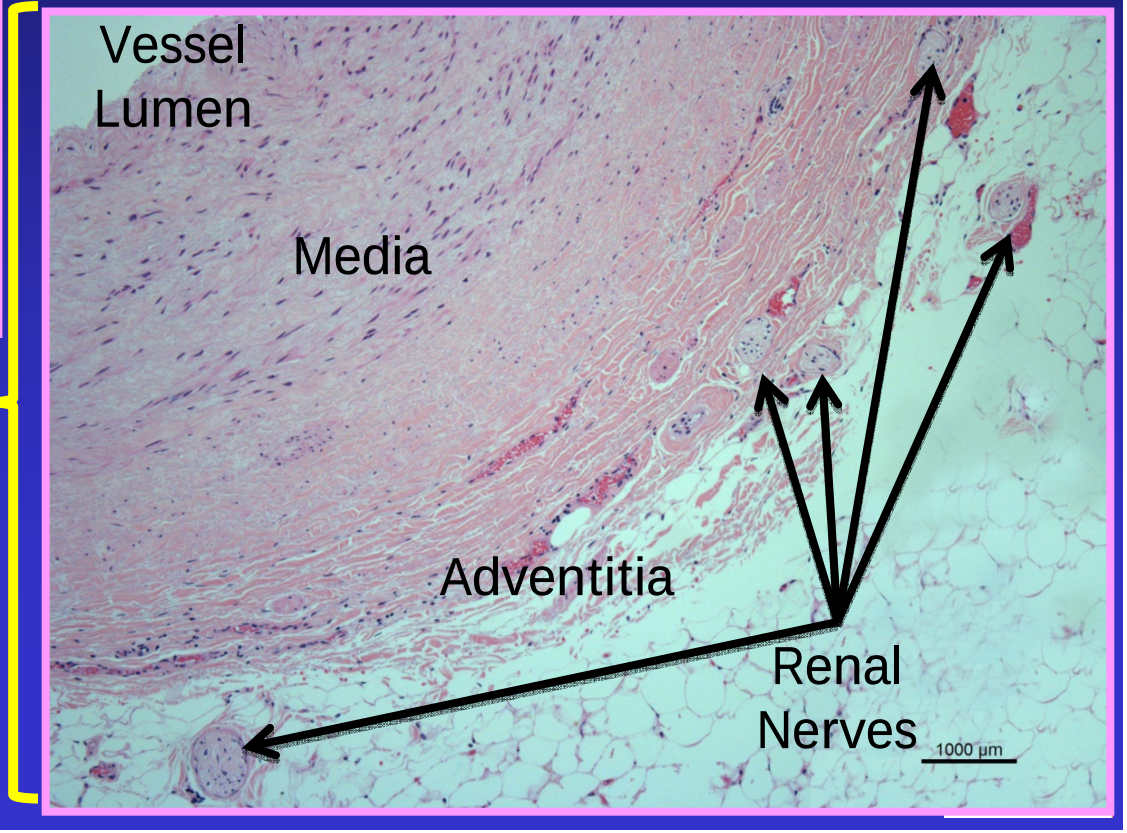
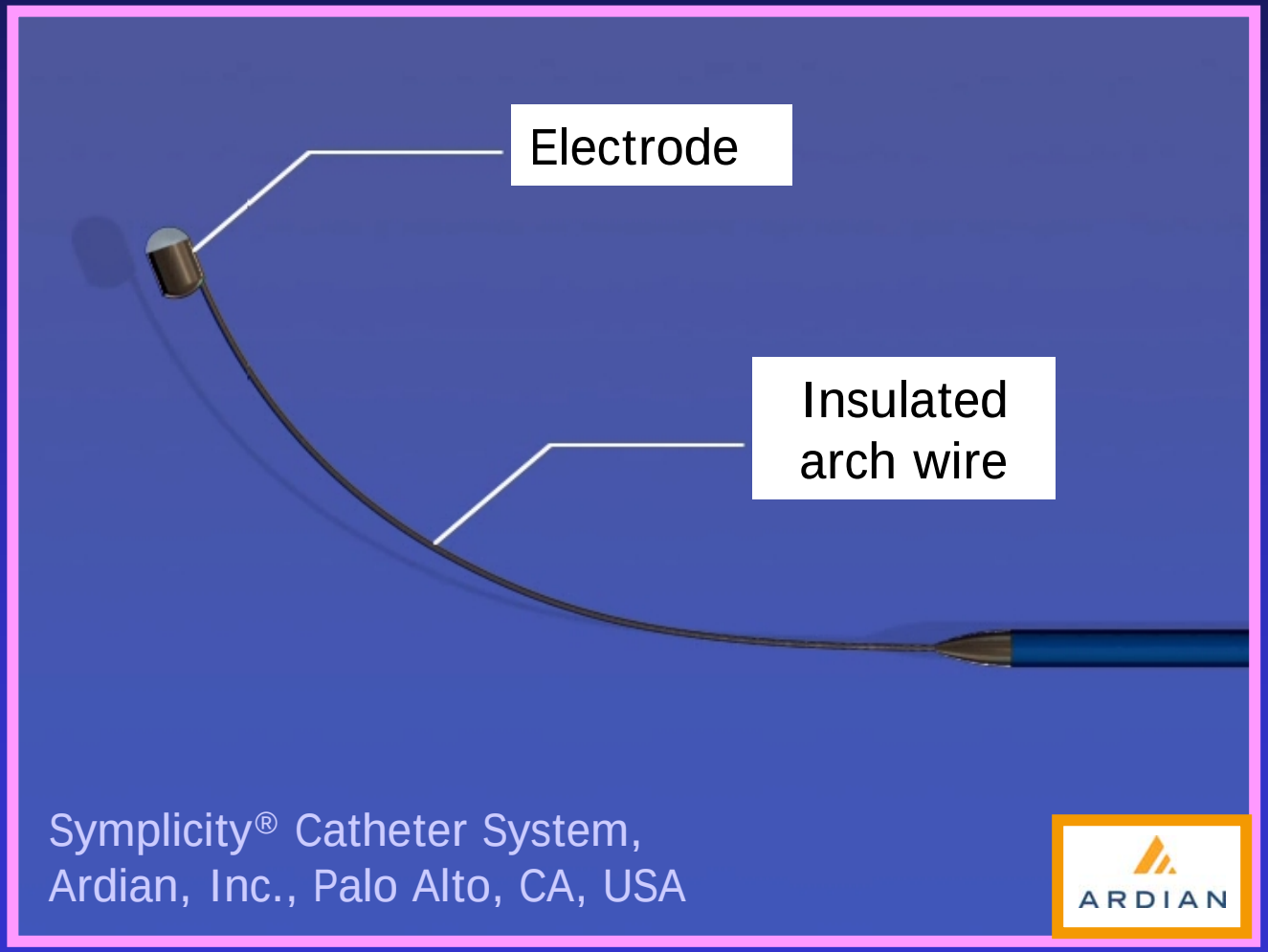


# RF Ablation Approach to Renal Sympathetic Denervation

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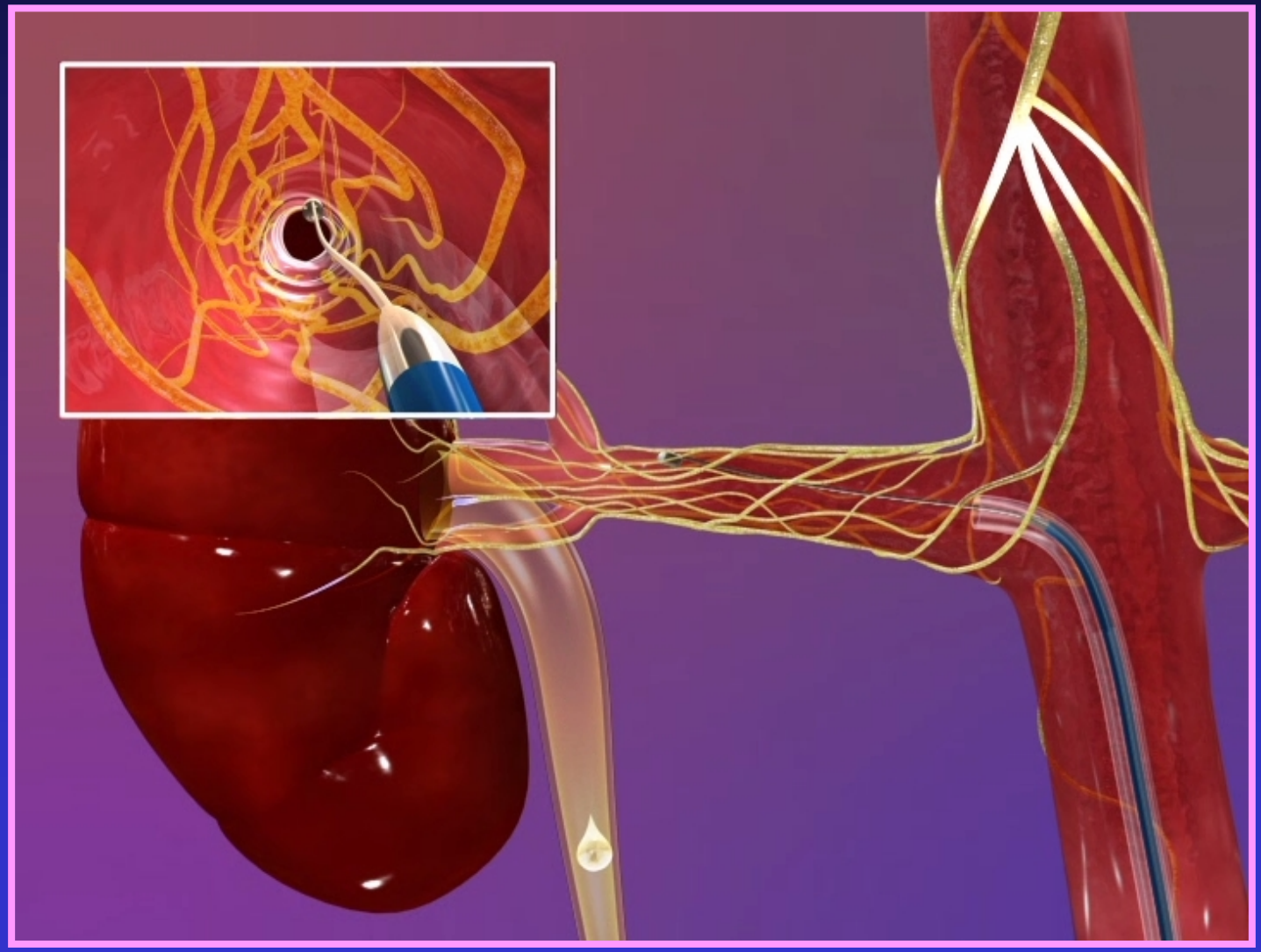
# Placement of Renal RF Catheter



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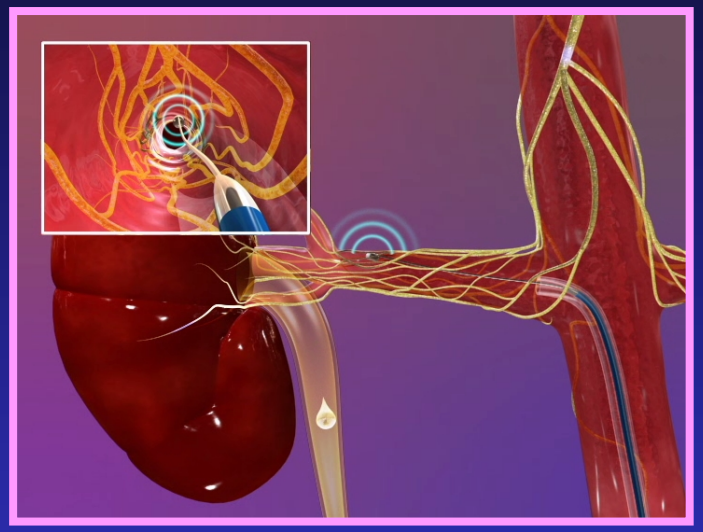
# Treatment by Renal RF Catheter



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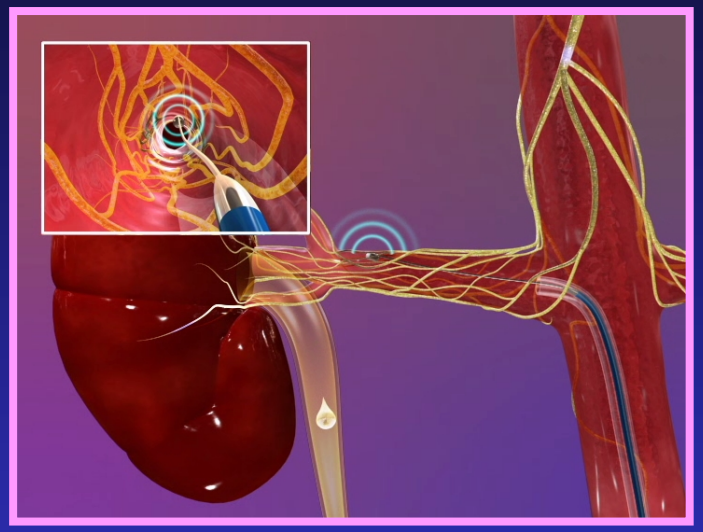

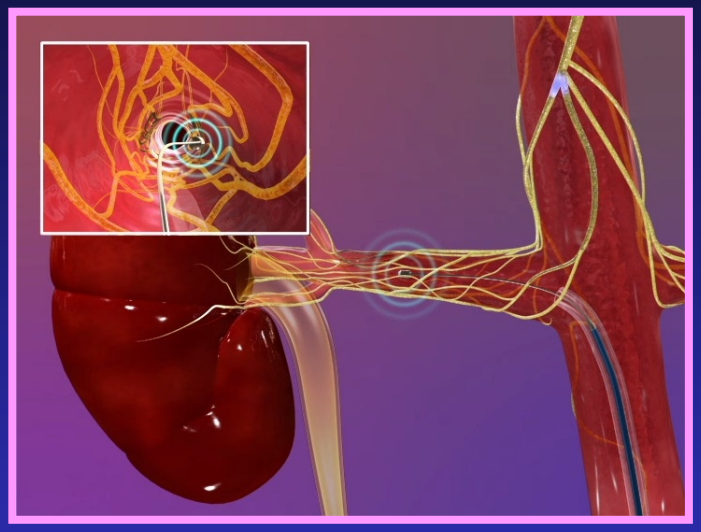

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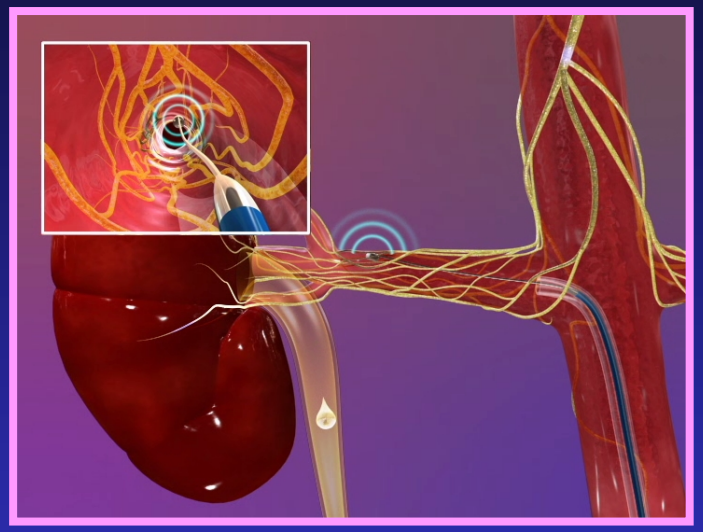
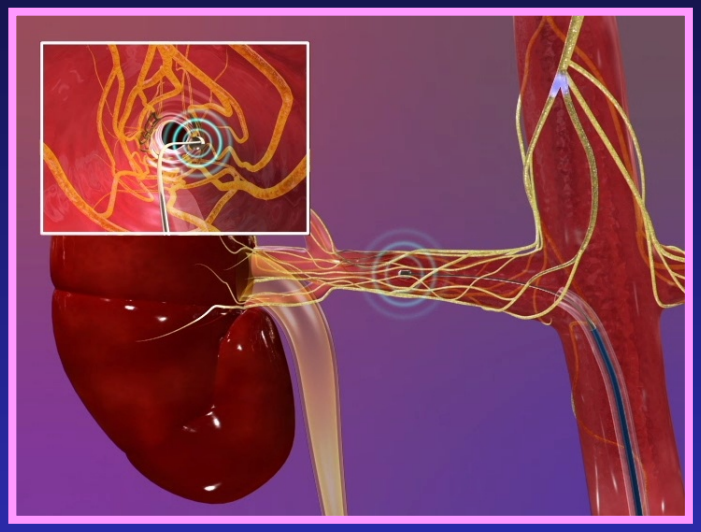
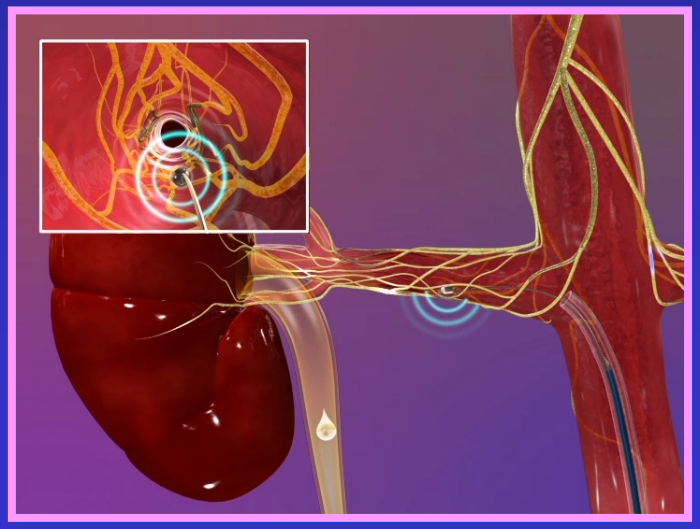
# Treatment by Renal RF Catheter







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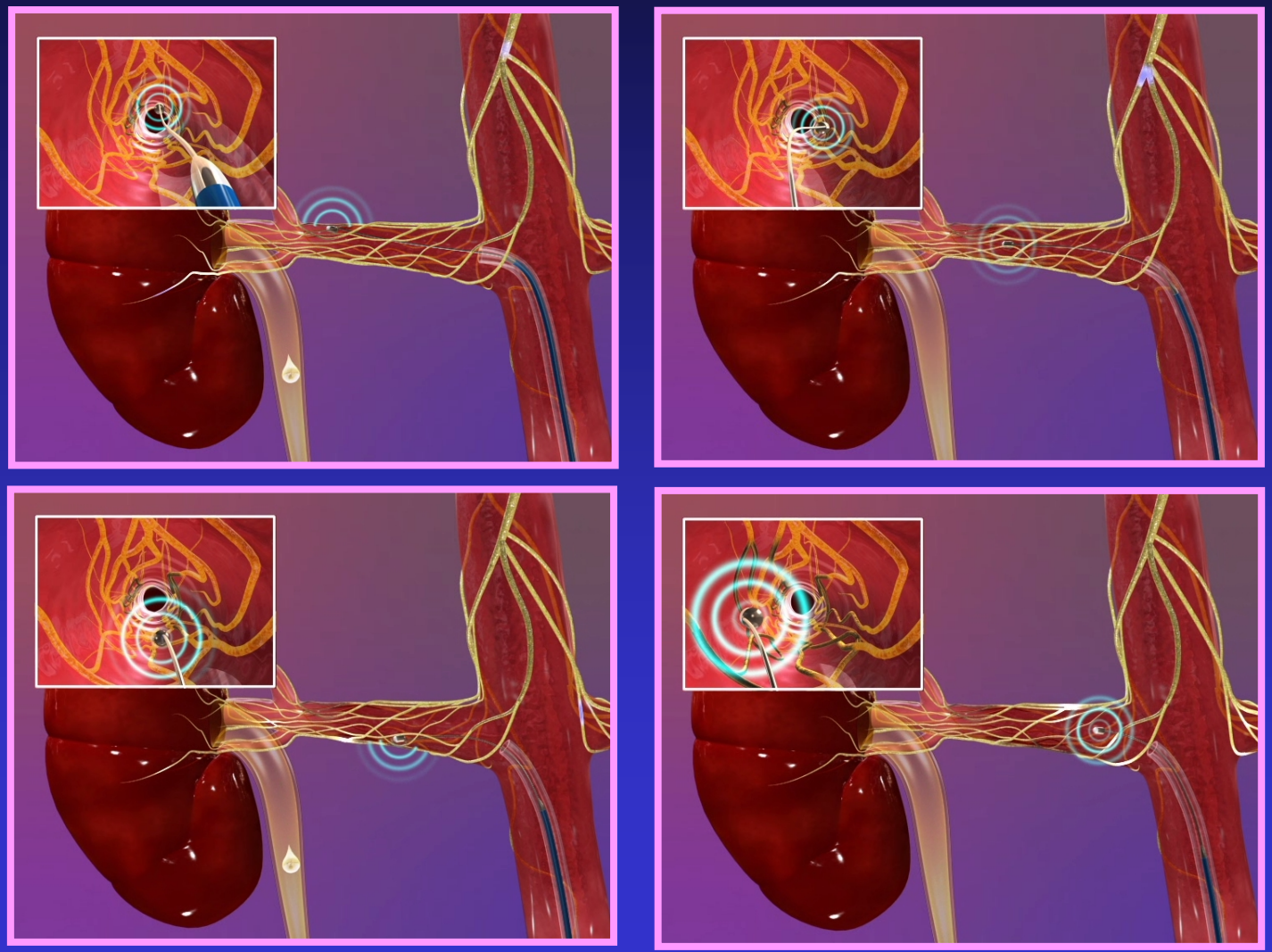
# Treatment by Renal RF Catheter



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# 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

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# Inclusion/Exclusion Criteria

***Key Inclusion Criteria***

- Office SBP ≥160 mmHg despite 3+ anti-hypertensive medications (including diuretic), or confirmed intolerance to medications
- eGFR (MDRD formula) of ≥ 45 mL/min/1.73m$^2$

***Key Exclusion Criteria***

- Known secondary cause of hypertension
- Type I diabetes mellitus
- Currently taking clonidine, moxonidine, or rilmenidine
- Renovascular abnormalities: significant renal artery stenosis, prior renal stenting or angioplasty, dual renal arteries

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# Study Endpoints

***Primary Endpoints***

- Peri-procedural and long-term safety
- Office blood pressure levels

*Secondary Endpoints*

- Ambulatory blood pressure monitoring
- Renal norepinephrine spillover rate
- Renal function (eGFR)

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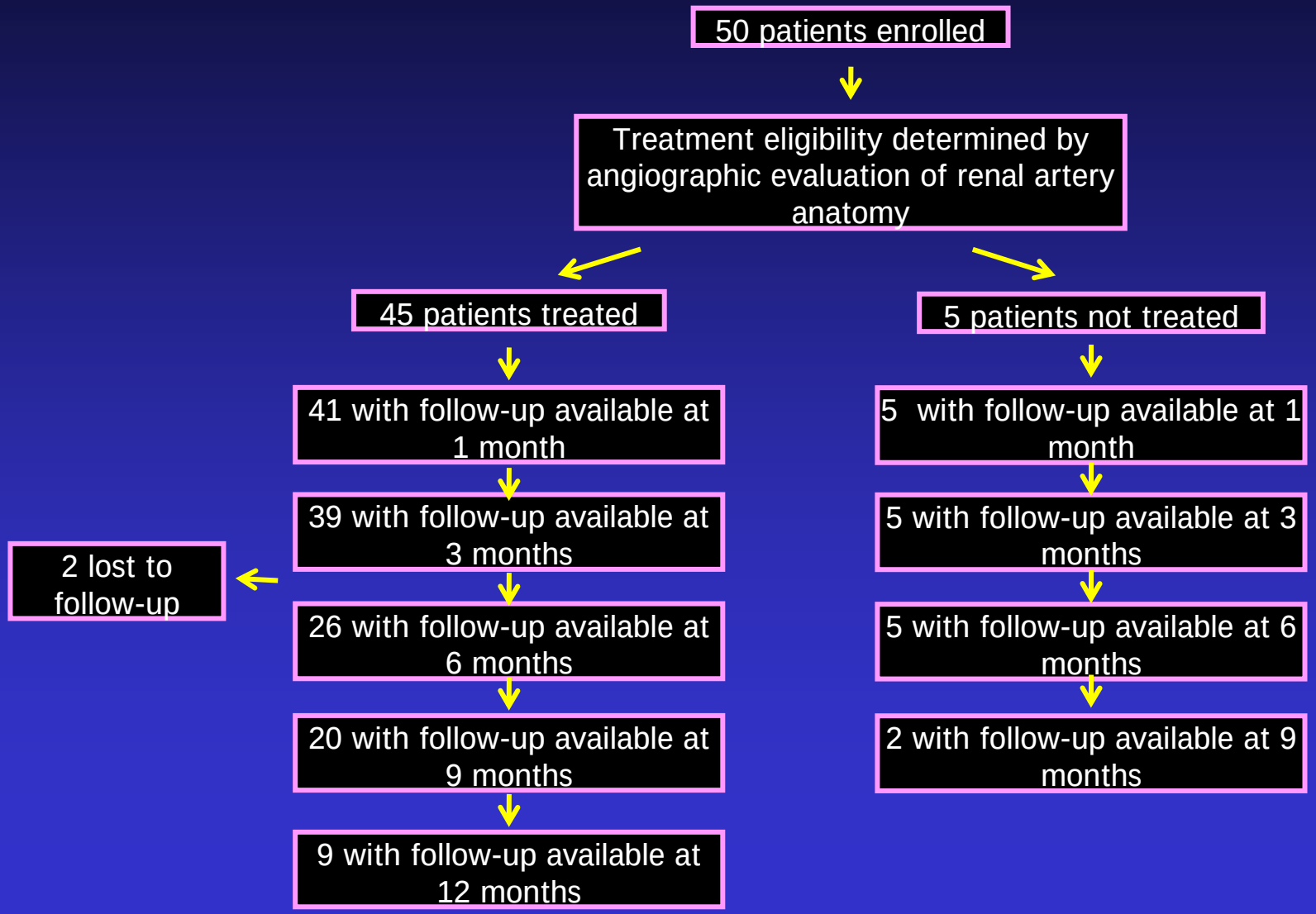
# Patient Disposition

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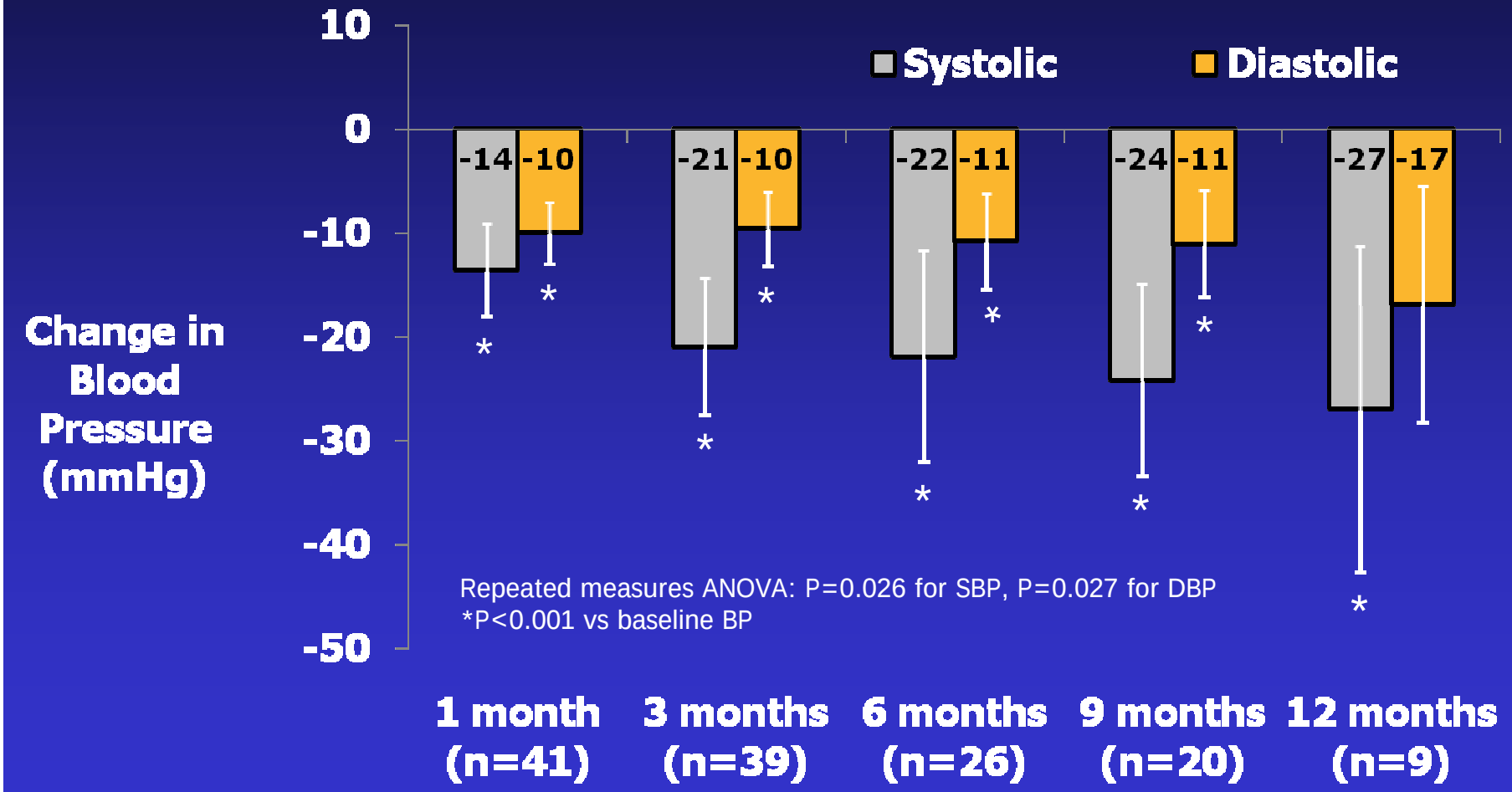
# Results

## *Office BP: All Treated Patients*




n=45

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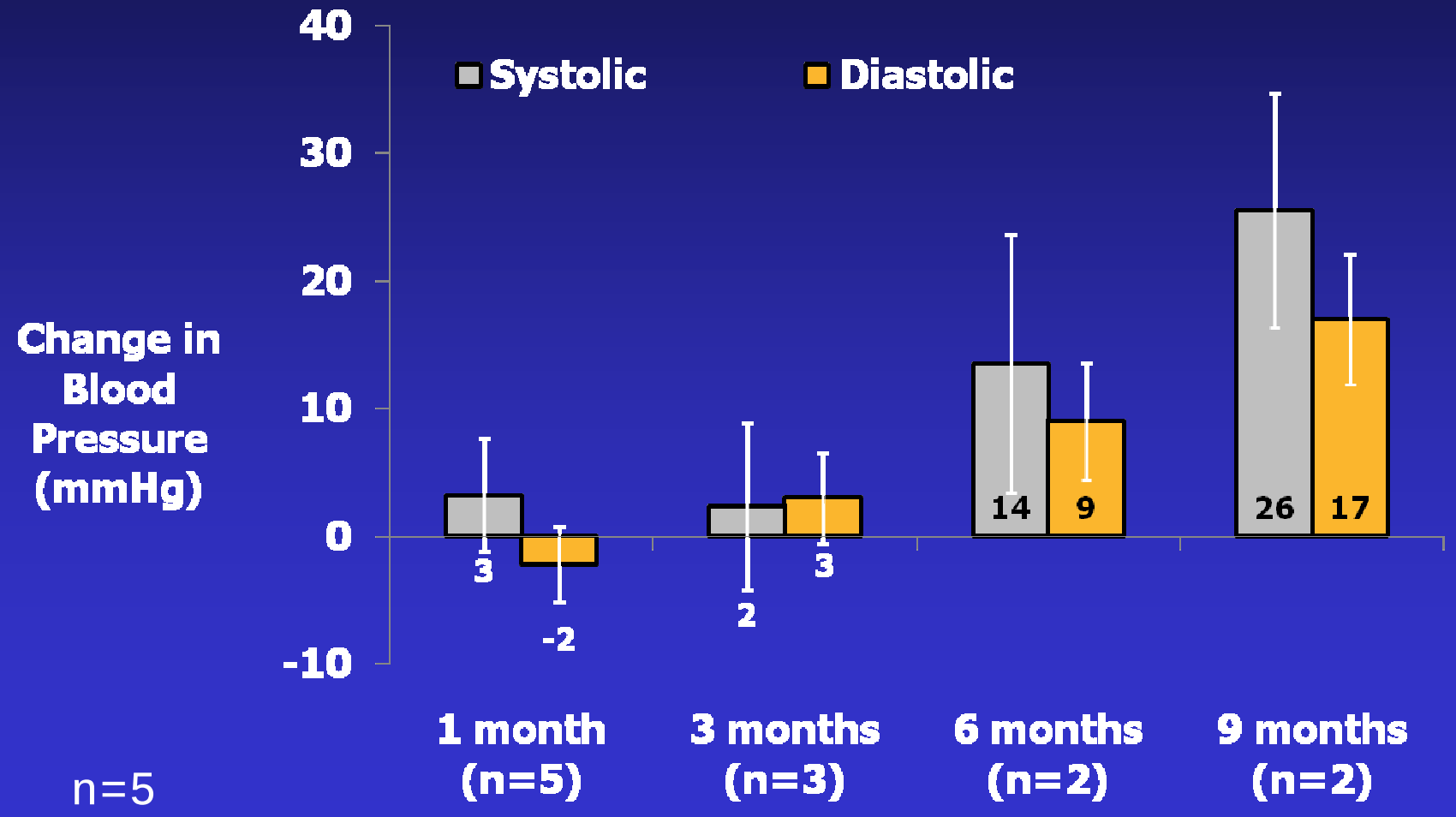
# Results

*Office BP: Untreated Patients*




n=5

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# Results

*Medication Changes*

- 4.7 ± 1.5 anti-hypertensive drugs at baseline; unchanged at patients' latest follow-up visit (p=NS)
- 3 patients required reduction of medications after normalization of BP
- 9 patients had their medications increased:
  - 5 were BP responders: >10mmHg BP reduction prior to medication increase
  - 4 were BP non responders

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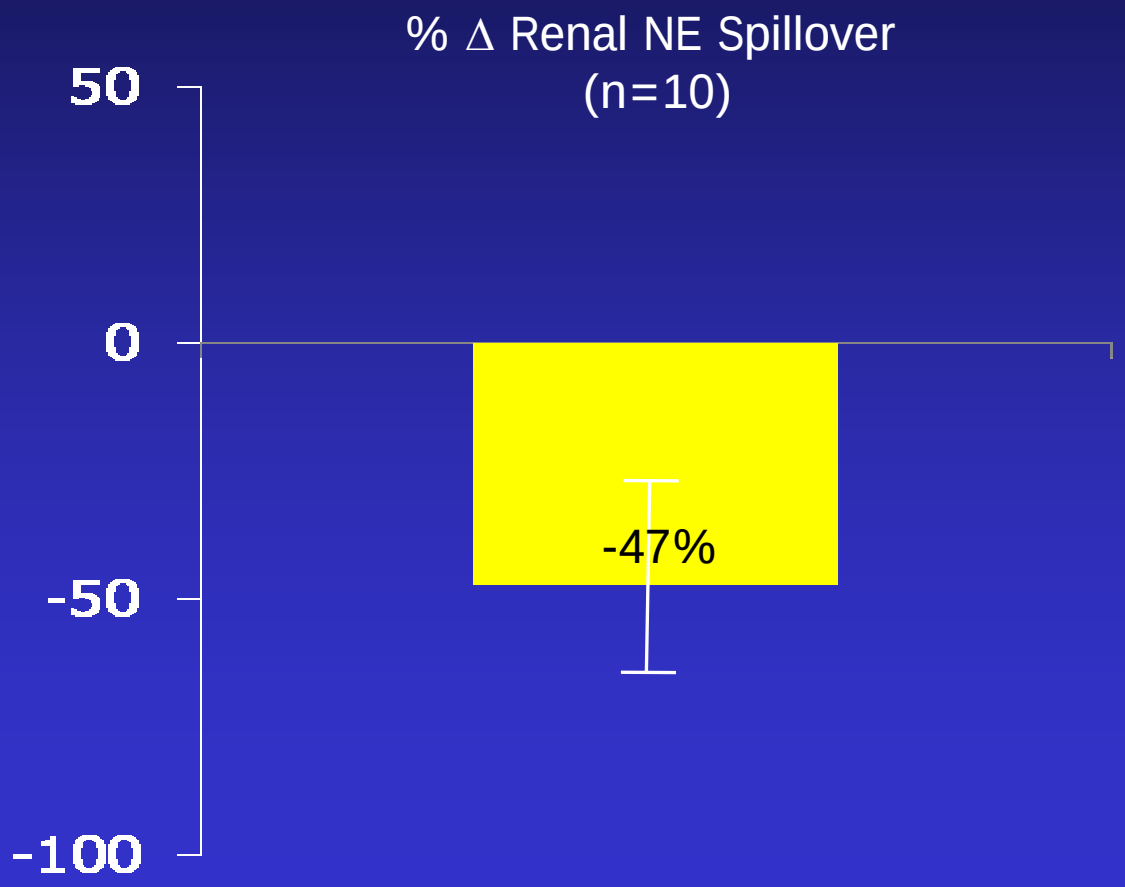
# Results

*Norepinephrine Data*

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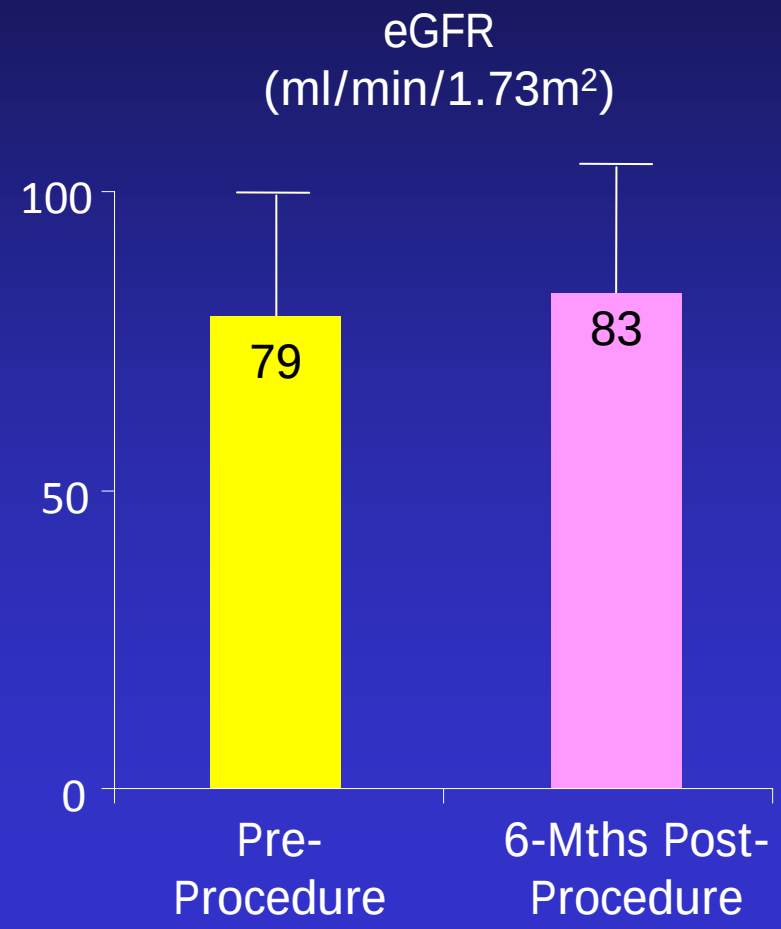
# Results

## *Renal Function*




n=25

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# Summary

- Therapeutic renal sympathetic denervation involves a brief, simple percutaneous procedure
- No major complications were observed to either the renal artery or the kidney
- Significant and sustained reductions in blood pressure were achieved in patients with resistant hypertension
- Achievement of denervation supported by significant reduction in renal norepinephrine spillover

# Randomized, Double-Blind, Placebo-Controlled Study of Intramyocardial CD34+ Cell Therapy for Refractory Angina

**Douglas W. Losordo, M.D.**
**on behalf of ACT34-CMI Investigators**

Northwestern University, Chicago, USA

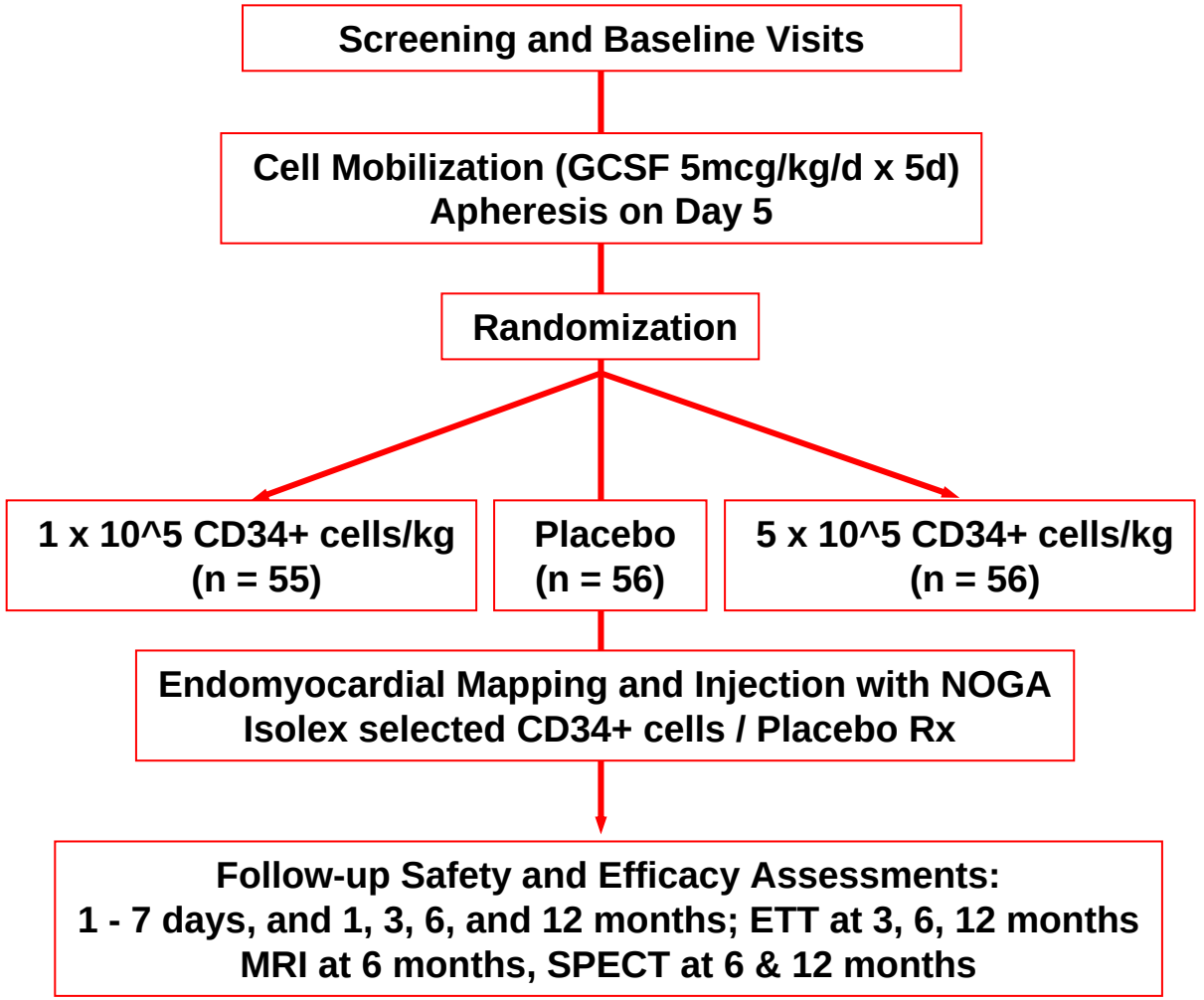
NORTHWESTERN UNIVERSITY

Baxter

# Phase II ACT34–CMI Study Design

**Subject population (n=167)**

- 21-80 yrs
- CCS class III or IV
- Angina
- Attempted “best” medical therapy
- Non-candidate for
- Surgical/Perc. revasc.
- Ischemia on SPECT
- 3-10 min. mod. Bruce protocol with angina or anginal equivalent at baseline



# Endpoints

## Safety

- Adverse event reporting, MACE, physical examination, vital signs, ECHO, laboratory parameters, revascularization procedures, hospitalization rates for cardiac related admissions and Emergency Department/Acute Care Service visits for cardiac related admissions will assess safety.

## Bioactivity

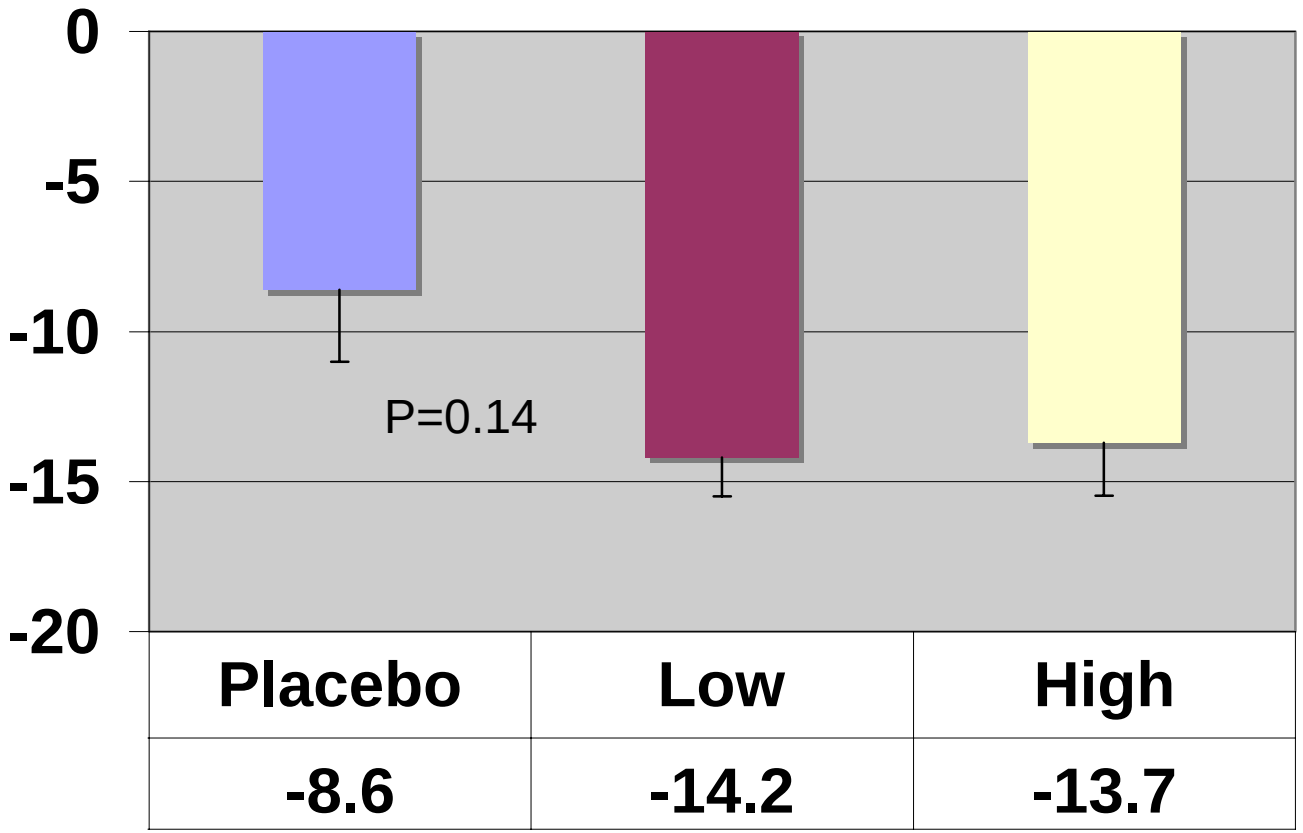
- Primary Efficacy variable is frequency of angina episodes per week, when comparing subjects receiving injection of CD34+ cells to placebo. Secondary Efficacy variables are divided into two categories, symptom relief and myocardial perfusion, and function measurement endpoints. Symptom Relief: ETT, anti-anginal medication, CCS functional class and QOL, and the combined rate of MACE events. Myocardial perfusion and function measurements: SPECT and cardiac MRI.

# Major Adverse Cardiac Events (12 Months)

| | Control | $1x10^5$ | $5x10^5$ | p-value |
|---|---|---|---|---|
| Any MACE | 25.0% | 12.7% | 14.3% | 0.194 |
| Death, MI, Urgent Revasc | 10.7% | 7.3% | 5.4% | 0.594 |
| Death, MI, Post-PCI MI, Urgent Revasc | 12.5% | 7.3% | 5.4% | 0.416 |
| Any MI | 7.1% | 9.1% | 5.4% | .707 |
| MI pre/injection | 3.6% | 1.8% | 1.8% | 1.000 |
| Death, MI, Urgent Revasc, Worse CHF, ACS | 21.4% | 9.1% | 8.9% | 0.123 |

# ACT-34 CMI: Reduction in Angina

**Anginal Episodes per Week**
**Change from baseline at 6 months**




**Poisson Regression with Extra Variability**

# ACT-34 CMI: Reduction in Angina

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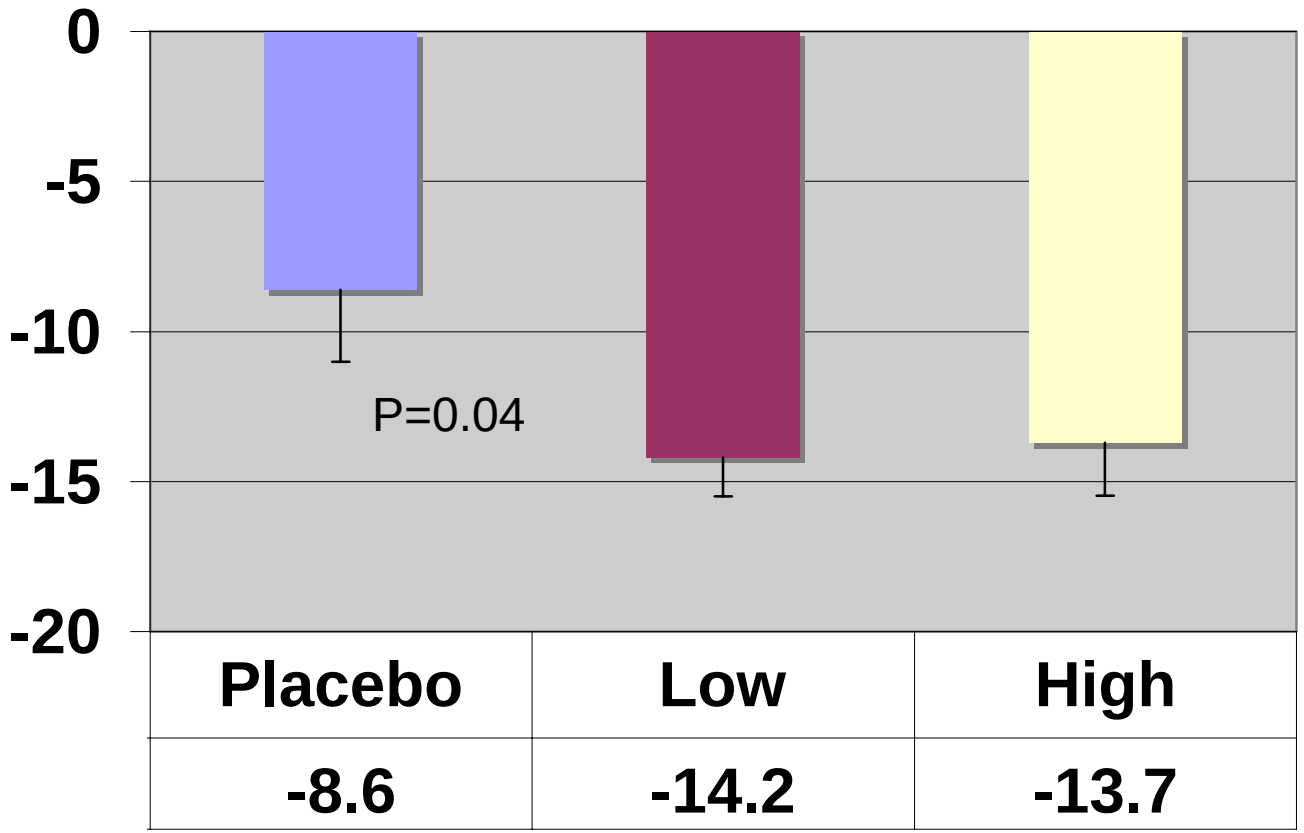
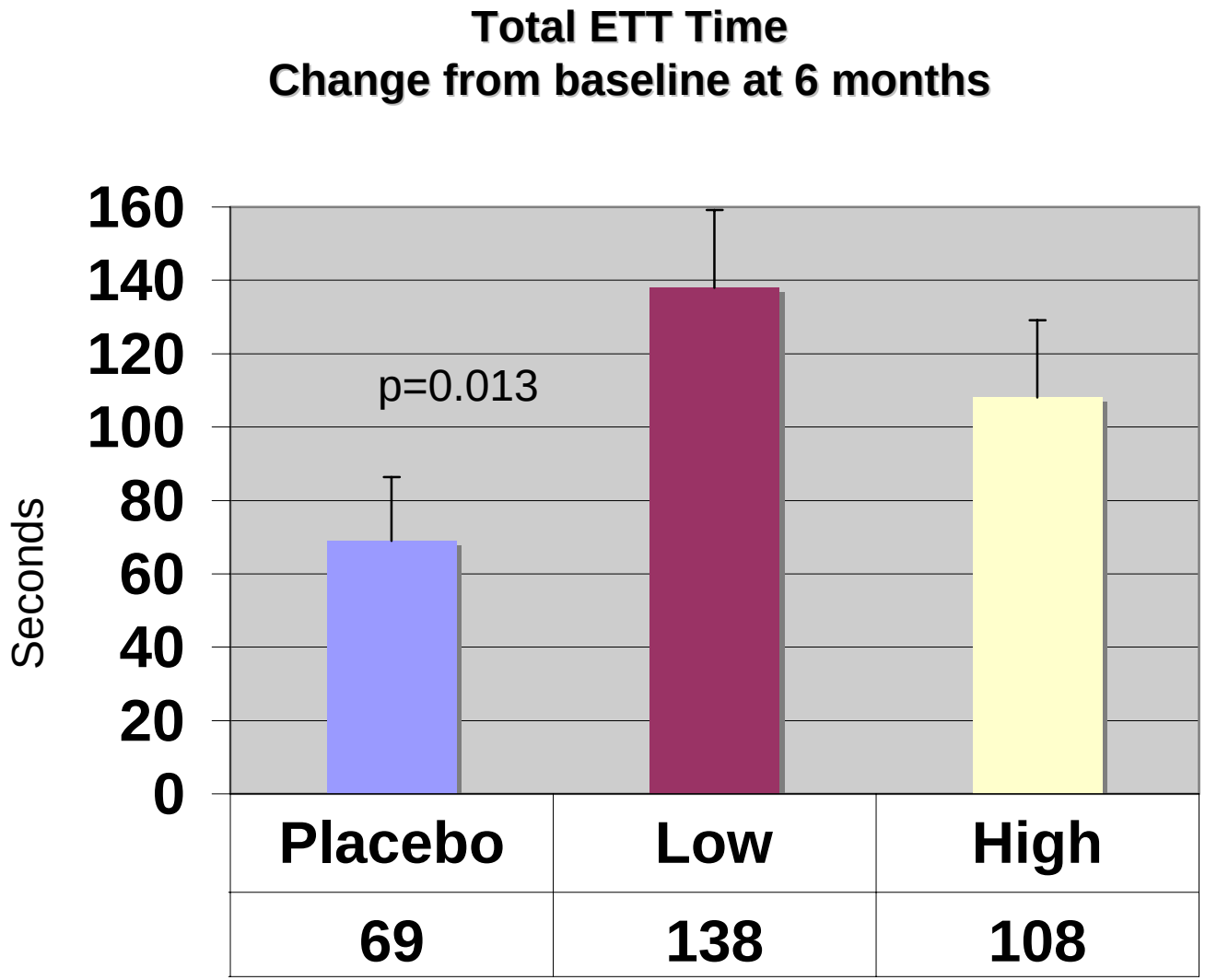



| Placebo | Low | High |
|---|---|---|
| -8.6 | -14.2 | -13.7 |

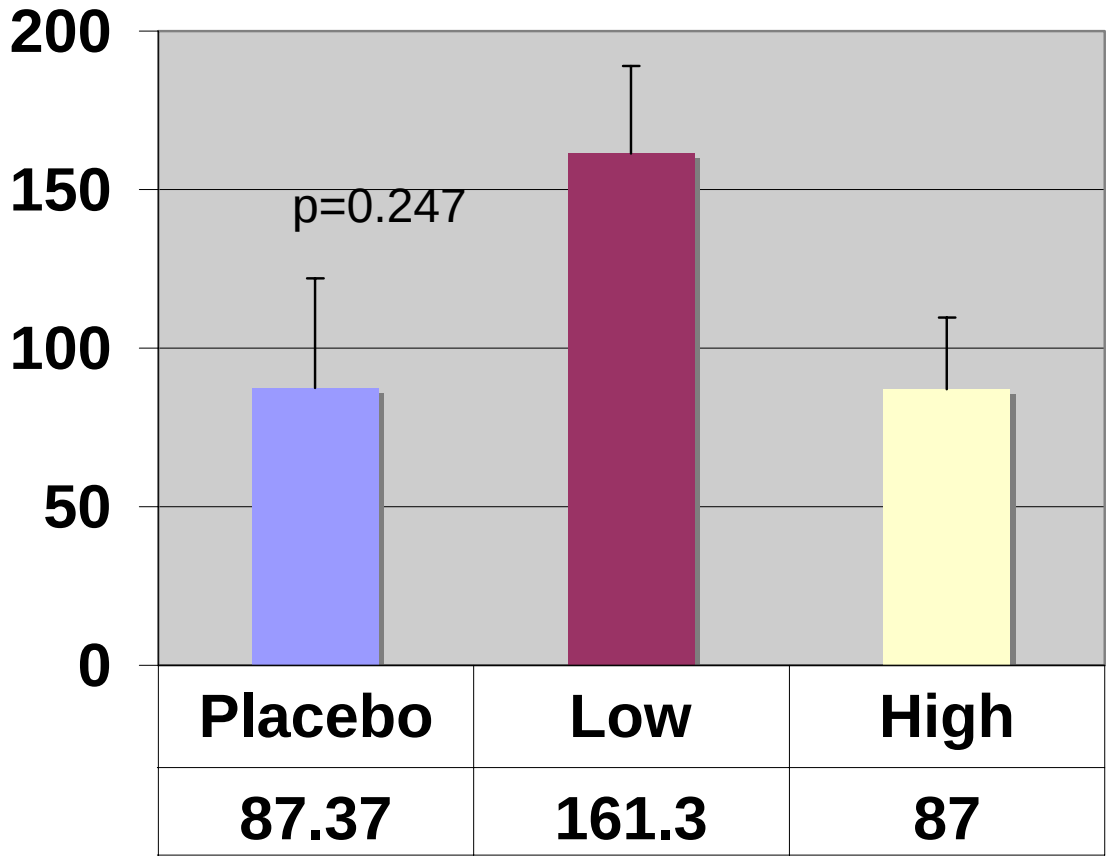
**Analysis of Variance (ANOVA)**

# ACT-34 CMI: Increase in Exercise Time



# ACT-34 CMI: Increase in Time to Angina

**Time to Angina**
**Change from baseline at 6 months**



# Conclusions

- 167 “no-option” refractory angina pts enrolled in RCT of intramyocardial autologous $CD34^+$ stem cell therapy
- Safety profile appears acceptable
- Significant improvement in ETT - first demonstrated in this population
- Trend to reduced angina

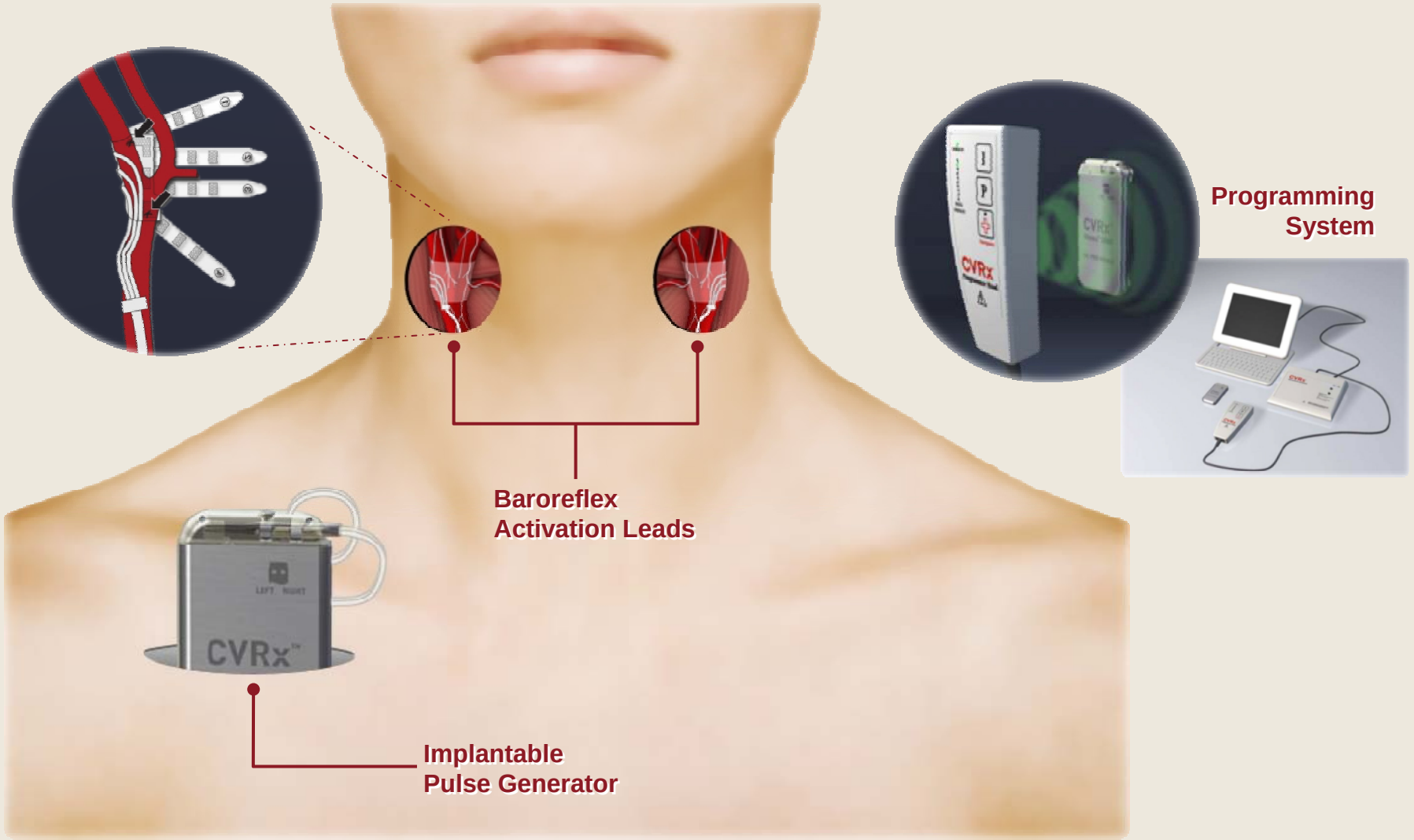
# Chronic Treatment of Resistant Hypertension with an Implantable Medical Device: Interim 3 Year Results of Two Studies of the Rheos® Hypertension System

Marcos Rothstein[1], Peter de Leeuw[2], Myriah Elletson[3]

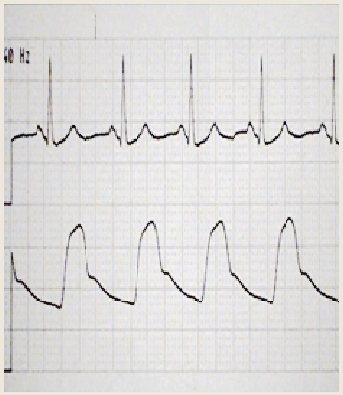
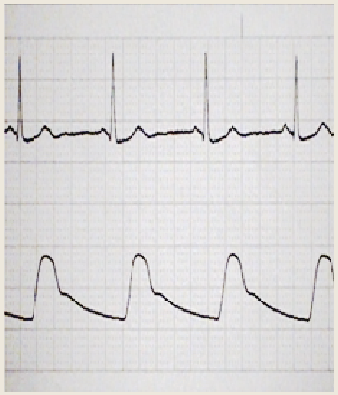
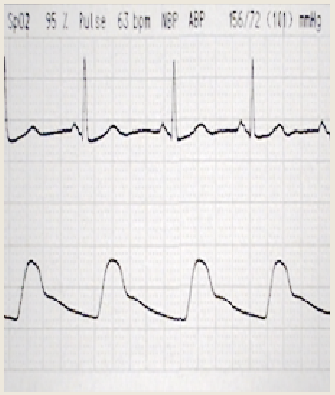
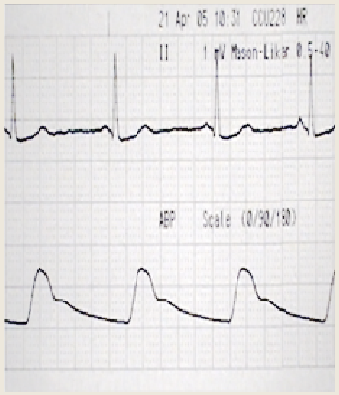
for the DEBuT and Rheos Feasibility Investigators

[1] Washington University School of Medicine
[2]Academisch Ziekenhuis Maastricht (AZM)
[3] CVRx, Inc.

# The CVRx® Rheos System

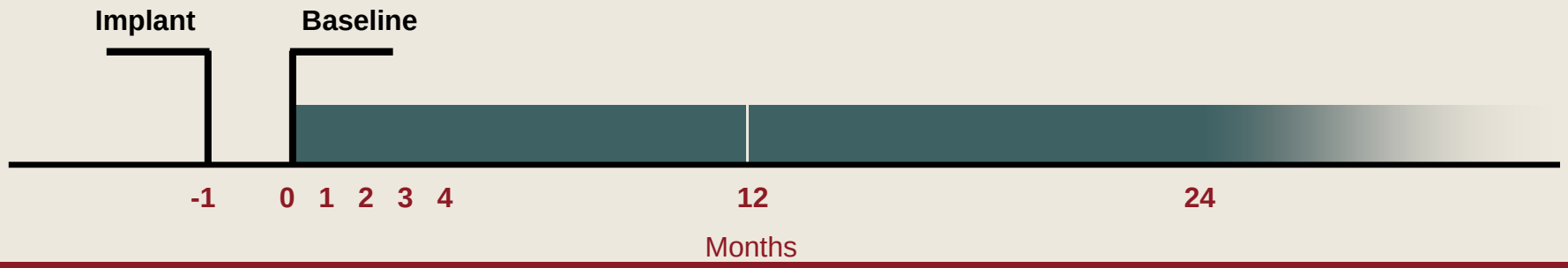


# Ability to Personalize and Control the Therapy

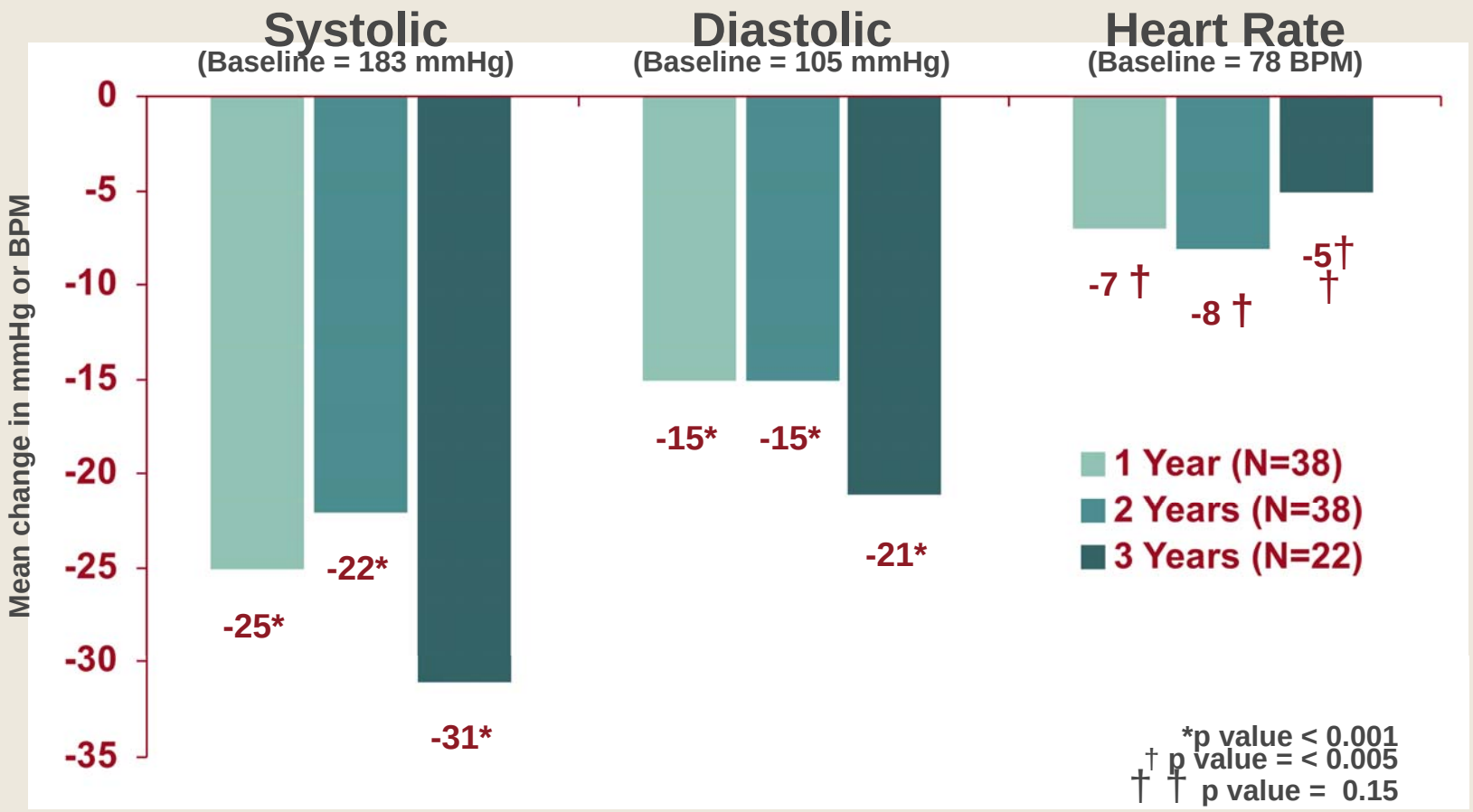
| | Control | 1 Volt | 2 Volts | 3 Volts |
|---|---|---|---|---|
| |  |  |  |  |
| **Heart Rate** bpm | 71 | 56 | 58 | 50 |
| **Blood Pressure** mmHg | 210 / 96 | 168 / 73 | 156 / 72 | 144 / 66 |

# Feasibility Trial Design

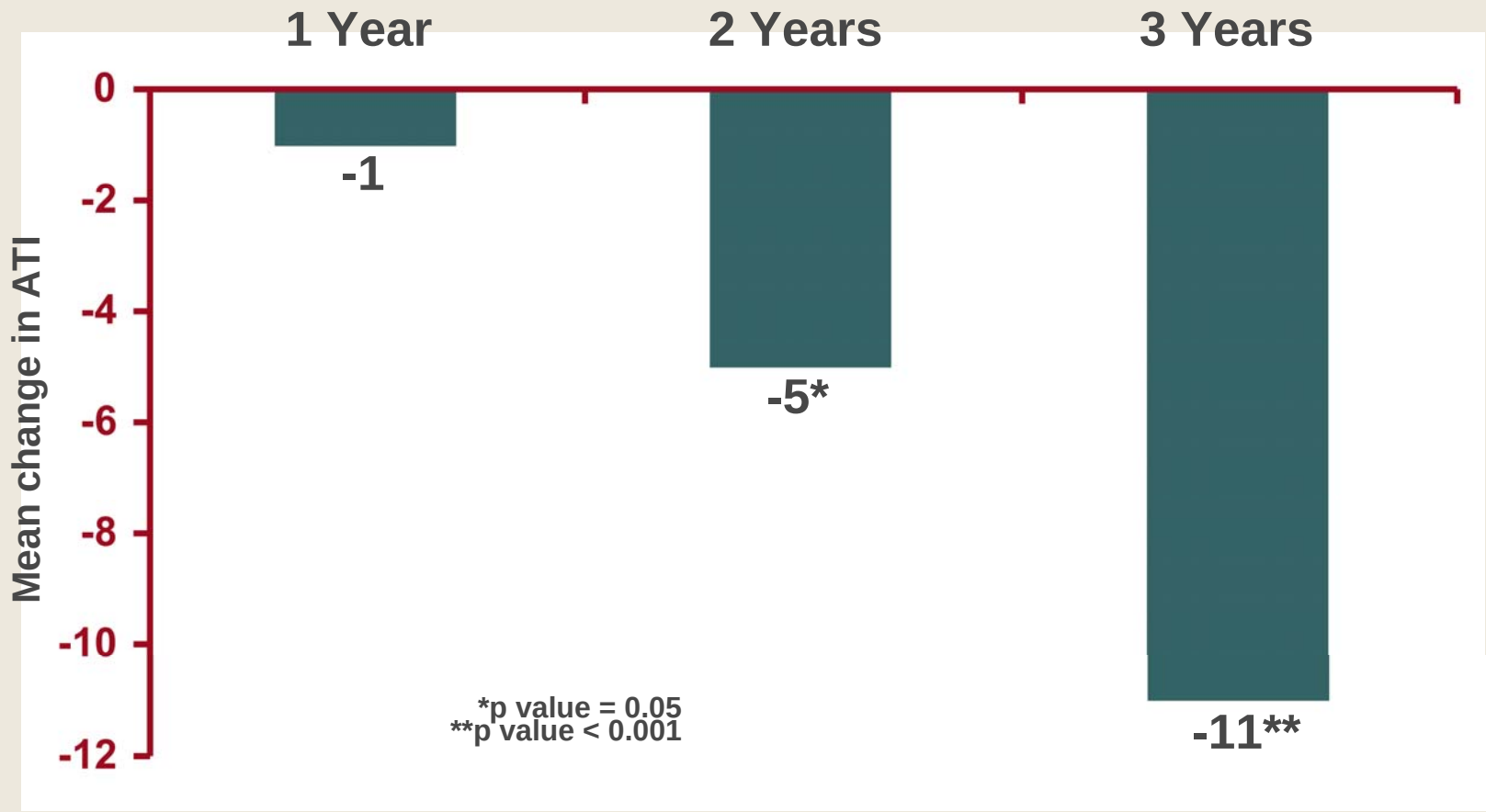
- Subjects implanted at both European and US centers
  - Multi-drug resistant systolic hypertension (SBP ≥ 160 mmHg)
  - 3+ anti-hypertensive medications with 1 diuretic
  - Must not have hypertension secondary to a treatable cause
  - Anti-hypertensive medications constant during the first 3 months of active treatment per protocol design
  - Continued annual follow-up



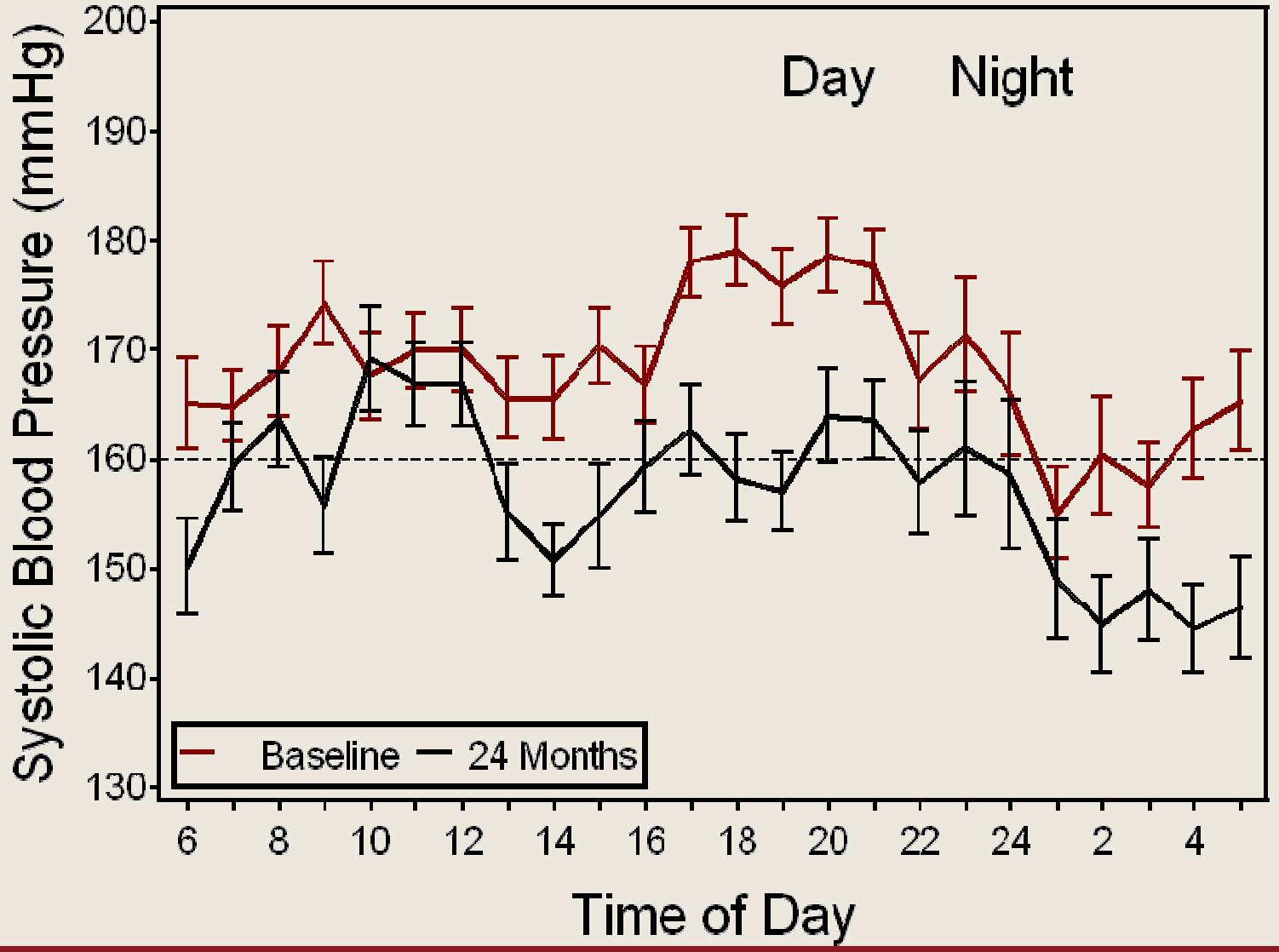
# Office BP Response to Rheos Therapy



# Change in Antihypertensive Therapeutic Index over Time



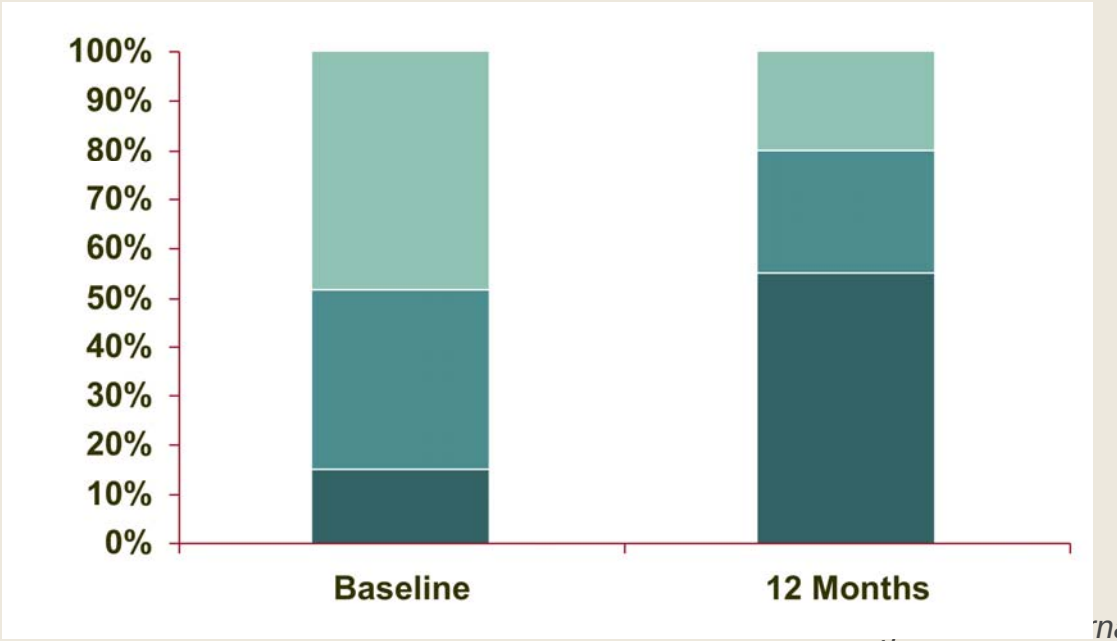
# Diurnal Variation Preserved (24-hour Ambulatory, N=19)



# Cardiac Structure and Function Improvements

| N=18 | Baseline | Δ 12 Months |
|---|---|---|
| LV Mass Index (g/m$^2$) | 132.8 ± 33.3 | –25.0 ± 18.2* |
| Left Atrial Dimension (mm) | 44.1 ± 8.1 | –2.4 ± 3.5* |
| Mitral E Wave Velocity (cm/s) | 85 ± 19 | –5 ± 14 |
| Mitral A Wave Velocity (cm/s) | 83 ± 22 | –10 ± 13* |

Values: mean ± SD *p value <0.05




*nal of Cardiac Failure* 2008;14(No. 6S Suppl):S48.

## Conclusions

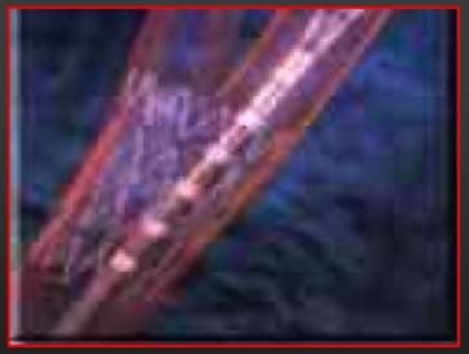
- Baroreflex hypertension therapy demonstrates clinically meaningful and sustained reduction in blood pressure in subjects with drug resistant hypertension
- The Rheos therapy also has been shown to improve cardiac structure and function
- These findings merit further investigation of this chronic device-based approach for hypertension management
- A randomized, blinded pivotal trial approved by FDA is underway

# Dedicated Bifurcation Stents

AST petal

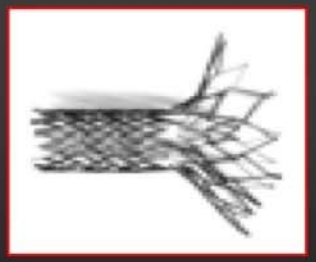
Guidant frontier

Trireme



Devax (+ BA9)

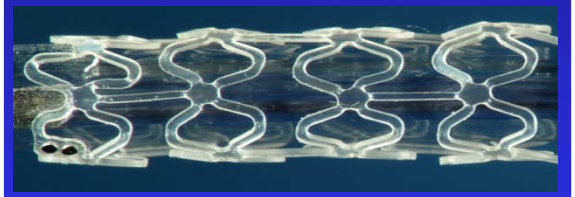
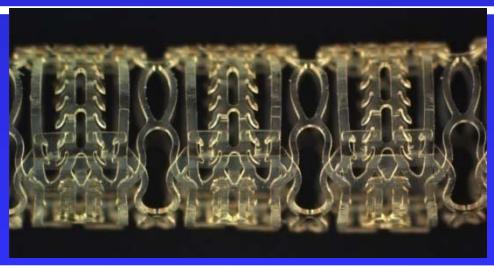
“true” bifurcation designs



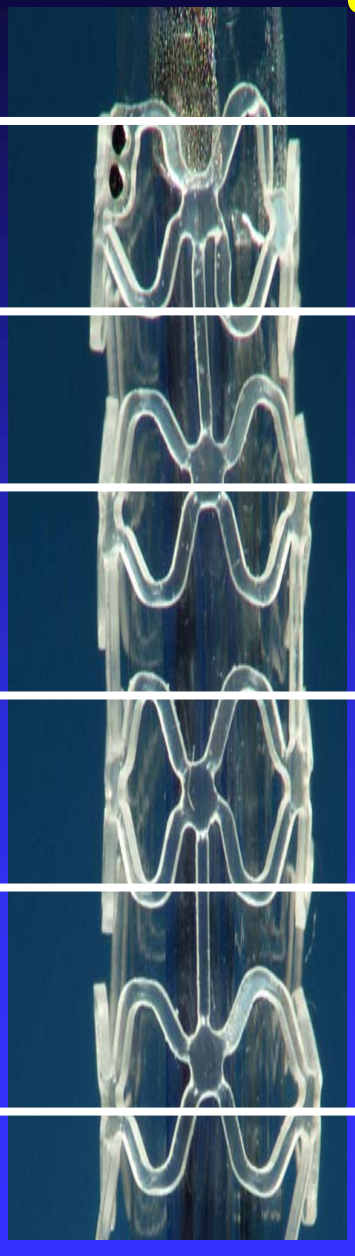
sidebranch designs

# Bioabsorbable Stents Programs: Overview

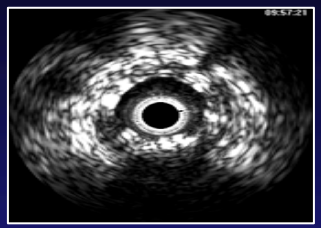
Clinical

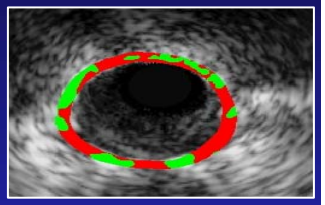
| Company | Picture | Polymer / Drug | Features |
|---|---|---|---|
| **Igaki-Tamai** (2000) |   | **PLLA PLLA plus Tranilast** | **Zig-zag design deployed with a heated balloon** |
| **Biotronik** (2006) |  | **Mg alloy** | **Balloon expandable design** |
| **Abbott (BVS)** (2007) |  | **PLLA with everolimus** | **Balloon expandable** |
| **Reva Medical** (2008) |  | Tyrosine poly carbonate with Iodine for radio-opacity | Design has ratchet links for deployment |
| **BTI** (2008) |  | Salicylic acid blended into polymer (PLA or adipic acid) with sirolimus | **Balloon expandable** |

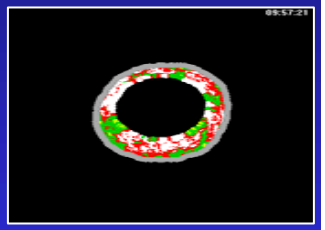
# The Absorb trial: imaging follow-up at 6 months and 2 years

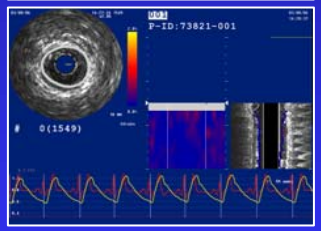


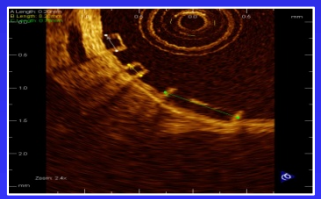
- QCA
- **Echogenicity**
- IVUS, IVUS-VH
- Palpography
- OCT
- MSCT — 18 months

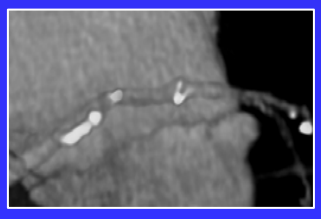




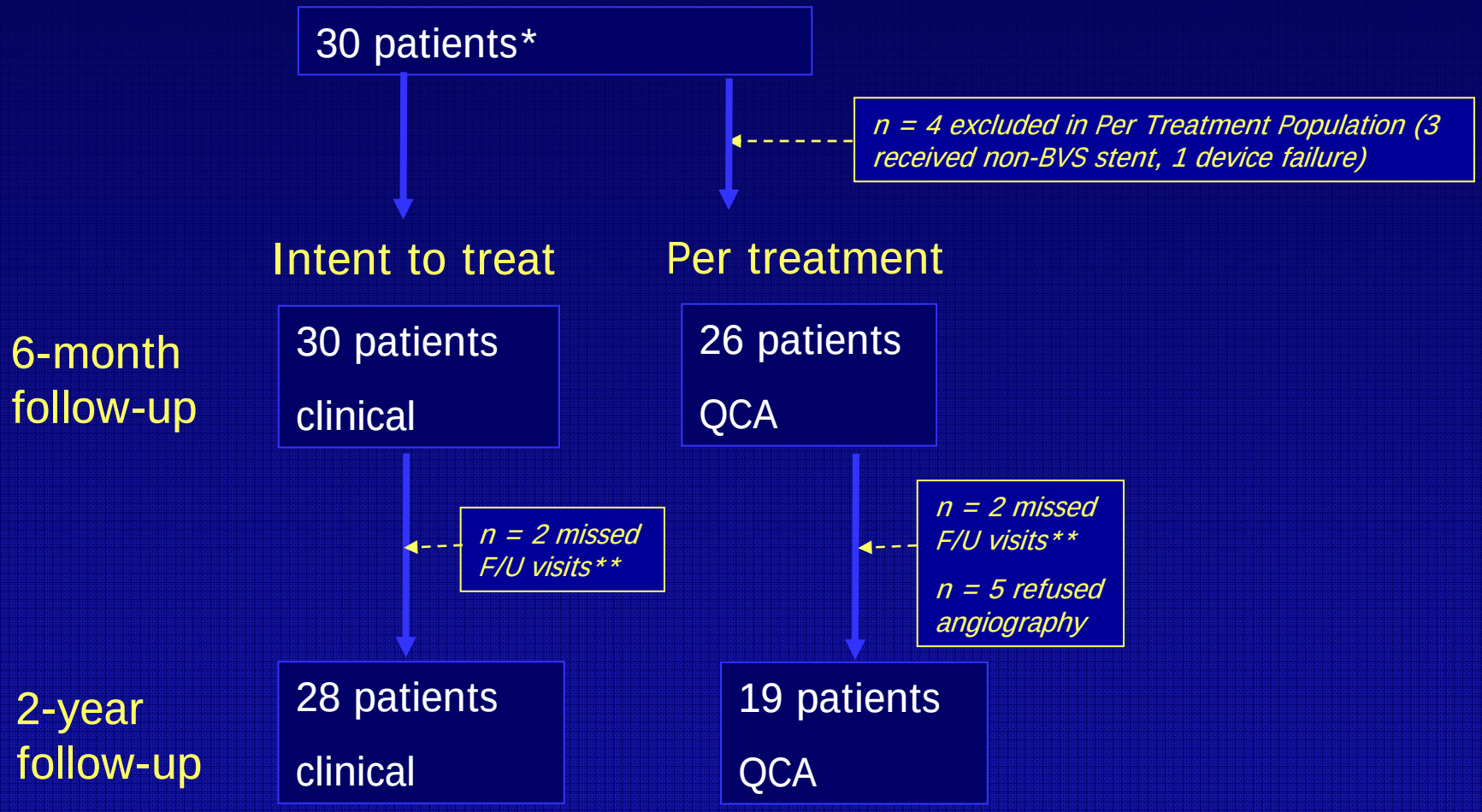






# Clinical Study Overall Population




* Intent-to-treat population

** One patient missed the 9, 12, 18 month and 2 year visits. One patient died from a non-cardiac cause 706 days post procedure

J. Ormiston, TCT 2008

# Clinical Results at 6, 12 and 24-Months: Intent to treat

| Hierarchical | 6 Months<br>30 Patients | 12 Months<br>29 Patients** | 24 Months<br>28 Patients** |
|---|---|---|---|
| **Ischemia Driven MACE** | 1 (3.3%)* | 1 (3.4%)* | **1 (3.6%)*** |
| **Cardiac Death** | 0 (0.0%) | 0 (0.0%) | **0 (0.0%)** |
| **MI** | 1 (3.3%)* | 1 (3.4%)* | **1 (3.6%)*** |
| **Q-Wave MI** | 0 (0.0%) | 0 (0.0%) | **0 (0.0%)** |
| **Non Q-Wave MI** | 1 (3.3%)* | 1 (3.4%)* | **1 (3.6%)*** |
| **Ischemia Driven TLR** | 0 (0.0%) | 0 (0.0%) | **0 (0.0%)** |
| **by PCI** | 0 (0.0%) | 0 (0.0%) | **0 (0.0%)** |
| **by CABG** | 0 (0.0%) | 0 (0.0%) | **0 (0.0%)** |

No new MACE between 6 and 24 months

*Same patient – this patient also underwent a TLR, not qualified as ID-TLR (DS = 42%)
** One patient missed the 9, 12, 18 month and 2 year visits. One patient died from a non-cardiac cause 706 days post procedure
*** MACE - Composite endpoint comprised of cardiac death, myocardial infarction (MI) and ischemia-driven target lesion revascularization (TLR) by PCI or CABG.

J. Ormiston, TCT 2008

# Stent Thrombosis through 2 Years – Intent to treat

Per protocol and per ARC definition

**0 – 2 Years**

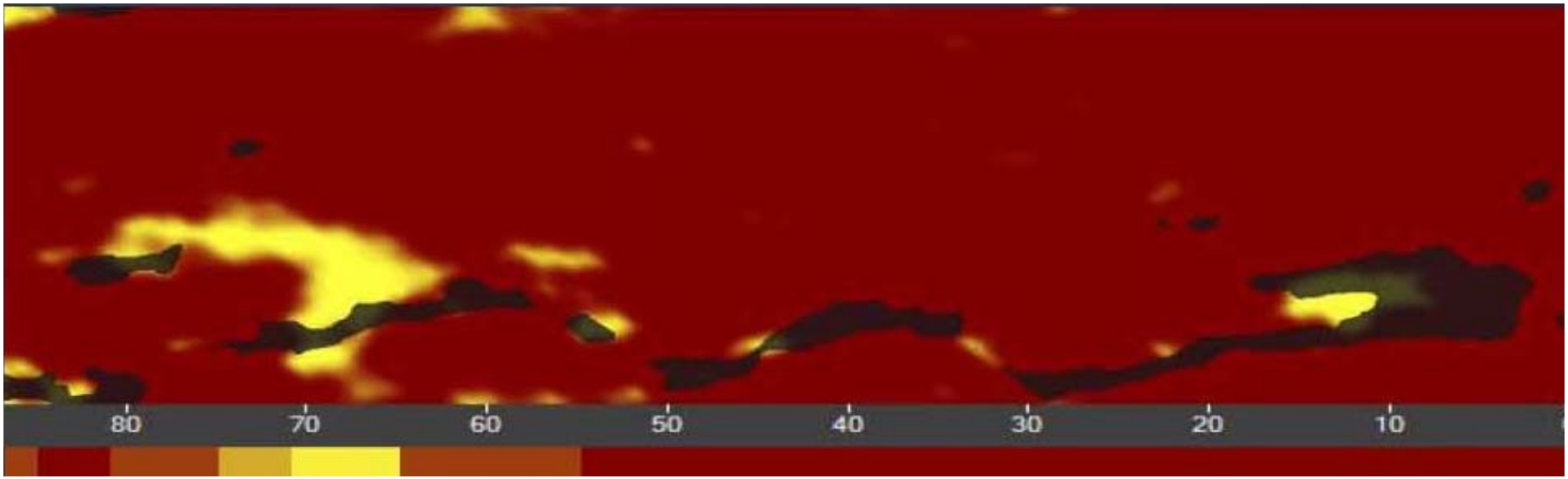
| | | |
|---|---|---|
| **Acute (< 1 day)** | **0 (0.0%)** | **N = 30** |
| **Sub-Acute (1 – 30 days)** | **0 (0.0%)** | **N = 30** |
| **Late (> 30 days – 1 year)** | **0 (0.0%)** | **N = 29** |
| **Very Late (> 1 year)** | **0 (0.0%)** | **N = 29** |

No stent thrombosis up to 2 years

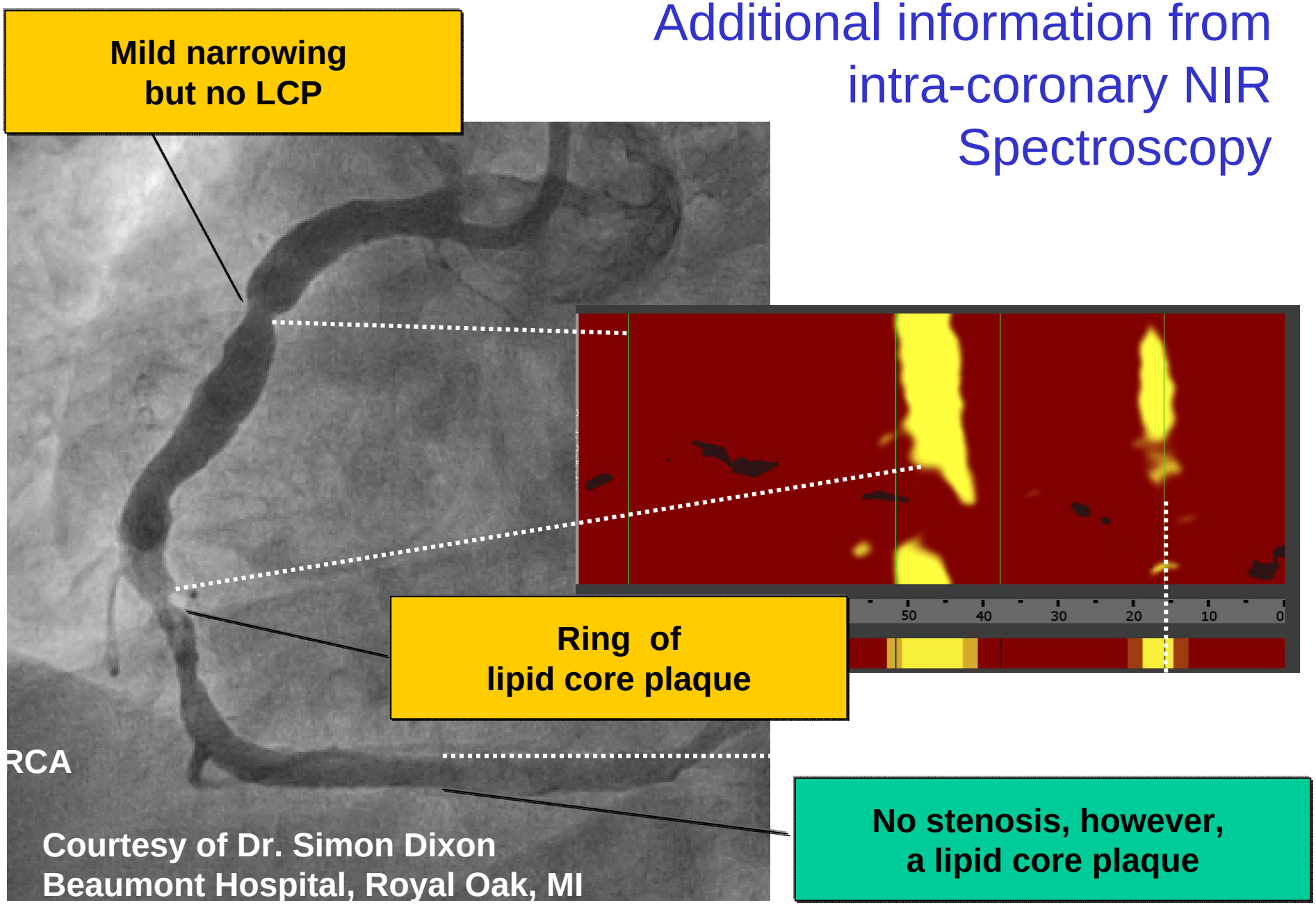
One patient stopped Clopidogrel a few days after the 2-Year visit
All the other patients stopped before 2-Year

J. Ormiston, TCT 2008

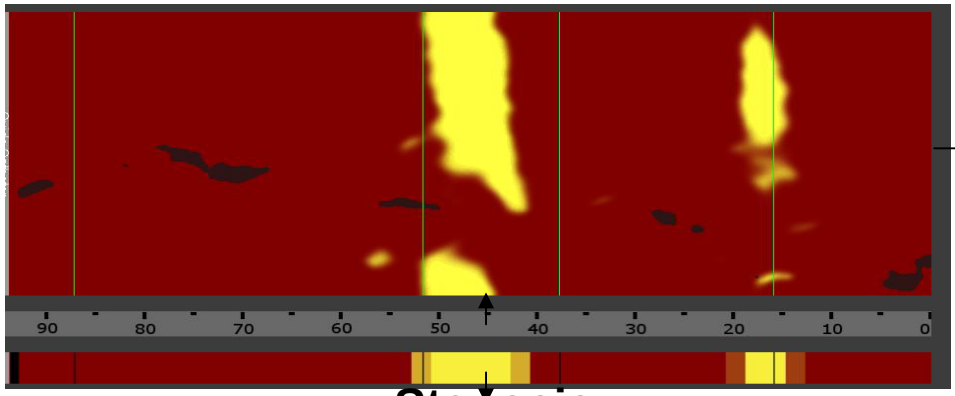
# Chemogram of a RCA in a DM/HC pig that died of sudden cardiac death 3 months later.



# Additional information from intra-coronary NIR Spectroscopy



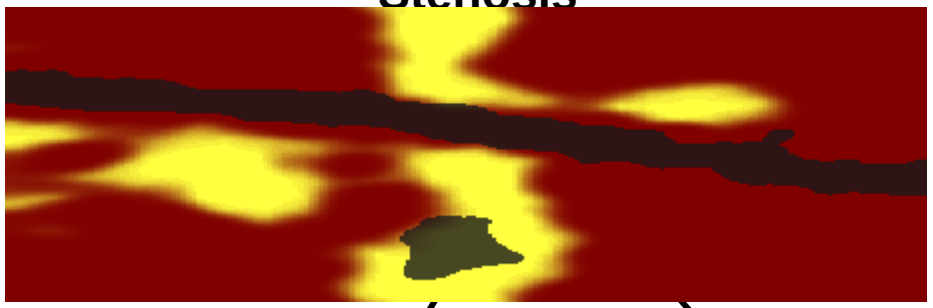
Chemogram of RCA with ring LCP at stenosis in 62 yo male




Distal embolization following dilation leading to MI and CPR

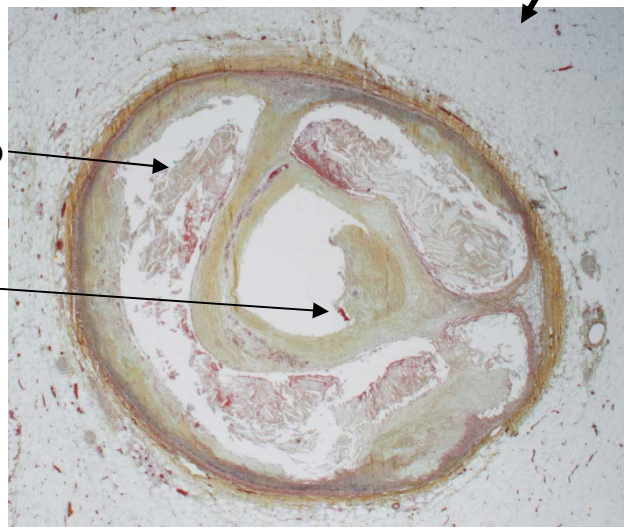
Stenosis

Similar chemogram with ring LCP from autopsy specimen of 48 yo male

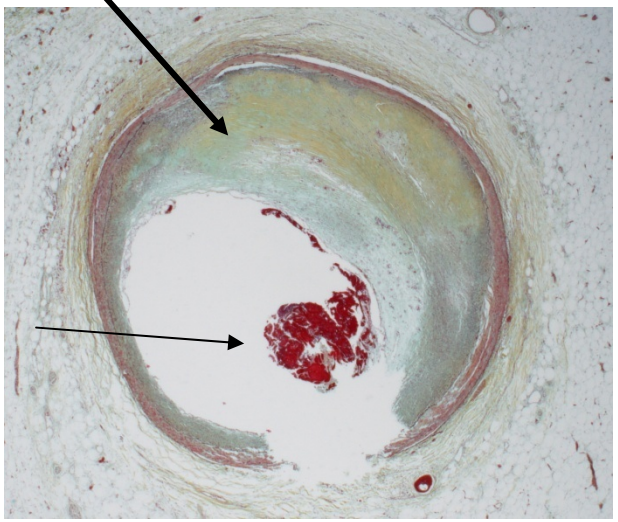


Sudden coronary death

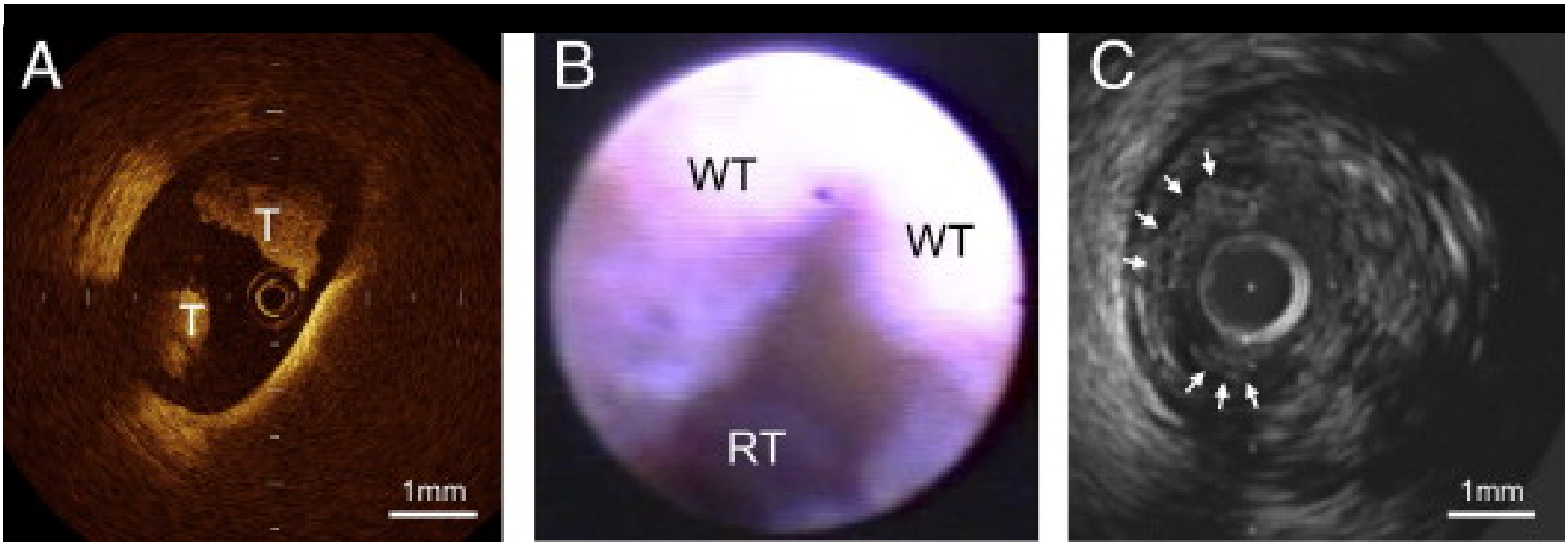
Massive LCP and remnant of fatal thrombus



Thrombus remnant

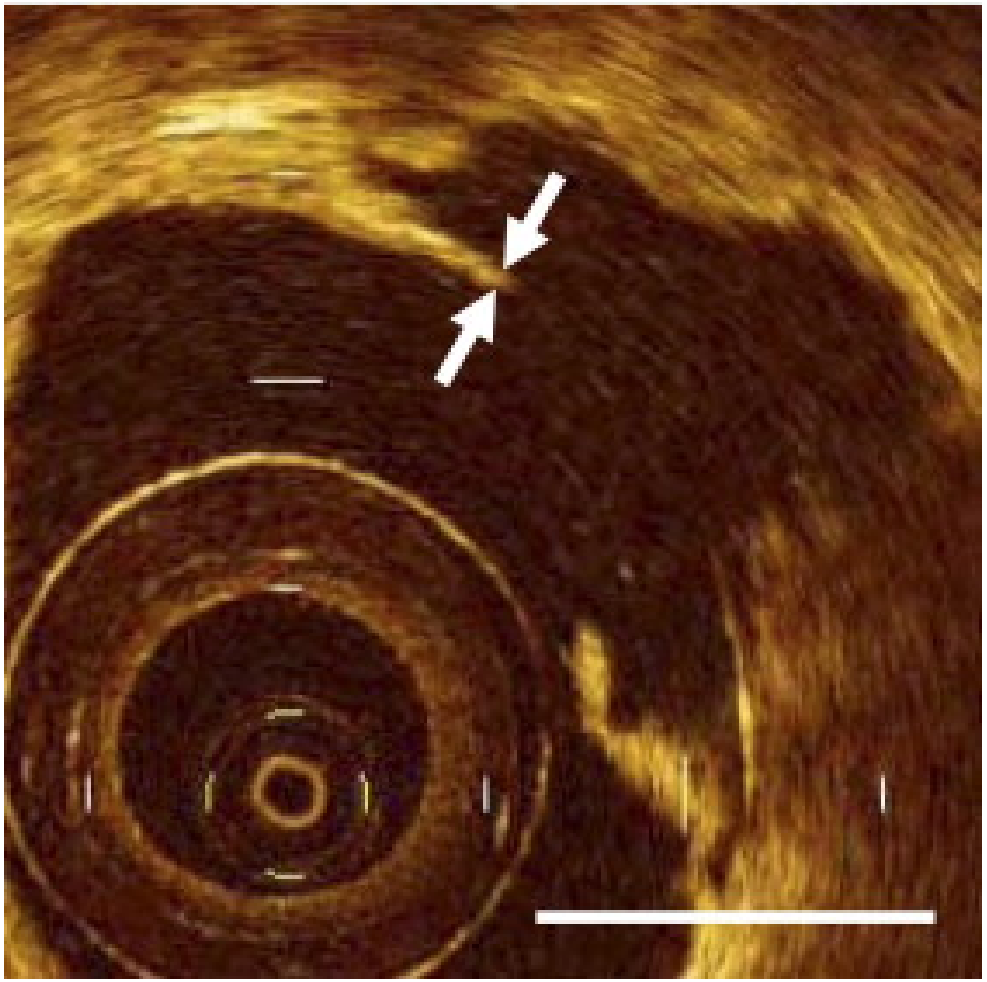


# Assessment of AMI culprit lesion morphology with OCT, angioscopy, IVUS




*Kubo et al J Am Coll Cardiol 2007;50:933*

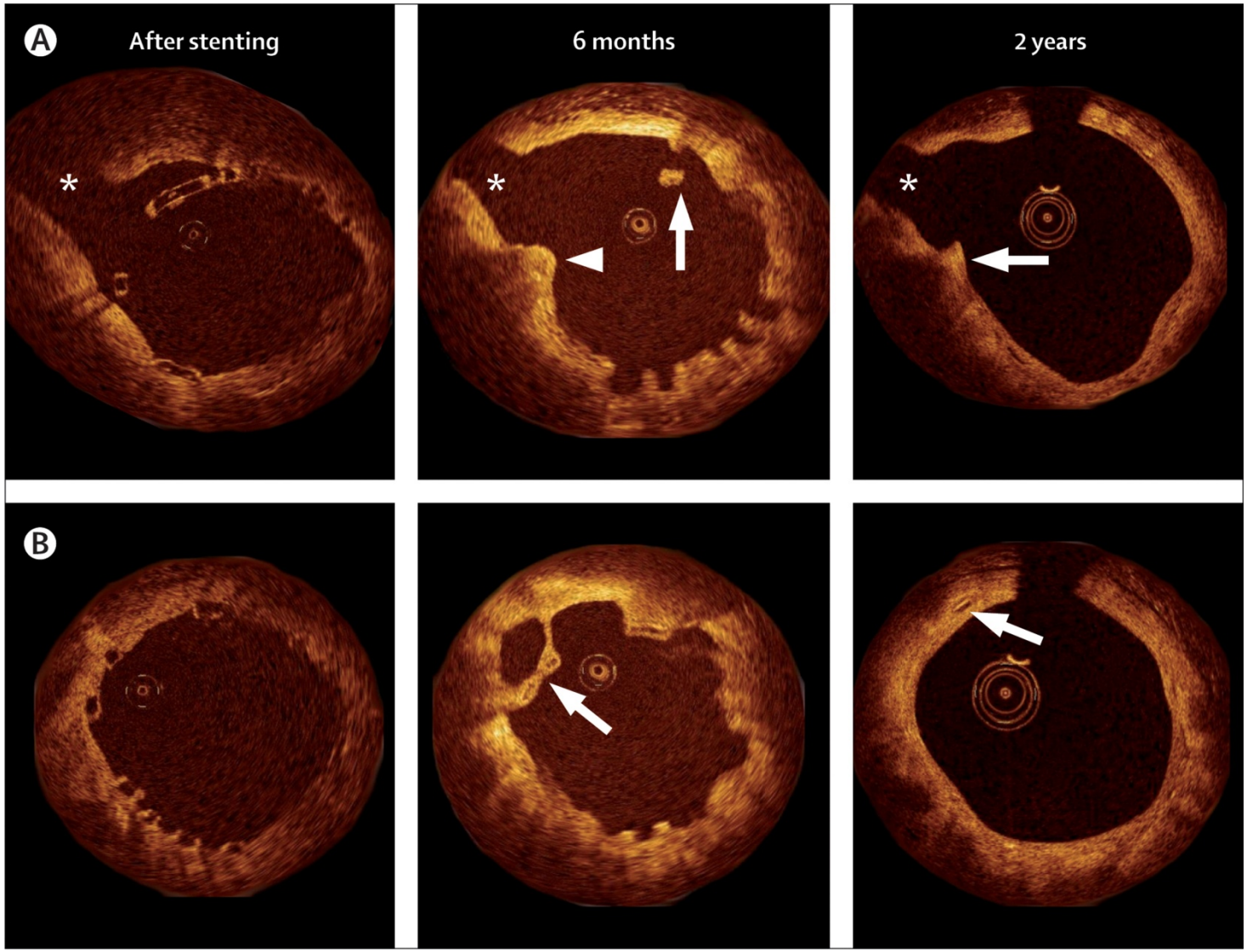
# Assessment of AMI culprit lesion morphology with OCT, IVUS, angioscopy



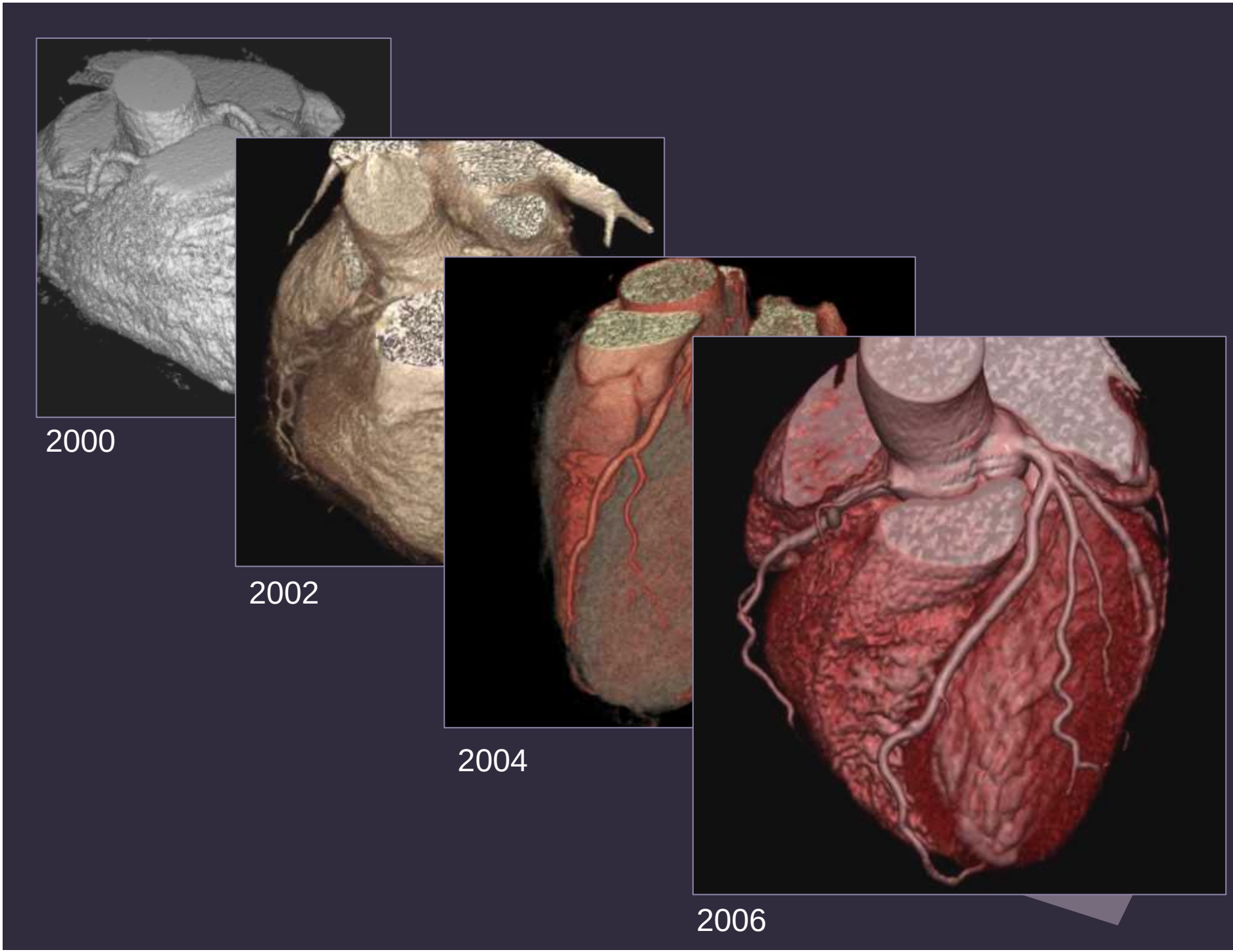
Measurement of fibrous cap thickness

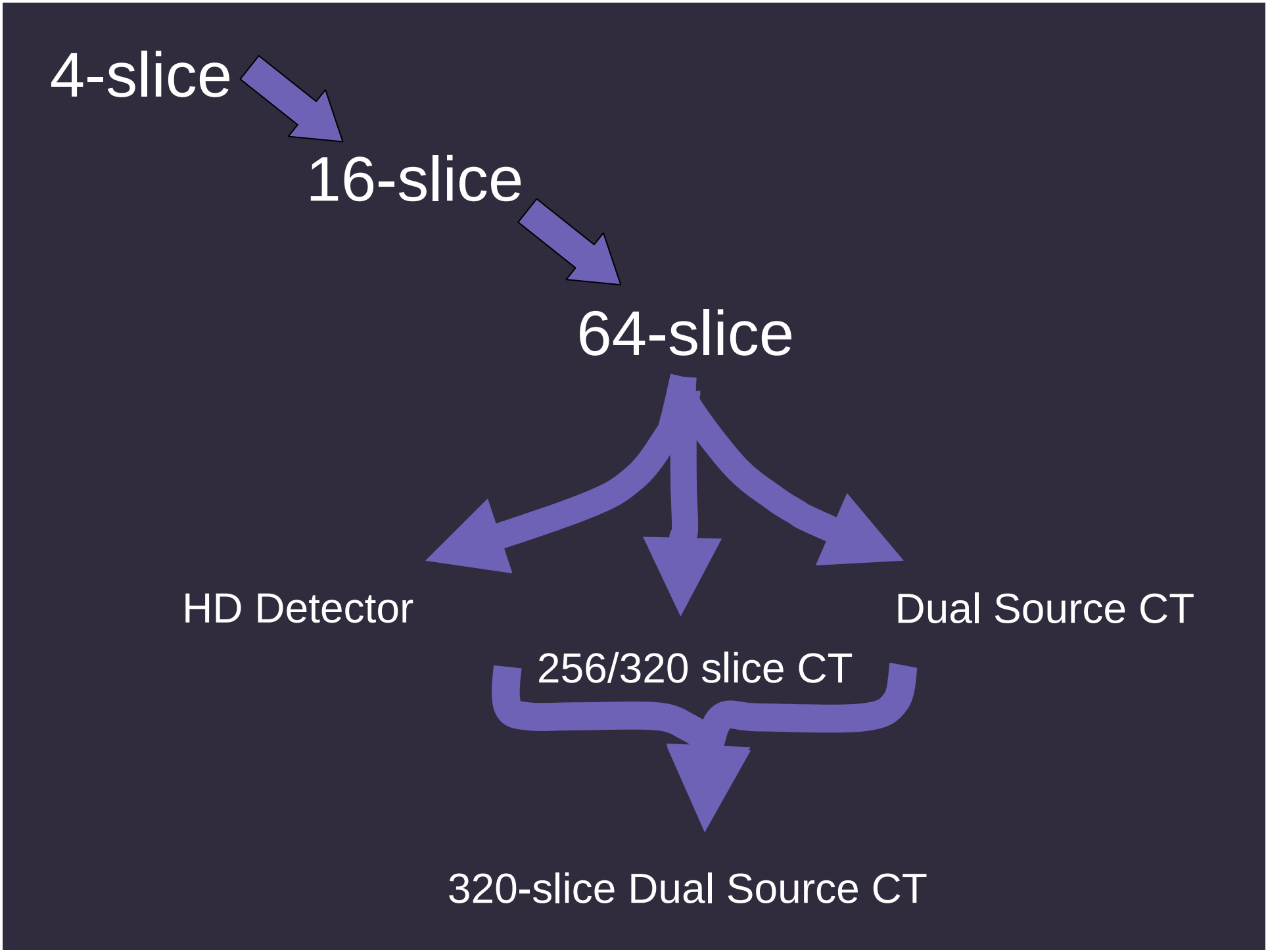
*Kubo et al J Am Coll Cardiol 2007;50:933*

# Serial assessment of stent struts with optical coherence tomography




*Serruys PW et al Lancet 2009;373:897*


2000
2002
2004
2006


4-slice
16-slice
64-slice
HD Detector
Dual Source CT
256/320 slice CT
320-slice Dual Source CT

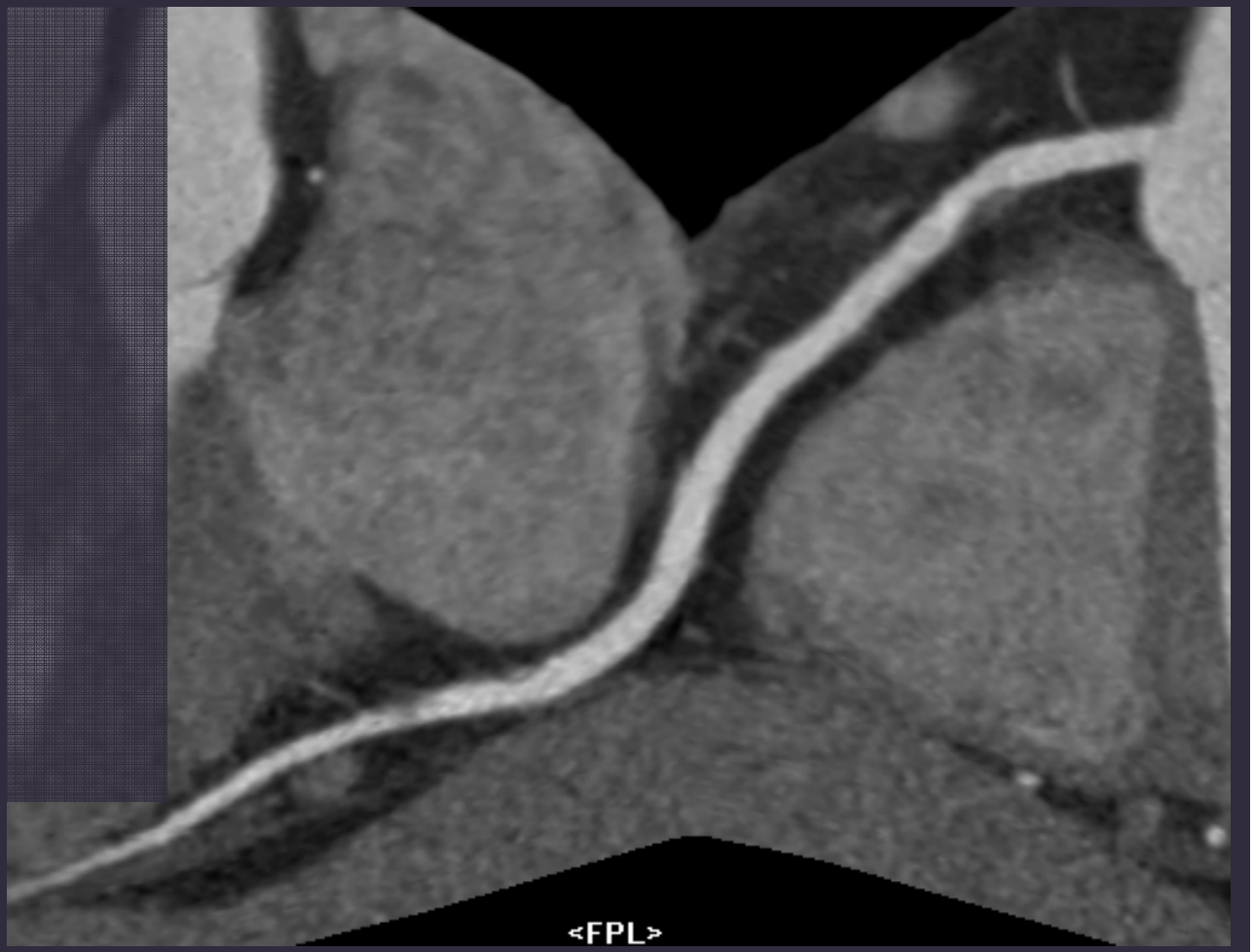
# Techniques to Enhance Accuracy of CTA

New scan technology with

- Better coverage
- Better temporal resolution

Diligent scanning

- Good breathhold
- Nitrates
- Contrast timing
- Low heart rate

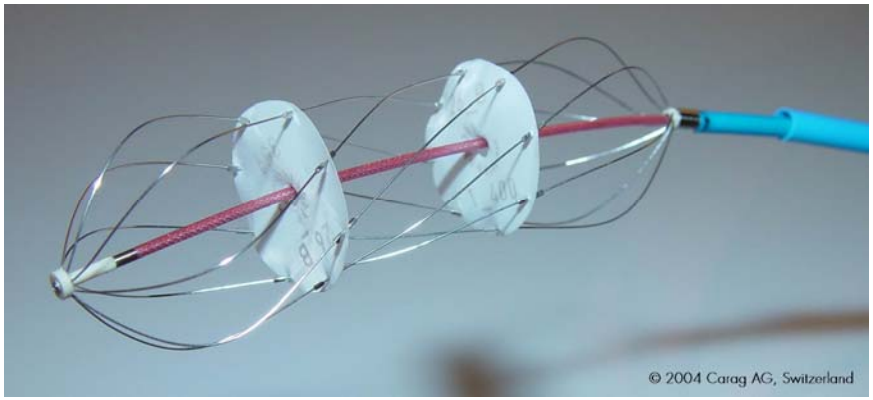


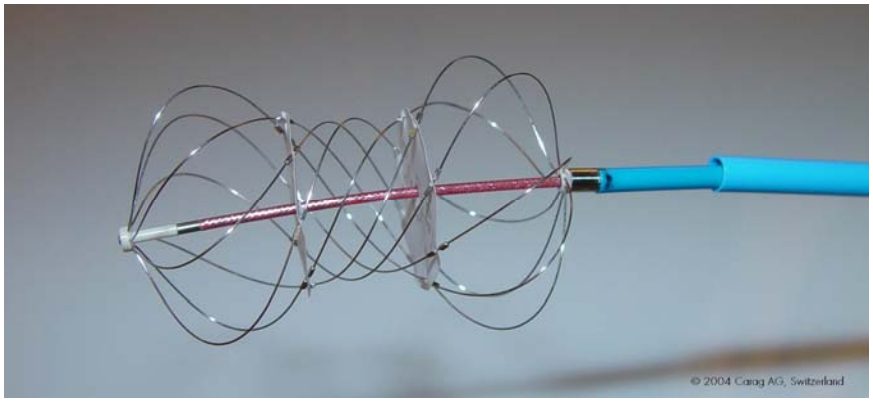
# Structural Heart Interventions

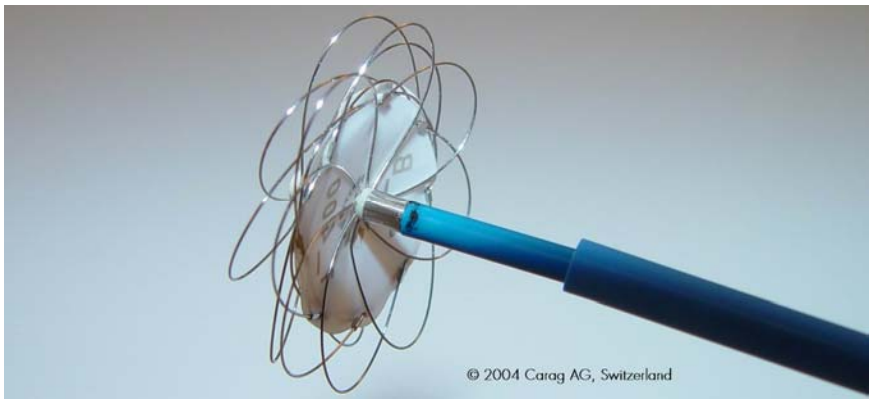
- ASD, PFO closure
- VSD closure
- Patent ductus closure
- Left atrial appendage closure
- Paravalvular leak closure
- Stenting of coarctation
- Heart failure treatment
- Valves
  - Mitral valve repair
  - Aortic valve implantation

# Solysafe®

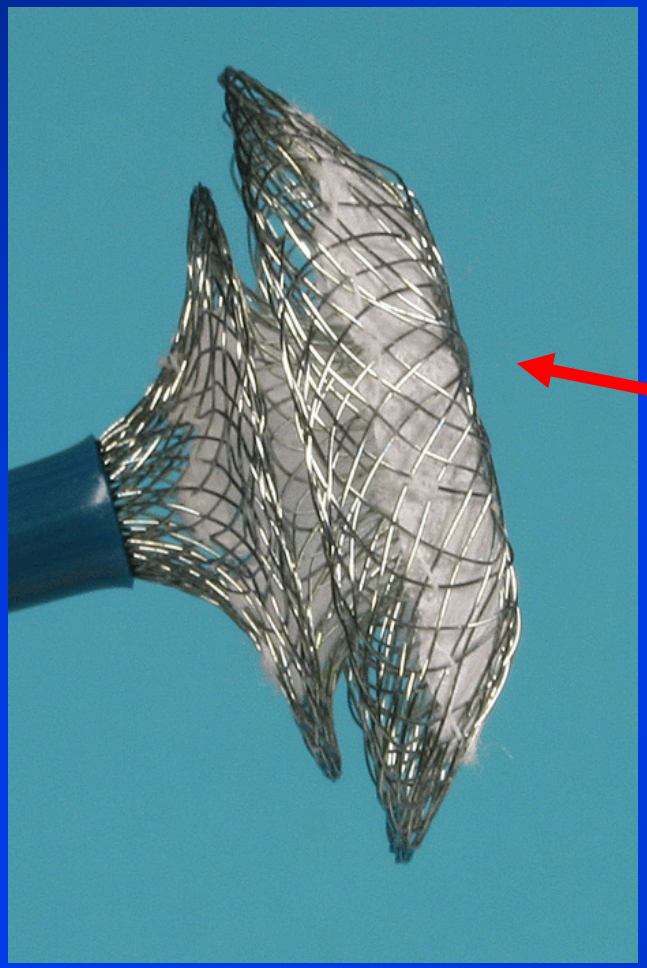
- Self-centering
- Phynox wires
- Polyester patches
- In the defect, wire-holders are moved towards each other
- Clicking mechanism keeps the wire-holders together
- Short 10 F introducer



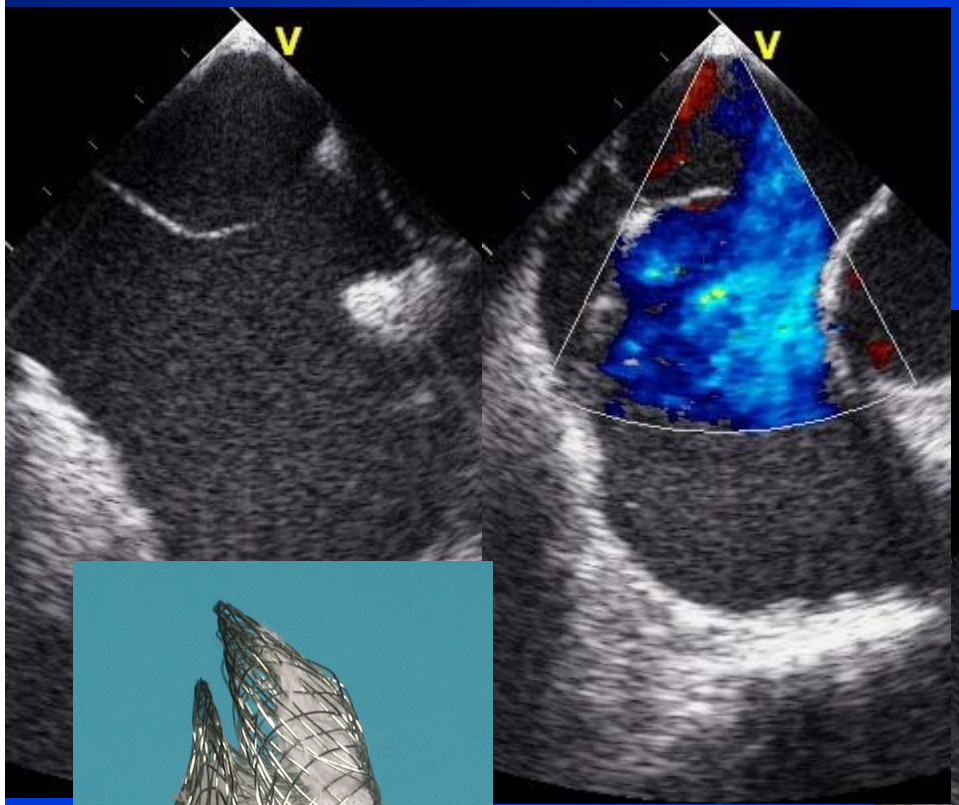



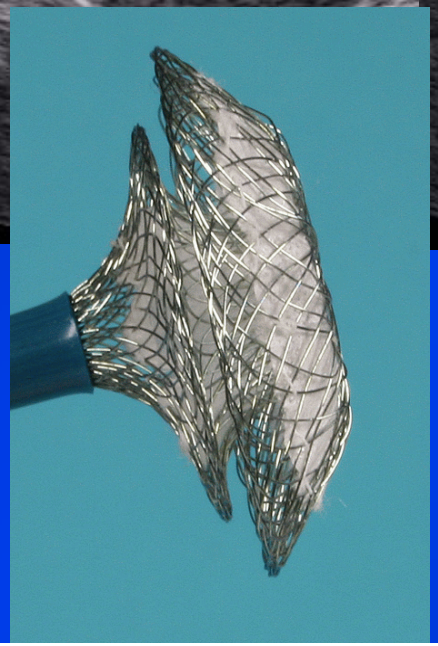
# Occlutech ASD Occluder

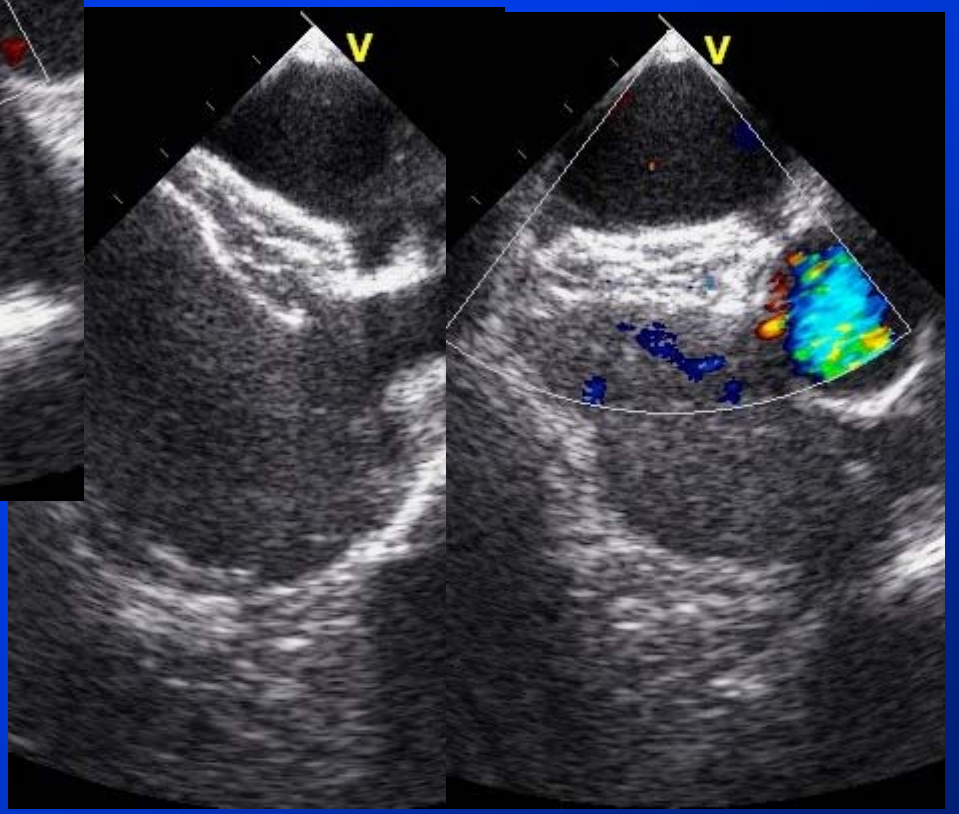


- Similar to the Amplatzer ASD Occluder
- No left atrial hub

# Occlutech ASD

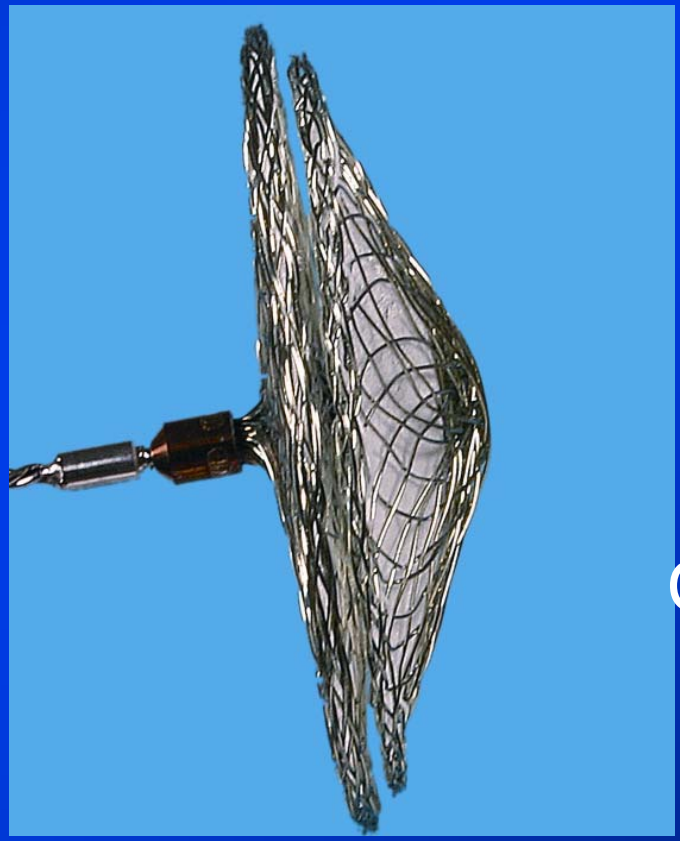






CE Mark

# Occlutech PFO Occluder



CE Mark

Single layer PFO  Double layer PFO

Similar to Amplatzer but no left atrial hub

# Nitocclud PFO

- Nitinol
- One single wire
- Fabric on the left side
- Very flexible delivery system
  - No tension between delivery cable and device before release

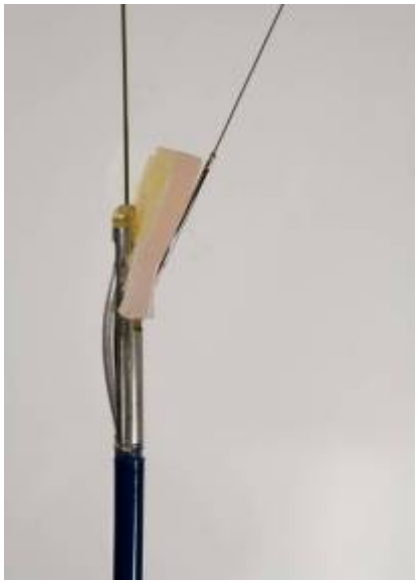
EU trial is planned

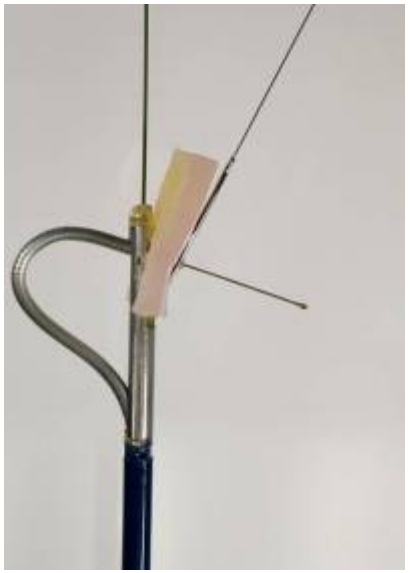
Courtesy F Freudenthal

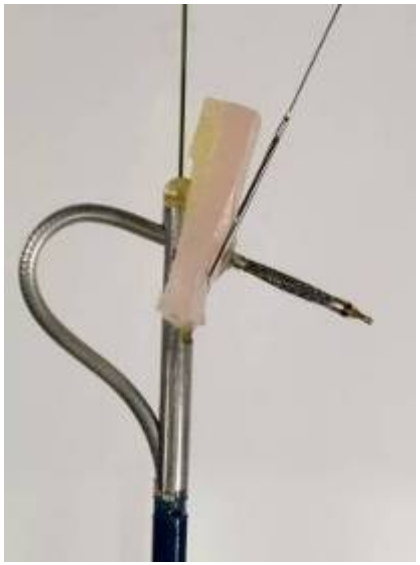
# CoAptus: A New Approach of Non-device Closure

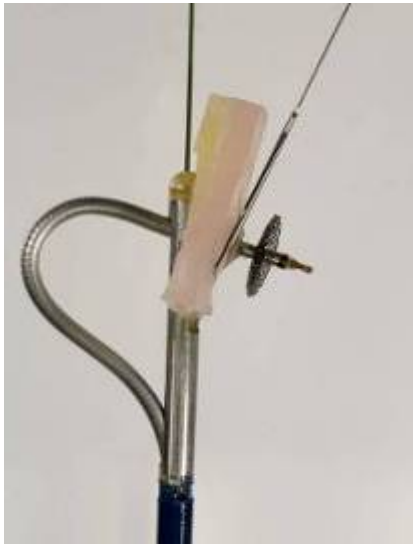
- Using radiofrequency
- Septum primum and septum secundum are coapted mechanically
- Then energy is applied
- Thereafter, the device is removed leaving nothing behind

# Device Design & Procedural Steps

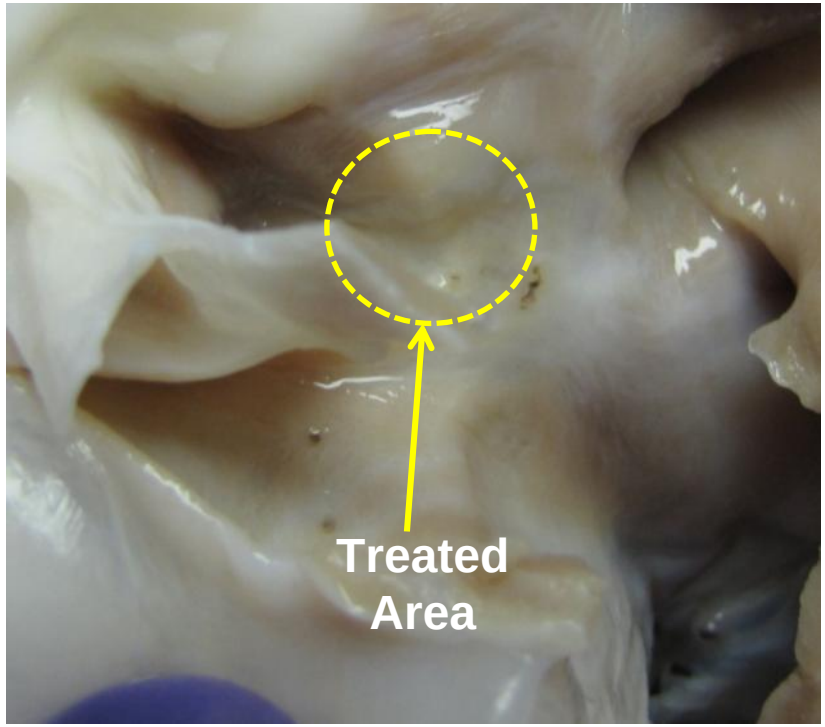


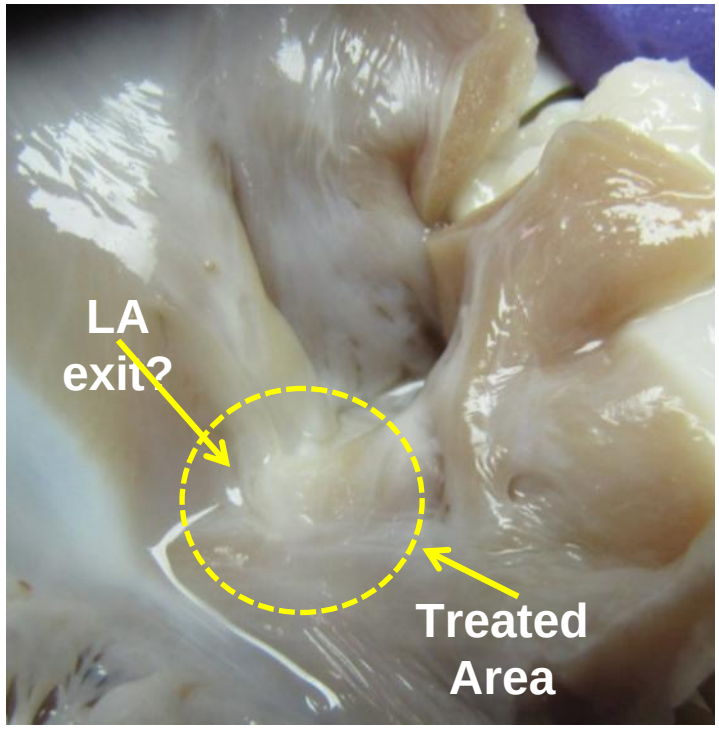






# 28 day

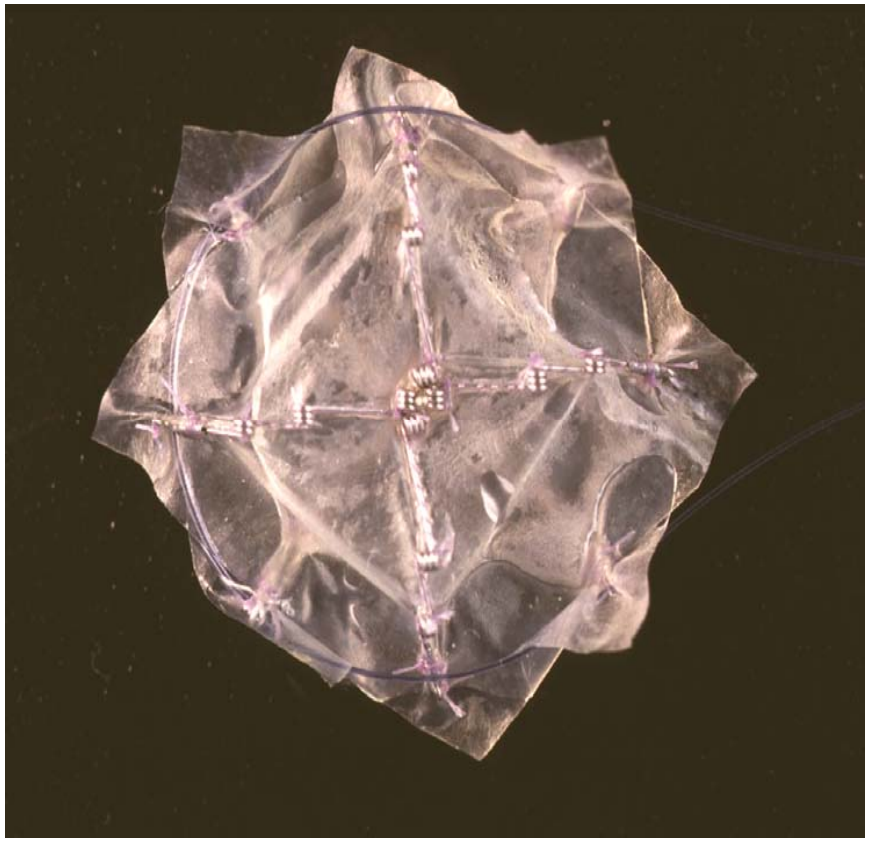


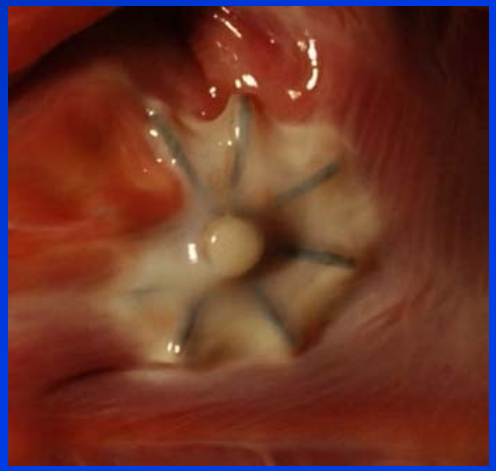

**RA** **LA**

# BioSTAR (NMT)

- CardioSEAL® framework
- STARFlex® self-centering mechanism
- Bioresorbable collagen matrix, heparin coating
- The metallic framework is not bioresorbable



# BioTREK™ Bioabsorbable Septal Repair



6 months

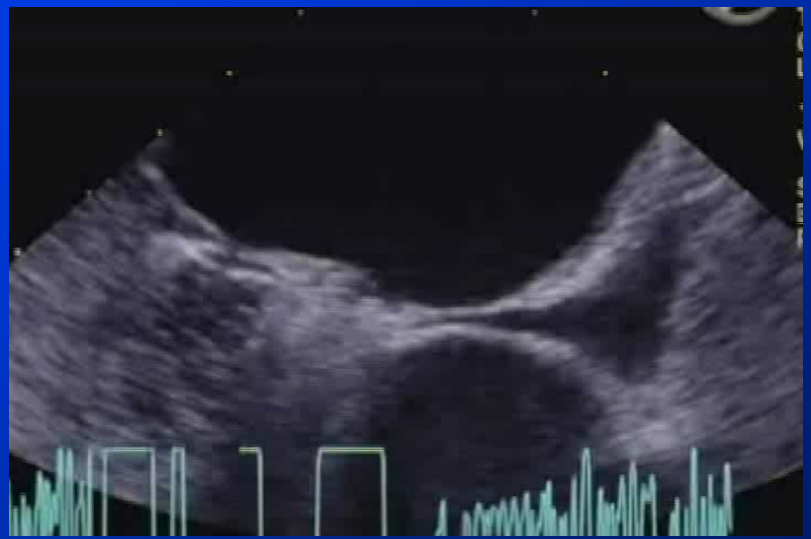
- 100% absorption over time
- novel bioabsorbable polymer (P4HB)
  - absorbs as a non-inflammatory natural metabolite
- easily repositionable and retrievable
- radiopaque and echogenic
- currently in pre-clinical studies

Explant photo courtesy of Aaron V. Kaplan, MD and Ebo D. de Muinck, M.D. Ph.D., Dartmouth Medical School (USA)

# PFO In-Tunnel Devices

# The SeptRx- System

- Nitinol frame and Nitinol wire mesh
- Left and right atrial anchors
- Sits within the PFO tunnel



- EU trial with the Gen-2 device will start this year

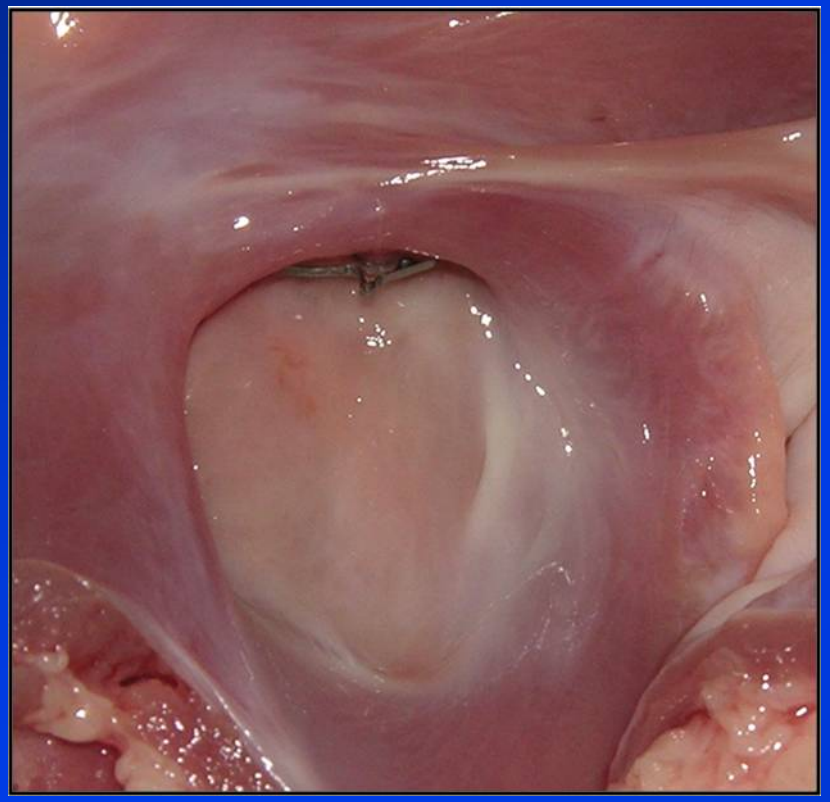
# Coherex EF

Designed to "Stent" the PFO tunnel

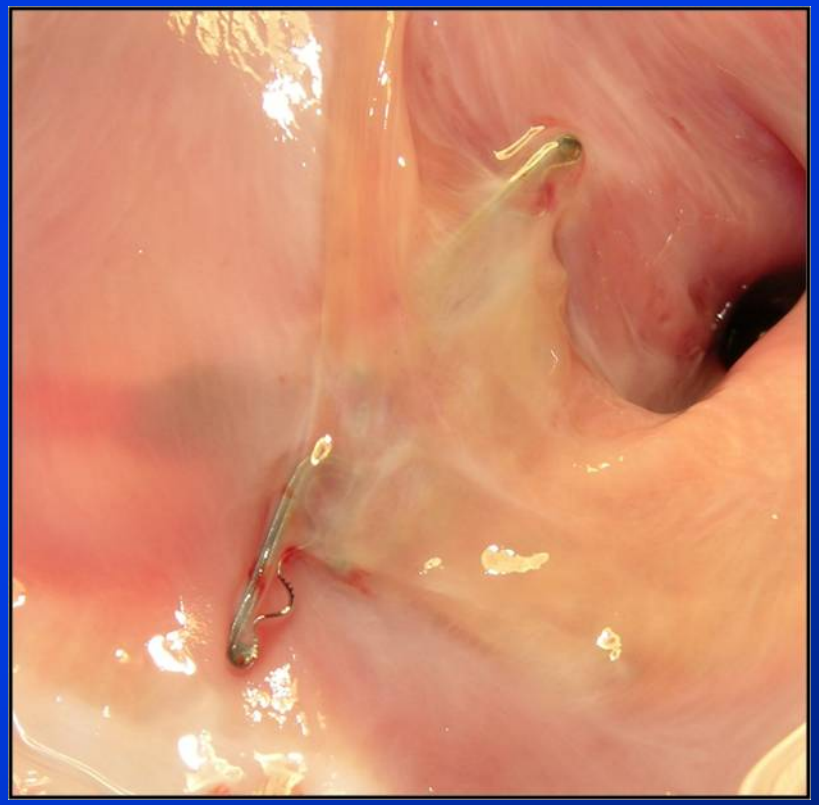
Nitinol and Polyurethan

# Coherex

## Pig Model – 30 days



RA View



LA View