BIOABSORBABLE DEVICES IN CONGENITAL HEART DISEASE

John P. Breinholt, M.D., FACC, FSCAI
Riley Hospital for Children
Indiana University School of Medicine

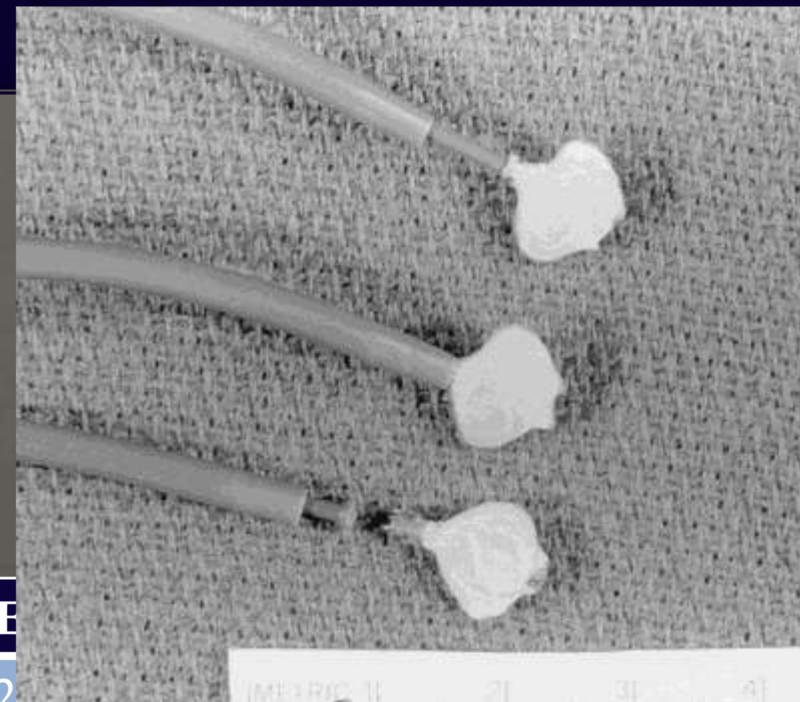
DISCLOSURES

- Abbott Vascular
  - Investigator Sponsored Study grant

HISTORY

- Catheter implantable devices
  - Occlusion devices
  - Stents
  - Valves
- Refinement – device evolution

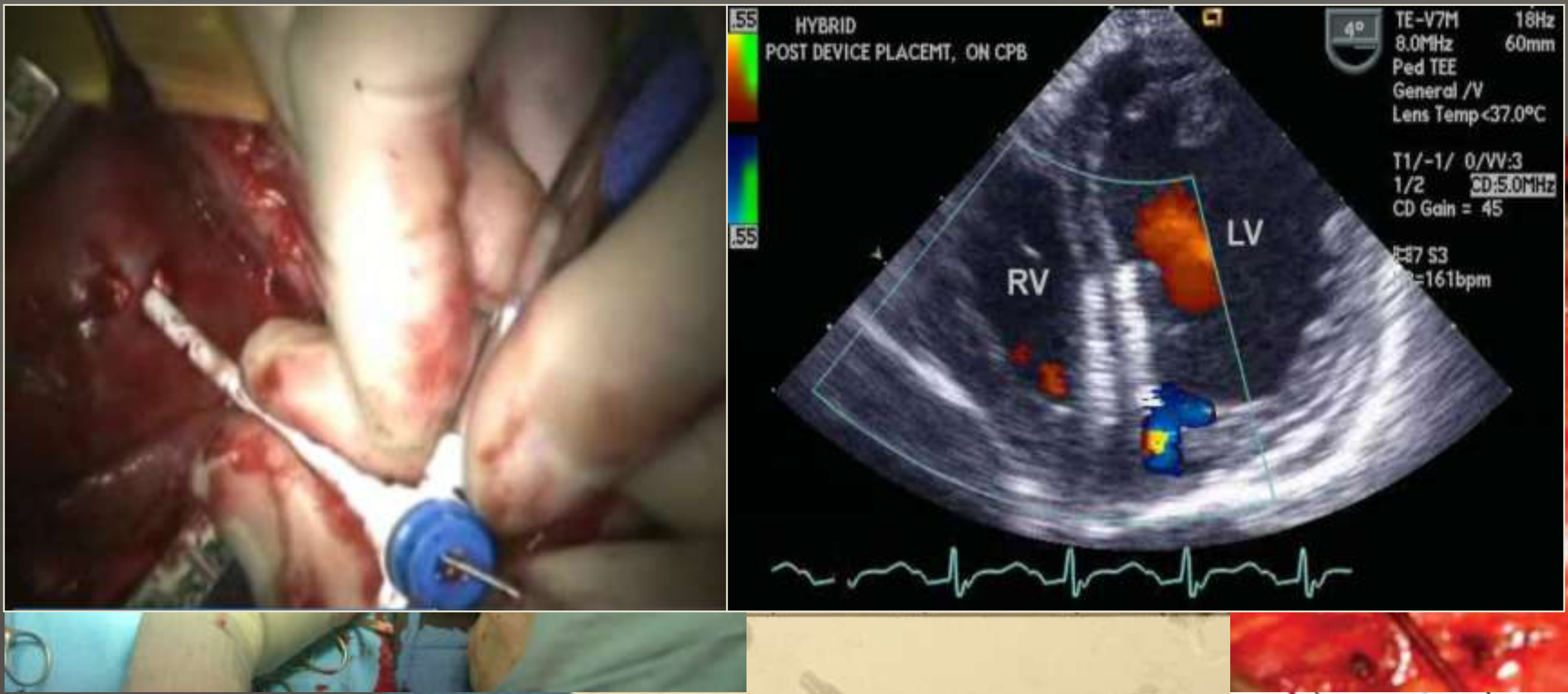
YEAR	DEVICE	SHE
1967	Ivalon plug	16-2
1979	Rashkind Umbrella	8-11 F
1993	Botalloccluder	10-16 F
1996	GGVOD	8 F
2003	Amplatzer ADO	5+ F
2013	Amplatzer ADO II	4+ F

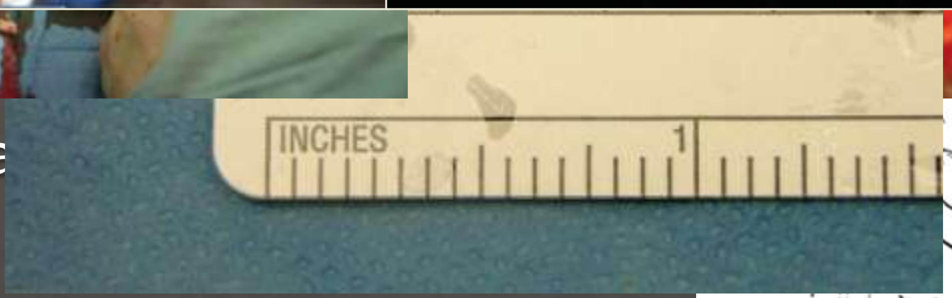


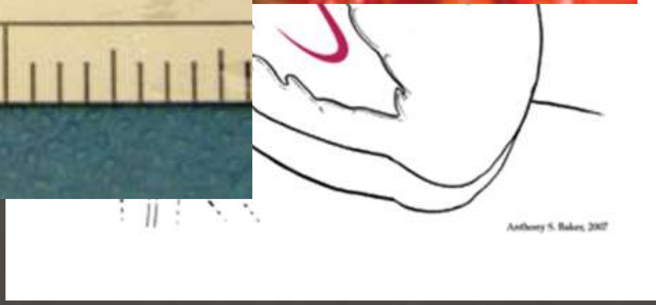
CHALLENGES

- Why can't we simply place big devices in small children?
  - Navigation issues
    - Do not tolerate complex catheter passes
      - VSD closure
    - Do not tolerate large caliber delivery sheaths across multiple valves
      - Pulmonary artery stent placement
  - Device size
    - Septal devices too large for surrounding structures
    - Stent length may be too long for the target site
      - Branch pulmonary artery stenosis – stent can "jail" side branches
      - Stents that are sufficiently short do not dilate to "adult size"

CURRENT ALTERNATIVES







- Intraopera

CURRENT CHALLENGES

- Interventional options for small children are inferior to those for their older counterparts
- Interventional Challenges
  - Coarctation of the Aorta
  - Branch Pulmonary Artery Stenosis

COARCTATION

- Comparison of angioplasty and surgery for unoperated coarctation of the aorta
  - "Immediate gradient reduction is similar after balloon coarctation angioplasty and surgical treatment…
  - The risks of aneurysm formation and possibly restenosis after angioplasty are higher than after surgery"

Shaddy *et al.* Circulation 1993

- Long-term randomized comparison of balloon angioplasty and surgery for native coarctation of the aorta in childhood
  - No difference
    - Resting BP, coarctation gradient, exercise performance, reintervention rate
  - Higher incidence of aneurysm formation with angioplasty vs. surgery
    - 35% vs. 0%

Cowley *et al.* Circulation 2005

COARCTATION

- **Comparison of surgical, stent, and balloon angioplasty treatment of native coarctation of the aorta**
  - “Stent patients had significantly lower acute complications compared with surgery patients or angioplasty patients”
  - “At short-term and intermediate follow-up, stent and surgical patients achieved superior hemodynamic and integrated aortic arch imaging outcomes”

2011 JACC – Forbes *et al.*

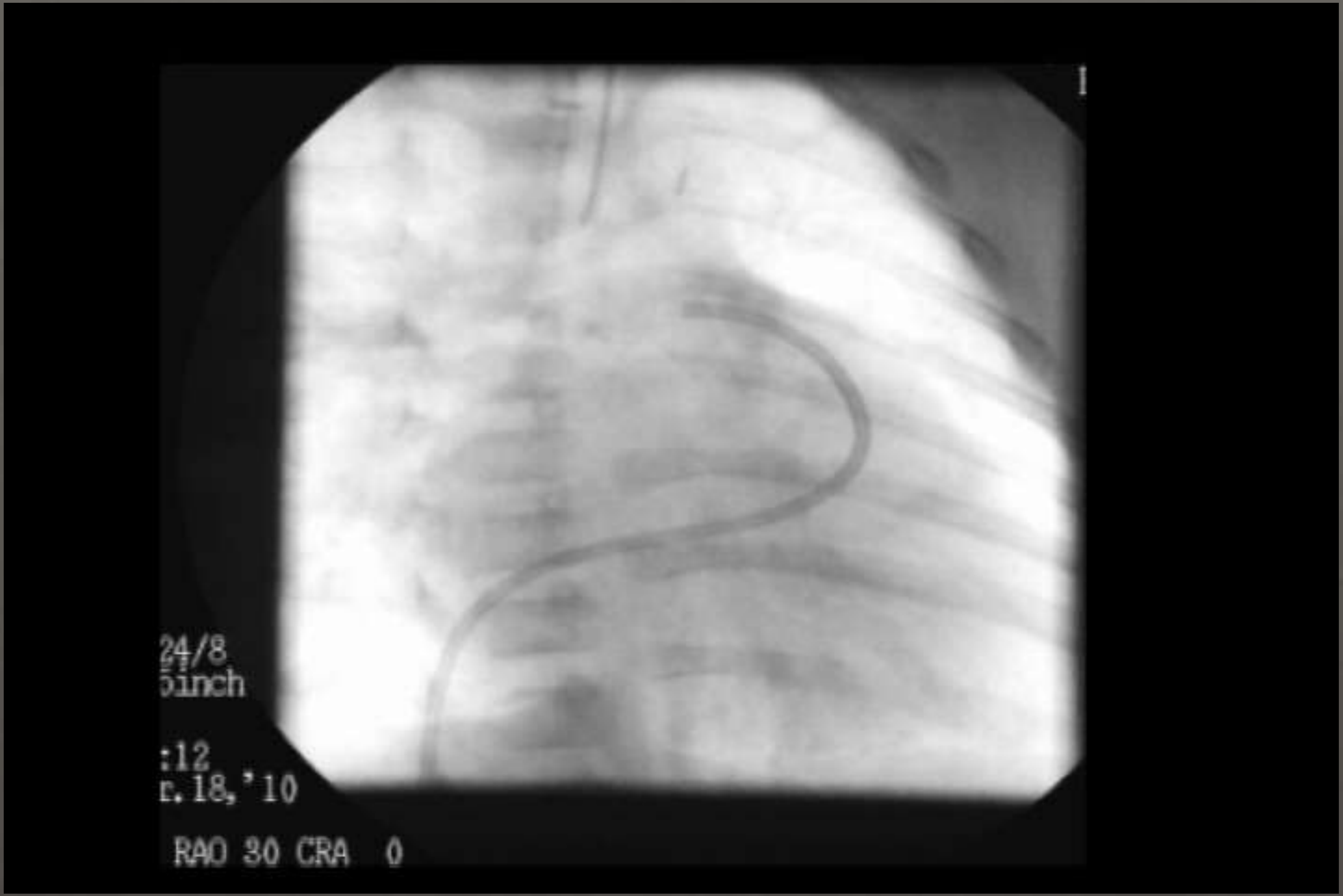
COARCTATION

How the studies differ…

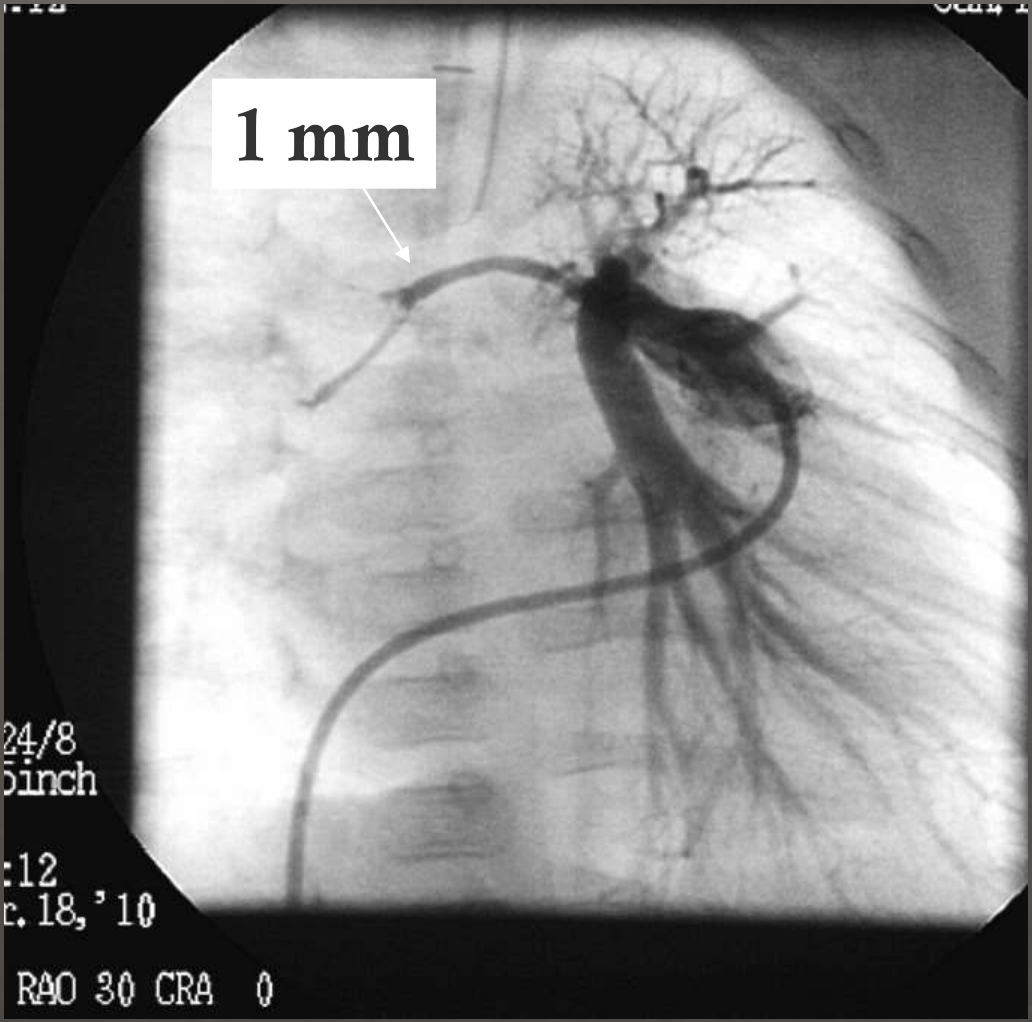
	AGE (yrs)			
	Angioplasty	Surgery	Stent	p value
Shaddy	6.3 ± 2.0	5.7 ± 2.1		NS
Forbes	9.0 ± 8.0	10.0 ± 9.7	**16.6 ± 10.9**	<0.001

	WEIGHT (kg)			
	Angioplasty	Surgery	Stent	p value
Shaddy	21.6 ± 8.1	19.5 ± 4.8		NS
Forbes	30 ± 21	35 ± 24	**55 ± 24**	<0.001

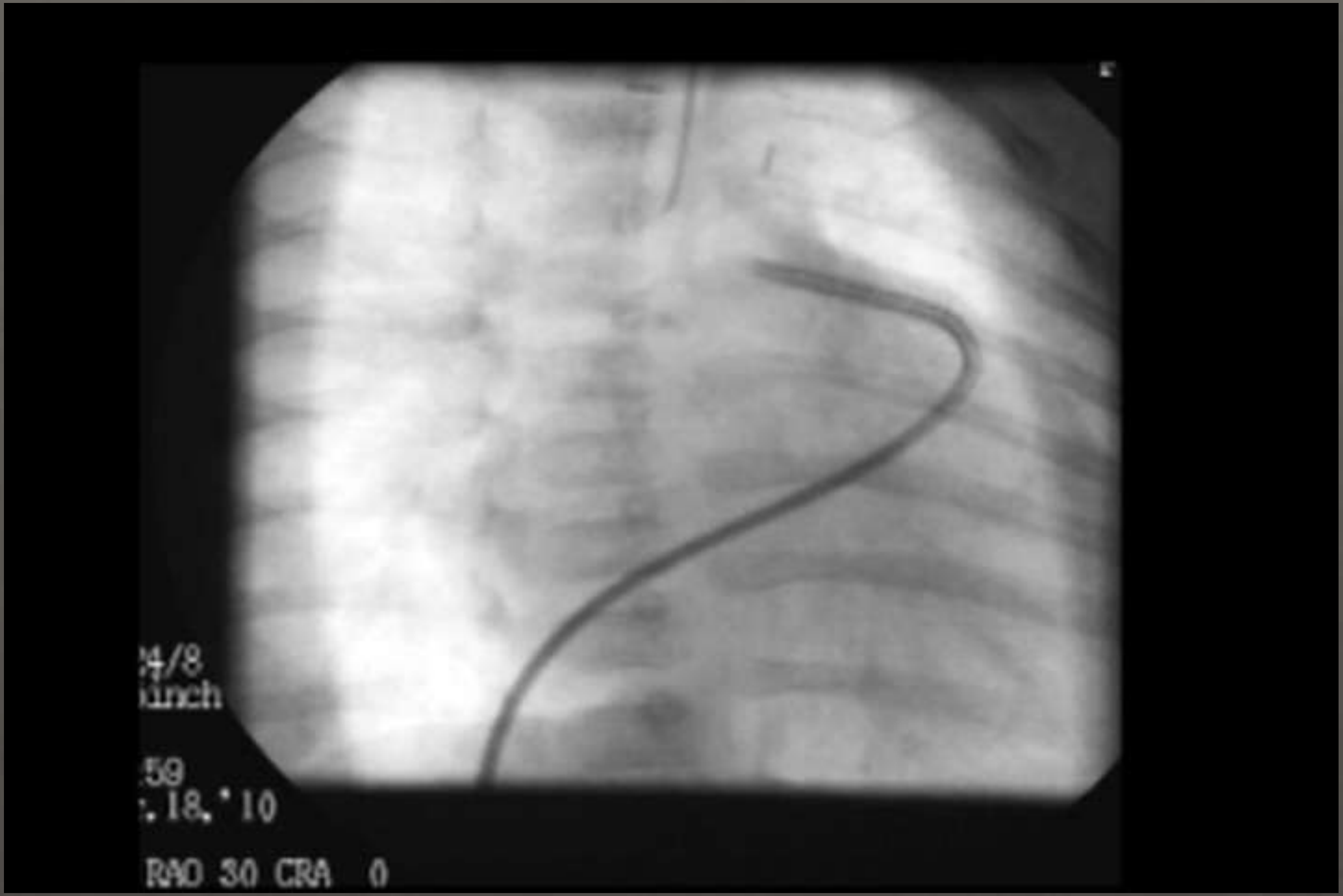
PULMONARY ARTERY STENOSIS



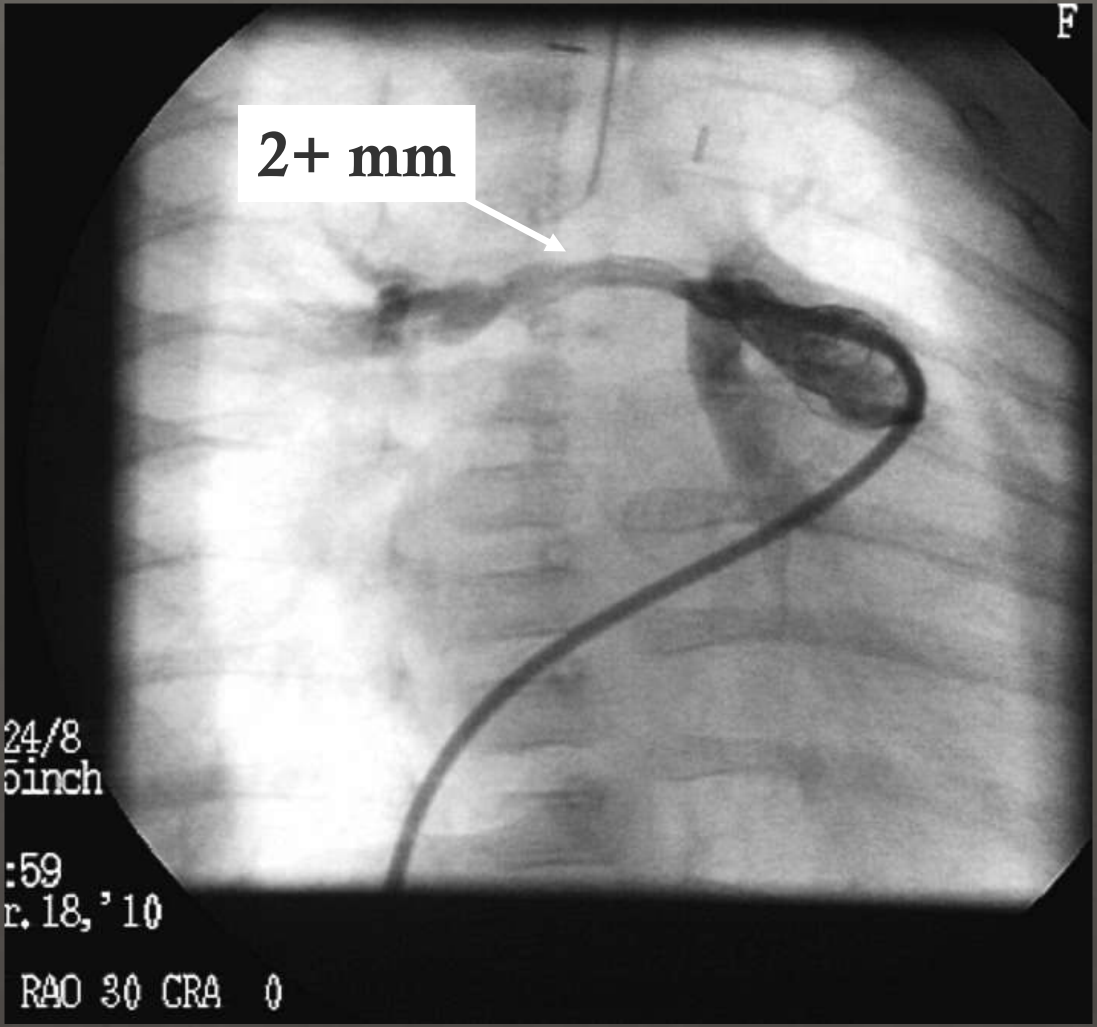
PULMONARY ARTERY STENOSIS



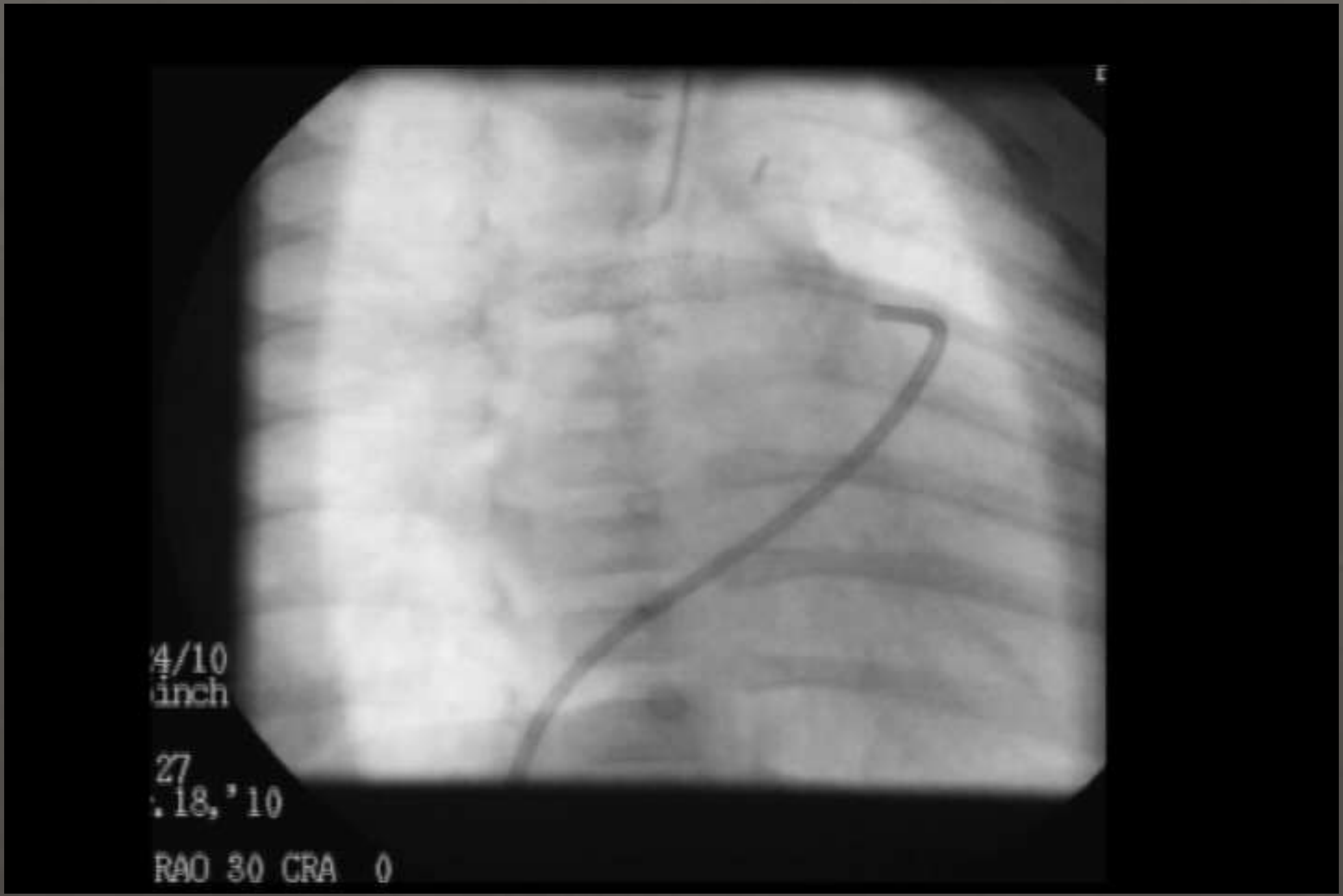
PULMONARY ARTERY STENOSIS



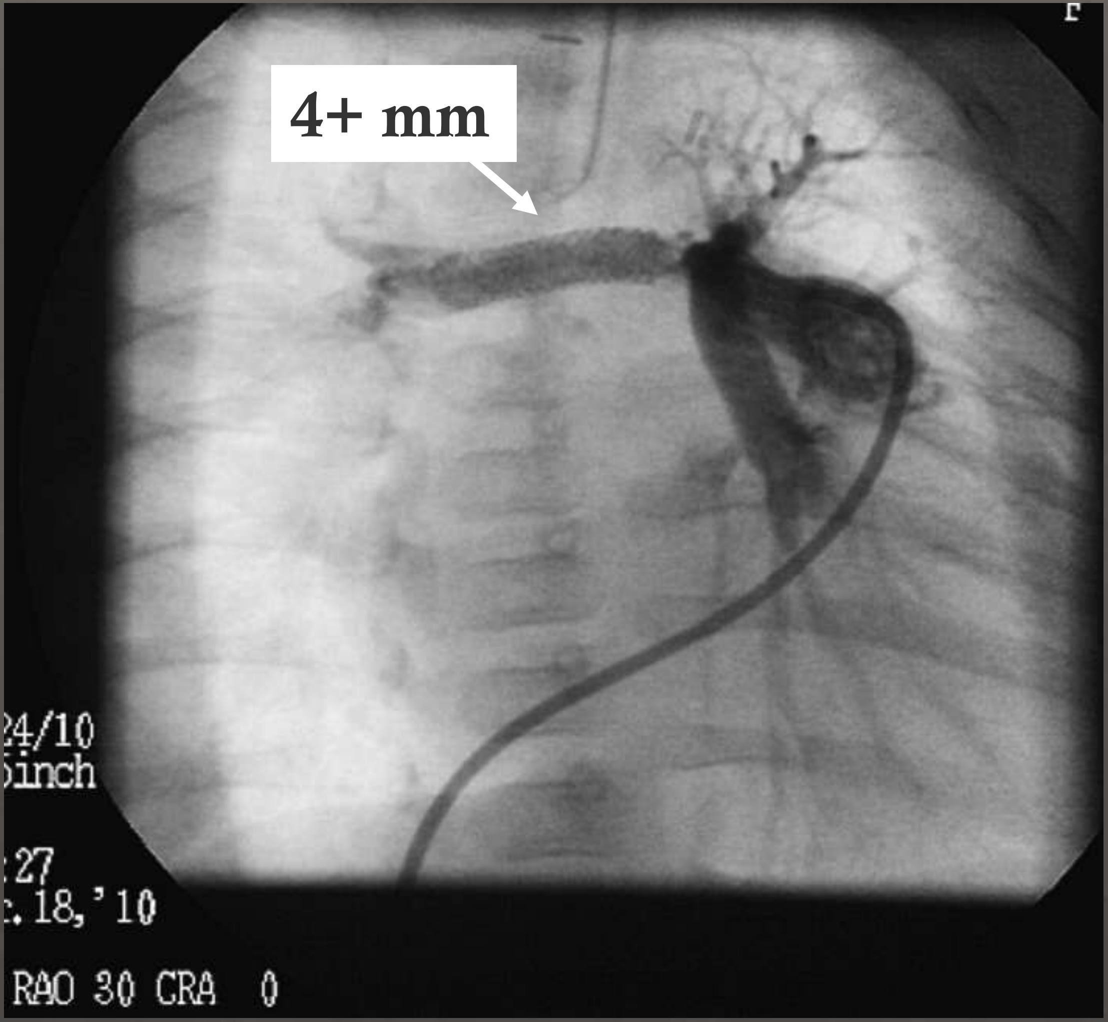
PULMONARY ARTERY STENOSIS



PULMONARY ARTERY STENOSIS



PULMONARY ARTERY STENOSIS

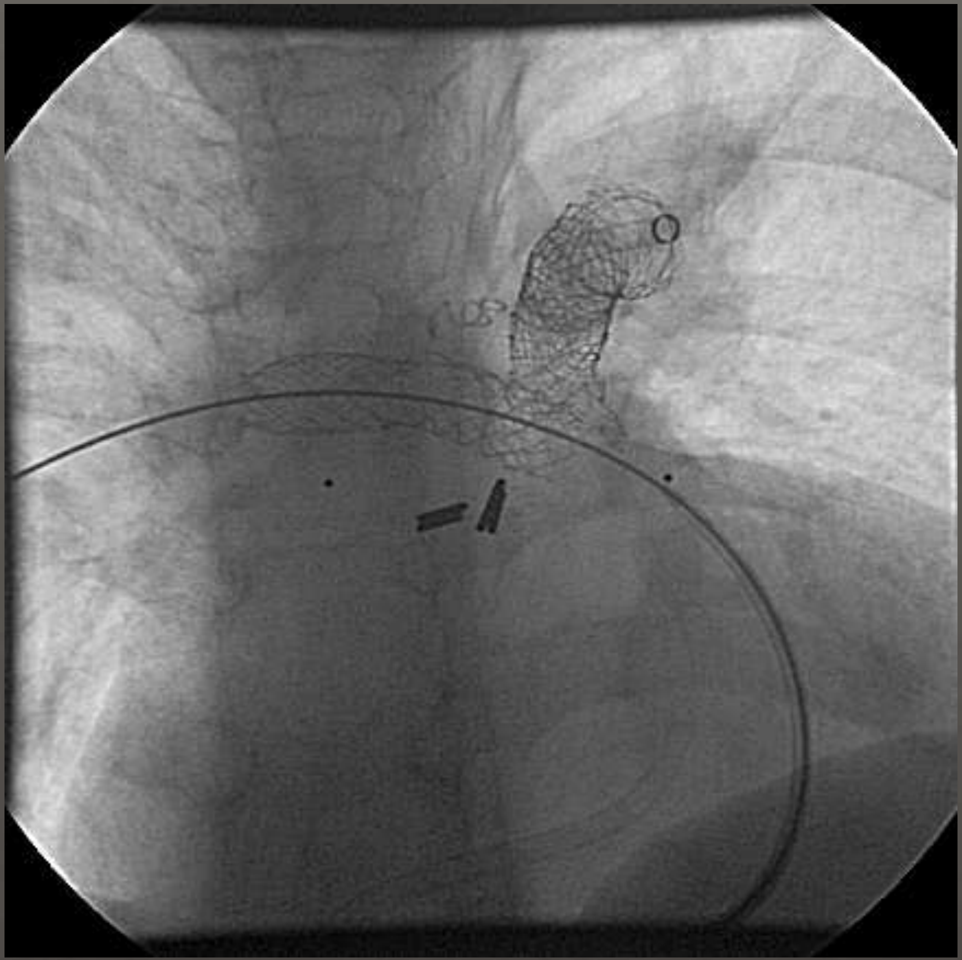


OUTCOMES

- Acute result is excellent
- Future issues
  - Cannot dilate stent further
  - Will require surgical retrieval **vs.** longitudinal incision and patch angioplasty **vs.** balloon angioplasty fracture
- Problems
  - Increased risk of surgical intervention
  - Easier for surgeons to perform angioplasty without interference from stents

OUTCOMES

Is this the desired outcome?



WHAT IS NEXT ?

- How can we achieve the acute results without the later challenges and risks?

- Sometimes the problem is NOT that you need to get something big into a small patient

- **Something small is exactly what is needed … at the time**

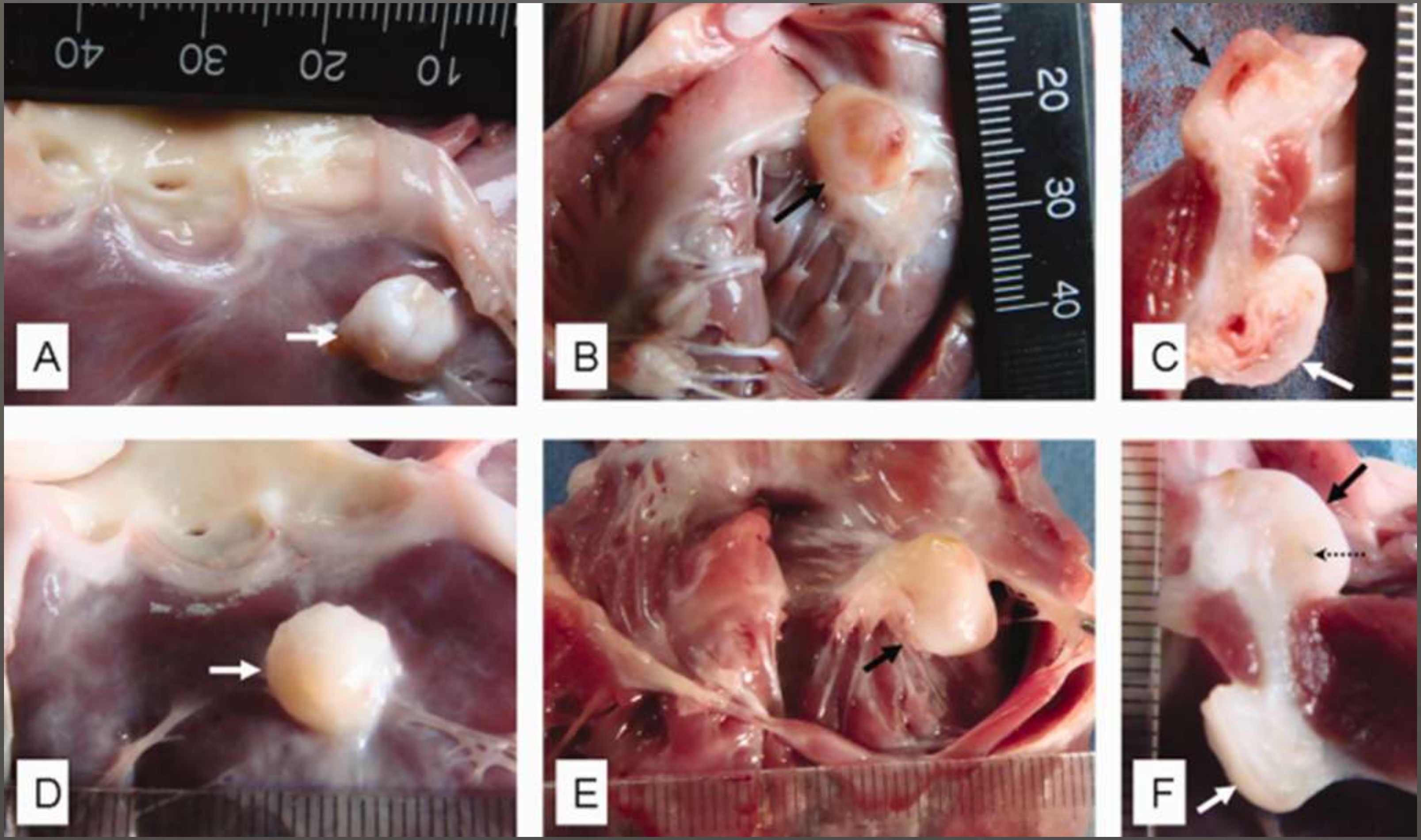
BIODEGRADABLE PRODUCTS

ADVANTAGES

- Temporary effects: when only short term result is needed
- Overcomes problem of being “big enough for an adult”
  - No need to re-dilate to accommodate somatic growth
  - Later interventions done without concern of existing hardware
  - Decrease complexity of surgical procedures / device manipulation unnecessary
- Allow restoration of vascular compliance
  - Possible positive remodeling and later growth
- Decrease risk of arrhythmia
- Possible modality for drug or gene therapy delivery

SEPTAL DEFECTS

•



– Huang, et al. Catheter Cardiovasc Interv 2013;81:324-330

SEPTAL DEFECTS

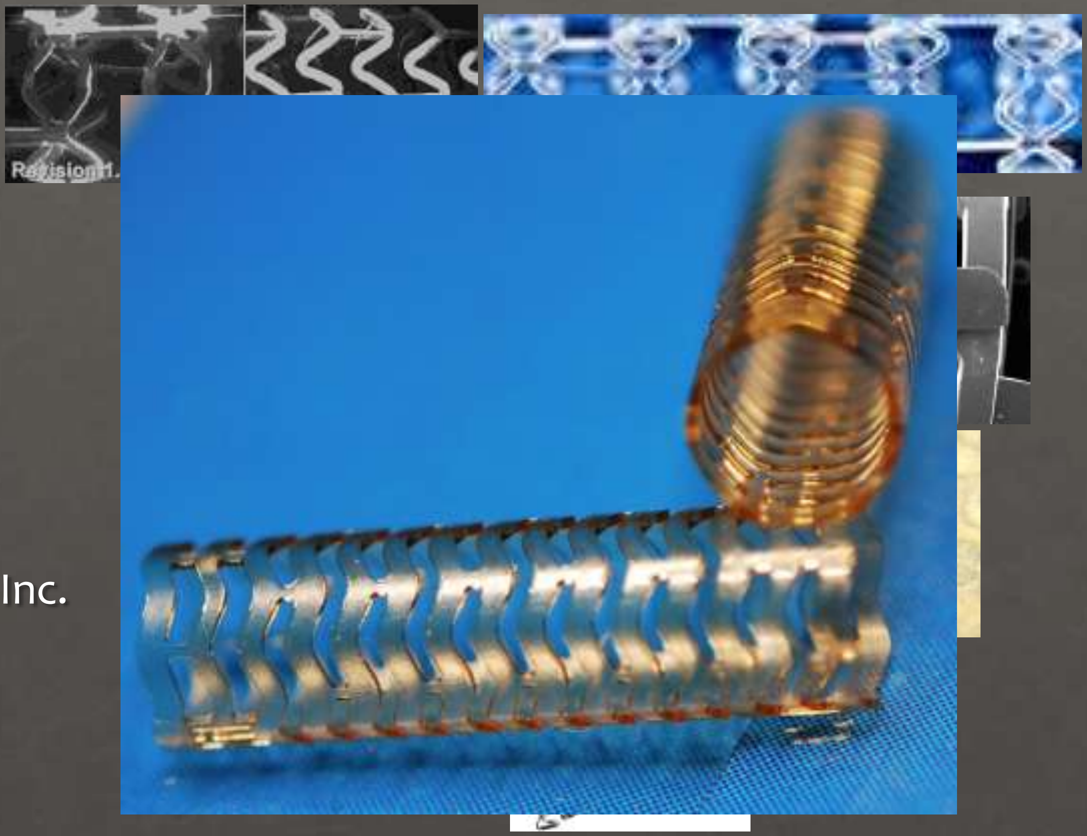
- Possible benefits
  - Device endothelializes → dissolves → tissue septum
  - A non-rigid septum may improve atrial mechanics and reduce likelihood of erosion
  - Biodegradable devices may reduce the risk of AV block
    - Perimembranous VSDs

BIOABSORBABLE STENTS

CORONARY STENTS – HUMAN STUDIES

- Igaki-Tamai
  - PLLA
  - Kyoto Medical Planning Co., Ltd.

- Abbott ABSORB
  - PLLA
  - Abbott Vascular



- REVA
  - Tyrosine Polycarbonate
  - RevaMedical, Inc.
- BTI
  - PAE - Salicylate
  - Bioabsorbable Therapeutics, Inc.
- Biotronik DREAMS
  - Magnesium alloy

BIOABSORBABLE STENTS

WORK IN PROGRESS

Abbott
- PLLA stent
- PDLLA coating
- Everolimus drug

Medtronic
- Specific target applications to meet unique clinical needs
- Material development focused on less than 6- month degradation
- Ongoing stent design, evaluation and development

Reva
- Tyrosine-based polycarbonate
- Paclitaxel abluminal delivery
- Slide-and-lock design

Cordis
- PLGA/PCL-PGA
- Balloon-expandable
- Longer drug elution than Cypher

Biotronik
- Magnesium alloy (93% Mg)
- Have looked at 7 new alloys and 3 new designs
- Pimecrolimus-eluting stent under development

ART
- PLLA stent made from amorphous polymer
- Balloon-expandable
- Claim of positive remodeling

Biosensors
- PLLA/PLDA stent
- Self-expanding with retractable sheath

Igaki-Tamai
- PLLA material
- Polycaprolactone coating
- DES preclinical studies with ST638, ST494
- Balloon-expandable with covered sheath system

OrbusNeich
- PLGA/PCL-PGA stent
- Abluminal drug coating
- Luminal EPC capture

BTI
- Salicylic acid-based surface eroding stent
- Sirolimus eluting

Endovasc, Inc. (BioFlow, Inc.)
- Biodegradable stent for ureteral applications

TissueGen
- PLLA stent
- Spiral helical design
- Claim of growth factors/enzymes delivery

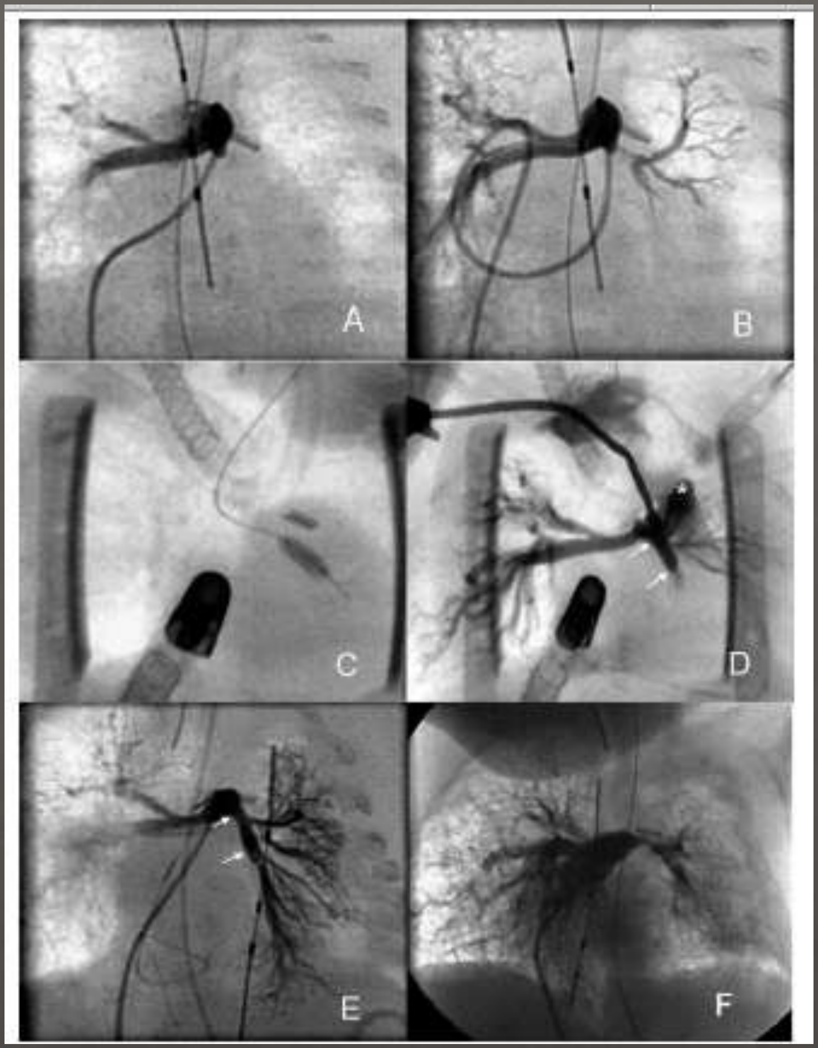
Tepha
- Combination: polyester based "TephaFLEX" and PLLA for added strength

Sahajanand
- PLLA and heparinized PLLA stent with genistein drug
- Balloon-expandable

Amaranth
- PLLA, self-expanding stent
- Multiple drug delivery
- Peripheral indication

BIOABSORBABLE STENTS

- Compassionate use of a magnesium alloy stent in premature newborn with LPA stenosis
  - B – LPA stenosis
  - D – Immediately post implant
  - E – 1 week post implant
    - White arrows identify stent site
  - F – 1 month post implant

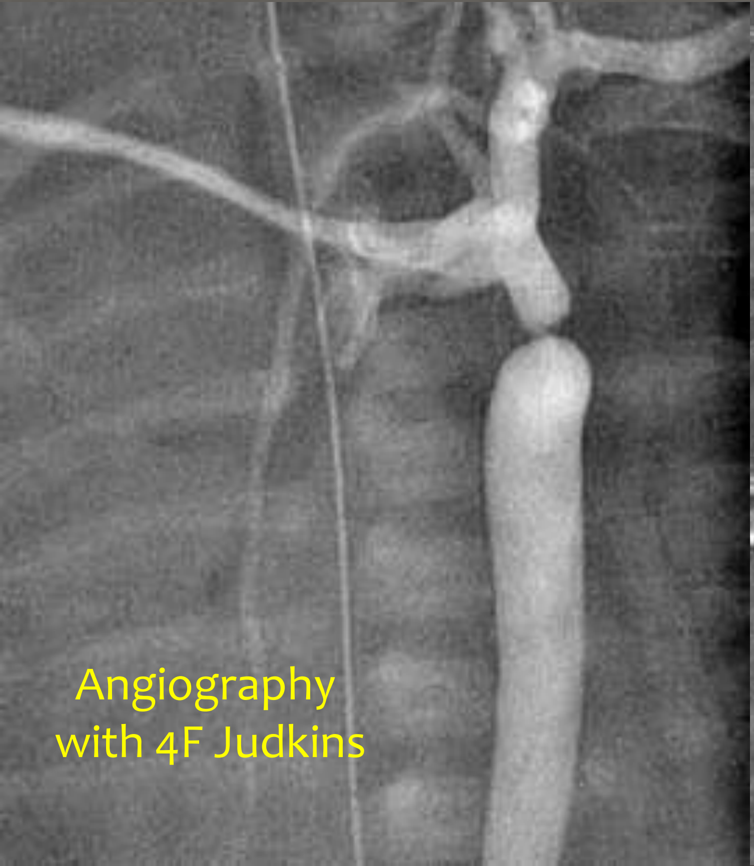


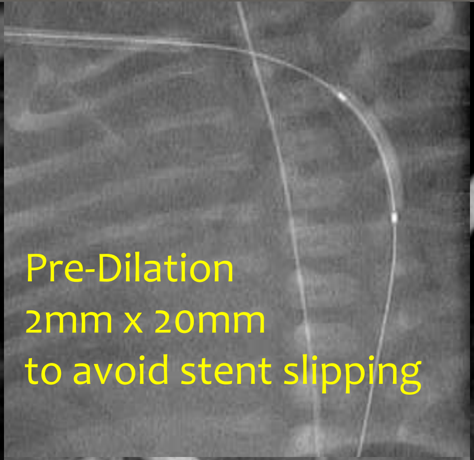
Zartner P *et al*. CCI 66:590-4,2005 ; 69:443-446, 2007

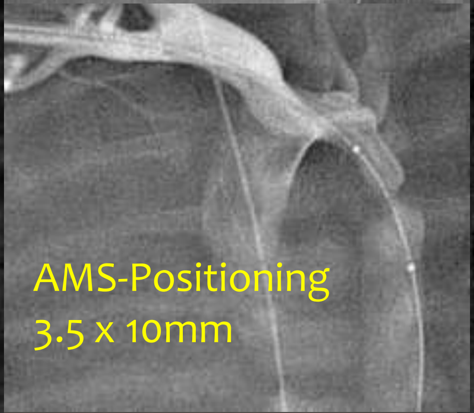
COARCTATION

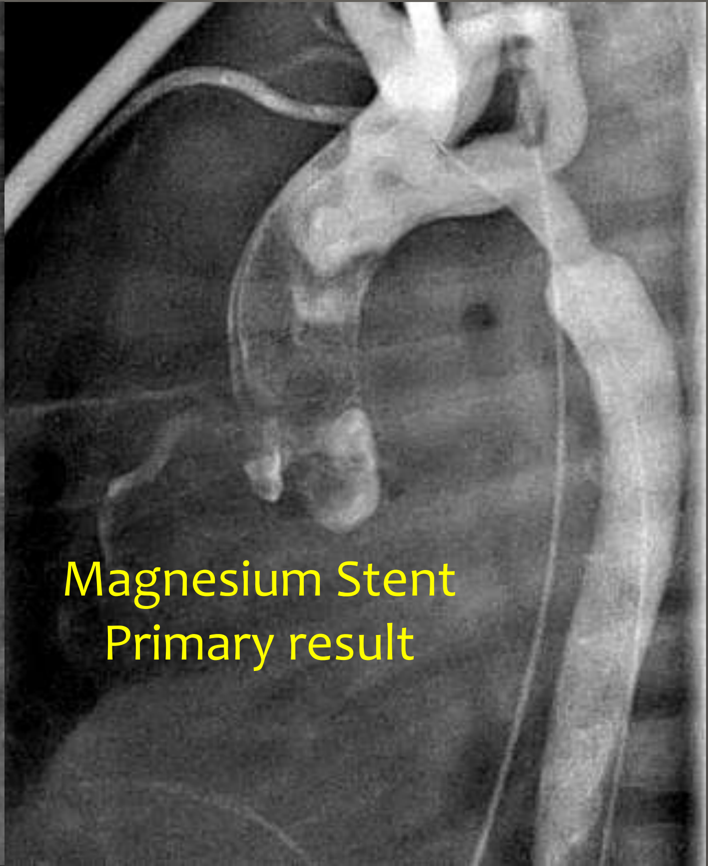
- Native CoA in a premature infant
- Access: right axillary artery
- Mg stent – 3.5 mm x 10mm

– courtesy of Dietmer Schranz



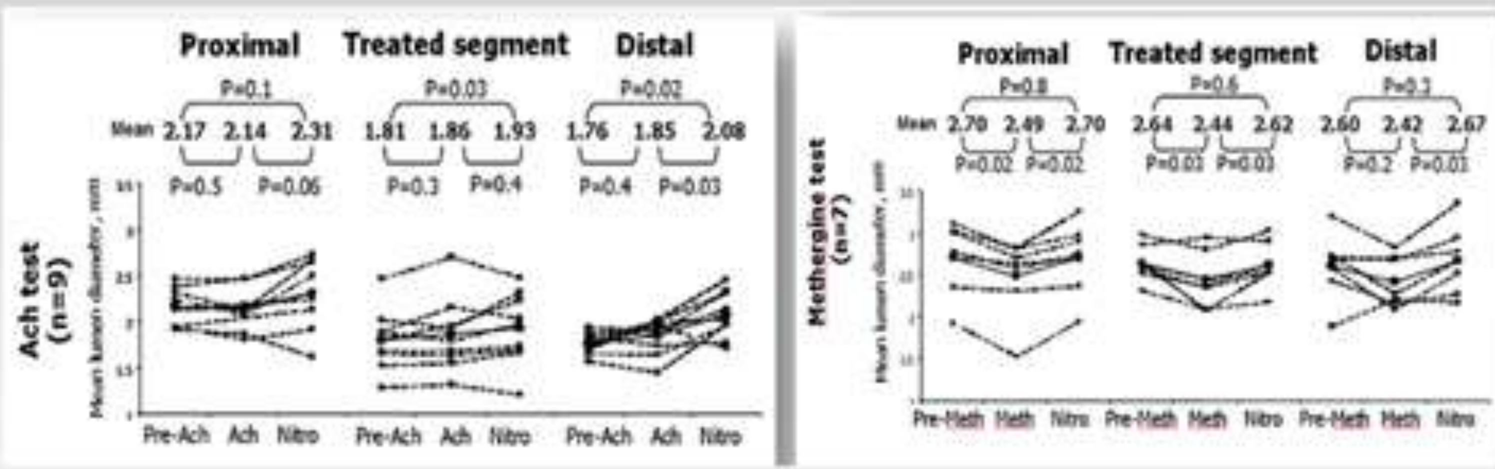






ABBOTT ABSORB STENT

ABSORB: Vasomotor Function Testing



The reappearance of vasomotion in the proximal, distal, as well as treated segments in response to methergine or acetylcholine suggests that vessel vasoreactivity has been restored and that a physiological response to vasoactive stimulus might occur anew.

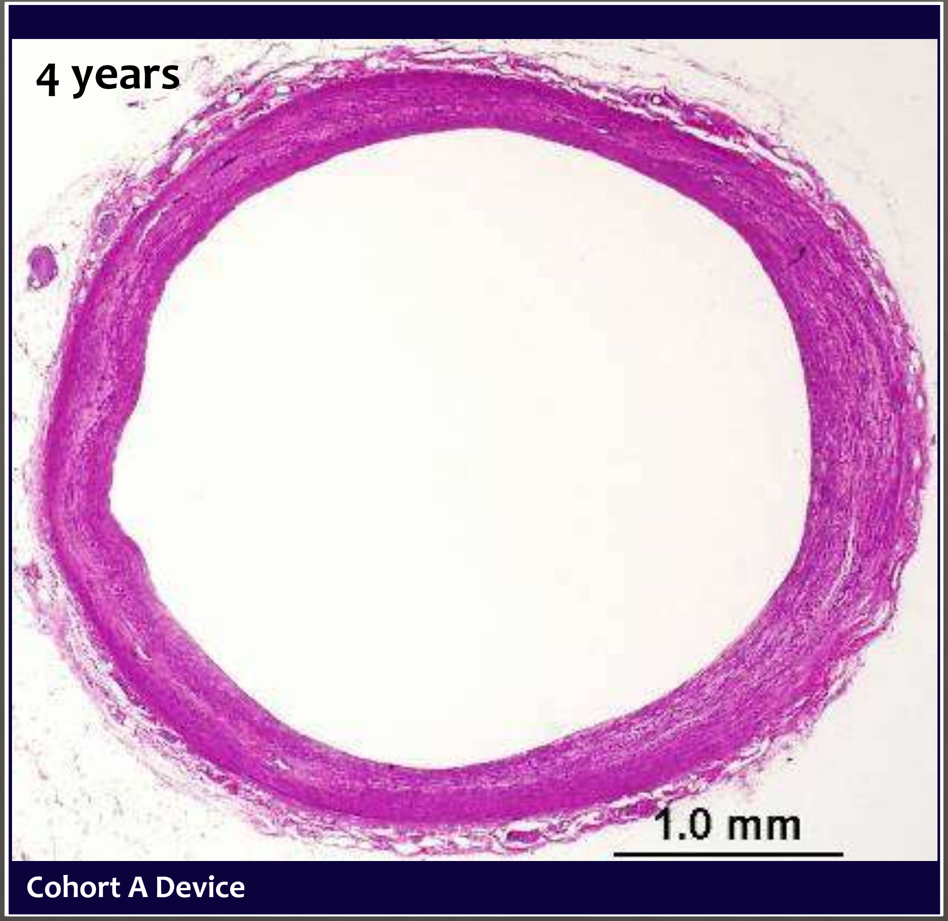
– Serruys *et al. Lancet* 2009;373:897-910

VASCULAR RESPONSE

- Mass loss data suggests 100% of material mass lost by 2 years
- Although the shape of struts still apparent at 2 years, there has been gradual replacement with provisional matrix
- No inflammation around the pre-existing strut regions

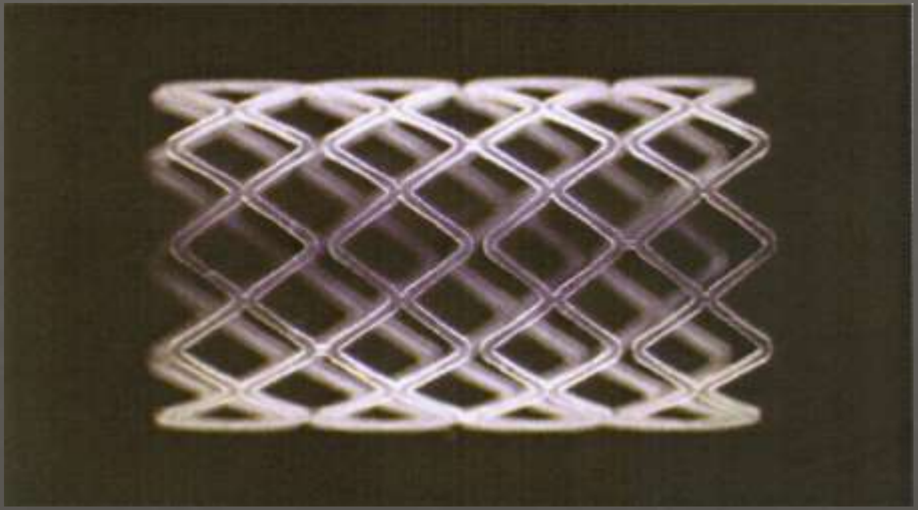
- 3 years – struts fully replaced by tissue
- 4 years – strut sites are indiscernible

Porcine coronary arteries



– courtesy of Abbott Vascular

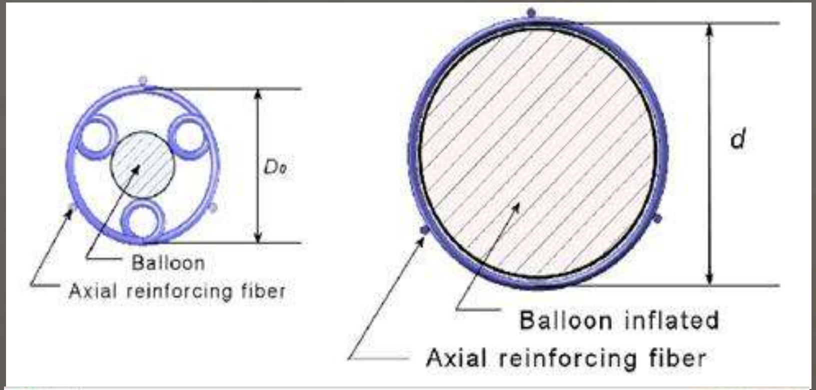
BIODEGRADABLE STENTS

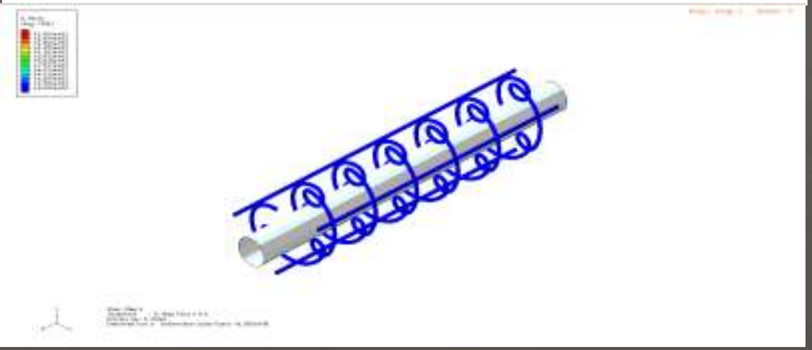


- Prototype
  - Early profile of a PediaStent biodegradable stent

UTSW: NOVEL BDS DESIGN

- Poly-L-Lactic acid (PLLA)
- Fibers melt extruded
  - PLLA pellets at 180°C
  - Drawn to 100 µm
- Novel BDS design
  - Balloon expandable
  - Internally coiled PLLA stent
  - Longitudinal fibers
  - Platinum tip markers for visibility





FINITE ELEMENT ANALYSIS

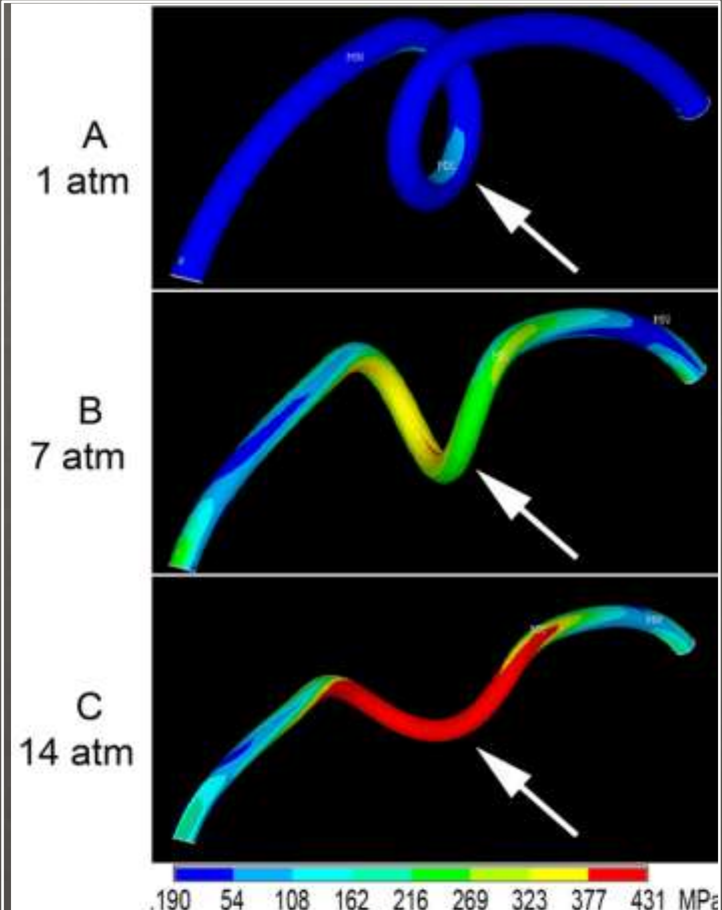


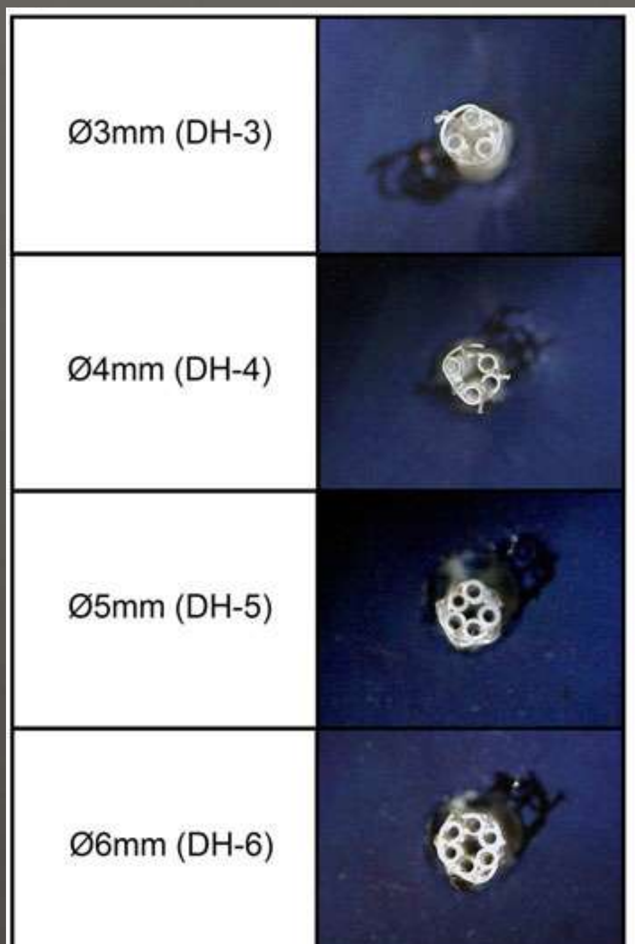
Fig. 1 Expanded coils of the stent at (A) 1 atm, (B) 7 atm, (C) 14 atm

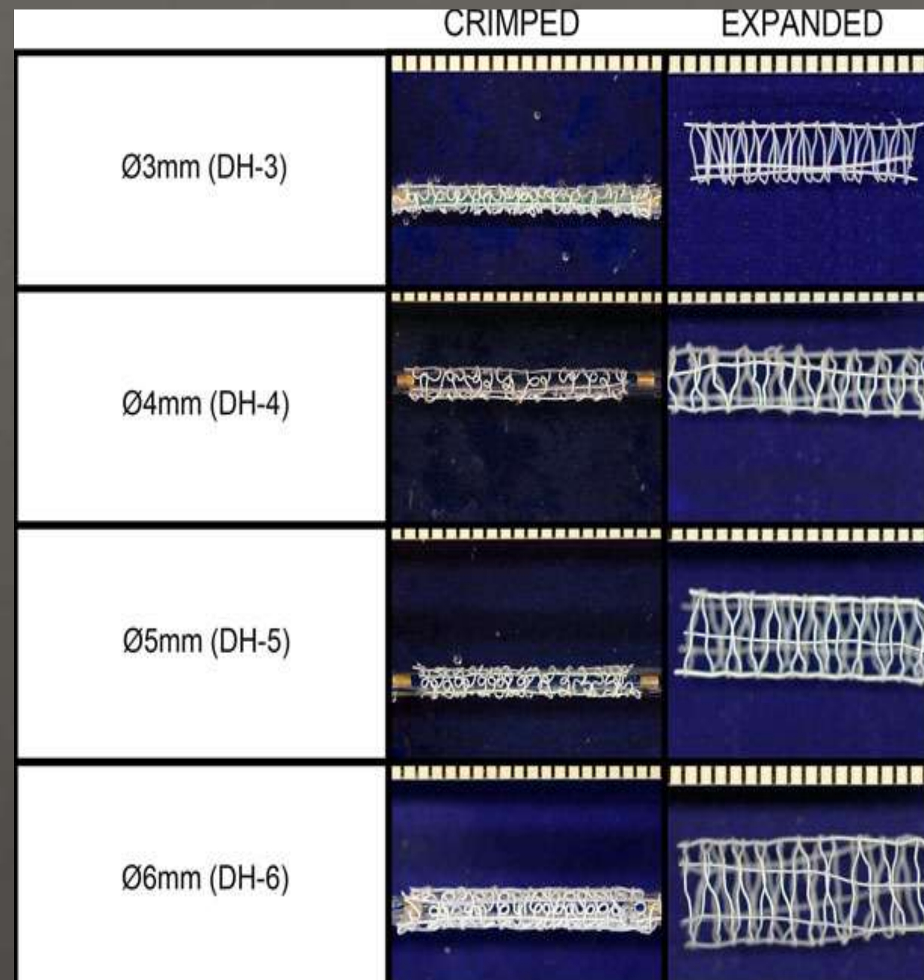
- Predicts expansion
- Validated in bench testing
- Permanent set caused by plastic yielding in torsion
- Localized to last converted portion of inner coil (white arrow)

Welch et al. Characterizing the expansive deformation of a bioresorbable polymer fiber stent. Annals of biomedical engineering 2008;36:742-51

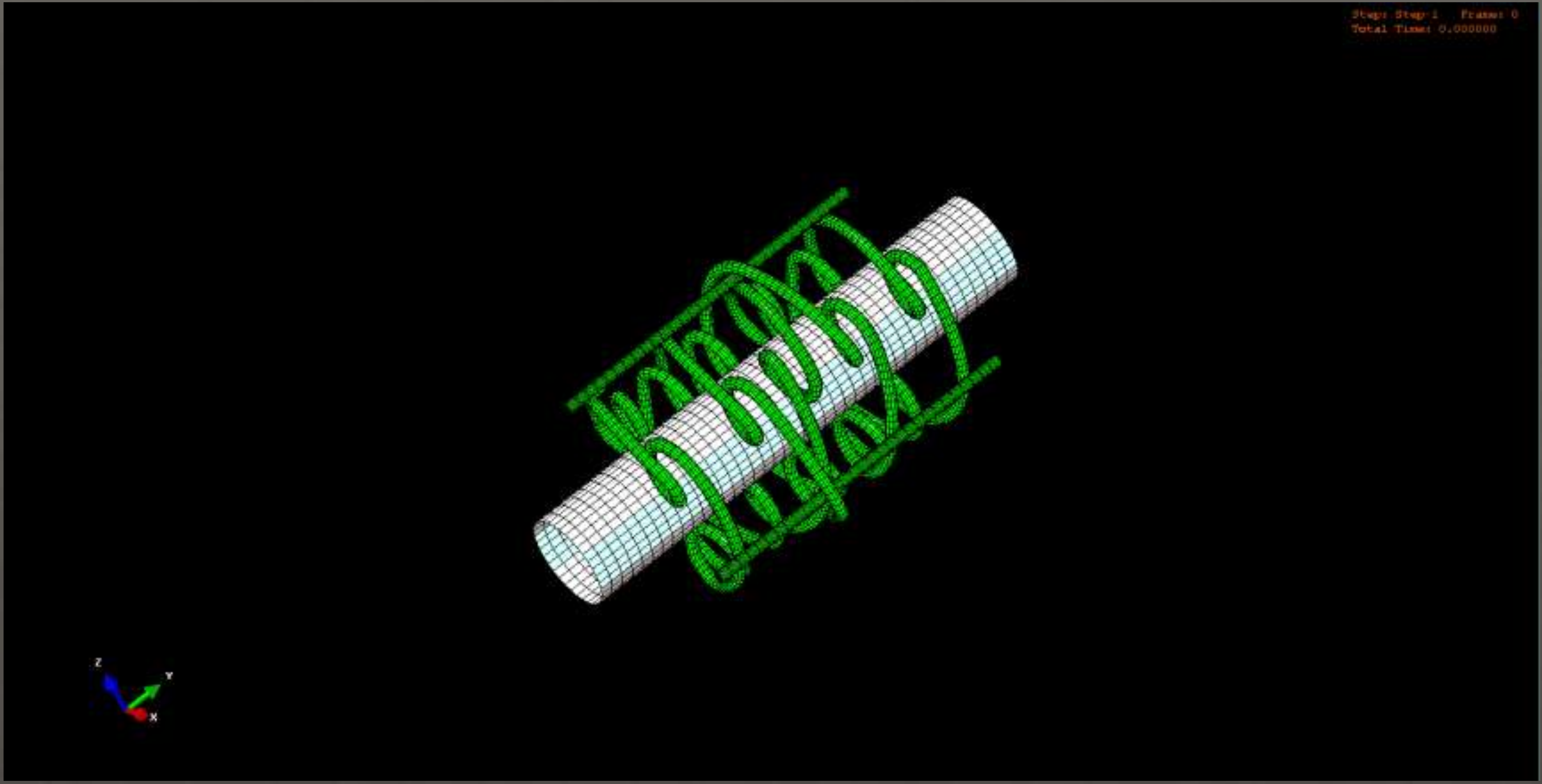
DOUBLE OPPOSED HELIX STENTS

Inner loop configuration



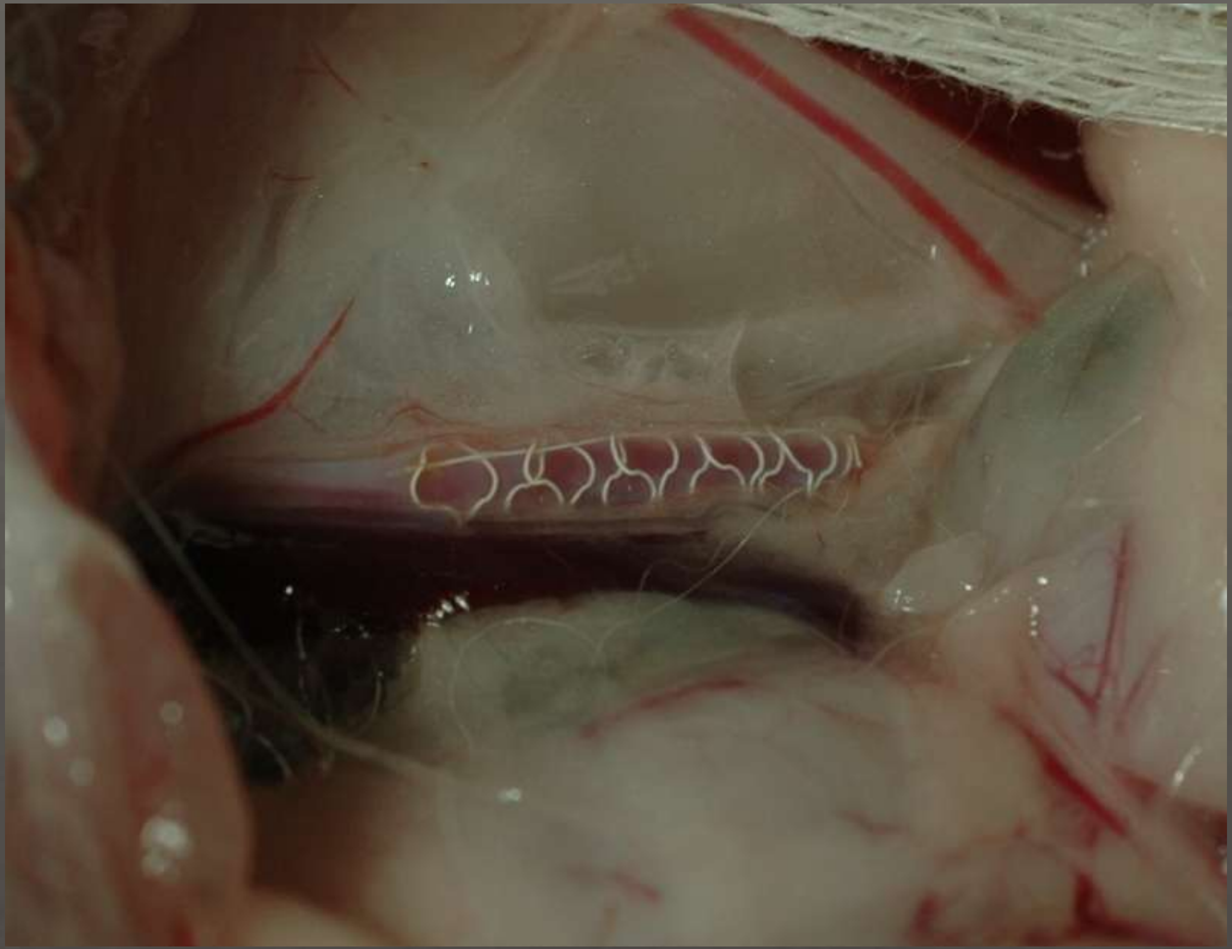


DOUBLE OPPOSED HELICAL BDS
COMPUTER MODEL STENT EXPANSION

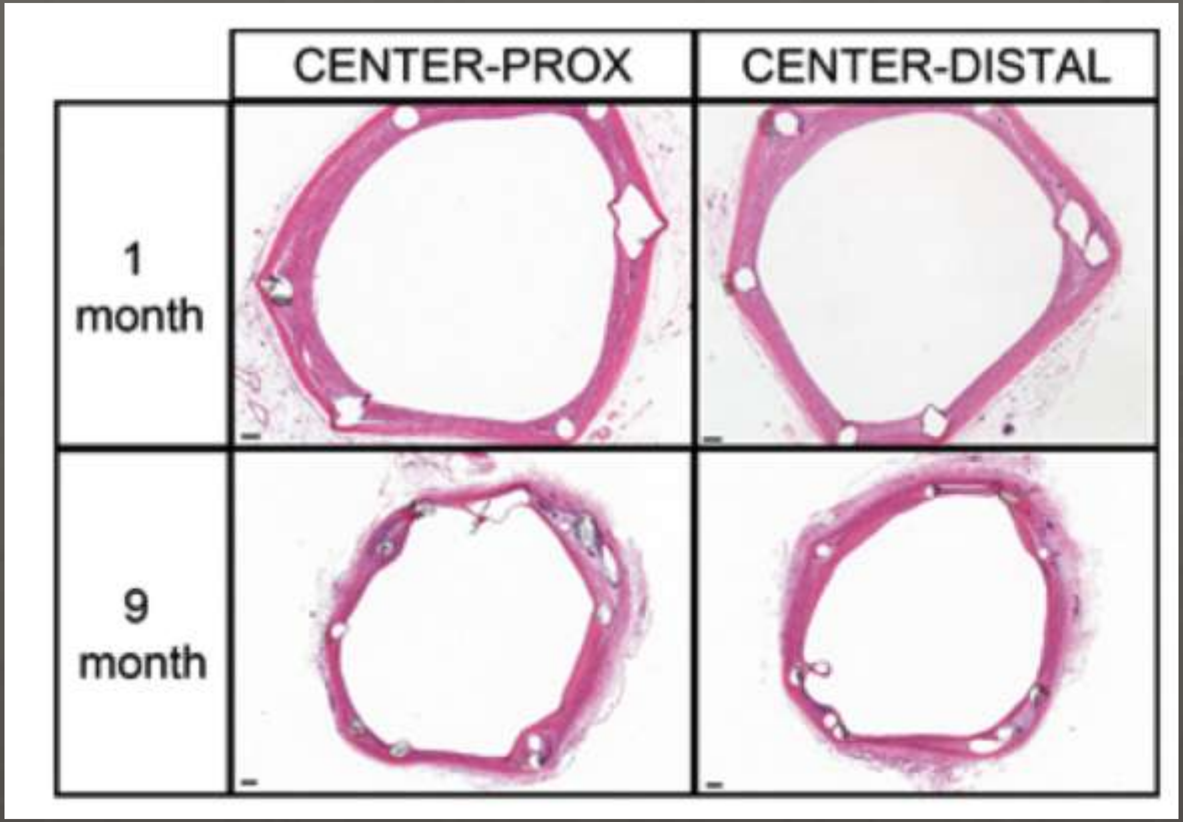


DH STENT APPOSITION

Dual Helical

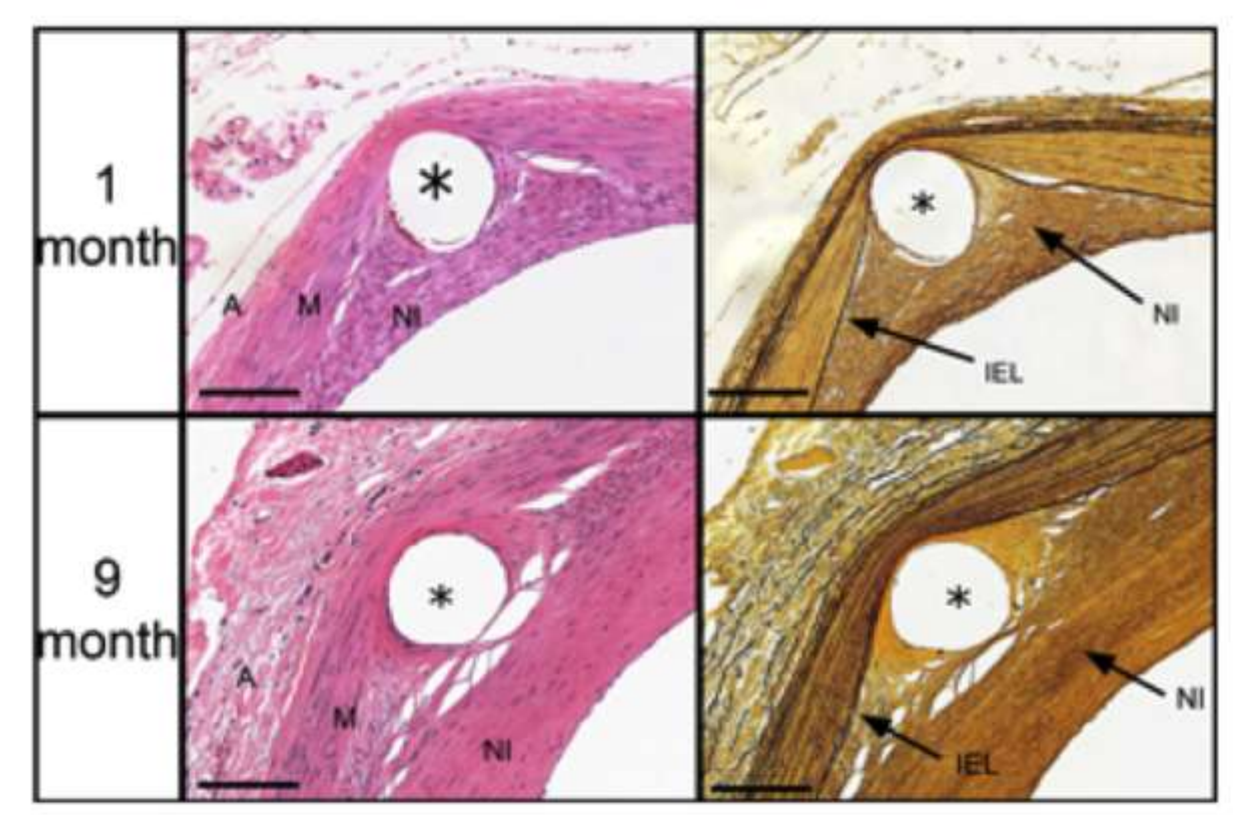


MMW LUMINAL SUPPORT: MAINTAINED AT 9 MONTHS



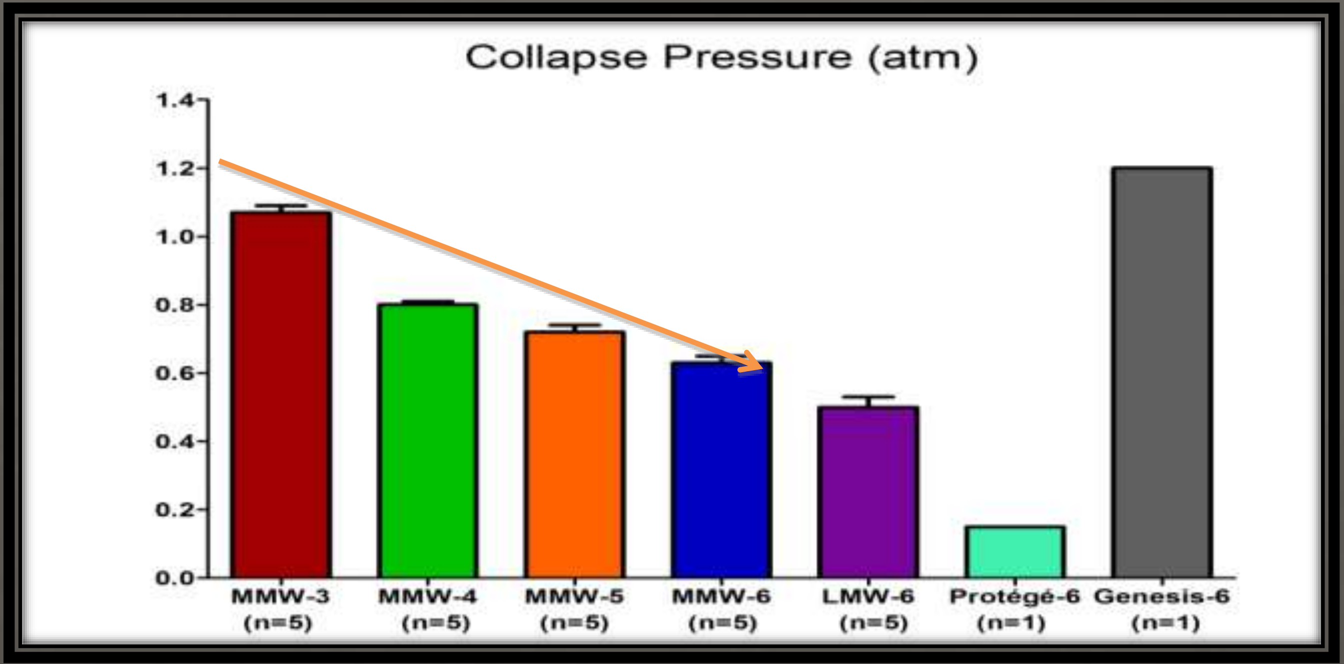
Sections of rabbit iliac artery and lower descending aorta stained with H&E illustrating luminal suport at the proximal and distal sections of the stent. The vessels are supported by the stent are wide and patent. Bar = 100 µm.

NEOINTIMAL RESPONSE: 9 MONTHS



A contiguous section H&E stain and Hart's elastin at 1 month and 9 month at 20x magnification (the neointimal response is evident (NI). The internal elastic lamina (IEL) is intact. Bar = 100 µm.

CHD GOAL > 6MM DIAMETER



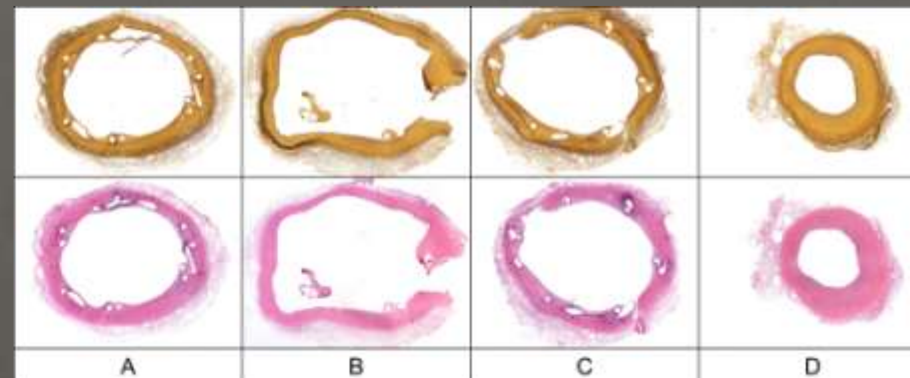
Options:

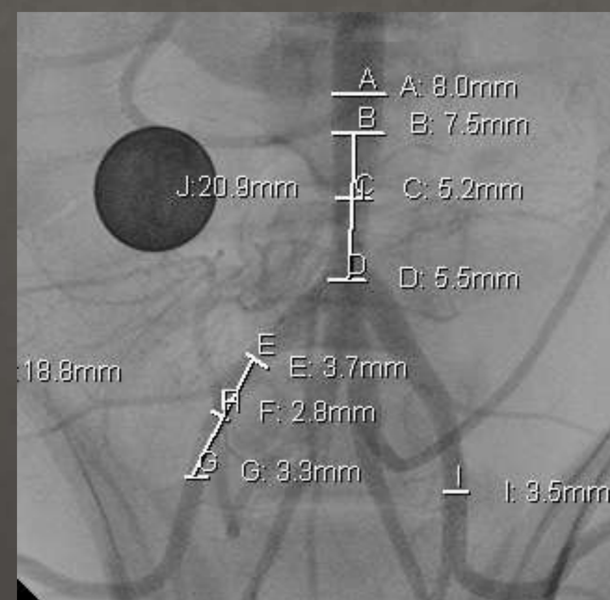
- more material (triple opposed helix)
- thicker fiber
- blended fiber
- increase MW

8MM STENTS IN DAO: 1 MONTH

Proximal Central Distal

1m





16-20kg minipigs.
9Fr sheath
8mm too small for species
9 month follow-up

9 MONTH FOLLOW-UP

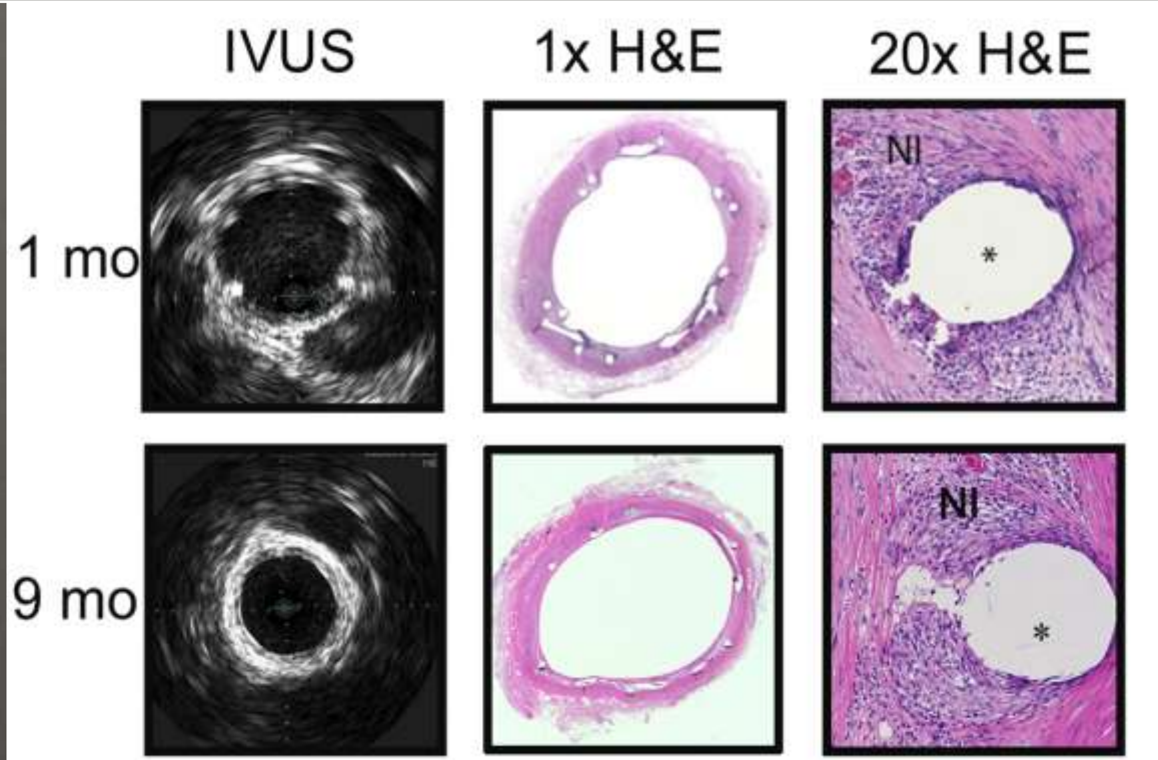


Fig. 16.IVUS and H&E staining of 8 mm PLLA stent in DAO at 1 and 9 months. * = stent strut; NI = neointima

EXPANSION OF 10 AND 12MM

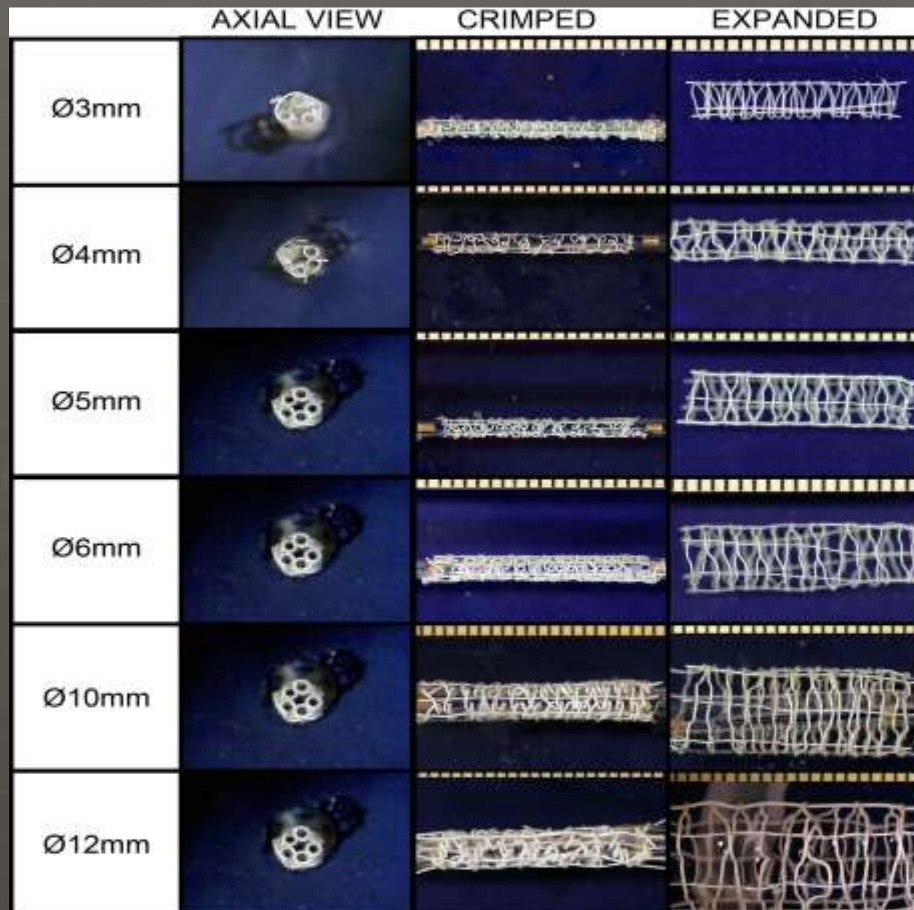


Fig. 4 Displaying the different diameter sizes noting the number of coils per design for the crimped and expanded stents.

REMAINING QUESTIONS

- How will the stent behave in the large vessels?
  - Radial strength at larger diameters
  - Effect of aorta pulsatility
- Vessel response as stent loses radial strength?
  - Vessel recoil or restenosis
  - Retain expanded diameter, requiring later reintervention
  - Allow later somatic growth of vessel
- Will fragments embolize after differential dissolution?
  - Where will fragments go?
- What happens when the device dissolves?
  - Will ASDs/VSDs *recanalize* as device dissolves?

SUMMARY

- Many procedures cannot be offered due to restraints in devices or attributes of patients
- Our smallest patients cannot benefit from some of our more refined techniques
- Biodegradable devices provide an important solution
  - Overcome the limitations of permanent devices
  - Allow small devices to be implanted without concern for somatic growth
- Loss of the device's rigid scaffold may restore functionality to the target vessel or cardiac region
- These devices will allow us to expand the reach of procedures
  - Avoid unnecessary surgeries
  - Include neonates and small children

Thank you