

# Paclitaxel-Eluting Balloon Valvuloplasty to Prevent Restenosis in an Animal Model of Aortic Stenosis

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# Potential conflicts of interest

**Speaker's name: K Spargias, MD**

**■ I have the following potential conflicts of interest to report:**

- Research contracts**
- Consulting
- Employment in industry
- Stockholder of a healthcare company
- Owner of a healthcare company
- Other(s)

**I do not have any potential conflict of interest**

## BAV and Restenosis components

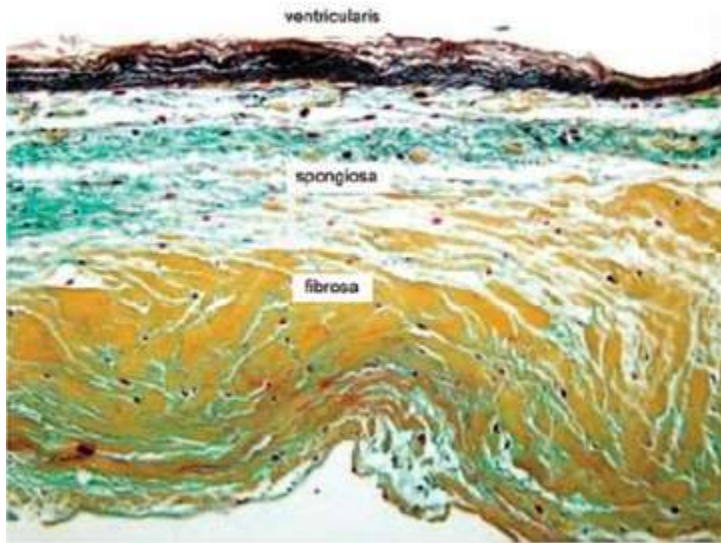
### ■ Recoil

- Immediate in ~20% of patients no acute improvement (no change or  $\leq 0.1 \text{ cm}^2 \uparrow$  in AVA)
- Late (12h to 30 days) conflicting data

### ■ Hyperplastic reaction

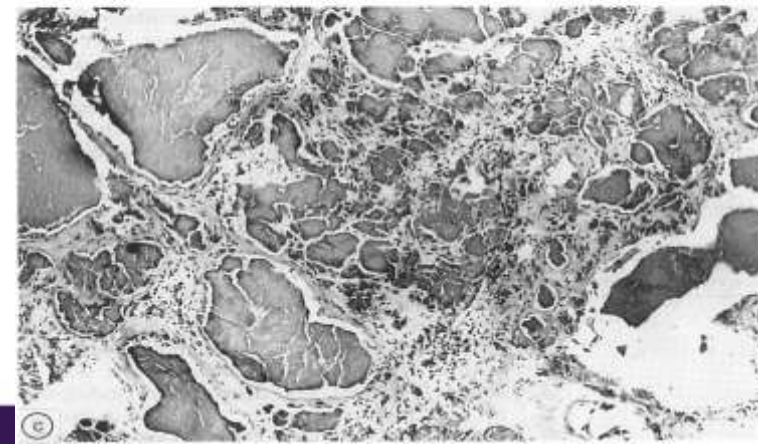
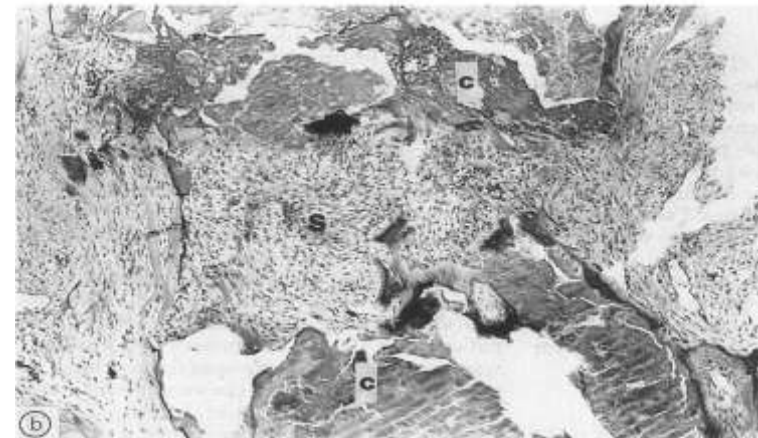
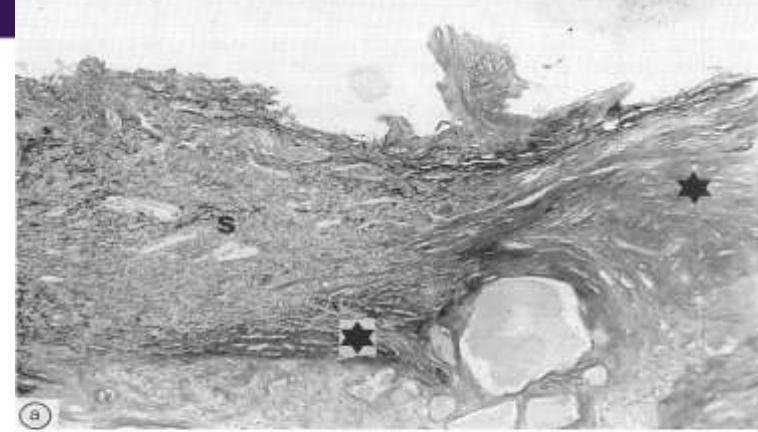
Histologic changes in restenosed valves differ from those seen initially in calcific AS and they exhibit:

- Zones of active capillary growth
- Zones of cellular proliferation
- Granulation tissue
- Fibrosis
- Ossification



Normal AV leaflet

Post-BAV AV leaflets



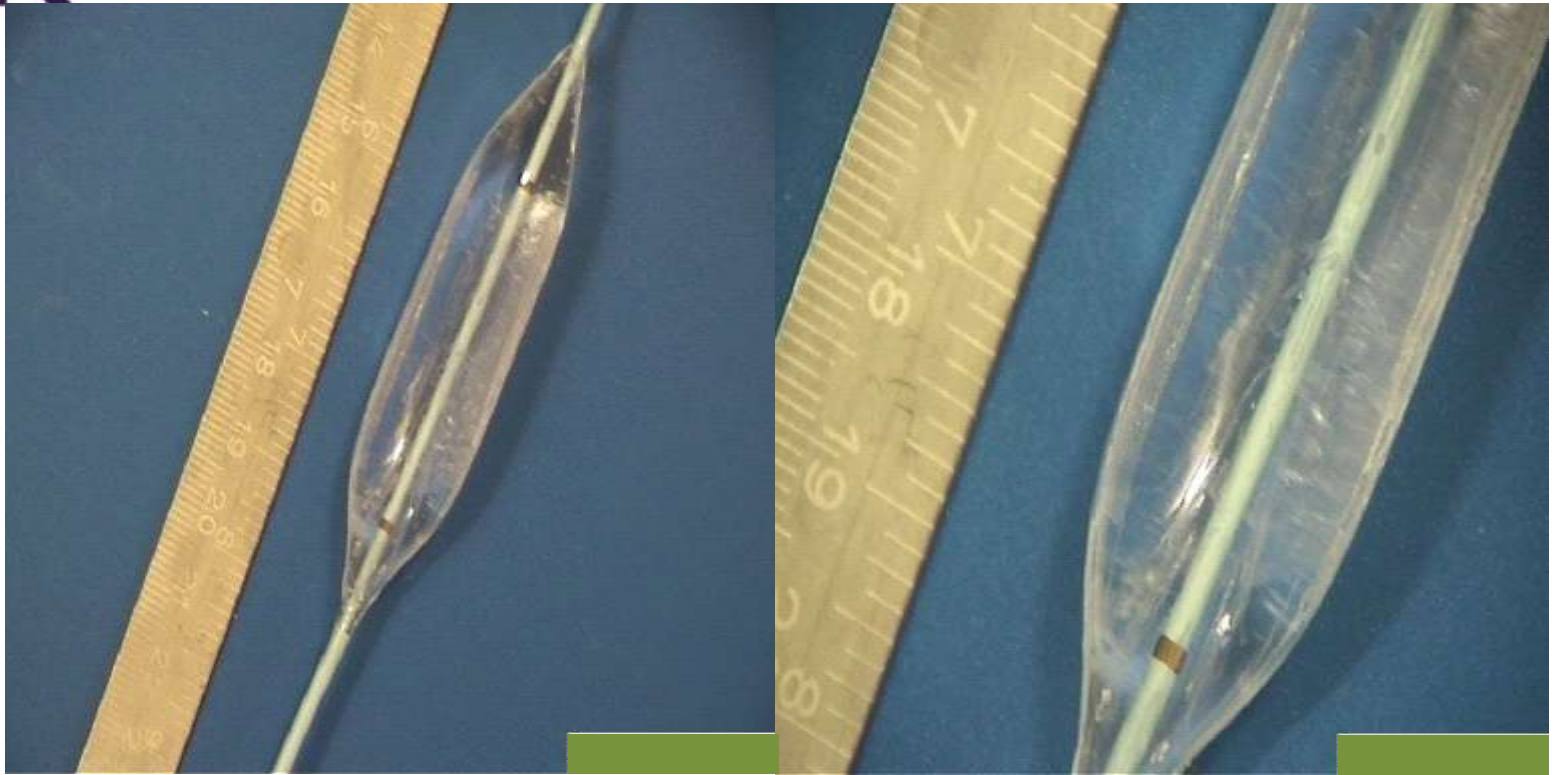
- The scarring component of restenosis is evident as early as a few days postBAV
- Young scar tissue gradually fills up splits between commissures, small tears or lacerations in the collagenous valve stroma and fractures in calcifications

Feldman et al, CCD1993;29:1-7. Hara et al, Circulation 2007;115:334-8.

Van den Brand et al, BHJ 1992;67:445-9. Serruys et al, EHJ 1988;9:782-94.

Safian et al, JACC 1987;9:655-60

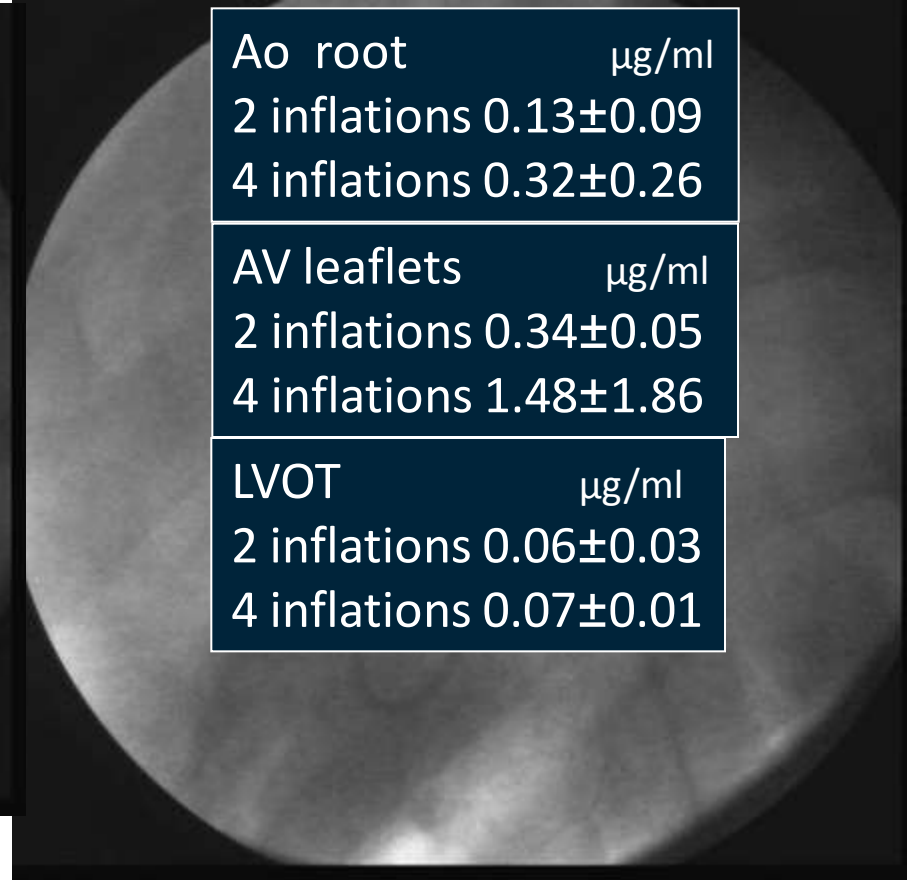
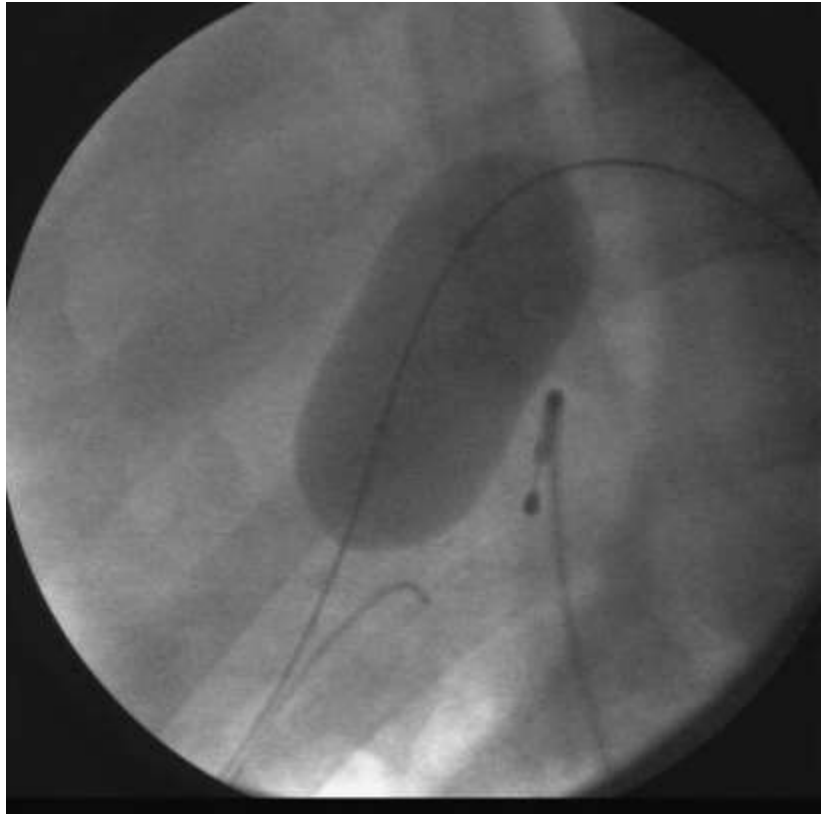
# Paclitaxel-eluting valvuloplasty balloon



## DIOR II™ Technology (Eurocor GmbH)

- Paclitaxel loading/balloon surface:  $3 \mu\text{g}/\text{mm}^2$
- Coating method: directly on balloon surface, 1:1 mixture of aleuritic & shellolic acid with Paclitaxel
- Complete drug release @ 30 sec

# Paclitaxel-eluting balloon valvuloplasty in healthy pigs: Tissue concentrations



- 8 healthy domestic pigs
- BAV with 22/24 mm paclitaxel-eluting balloons (3 µg/mm<sup>2</sup>, DIOR technology)
- Randomly 2 or 4 X 15-second inflations

# Study protocol based on an animal model of AS

- Cholesterol-rich diet (0.5% cholesterol) + 50000 IU/day Vit. D2\*



3 months

- General anaesthesia, TTE
- Access : right carotid artery, Aortography
- Pressure measurements of the ascending aorta and left ventricle
- BAV randomly with coated or uncoated balloon (8.0/20 mm, 3x10 sec)



3 weeks

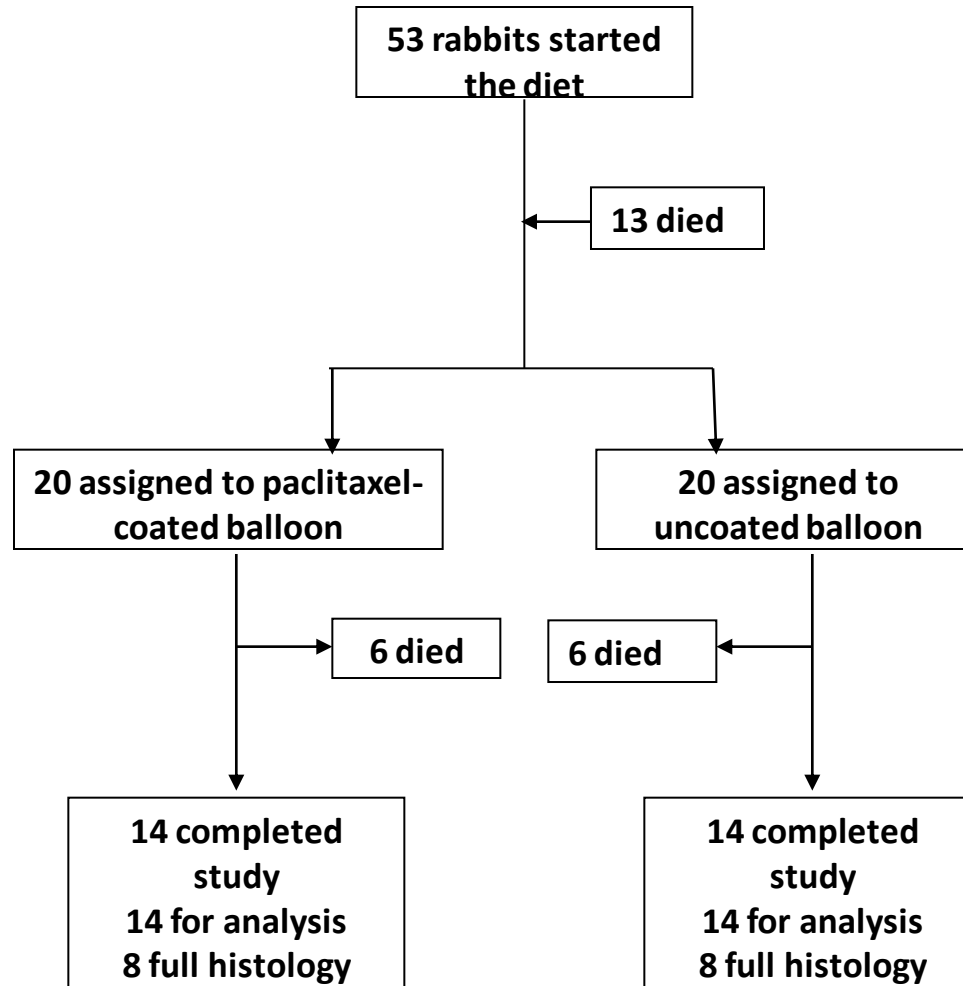
- General anaesthesia, TTE
- Access: right femoral artery, Aortography
- Pressure measurements of the ascending aorta and left ventricle



- Histology (Masson's trichrom in all, PCNA in last 16)

\*Drolet et al, JACC 2003;41:1211

# Study flow chart





Echocardiography:  
thickened sclerotic  
aortic valve



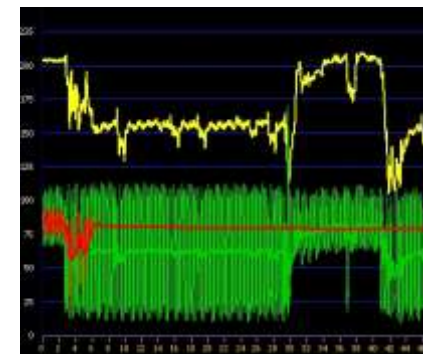
Pre-BAV



Positioning



BAV

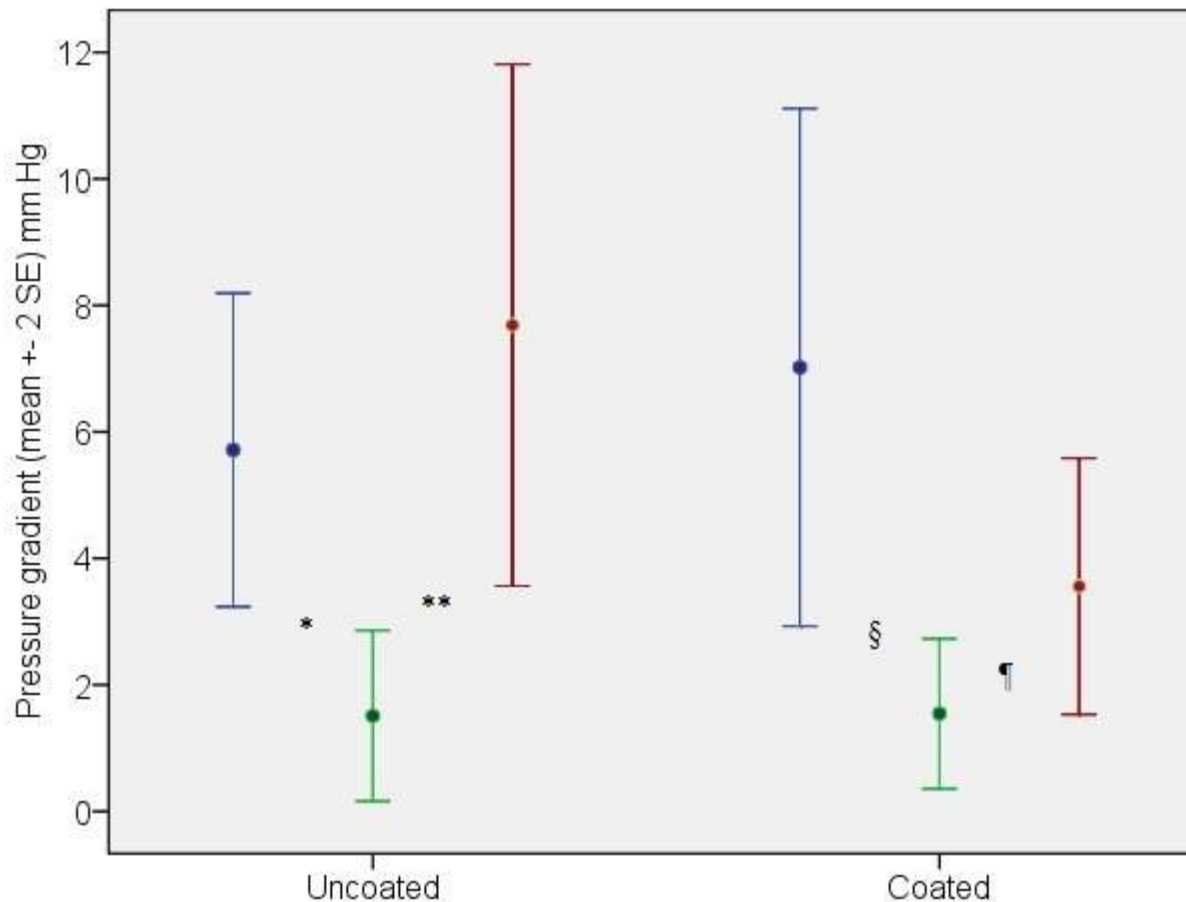


LV Aorta

## Invasive and echocardiographic data

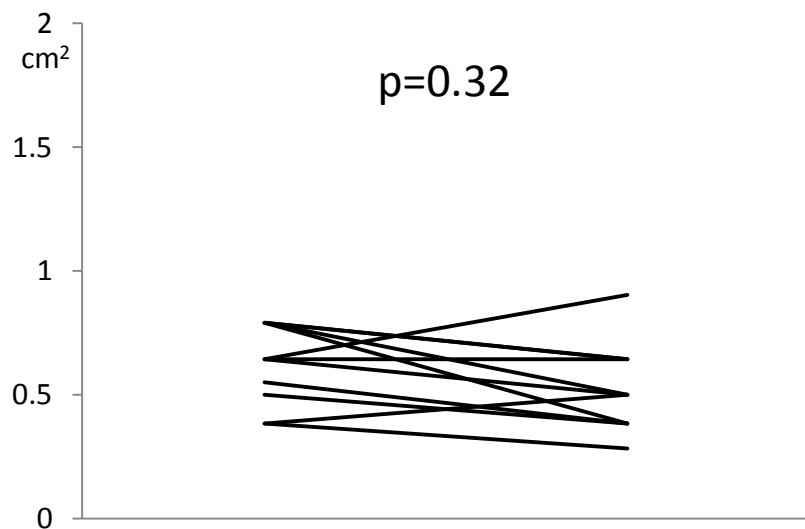
	Uncoated	Paclitaxel-coated	P value
	n=14	n=14	
<b>Pressure gradient*</b>	5.7±4.6	7.0±7.6	0.59
<b>Baseline (mm Hg)</b>			
<b>Pressure gradient</b>	1.5±2.5	1.5±2.2	0.97
<b>Post-BAV (mm Hg)</b>			
<b>Pressure gradient</b>	7.7±7.7	3.6±3.7	0.08
<b>Follow-up (mm Hg)</b>			
<b>Aortic valve area</b>	0.63±0.14	0.58±0.17	0.42
<b>Baseline (cm<sup>2</sup>)</b>			
<b>Aortic valve area</b>	0.62±0.16	0.58±0.19	0.55
<b>Post-BAV (cm<sup>2</sup>)</b>			
<b>Aortic valve area</b>	0.58±0.22	0.83±0.49	0.10
<b>Follow-up (cm<sup>2</sup>)</b>			

## Mean transvalvular pressure gradients

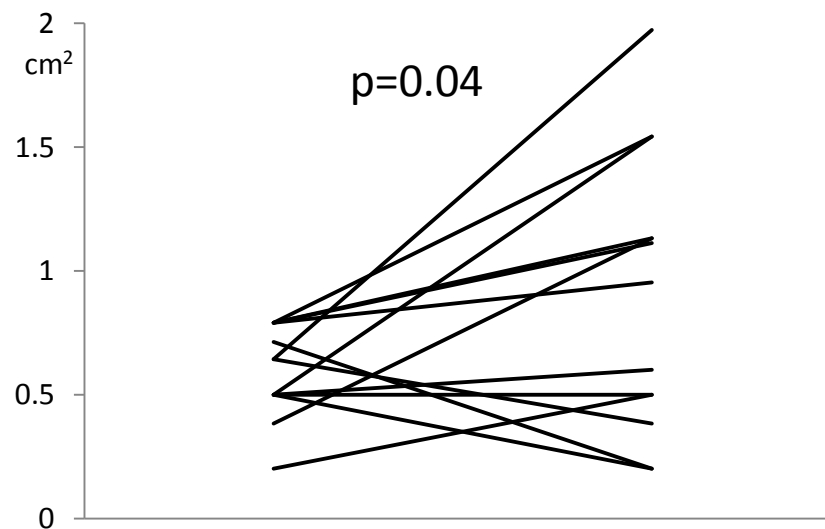


Blue lines: baseline, green lines: post-BAV, brown lines: follow-up. \*0.01, \*\*0.02, §0.004, ¶0.15

## Aortic valve area post-BAV and at follow-up



Uncoated

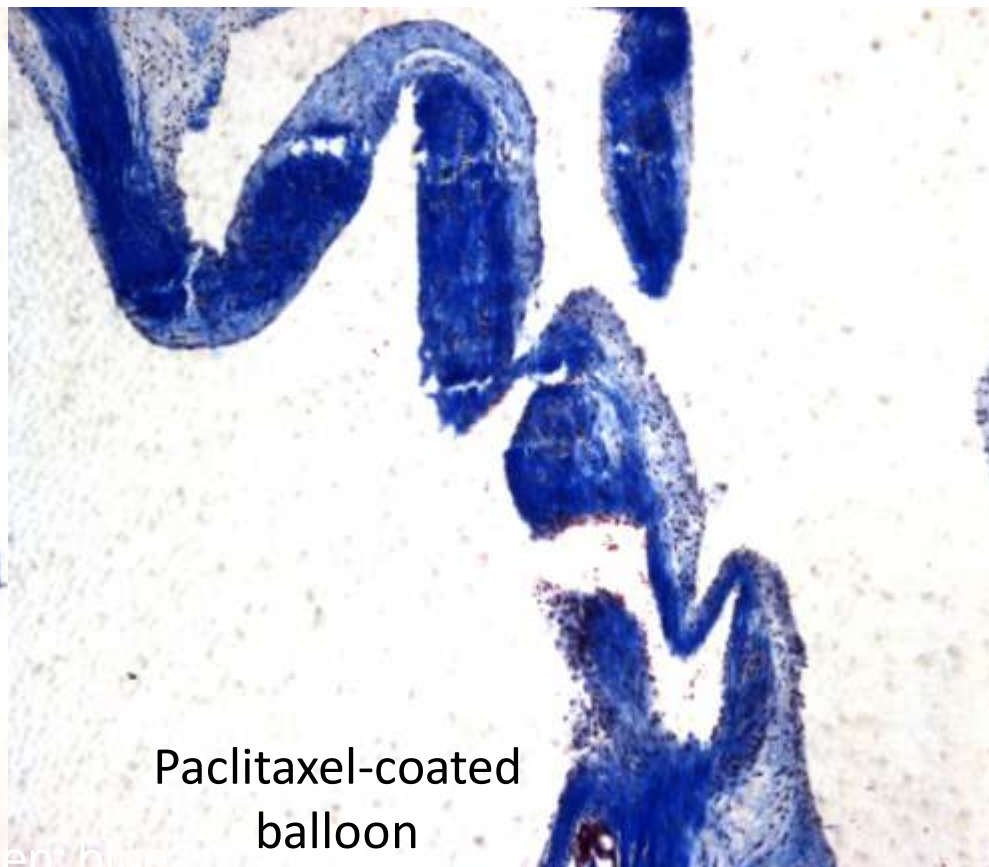


Paclitaxel-coated

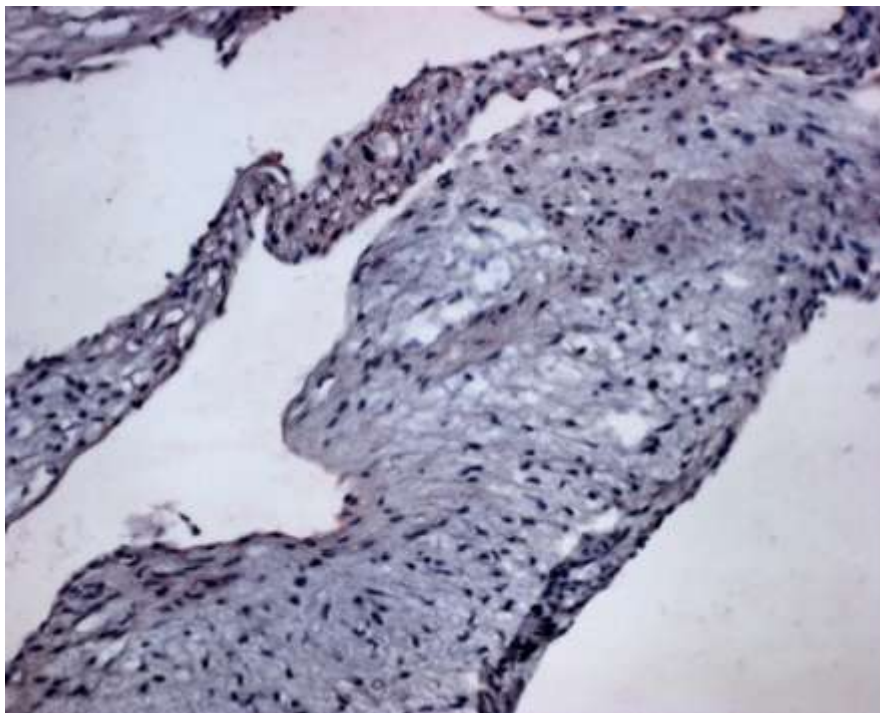
## Echocardiographic data

	Uncoated n=14	Paclitaxel-coated n=14	P value
IVS diastolic (cm)	0.30±0.04	0.29±0.06	0.69
IVS systolic (cm)	0.42±0.09	0.44±0.08	0.45
PW diastolic (cm)	0.38±0.12	0.37±0.09	0.85
PW systolic (cm)	0.49±0.08	0.52±0.06	0.33
EDD (cm)	1.46±0.31	1.35±0.39	0.42
ESD (cm)	0.92±0.16	0.83±0.13	0.37
EDV (mL)	6.00±3.05	5.45±3.41	0.66
ESV (mL)	1.77±1.02	1.60±1.25	0.71
SV (mL)	3.67±1.89	4.14±2.18	0.10
FS (%)	31.9±4.71	37.3±7.02	0.02
EF (%)	69±6.85	74±9.58	0.14

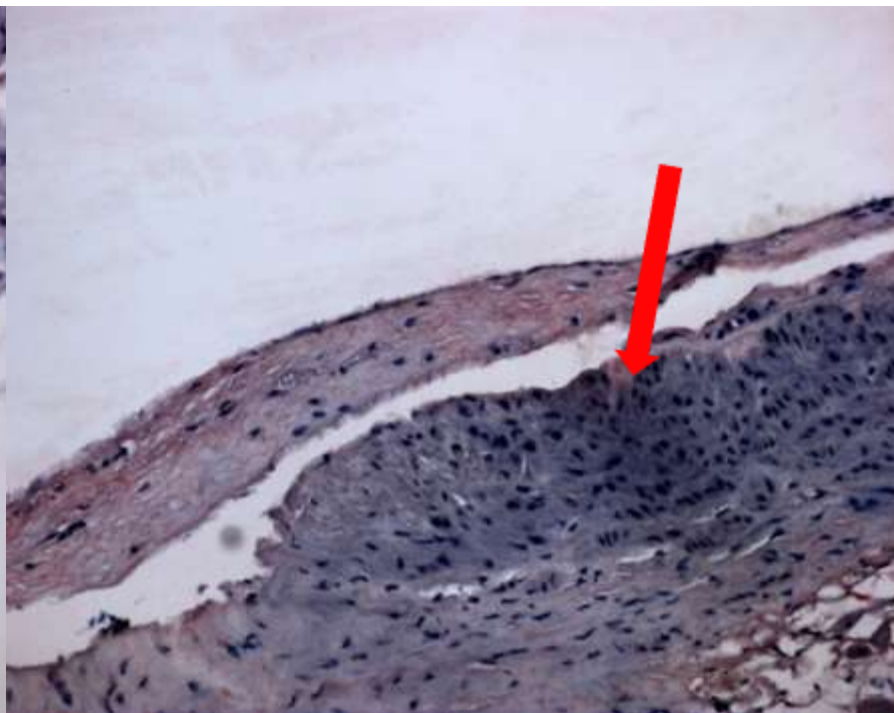
# Extracellular matrix deposition on AV leaflets post BAV: Masson`s trichrom staining



# Cell proliferation post BAV PCNA staining



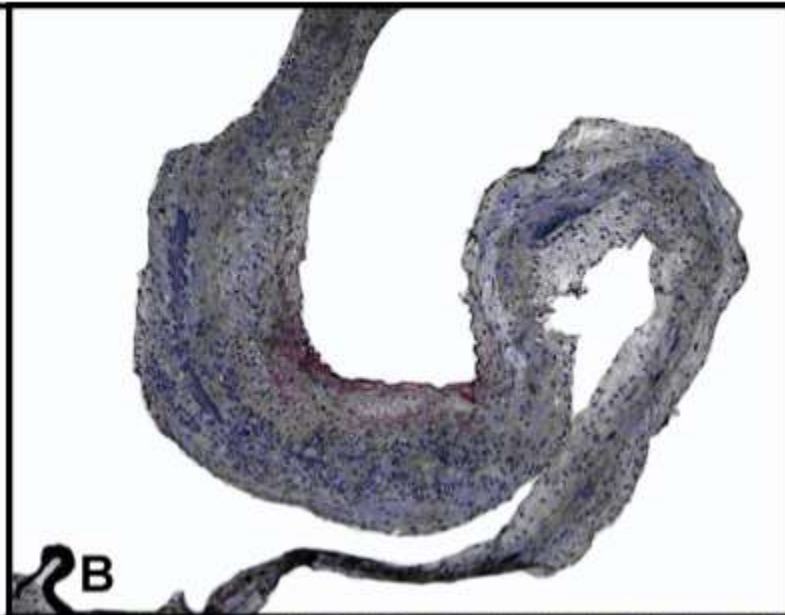
**Paclitaxel-Coated**



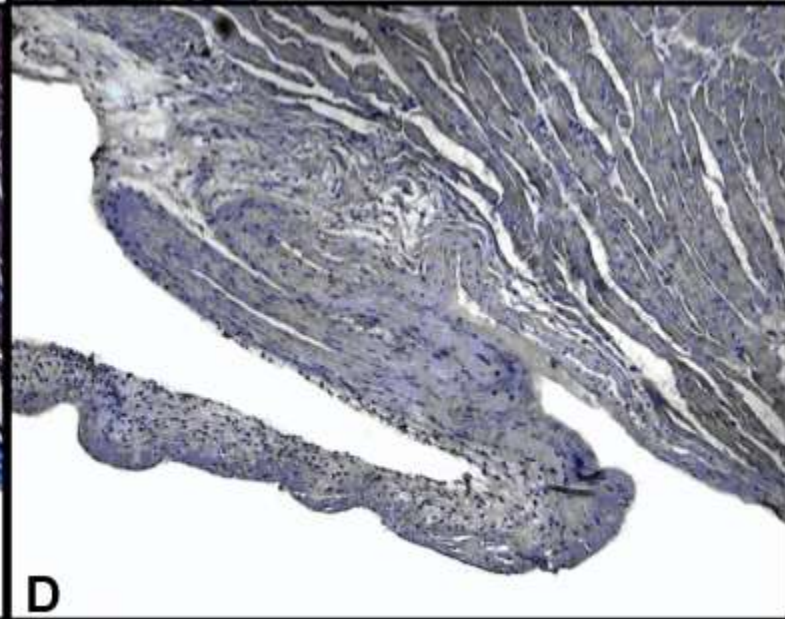
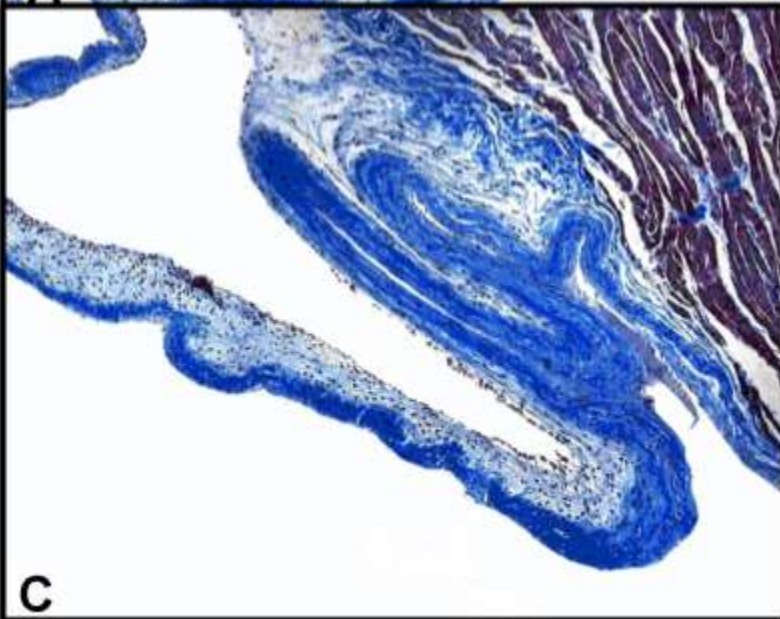
**Uncoated**

# Maisons trichrom (left) and PCNA (right) stainings

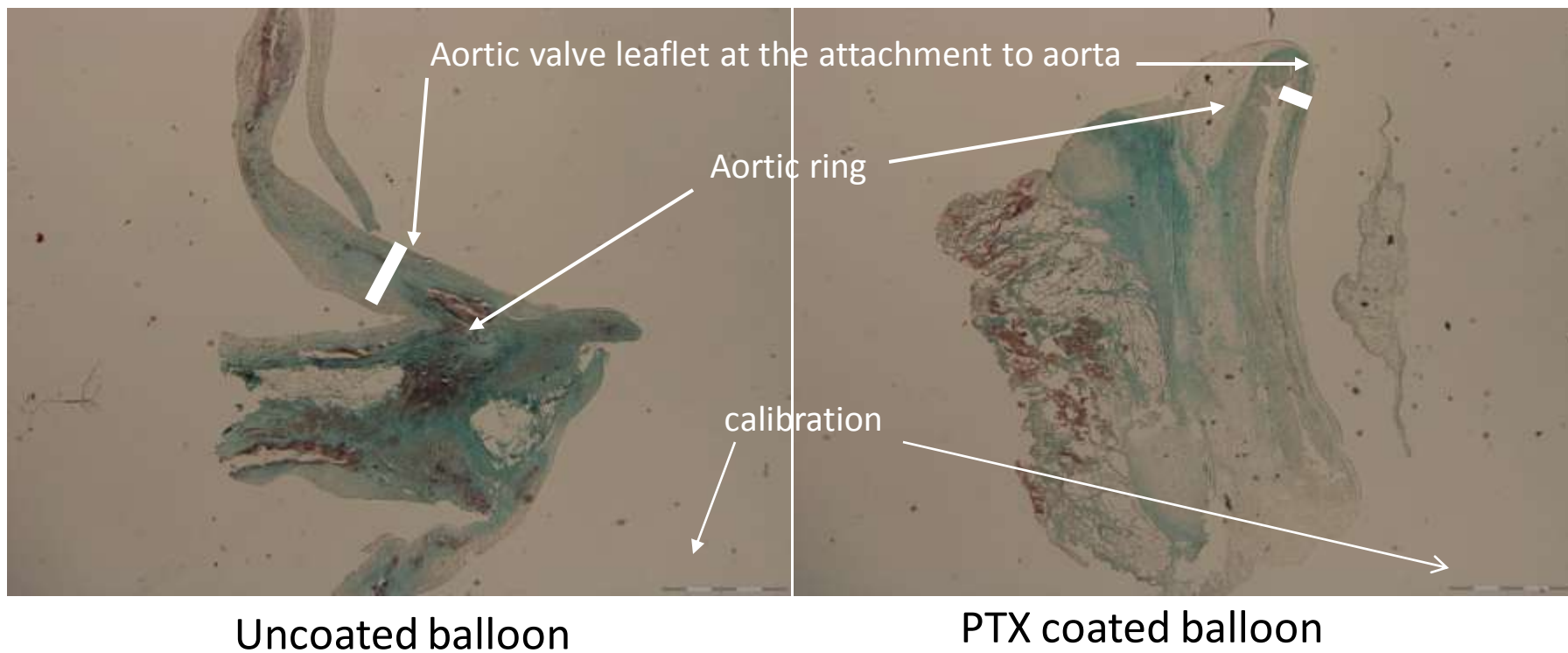
Uncoated



Paclitaxel coated



## AV leaflet thickness post-BAV



According to Rajamannan et al, Circulation 2005;112:I229

## Histology data

	Uncoated	Paclitaxel-coated	P value
	n=14	n=14	
<b>Leaflet thickness (mm)</b>	0.71±0.17	0.60±0.15	0.03
<b>PCNA grade</b>	2.88±1.55	1.88±1.72	0.24
<b>n=16; 8 each group</b>			

PCNA: Proliferating Cell Nuclear Antigen staining

# Drug-eluting balloon valvuloplasty development

- The results of this study support a preventative effect of the paclitaxel-coated balloon on restenosis
- FIM pilot studies with clinical and ECHO FU for safety, efficacy (ongoing)
- Randomized studies vs. plain BAV balloon for comparative efficacy (?clinical outcomes)
- Consider and test other potential drugs (such as antiproliferative, ossification inhibitors)
- Determine clinical use in triaging AS patients in the era of PAVR

# Patient risk and treatment options

