

# **Late loss and late catch-up after polymer-free and polymer-containing DES**

angiographic versus clinical long term results

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# Agenda

1. **DES registry** from Munich
  - **Serial angiographic FU** at 6-8 months and 2 years
  - **Clinical FU** to 2 years
  
2. Two-year angiographic and clinical follow-up of **ISAR-TEST-3**
  - BP DES vs Cypher vs PF DES

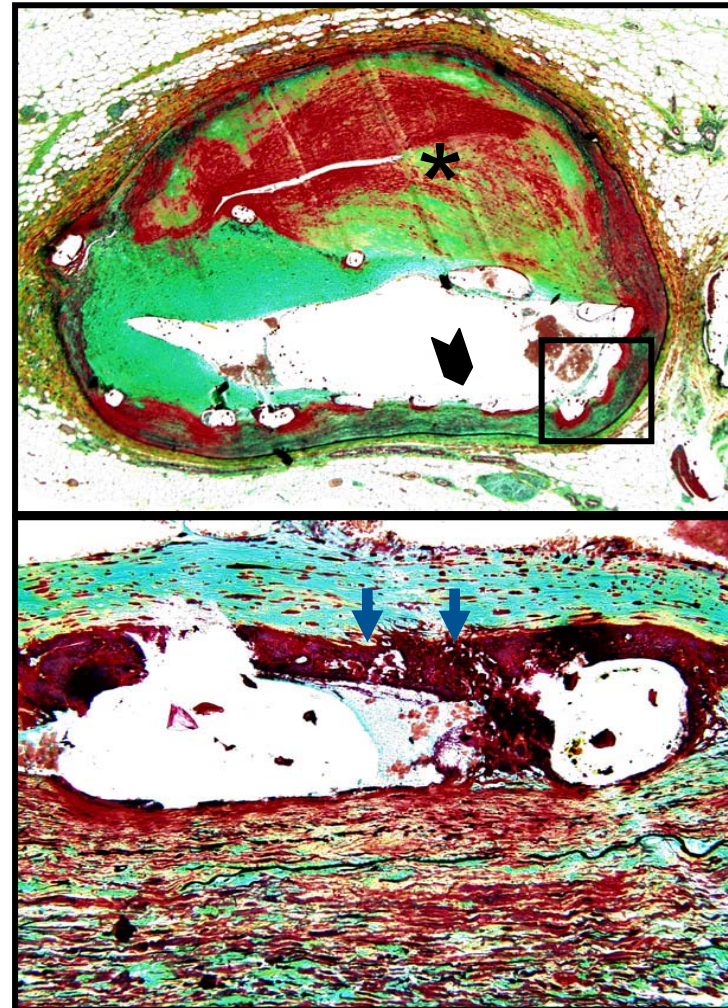
# Delayed Arterial Healing

*Incomplete  
Endothelialisation*

*Late Fibrin  
Deposition*

*Chronic  
Inflammation*

*Platelet Activation*



# Consequences of DAH

Excess of adverse events *late* (>12 months)  
after implantation in comparison with BMS



*Late Stent Thrombosis*

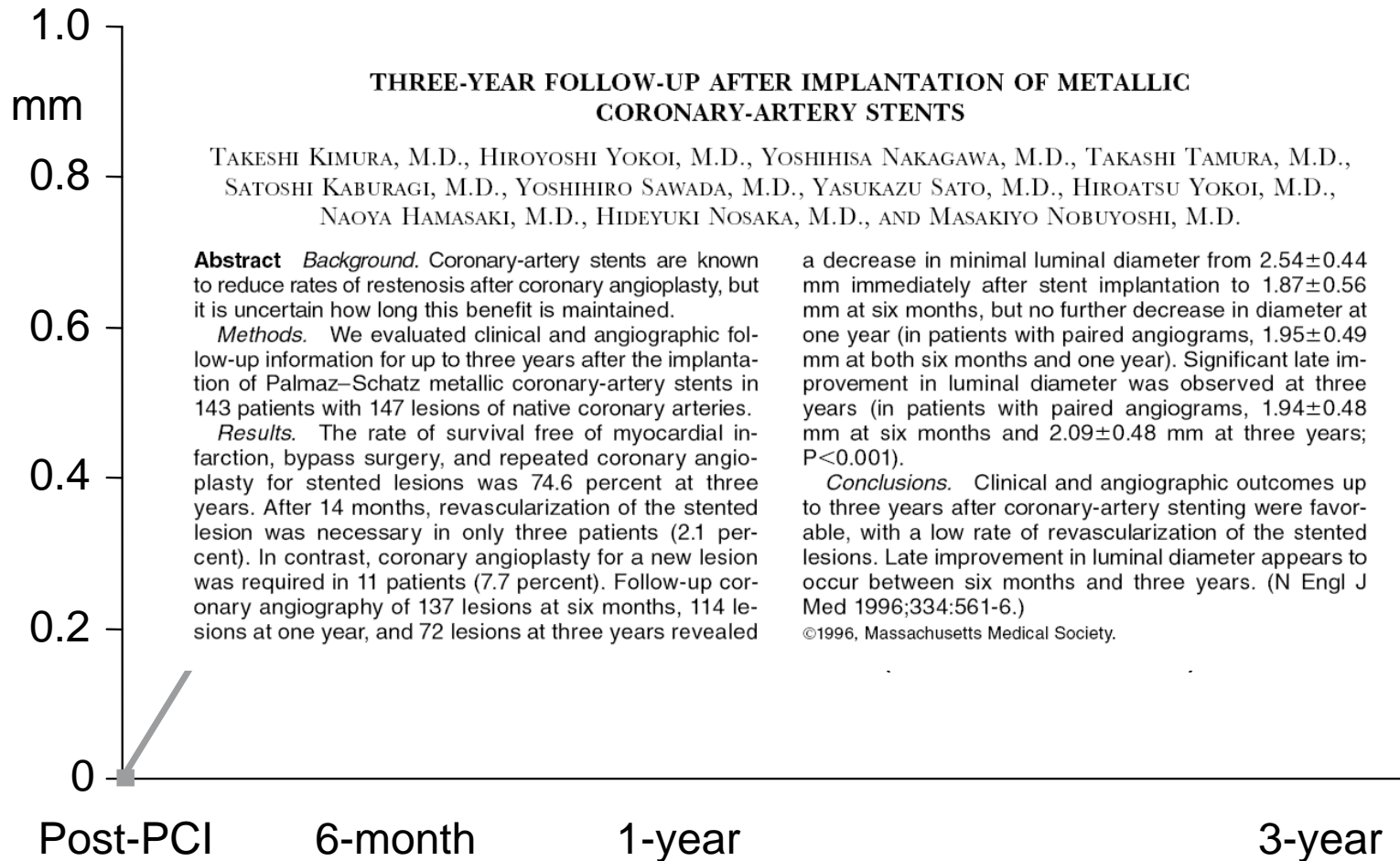


*Delayed Loss of  
Antirestenotic Efficacy*

Inflammatory Response to Durable  
Polymer Plays a Central Role

# Delayed Late Loss in BMS

## Late Luminal Loss



### THREE-YEAR FOLLOW-UP AFTER IMPLANTATION OF METALLIC CORONARY-ARTERY STENTS

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**Abstract Background.** Coronary-artery stents are known to reduce rates of restenosis after coronary angioplasty, but it is uncertain how long this benefit is maintained.

**Methods.** We evaluated clinical and angiographic follow-up information for up to three years after the implantation of Palmaz-Schatz metallic coronary-artery stents in 143 patients with 147 lesions of native coronary arteries.

**Results.** The rate of survival free of myocardial infarction, bypass surgery, and repeated coronary angioplasty for stented lesions was 74.6 percent at three years. After 14 months, revascularization of the stented lesion was necessary in only three patients (2.1 percent). In contrast, coronary angioplasty for a new lesion was required in 11 patients (7.7 percent). Follow-up coronary angiography of 137 lesions at six months, 114 lesions at one year, and 72 lesions at three years revealed

a decrease in minimal luminal diameter from  $2.54 \pm 0.44$  mm immediately after stent implantation to  $1.87 \pm 0.56$  mm at six months, but no further decrease in diameter at one year (in patients with paired angiograms,  $1.95 \pm 0.49$  mm at both six months and one year). Significant late improvement in luminal diameter was observed at three years (in patients with paired angiograms,  $1.94 \pm 0.48$  mm at six months and  $2.09 \pm 0.48$  mm at three years;  $P < 0.001$ ).

**Conclusions.** Clinical and angiographic outcomes up to three years after coronary-artery stenting were favorable, with a low rate of revascularization of the stented lesions. Late improvement in luminal diameter appears to occur between six months and three years. (N Engl J Med 1996;334:561-6.)

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## 1.

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## Durability of Antirestenotic Efficacy in Drug-Eluting Stents With and Without Permanent Polymer

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Olga Bruskina, MD,\* Albert Schömig, MD,\*† Adnan Kastrati, MD\*

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**Objectives** We sought to assess changes in antirestenotic efficacy of drug-eluting stents (DES) by restudying subjects at 2 time points after coronary stenting (6 to 8 months and 2 years) and to compare differences in time courses of late luminal loss (LLL) between 3 different DES platforms in use at our institution.

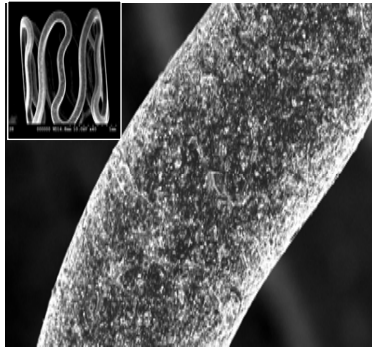
**Background** DES therapy is associated with low levels of LLL at 6 to 8 months. The temporal course of neointimal formation after this time point remains unclear.

**Methods** This prospective, observational, systematic angiographic follow-up study was conducted at 2 centers in Munich, Germany. Patients underwent stenting with permanent-polymer rapamycin-eluting stents (RES), polymer-free RES, or permanent-polymer paclitaxel-eluting stents (PES). The primary end point was *delayed* LLL (the difference in in-stent LLL between 6 to 8 months and 2 years).

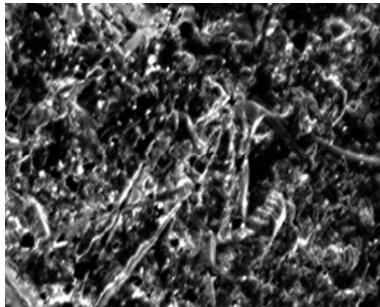
# Study Design

- 1. Permanent polymer sirolimus-eluting stent  
(Cypher)**
- 2. Polymer-free sirolimus-eluting stent  
(PF SES)**
- 3. Permanent polymer paclitaxel-eluting stent  
(Taxus)**

# ISAR Stent Types



100  $\mu\text{m}$



10  $\mu\text{m}$

## Stent Platform:

Thin-strut (87 $\mu\text{m}$ ) **microporous 316L  
Stainless Steel**

## Active Drug:

**Sirolimus**

## Coating:

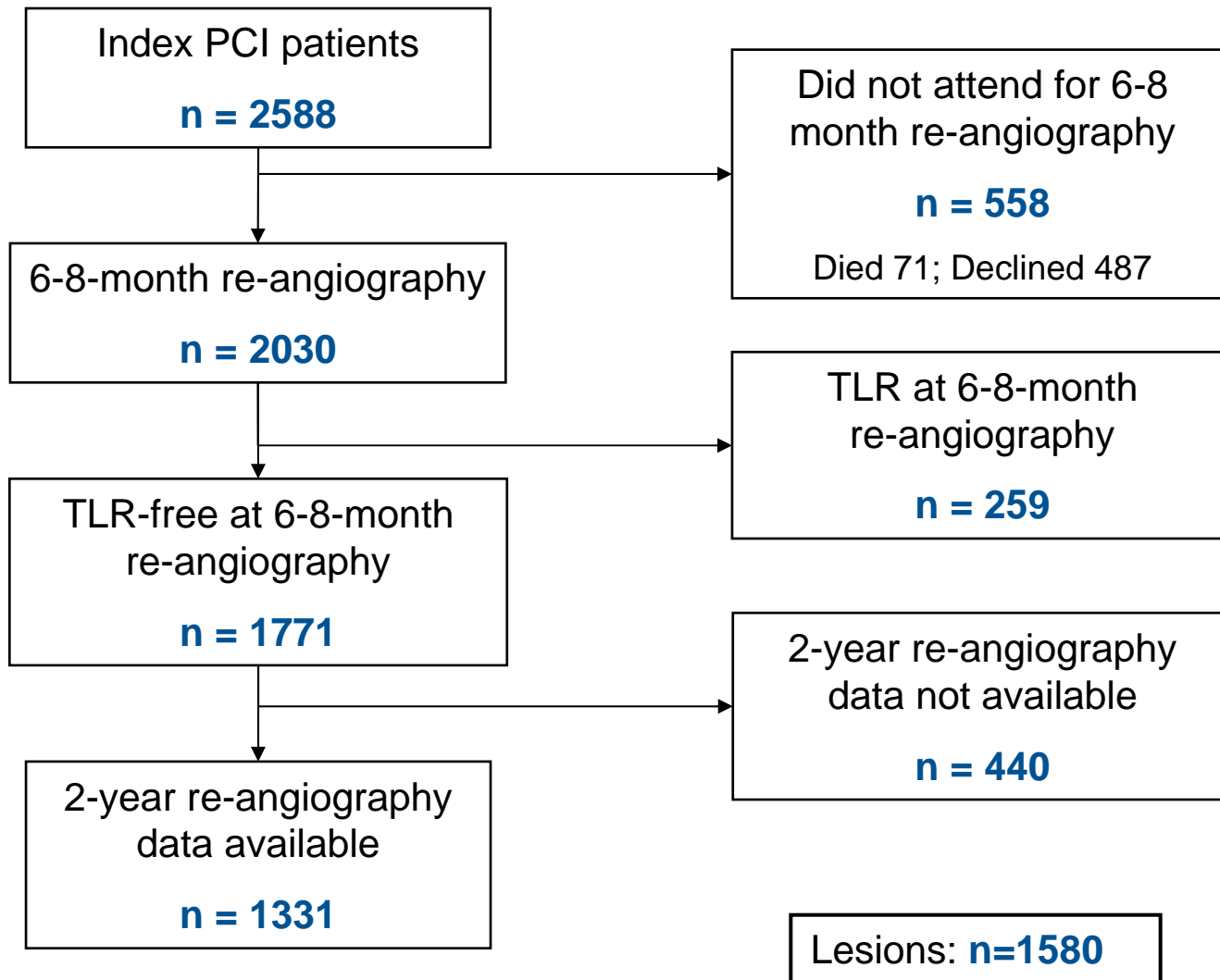
1. **PF DES: No polymer**; 480 $\mu\text{g}/\text{cm}^2$  sirolimus
2. **BP DES: Biodegradable polymer + shellac resin**; 180 $\mu\text{g}/\text{cm}^2$  sirolimus
3. **Dual DES: No polymer**; Probucol 120 $\mu\text{g}/\text{cm}^2$  + sirolimus 120 $\mu\text{g}/\text{cm}^2$

Developed in the setting of the ISAR-Project supported by the Bayerische Forschungsförderung

Wessely ATVB 2005; Hausleiter EHJ 2005; Mehilli Circulation 2006; Mehilli EHJ 2008;  
Steigerwald Biomaterials 2009; Byrne EHJ 2009; Byrne EHJ 2009



# Study Design



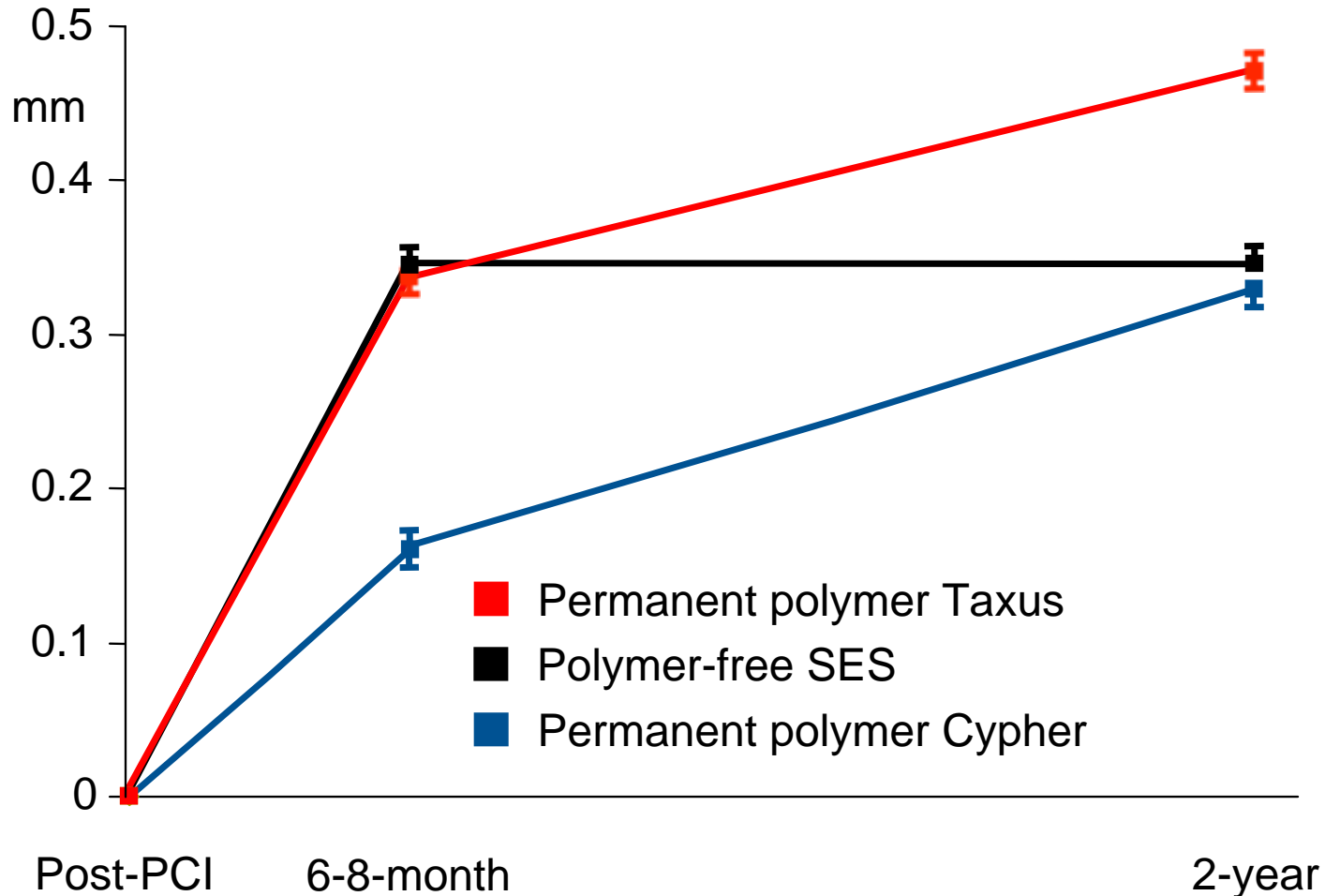
# Baseline Characteristics

	Cypher PP SES (n=1036)	PF SES ISAR (n=565)	Taxus PP PES (n=740)
Vessel size, mm	<b>2.70±.51</b>	<b>2.70±.49</b>	<b>2.71±.51</b>
Lesion length, mm	<b>14.1±7.8</b>	<b>13.6±6.5</b>	<b>13.4±7.7</b>
Diabetes mellitus	<b>29.6%</b>	<b>27.5%</b>	<b>28.1%</b>

# 2-Year Angiographic Outcomes

n=1580

Late Luminal Loss



# Late Lumen Loss

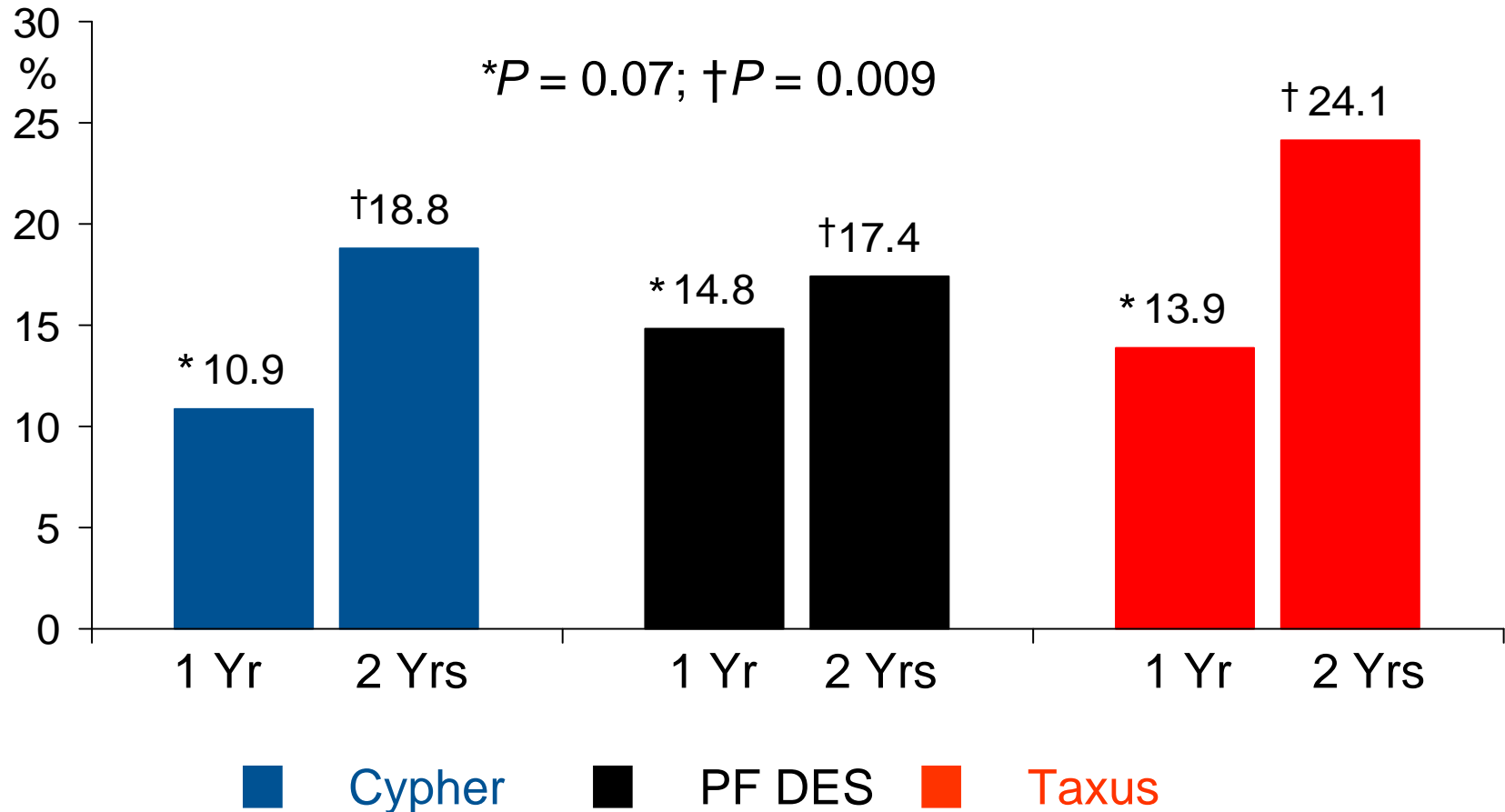
	Cypher (n=1036)	PF SES (n=565)	Taxus (n=740)
<b>Early</b> , mm 6-8 months	<b>0.16±.37*</b>	<b>0.35±.46</b>	<b>0.34±.44</b>
<b>Delayed</b> , mm 6-8 months → 2 years	<b>0.17±0.50</b>	<b>0.01±.42†</b>	<b>0.13±.50</b>

\*  $p < .001$  in favour Cypher; †  $p < .001$  in favour PF SES

# Clinical Restenosis

n=2030

## TLR at 6-8 months and 2 years



# Newer DES Platforms

**G2**

*Endeavor; Resolute*

*Xience-V*

**Next  
Gen**

*Biodegradable Polymer DES*

*Bioabsorbable Stent DES*

## 2.

## Randomised trial of three rapamycin-eluting stents with different coating strategies for the reduction of coronary restenosis: 2-year follow-up results

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### ABSTRACT

**Background:** Drug-eluting stent (DES) platforms devoid of durable polymer have potential to enhance long-term safety outcomes. The ISAR-TEST-3 study was a randomised trial comparing three rapamycin-eluting stents with different coating strategies. The present study examined 2-year outcomes of these patients and is the first large-scale trial to report longer-term outcomes with biodegradable polymer and polymer-free DES.

**Methods:** Patients with de novo coronary lesions in native vessels were randomly assigned to receive biodegradable polymer (BP; n = 202), permanent polymer (PP; Cypher; n = 202) and polymer-free (PF; n = 201) stents. The 2-year endpoints of interest were target lesion revascularisation (TLR), death/myocardial infarction (MI), stent thrombosis and delayed angiographic late luminal loss (LLL) between 6–8 months and 2 years.

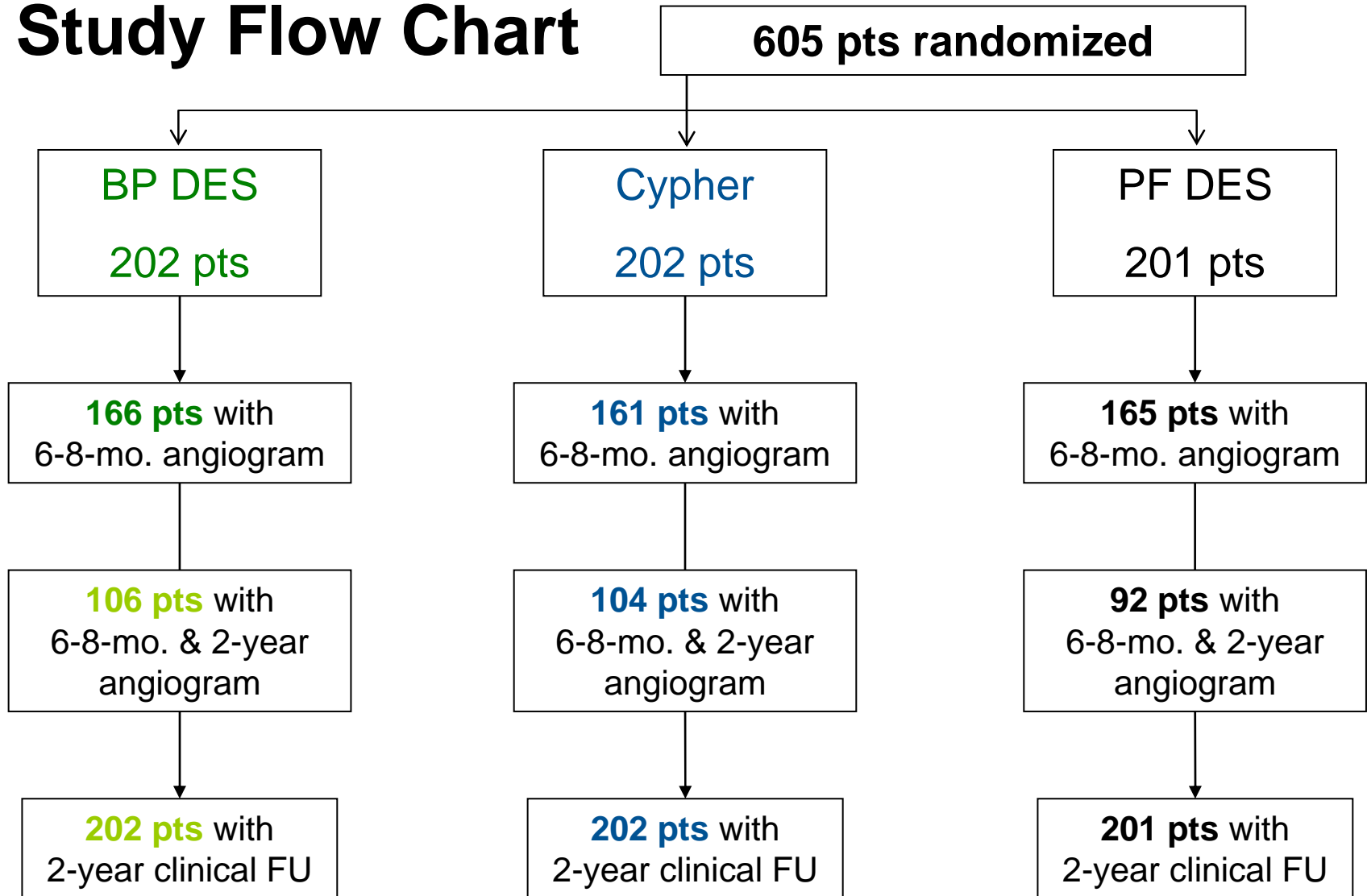
The Intracoronary Stenting and Angiographic Restenosis–Test Efficacy of Rapamycin-Eluting Stents with Different Polymer Coating Strategies (ISAR-TEST-3) study was a two-centre assessor-blinded randomised study examining the safety and efficacy of both novel polymer-free (PF) and biodegradable polymer (BP) rapamycin-eluting stents in comparison with the commercially available permanent polymer rapamycin-eluting stent (PP).<sup>8</sup> Results up to 1 year indicated that, whereas the antirestenotic efficacy of the PF stent was inferior to that of the PP platform, the BP stent achieved a similar antirestenotic efficacy to the PP stent. Potential benefits of DES platforms devoid of permanent polymer may be expected to appear only with longer-term follow-up.<sup>12–13</sup> The current analysis is the first large-scale study to

# ISAR-TEST-3 Study Design

- 1. Biodegradable polymer rapamycin-eluting stent  
(BP DES)**
- 2. Permanent polymer sirolimus-eluting stent  
(Cypher)**
- 3. polymer-free rapamycin-eluting stent  
(PF DES)**



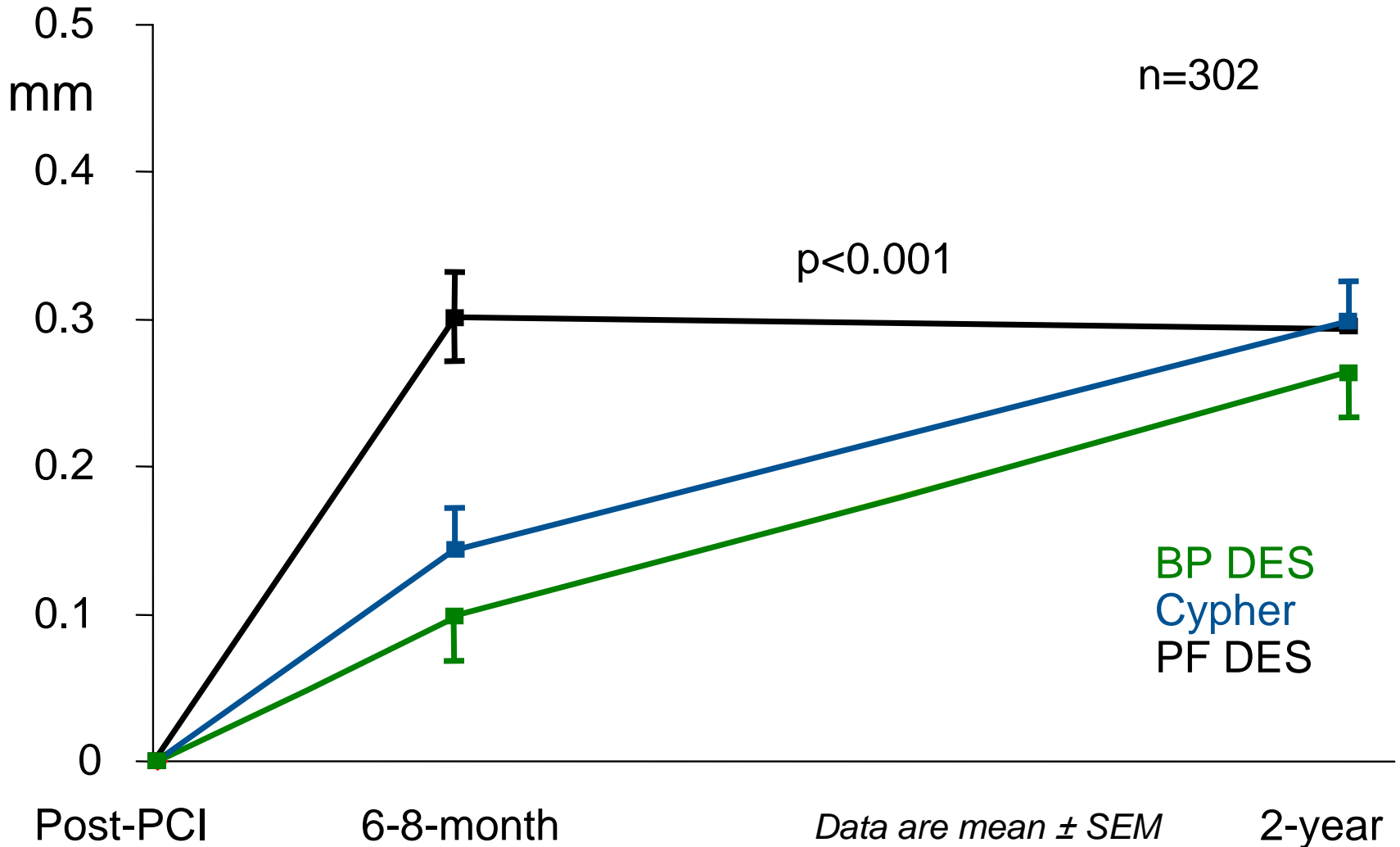
# Study Flow Chart



# Baseline Characteristics

	<b>BP SES (n=202)</b>	<b>Cypher (n=202)</b>	<b>PF SES (n=201)</b>
Vessel size, mm	<b>2.74±.51</b>	<b>2.75±.51</b>	<b>2.74±.45</b>
Lesion length, mm	<b>13.9±7.2</b>	<b>14.6±5.1</b>	<b>14.3±7.0</b>
Diabetes mellitus	<b>29%</b>	<b>26%</b>	<b>27%</b>

# ISAR-TEST-3: Late Luminal Loss to 2 Yrs



# Late lumen loss

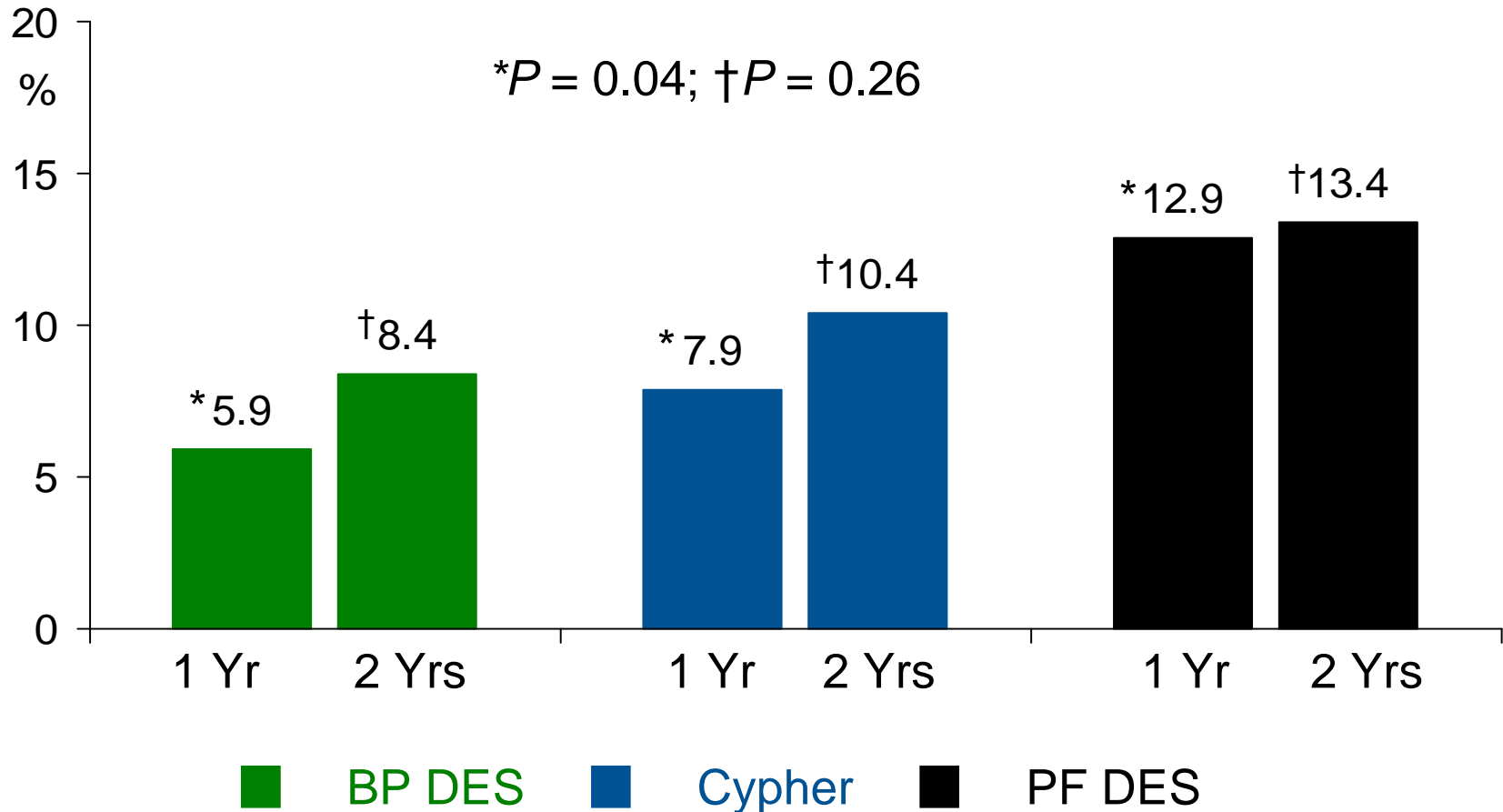
	<b>BP SES</b> (n=126)	<b>Cypher</b> (n=127)	<b>PF SES</b> (n=100)
<b>Early</b> , mm 6-8 months	<b>0.10±.29</b>	<b>0.14±.32</b>	<b>0.30±.31*</b>
<b>Delayed</b> , mm 6-8 months → 2 years	<b>0.17±.42</b>	<b>0.16±.41</b>	<b>-0.01±.36*</b>

\*  $p < .001$  for PF DES vs. Cypher and vs. BP DES

# Clinical Restenosis

TLR at 1 and 2 years

\* $P = 0.04$ ; † $P = 0.26$



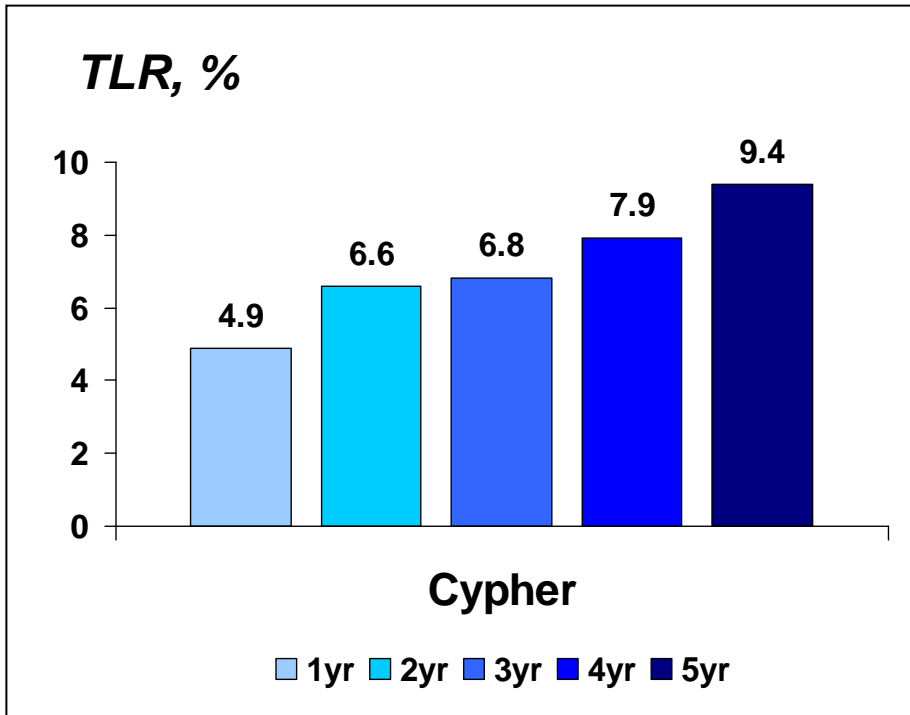
# Limitations

- Comparative analysis of delayed late loss (“late luminal creep”) is limited by the **exclusion of patients who undergo TLR at 6-8 months**
  - time zero is considered reset
  - inextricably related to efficacy of the study devices
- Any comparison of delayed late loss should be made in association with **overall 2-year TLR data**
- Interpretation of differences in “late luminal creep” should be considered **hypothesis generating**

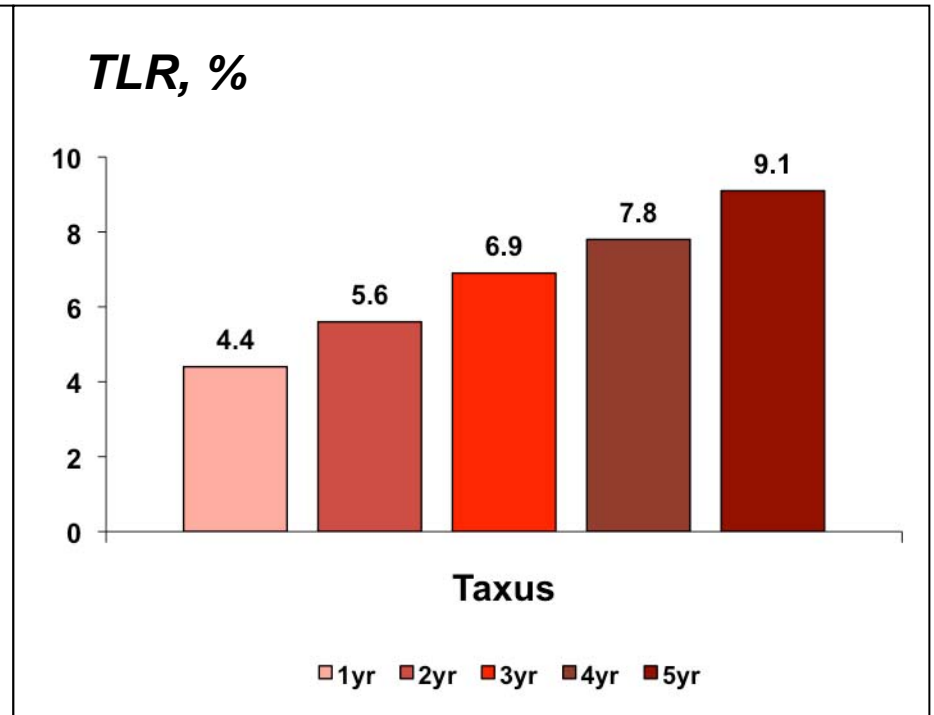
# Conclusions from ISAR experience

- DES therapy is associated with delayed late loss or **“late luminal creep”** between 6-8 months and 2 years
- This delayed late loss has been observed with...
  - **Permanent polymer DES (Cypher and Taxus)**
  - **Biodegradable polymer DES**
- ...but not with **polymer-free DES**
- Data on delayed late loss with the **Endeavor and Xience-V stents** will be available later this year

# Conclusions



**SIRIUS**



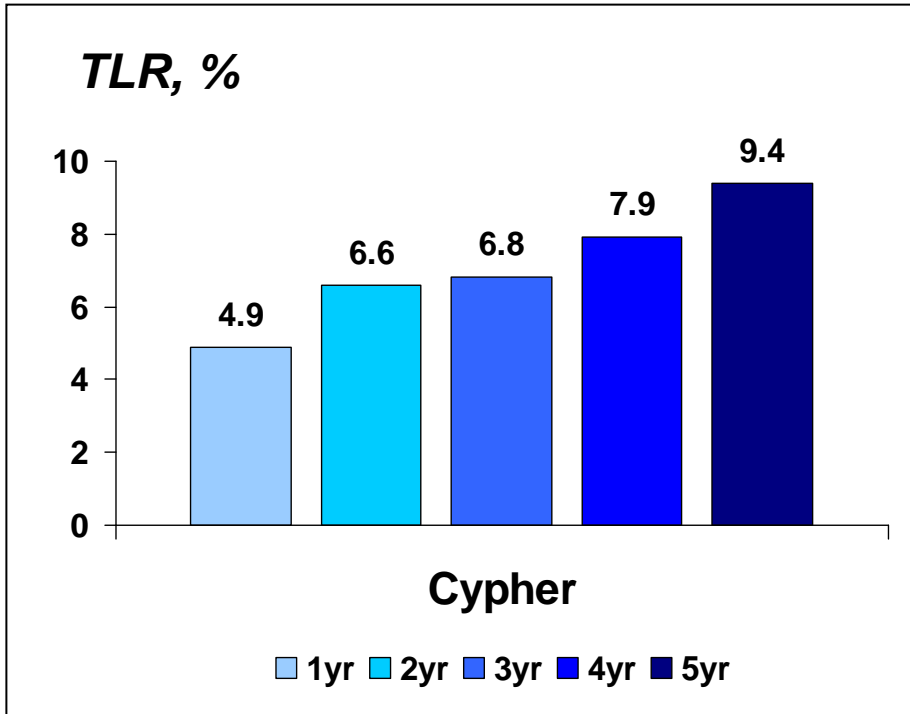
**TAXUS IV**

*Is our Understanding of  
DES-Restenosis Changing?*

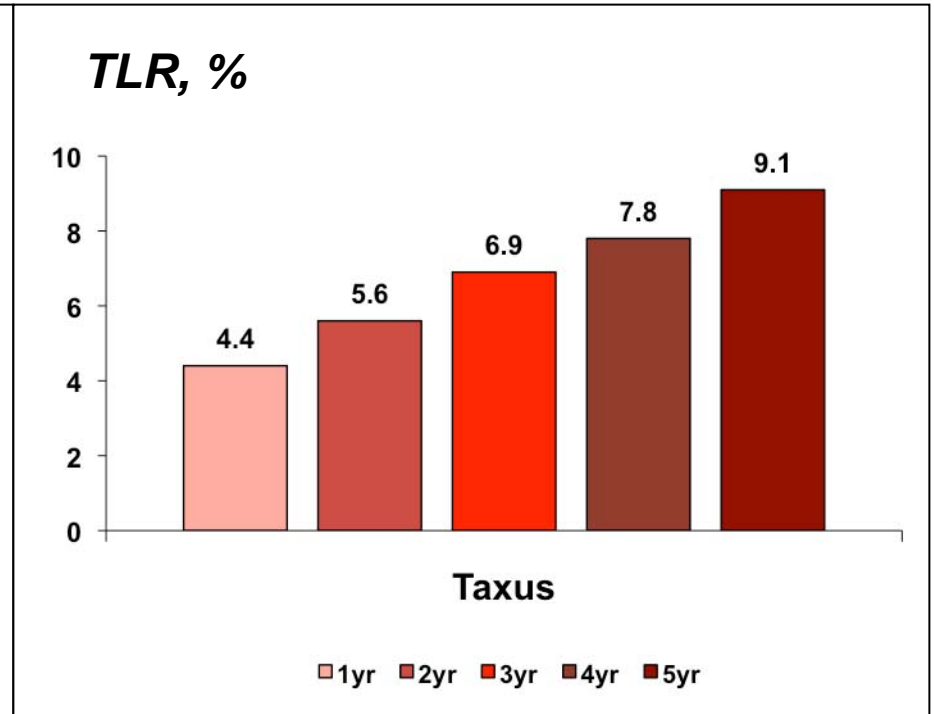
Finn et al. *JACC Interv* 2009



# Delayed Loss of AR Efficacy



**SIRIUS**



**TAXUS IV**

***Is our Understanding of  
DES-Restenosis Changing?***

Finn et al. *JACC Interv* 2009

# ISAR-TEST-2 Two-year FU

- 1. Permanent polymer sirolimus-eluting stent (Cypher)**
- 2. Polymer-free sirolimus- and probucol-eluting stent (Dual-DES)**
- 3. Permanent polymer zotarolimus-eluting stent (Endeavor)**

# Thank You

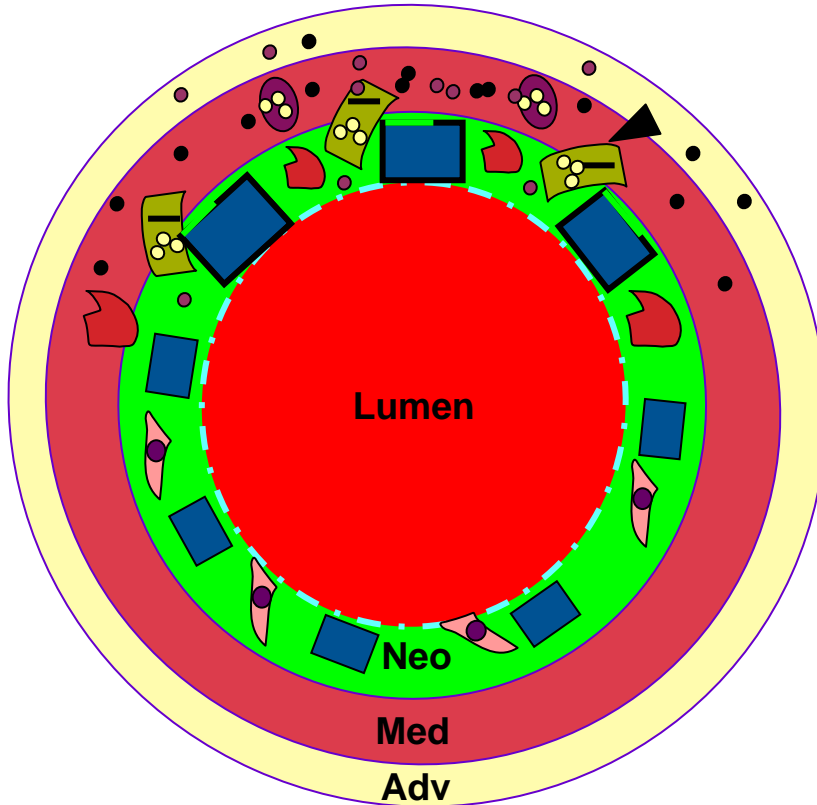


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# Arterial Response to BP



Biodegradable Polymers

