Endothelial Dysfunction Associated with DES: How Important?

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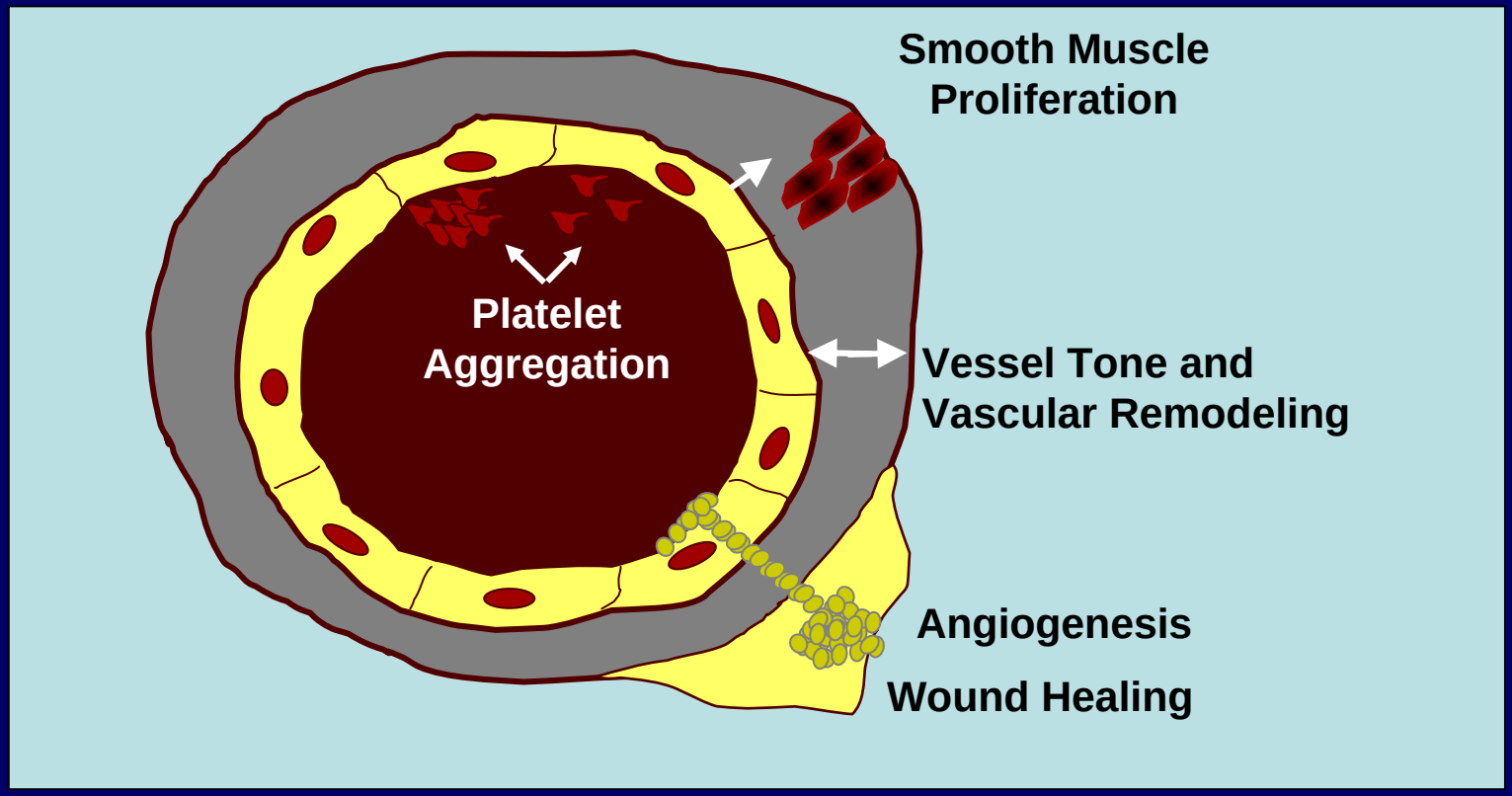
Conflict of Interest

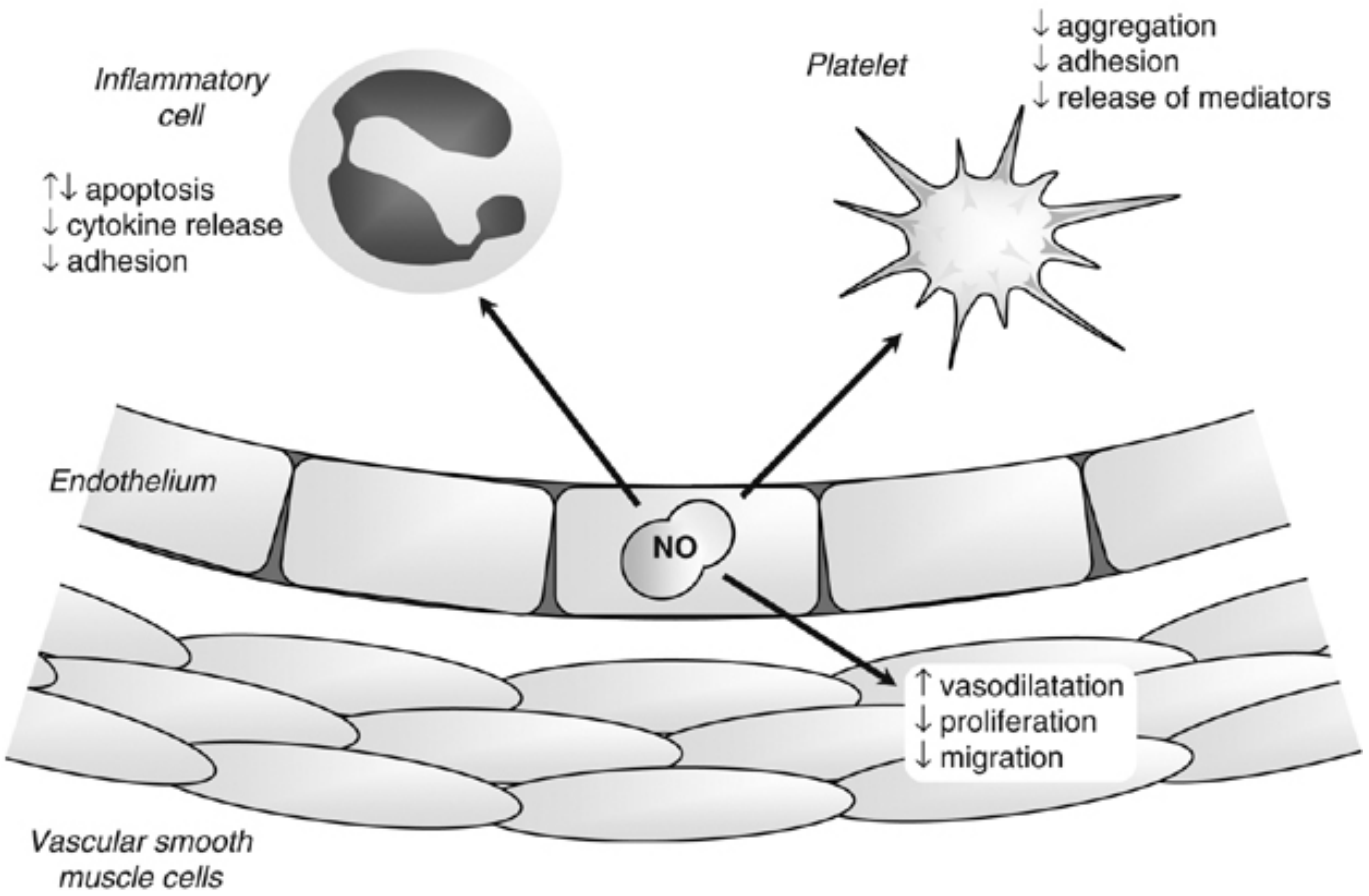
Scientific Advisory Board to

- Abbott Vascular
- Boston Scientific Corpoaration
- Cordis
- Medtronic

Functional Endothelium



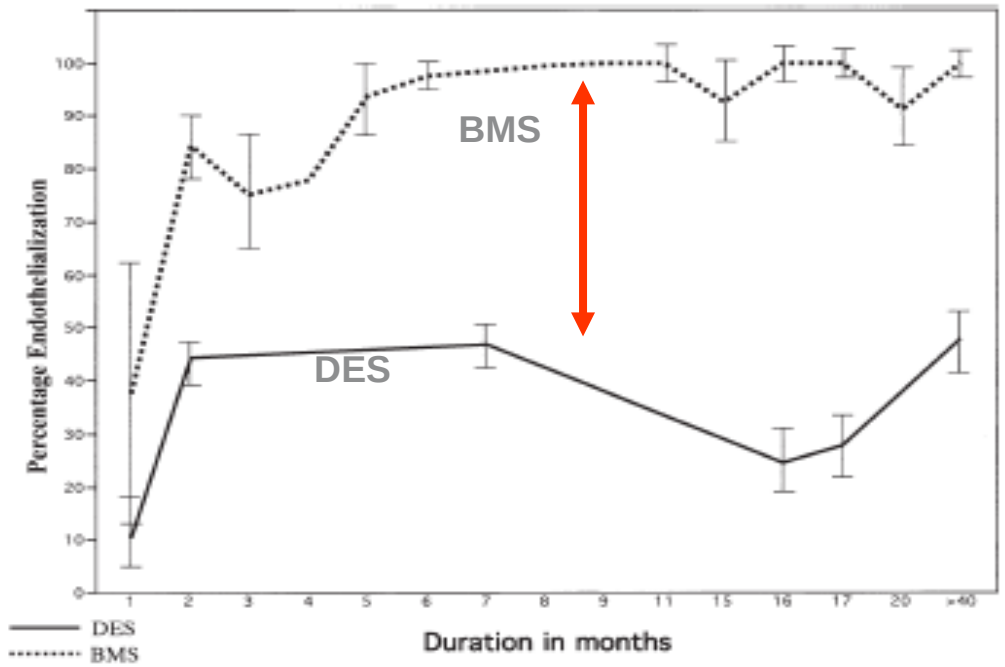
Biological Functions of Nitric Oxide



eNOS (Endothelial Nitric Oxide Synthase) is the protein that helps produce NO and is a marker of endothelial cell function

Reduced endothelial healing with DES

Clinical Pathology DES vs BMS



- **DES consistently show less endothelialization compared with BMS regardless of time point.**
- **Even beyond 40 mo DES are not fully endothelialized, whereas BMS are completely covered by 6 to 7 mo**

Joner et al. JACC 48:193;2006
Finn et al. Circulation 47;2007

Functional Endothelium

Synthesize eNOS and Nitric Oxide (NO)

- Normal vessels dilate in response to exercise, pacing or acetylcholine (ACH) stress
  - This response is dependent on endothelial production of NO
- Atherosclerotic vessels are characterized by having endothelial dysfunction and constrict in response to exercise, pacing or ACH
  - This is explained by either a loss of endothelial cells or loss of eNOS expression, NO production or inactivation of NO by superoxides
  - Exercise and pacing leads to release of catecholamines (constrictors), ACH directly constrict the smooth muscle

Cai H and Harrison DG. Circ Res 2000; 87: 840-844
Bonetti PO et al. ATVB 2003; 23: 168-175

Prognosis of Abnormal Endothelial Function in Native CAD or PAD

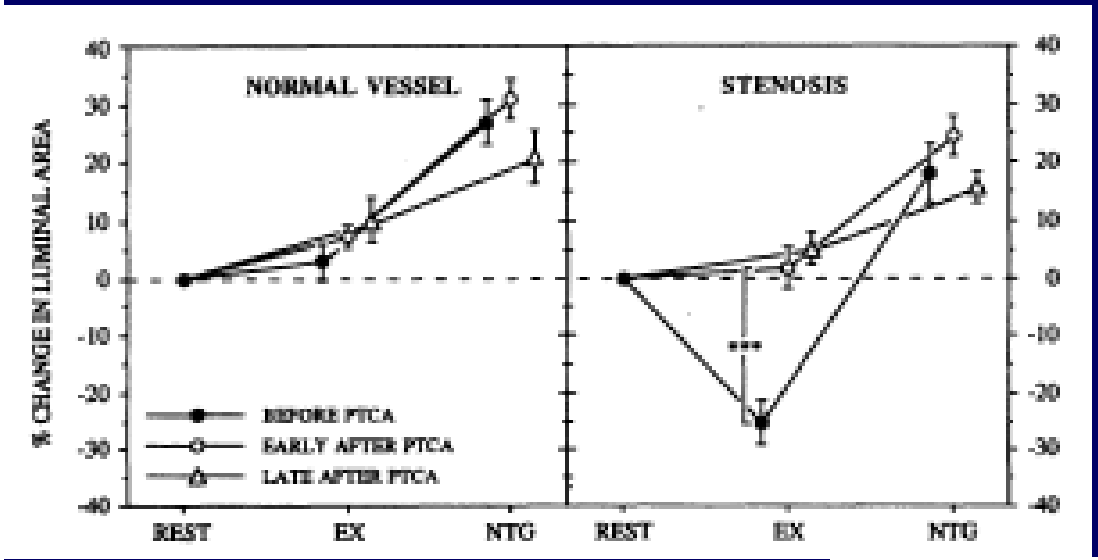
TABLE 2. Studies on the Prognostic Effect of Coronary and Peripheral Endothelial Dysfunction

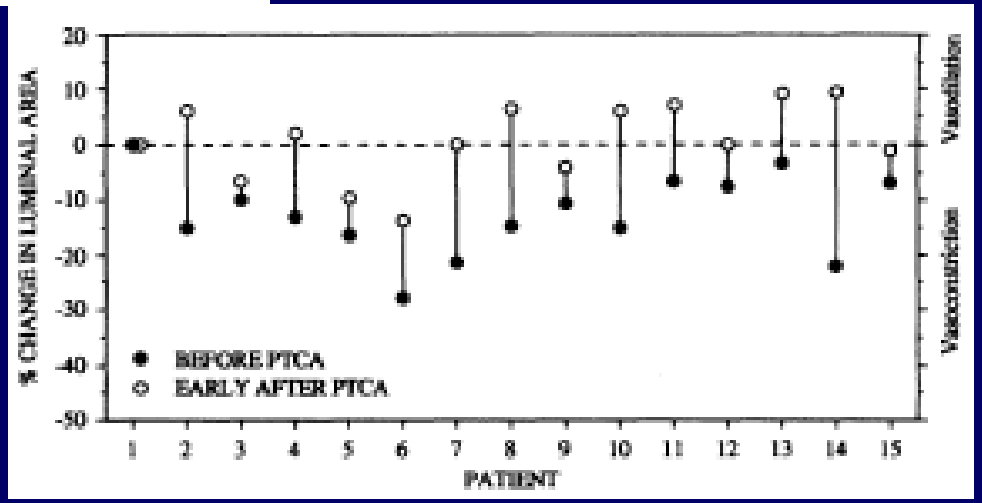
Study	n	Population	Assessment of End Function	Mean Follow-Up, months	Cardiovascular Event Rate, %			End Dysfunction as an Independent Predictor of Events
					Normal End Function	Mild End Dysfunction	Severe End Dysfunction	
Al Suwaidi et al[16]	157	Pts without significant coronary stenoses	Coronary microvasculature	28	0	0	24	Not assessed
Schächinger et al[47]	147	Pts with various stages of CAD	Coronary macrovasculature	80				Yes
Halcox et al[17]	308	Pts with/without CAD	Coronary micro-/macrovasculature	46				Yes
Perticone et al[51]	225	Pts with untreated hypertension	Forearm microvasculature	32	5	11	23	Yes
Heitzer et al[52]	281	Pts with CAD	Forearm microvasculature	54				Yes
Gokce et al[18]	187	Pts undergoing vascular surgery	Brachial artery	1	8		32	Yes

End indicates endothelial; Pts, patients.

Exercise-Induced Coronary Vasomotion and Balloon Angioplasty

Restoration of EC function measured early (4mo) or late (30mo) after PTCA

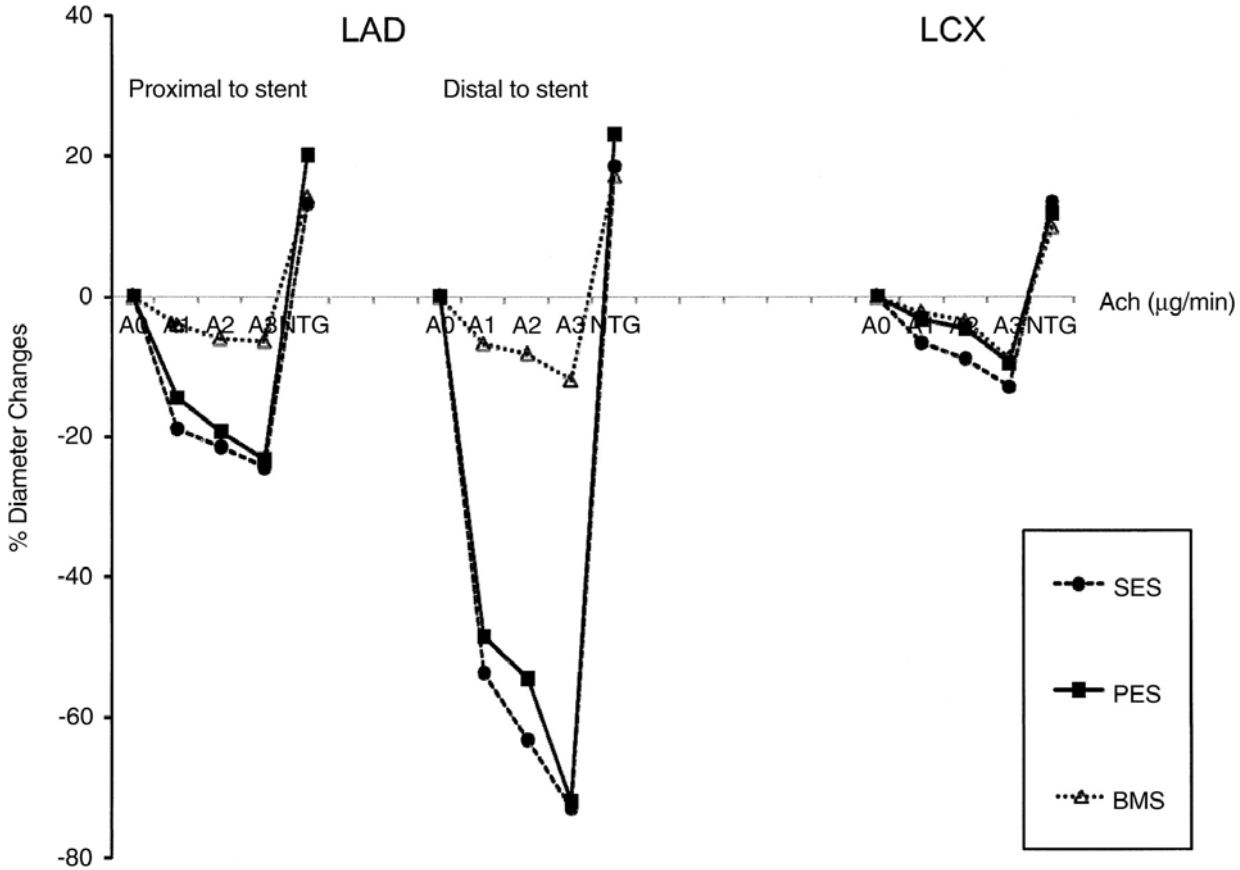




Suter M et al. *Circulation* 1992;85:86-9

EC function after Cypher or Taxus Implants

Clinical evaluation of ACH six months post-stenting



Kim, J. W. et al. J Am Coll Cardiol Intv 2008;1:65-71

Comparative DES Biocompatibility
Study design

- Cypher, Taxus, Endeavor and Driver stents were implanted in porcine coronary arteries

- Harvest tissues 28 days after stenting

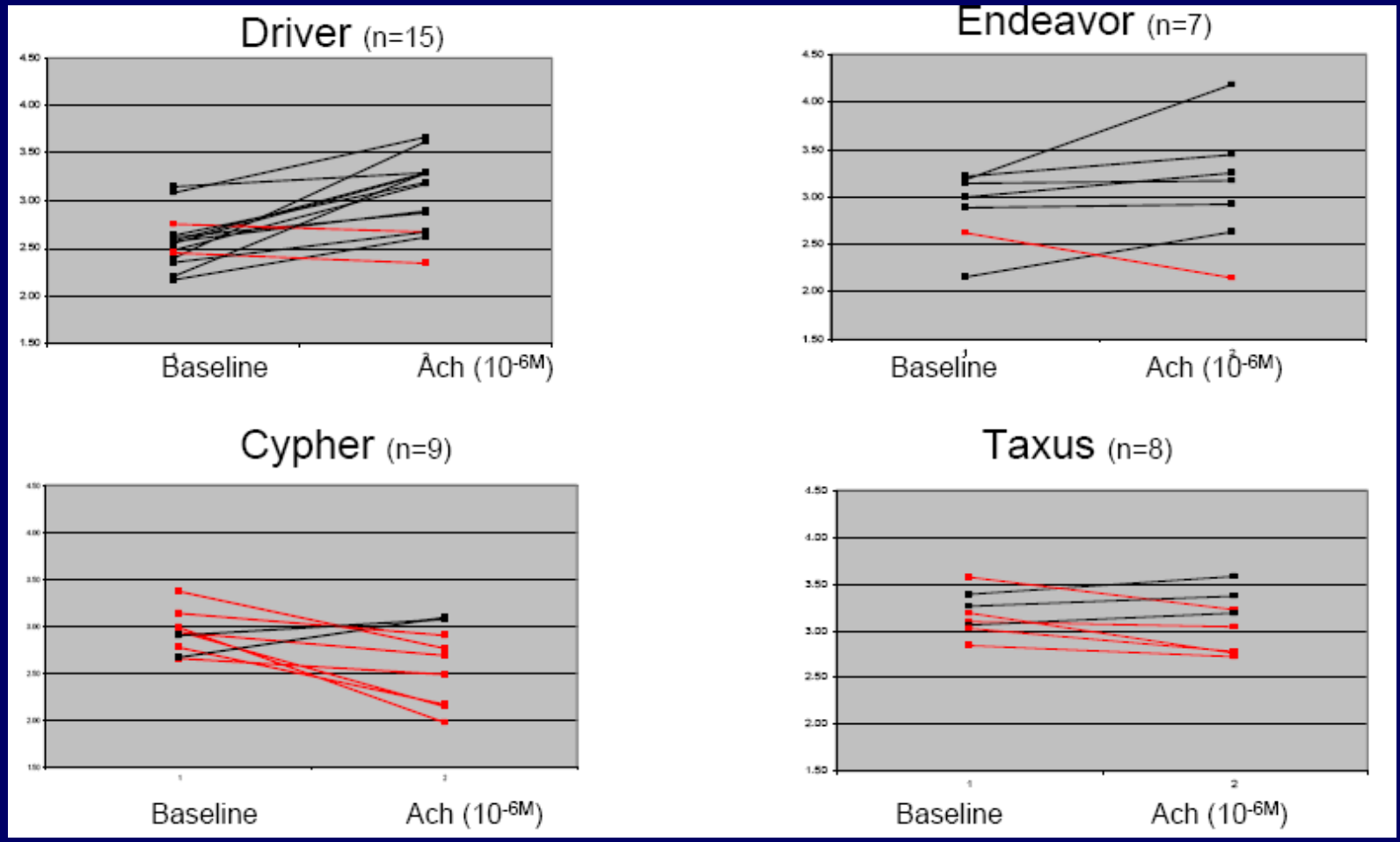
- Evaluate endothelial function
  - Acetylcholine challenge just prior to euthanasia

- Evaluate inflammation and polymer biocompatibility
  - Real Time RT-PCR to evaluate local expression eNOS
  - Histological with immunohistochemistry for EC, eNOS, etc.

Haraguchi et al. TCT. 2006

EC Function Assessed by ACH Challenge

28 Days After Stenting in Porcine Coronary Arteries

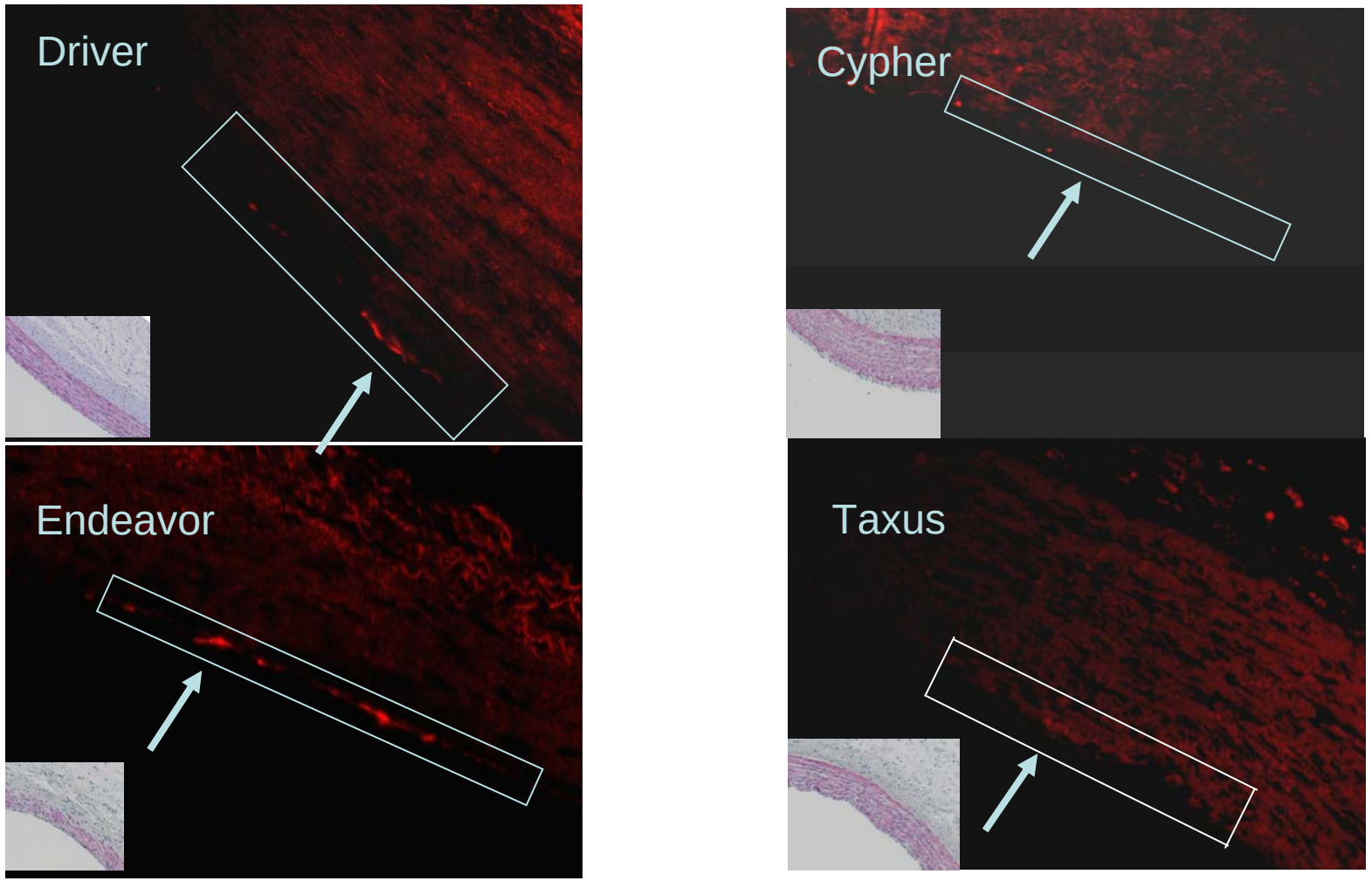


All vessels showed 100% endothelialization as determined by immunohistochemistry

Haraguchi et al. *TCT*. 2006

Localization of eNOS Protein

Immunohistochemistry



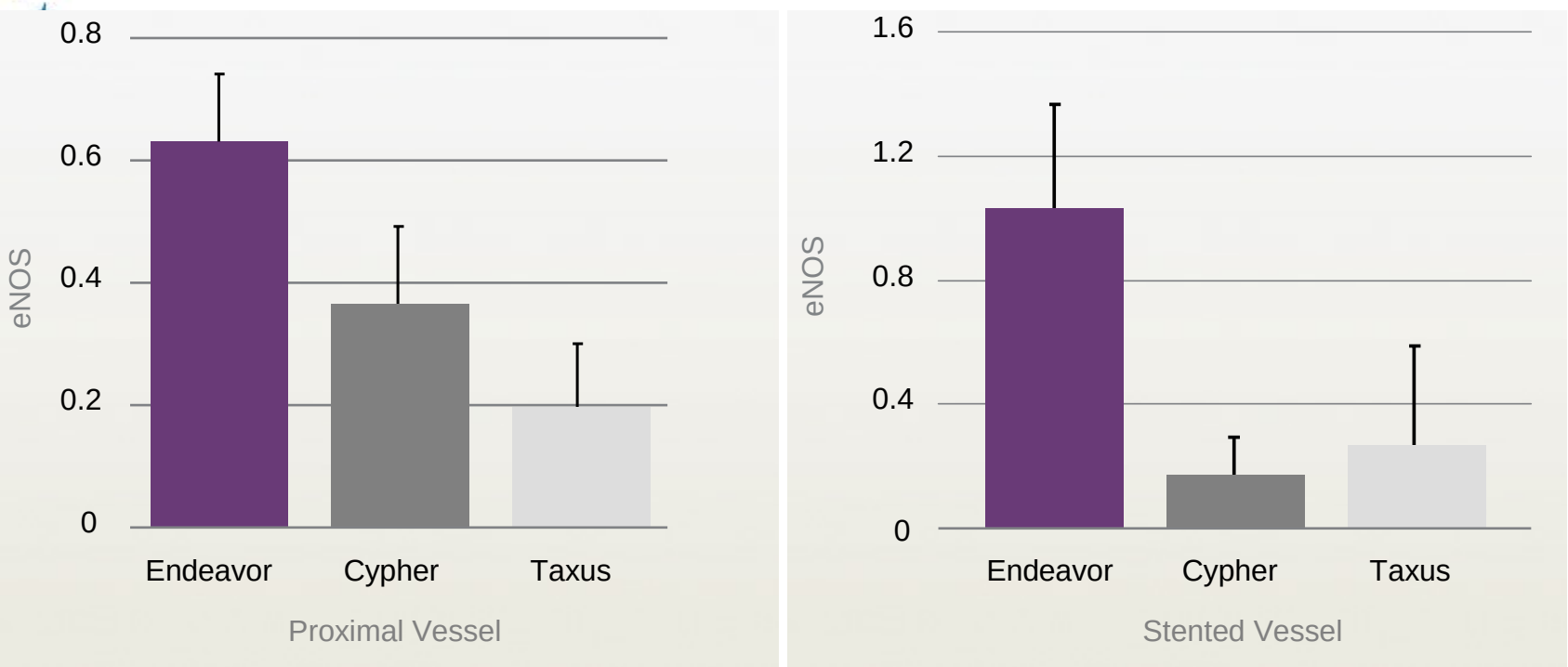
eNOS protein was localized on the luminal surface of vessels proximal to Endeavor and Driver stents

Haraguchi et al. *TCT*. 2006

Expression of eNOS mRNA

28 Days After Stenting by Quantitative Real Time PCR

eNOS, the protein that produces nitric oxide, is a marker of endothelial cell (EC) function



Both proximal and stented vessels have significantly more eNOS present with Endeavor stent than with either Cypher or Taxus

eNOS: endothelial nitric oxide synthase
Haraguchi *et al.,* Transcatheter Cardivoascular Therapeutics; Washington DC; October 22–27, 2006.

Haraguchi et al. *TCT*. 2006

Differences in EC Function

Are these due to drug or polymer effects?

To attempt to answer this question we compared Endeavor Resolute to Xience stents 28 days after implantation in porcine coronary arteries

- Both are low profile stents
- Both utilize similar drugs with equal potency (zotarolimus and everolimus)
- Drug elution is similar for each stent at 28 days
- Both demonstrate 100% endothelialization at 28 days in the pig coronary artery model as determined by SEM or immunohistochemistry

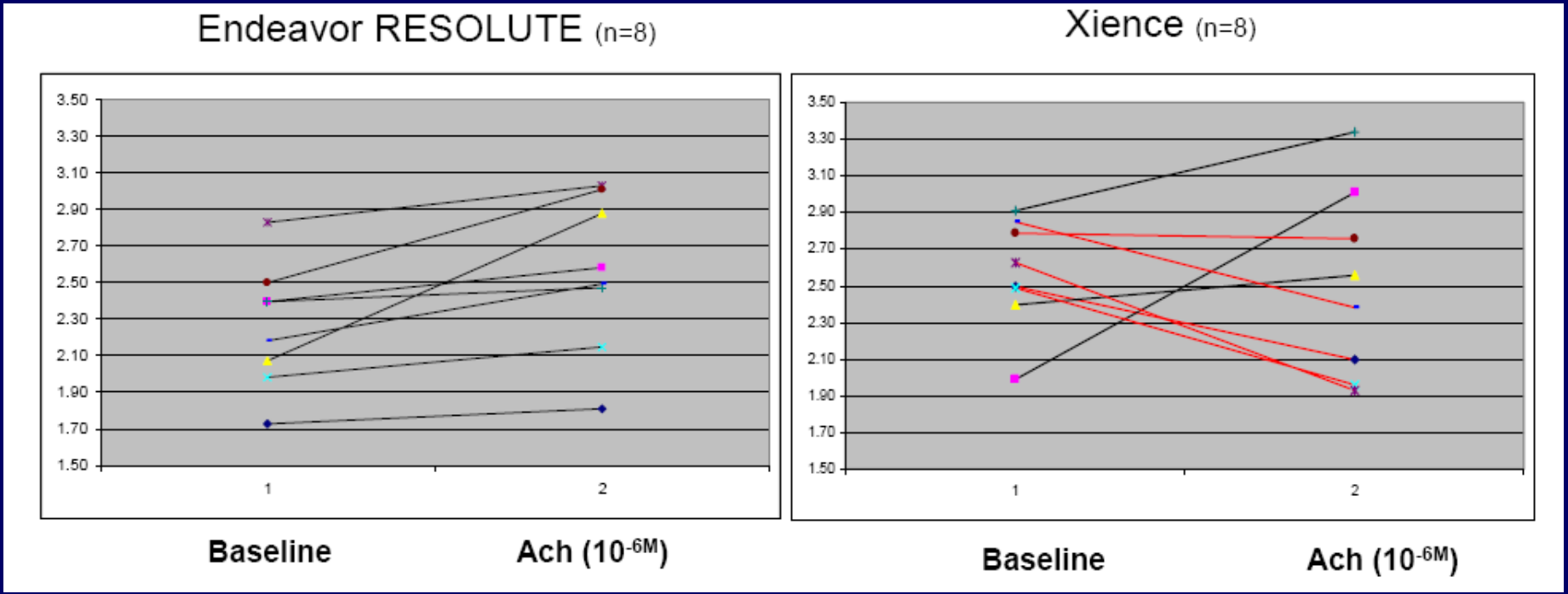
The major difference is that Endeavor Resolute uses the hydrophilic BioLinx coating while Xience utilizes the hydrophobic fluoropolymer coating for drug delivery

Wilcox. *TCT*. 2007

Caution: Endeavor Resolute utilizing the BioLinx polymer is an investigational device, not approved for US sale or commercial use

EC Function Assessed by ACH Challenge

28 Days After Stenting in Porcine Coronary Arteries



2.06 ± 0.58	Relative eNOS Expression	0.27 ± 0.26
0.67 ±1.52	Inflammation Scores	1.89 ± 1.95

Wilcox. *TCT*. 2007

Caution: Endeavor Resolute utilizing the BioLinx polymer is an investigational device, not approved for US sale or commercial use

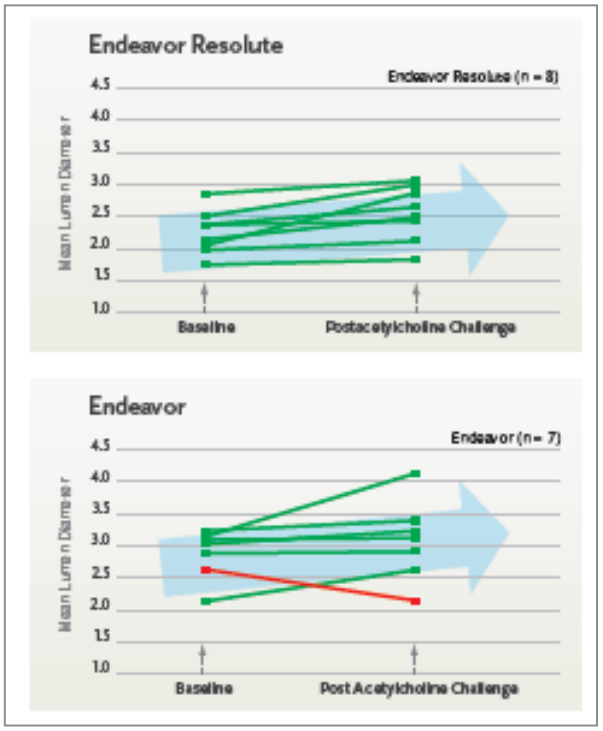
Acetylcholine challenge response

Proximal to stents implanted in porcine coronary arteries

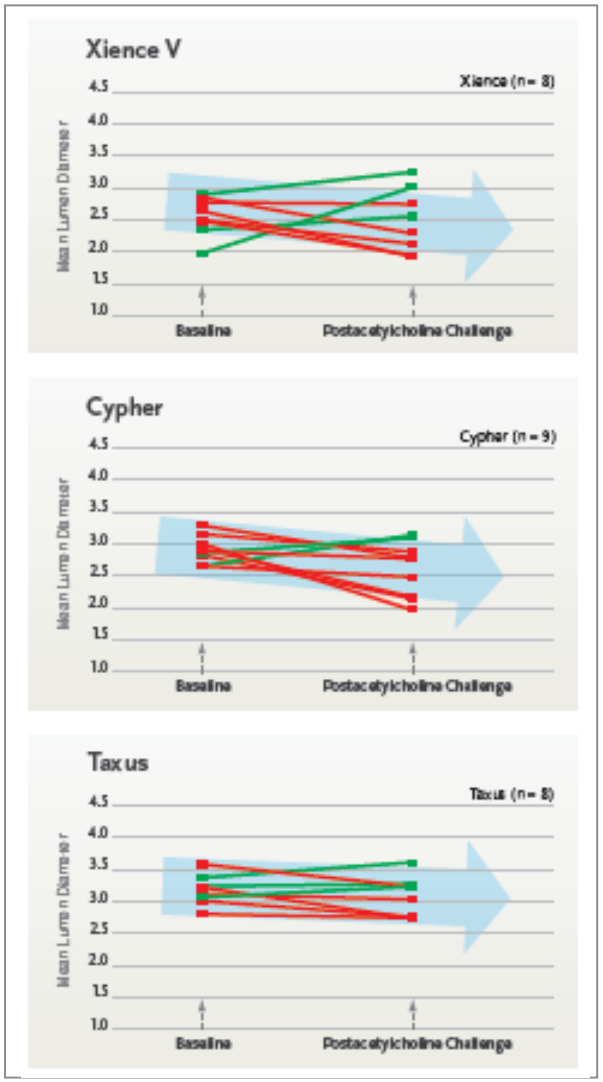
HYDROPHILIC

HYDROPHOBIC

Vasodilation



Vasoconstriction

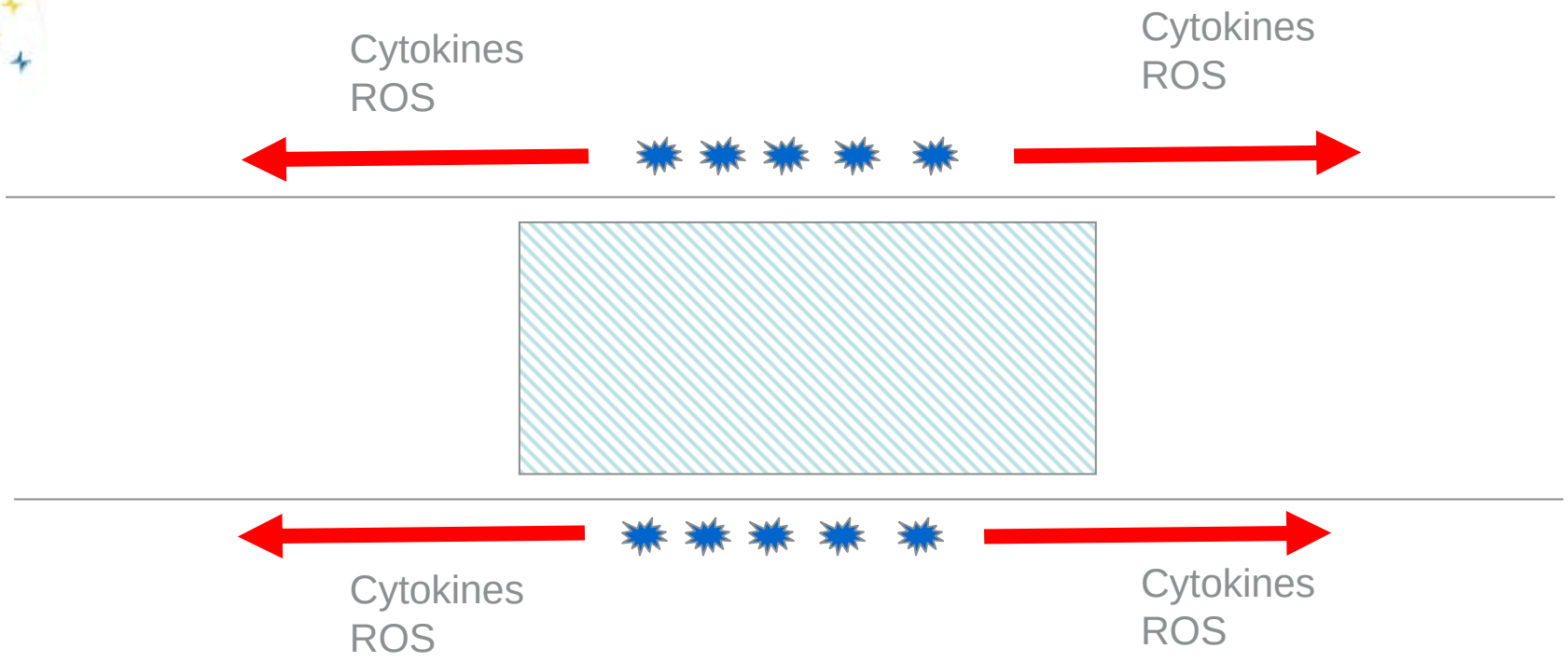


Endeavor and Endeavor Resolute stents show high eNOS levels, suggesting good NO production and a functional endothelium

Caution: Endeavor Resolute utilizing the BioLinx polymer is an investigational device, not approved for US sale or commercial use

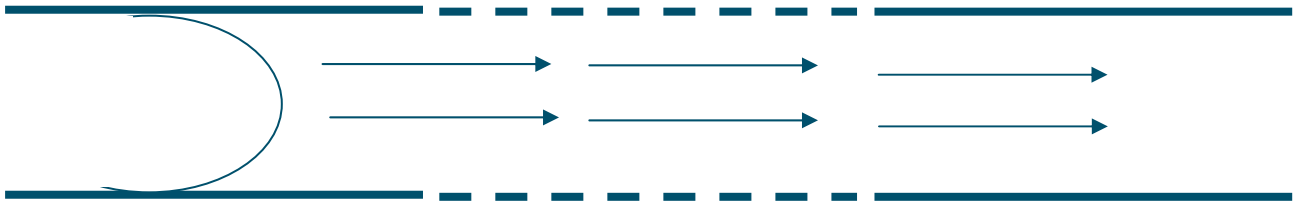
Inflammation is only found in the stented region

Why is this associated with vasomotor changes proximally and distally?

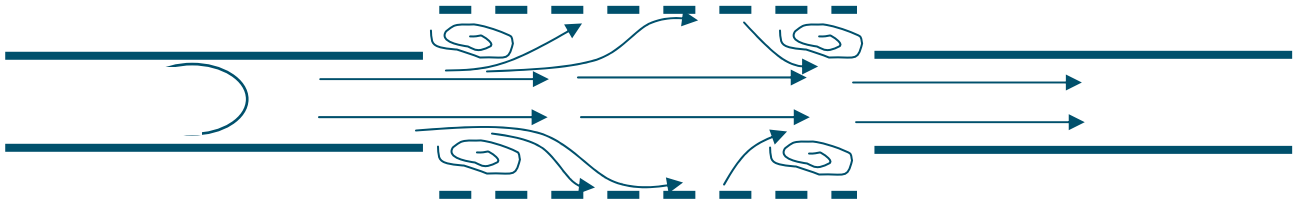


We hypothesize that inflammation exerts paracrine actions by releasing cytokines and ROS that affect the adjacent segments

Flow disturbance associated with EC dysfunction



Normal Laminar Flow



Proximal Vasoconstriction creates areas of disturbed flow within the stent segment leading to further EC injury and platelet activation

Clinical: Vessel Function

Methods

- Randomly treated with IVUS guided intervention using single stent to the mid segment of left anterior descending artery in patients with stable angina.

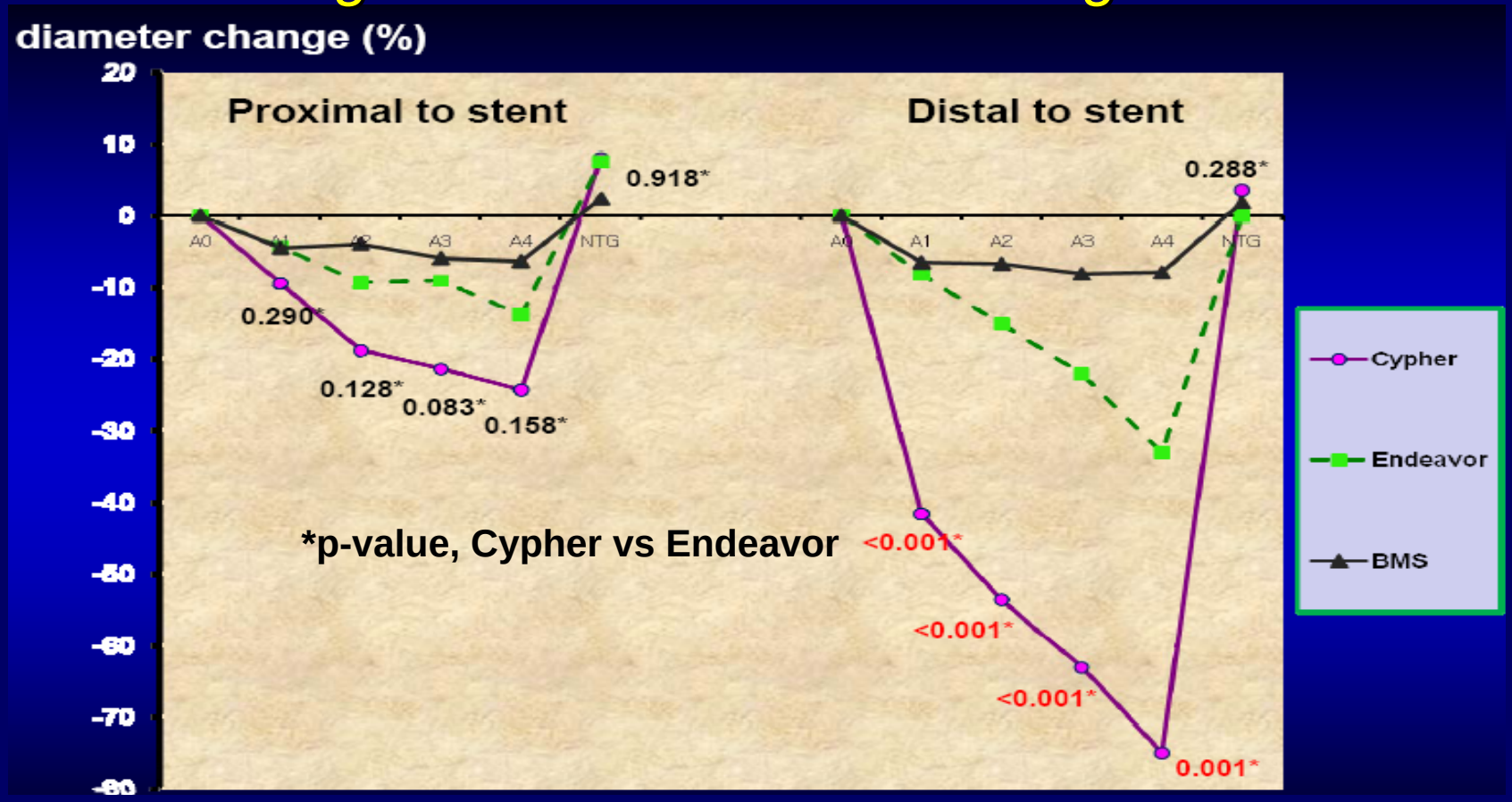
30 DES patients (15 SES, 15 ZES)
versus
10 control patients (Driver™)

- **Endothelial function was prospectively estimated at pre- and post-intervention 6 months follow-up.**
  - **Incremental dose of acetylcholine into the left coronary ostium**
  - **10, 20, 50, 100 μg over 1-min**
  - **each 5 min interval between doses**
  - **The infusion was stopped if > 90 % vasoconstriction was induced.**
  - **Maximum tolerable dose was followed by nitrate (200 μg/min)**

JW Kim et al. ACC 2007

Endeavor Clinical: Vessel Function

ACH Challenge Six Months Post-Stenting in Humans



- **ACH dose dependent vessel constriction with Cypher is significantly different vs Endeavor**
- **This constriction in response to acetylcholine (ACH) with Cypher suggests vessel dysfunction**

JW Kim et al. ACC 2007 NTG=Nitroglcerine

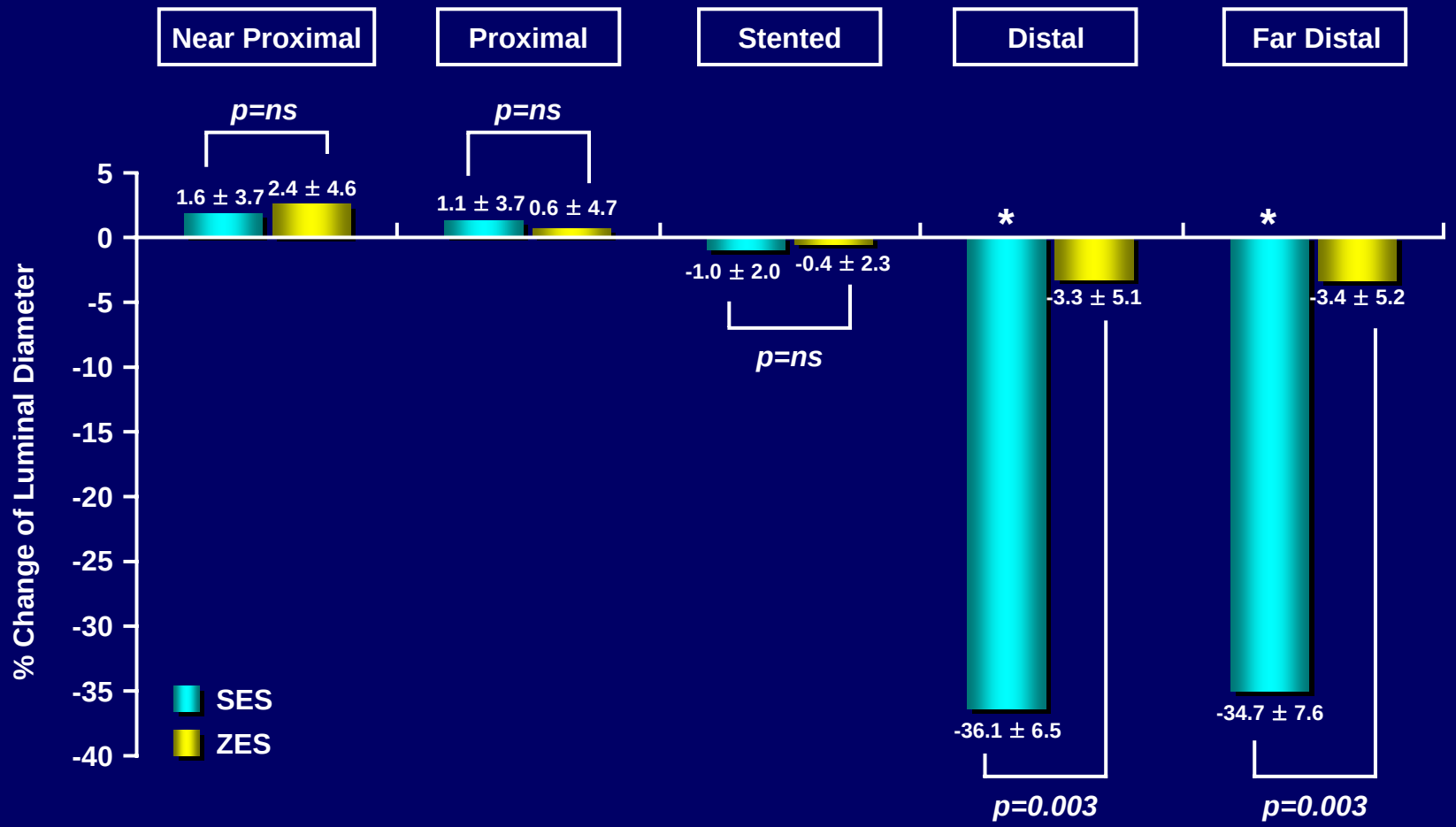
Long-Term Coronary Endothelial Function After Endeavor Implantation

A 9 month comparison between Zotarolimus eluting and Sirolimus eluting stents

Dong Il Shin et al International Heart Journal 2008; 49:639-652

Endothelium Dependent Vasomotion

Diameter Change in Response to ACH



Shin, DI et al. Int Heart J 2008;49:639-652

Interference of Drug-Eluting Stents With Endothelium-Dependent Coronary Vasomotion

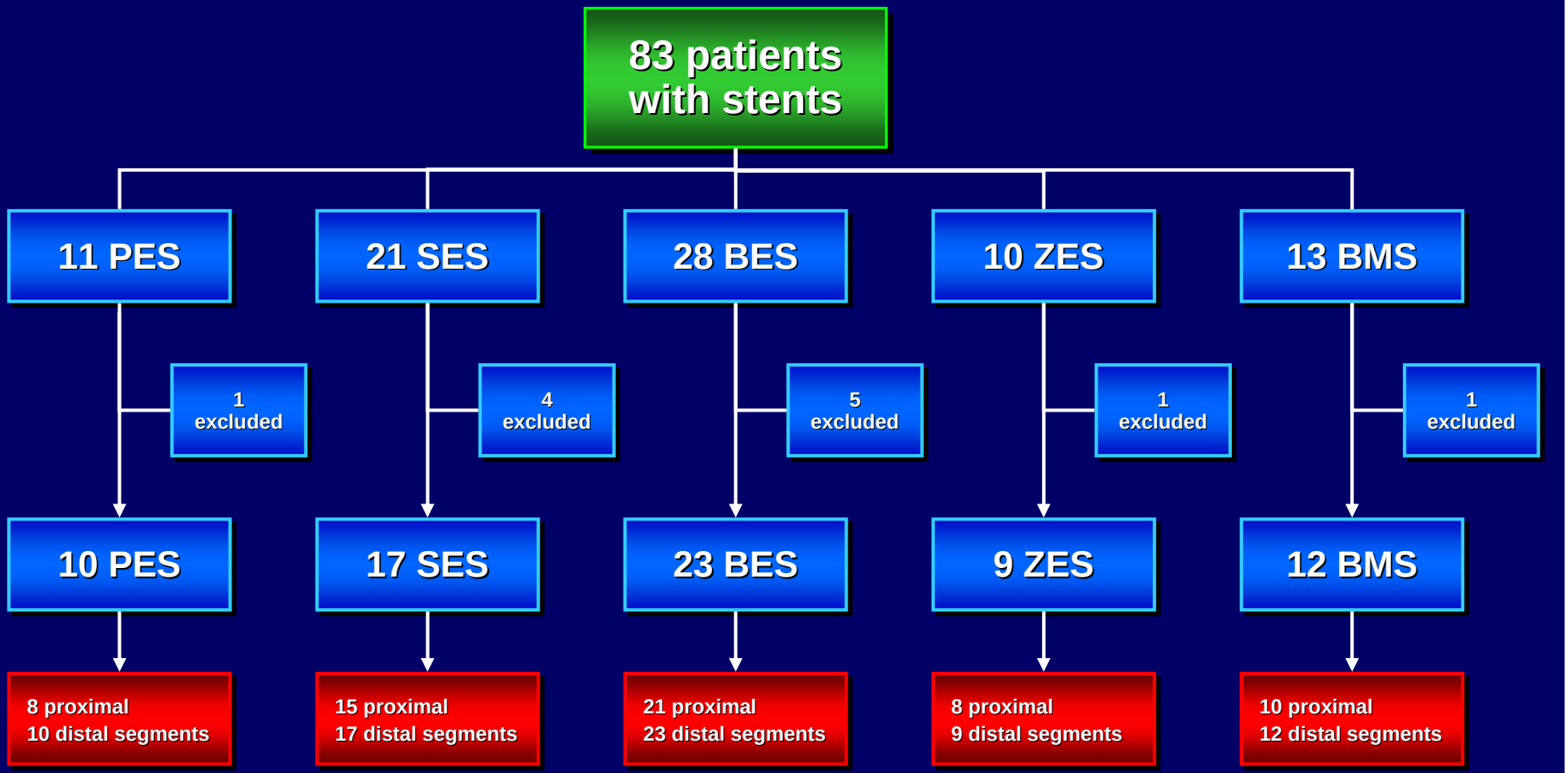
Evidence for Device Specific Responses

Hamilos, M. et al. Circulation Cardiovascular Interventions: 2008;1:193-200

Study Design

Patient Flowchart

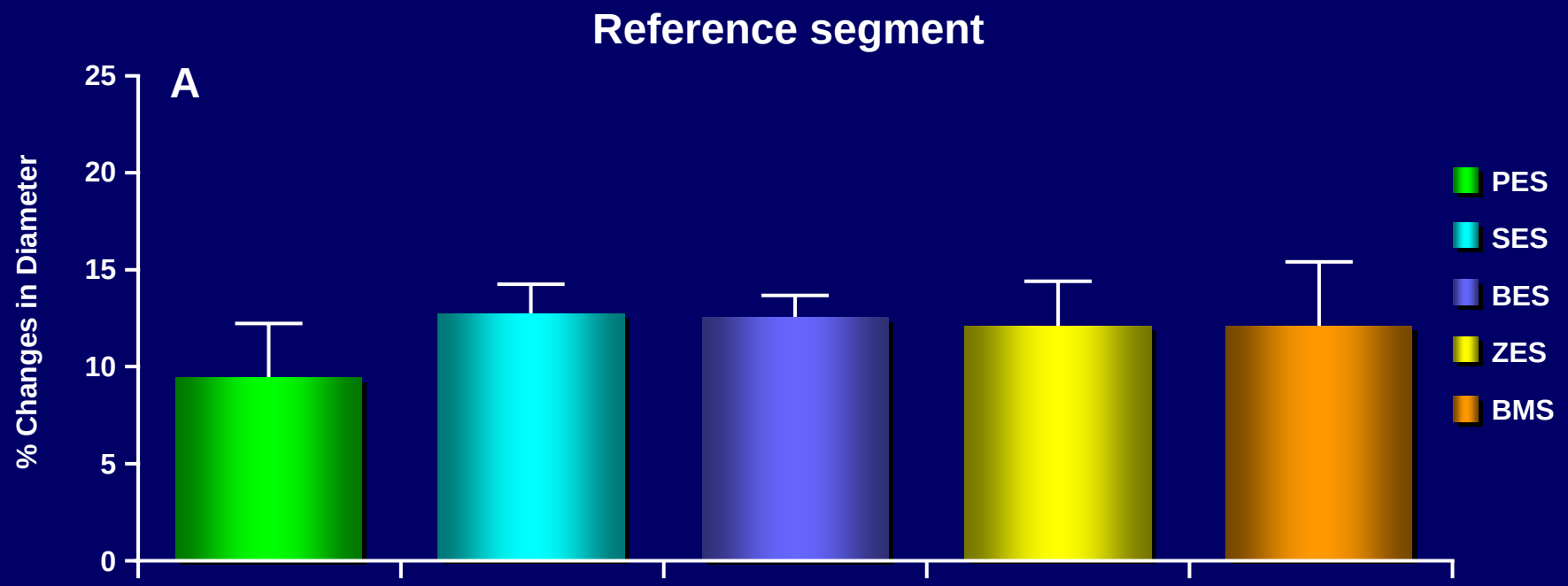
Figure 1. Flow chart of the study. Patients were excluded from the analysis because of in-stent restenosis (n=3), insufficient quality of the angiogram (n=4), or constriction of the reference segment (n=5)



Changes in Diameter

From Baseline

Figure 2. Percent changes in mean diameter from baseline (mean±SEM) in all stent groups, at reference (A), proximal (B), and distal (C) segment

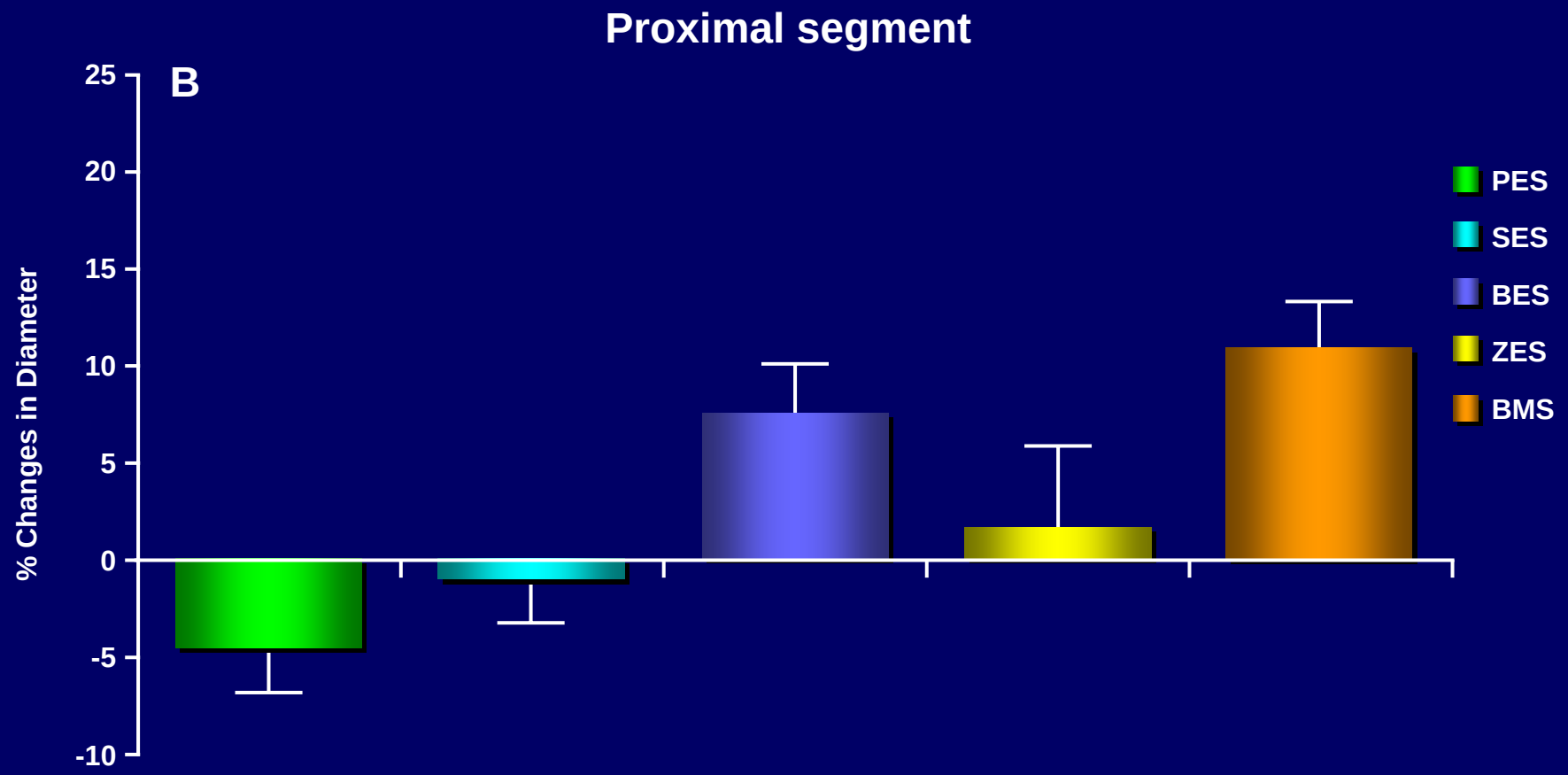


Hamilos, M. et al. Circ Cardiovasc Intervent. 2008;1:193-200

Changes in Diameter

Proximal Segment

Figure 2. Percent changes in mean diameter from baseline (mean±SEM) in all stent groups, at reference (A), proximal (B), and distal (C) segment

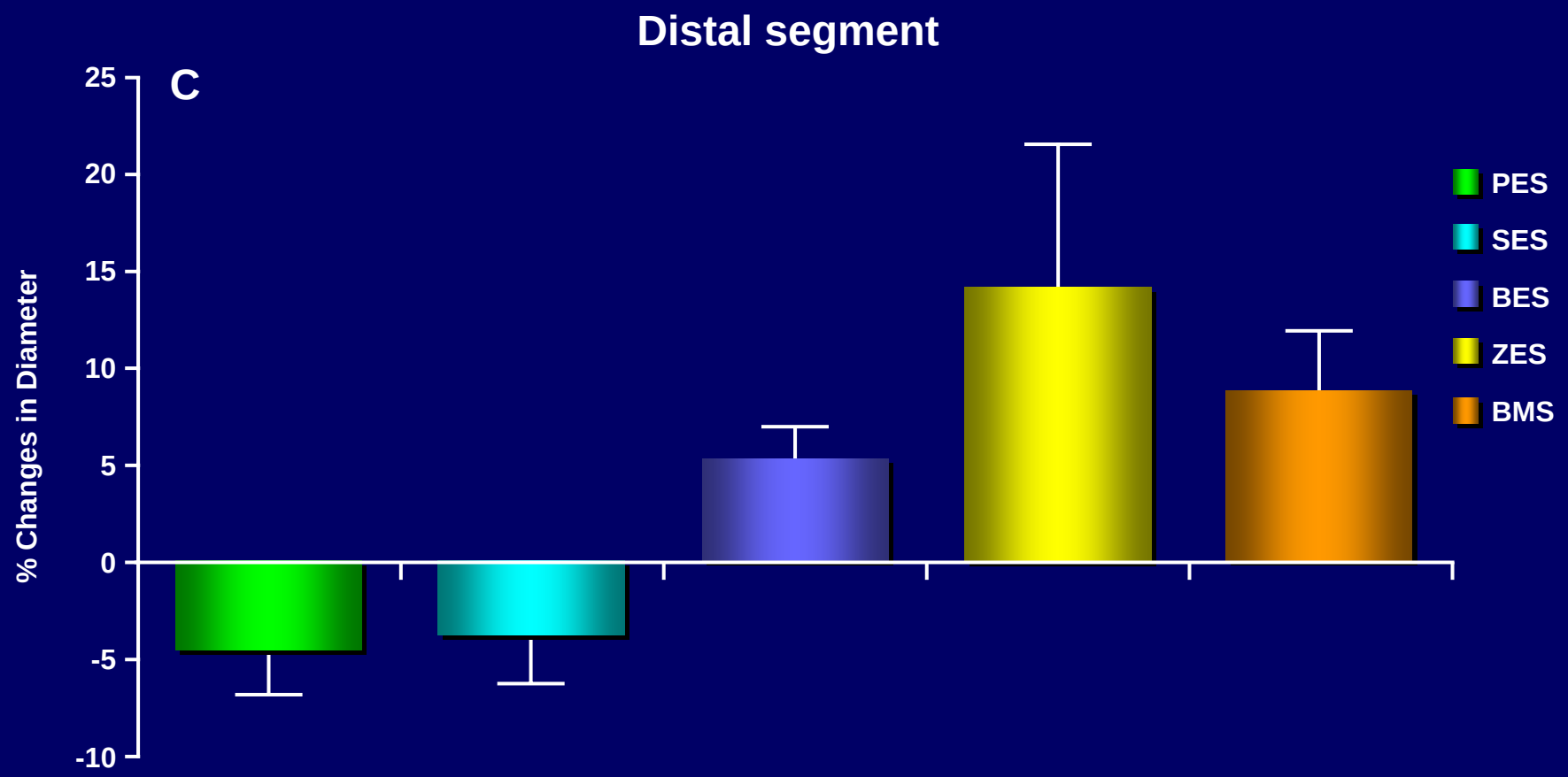


Hamilos, M. et al. Circ Cardiovasc Intervent. 2008;1:193-200

Changes in Diameter

Distal Segment

Figure 2. Percent changes in mean diameter from baseline (mean±SEM) in all stent groups, at reference (A), proximal (B), and distal (C) segment

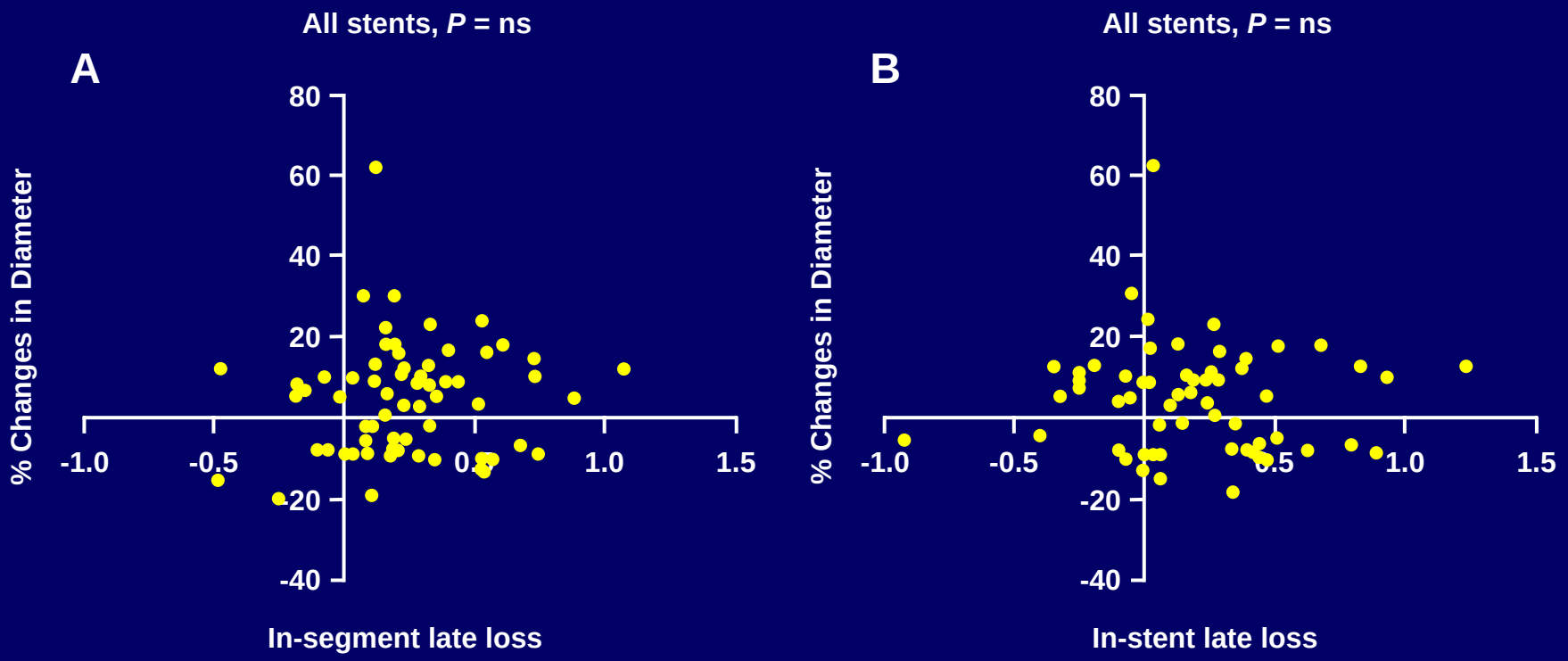


Hamilos, M. et al. Circ Cardiovasc Intervent. 2008;1:193-200

Vasomotion and Late Loss

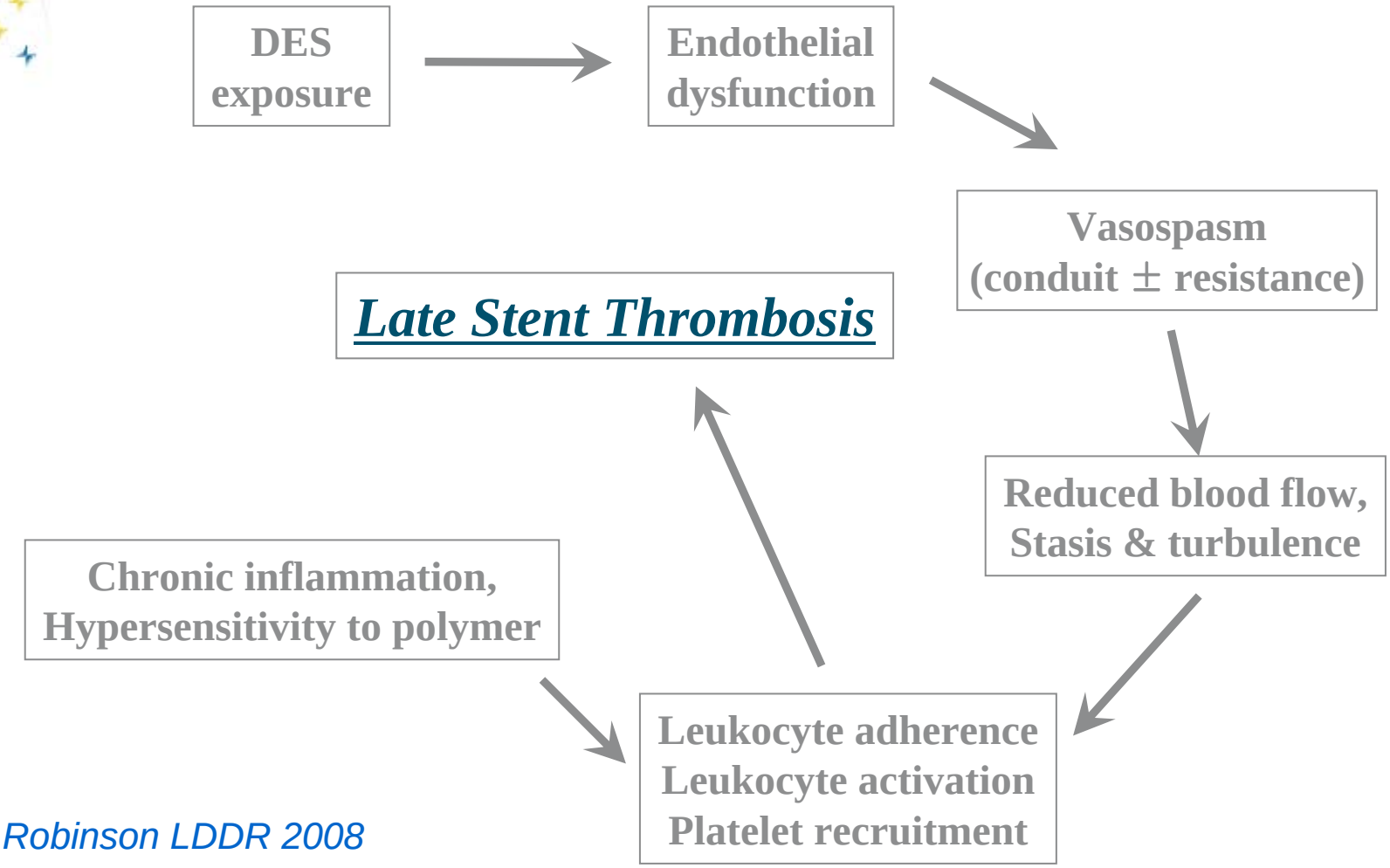
No Correlation Found

Figure 4. Scatterplots of in-segment late loss (A) and in-stent late loss (B) against vasomotion in the distal segment. There is no correlation between the variables



Hamilos, M. et al. Circ Cardiovasc Intervent. 2008;1:193-200

Relevance of Vasomotor Dysfunction to Late DES Thrombosis



K. Robinson LDDR 2008