CiloTax Stent™
Dual Drug-eluting Stent

13th
Angioplasty
Summit 2008

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Current DES Systems

Efficacy & Safety Issues

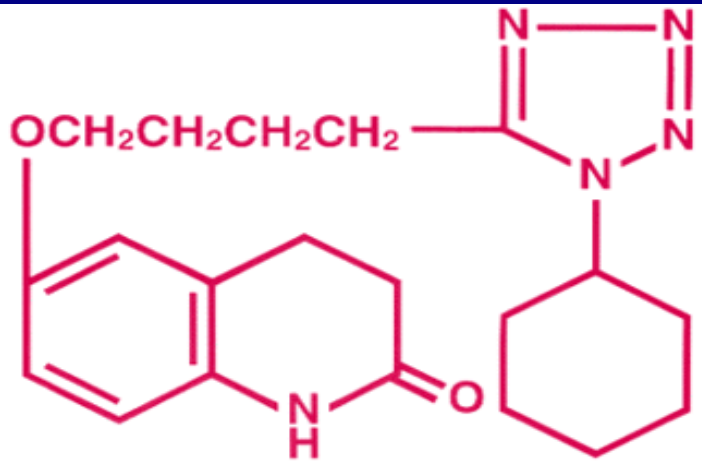
- **Restenosis results from multiple mechanisms & remains a significant problem in complex lesions.**
- **Stent thrombosis is a rare (0.2-1.8%), but feared complication of PCI associated with a high mortality.**

Co-drug Eluting Stent

Potential Advantages

- **Current DES have used single agents, which is focusing on SMC proliferation.**
- **Co-drug DES may allow differential targeting with synergism and minimal toxicity.**

Cilostazol



Chemical name : 6-[4-(1-cyclohexyl-1*H*-tetrazol-5-yl) butoxy]-3, 4-dihydro-2(1*H*)-quinolinone

Molecular formula : $C_{20}H_{27}N_5O_2$

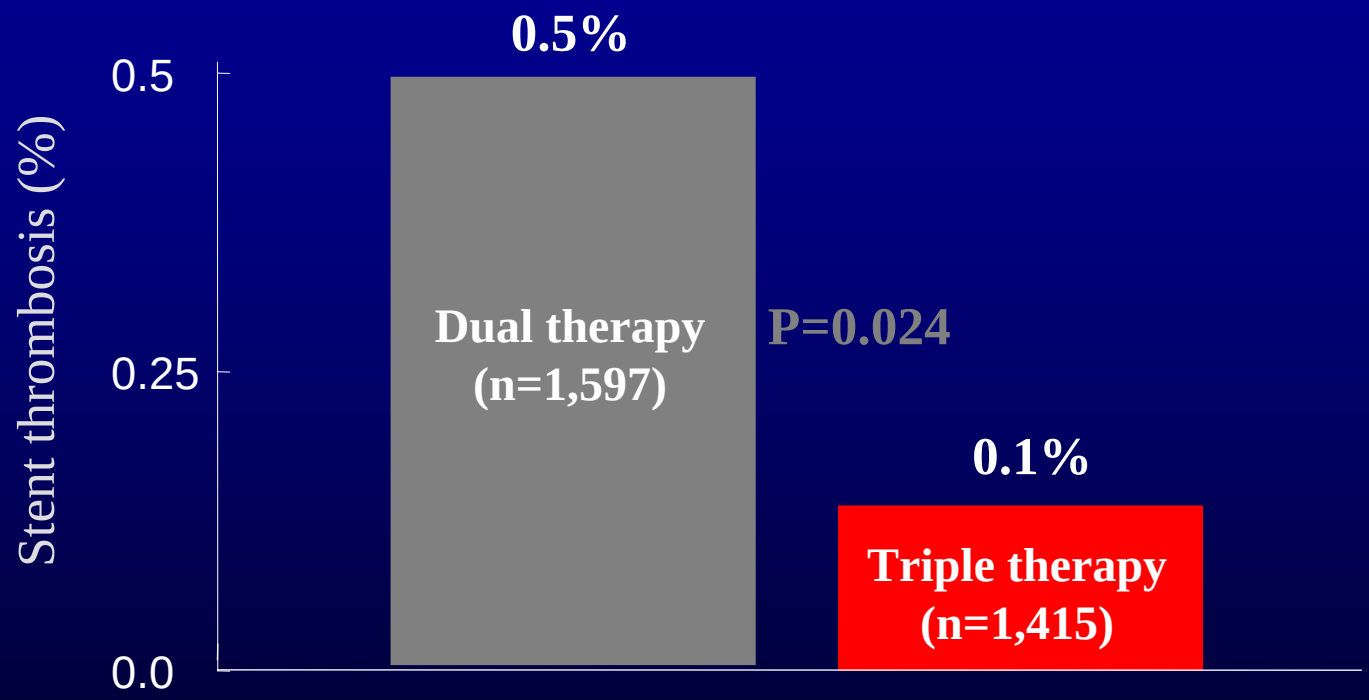
Molecular weight : 369.47

A PDE III inhibitor

Pharmacologic Effects

- **antiplatelet**
- **antiproliferative (VSMC)**
- **EC protection**

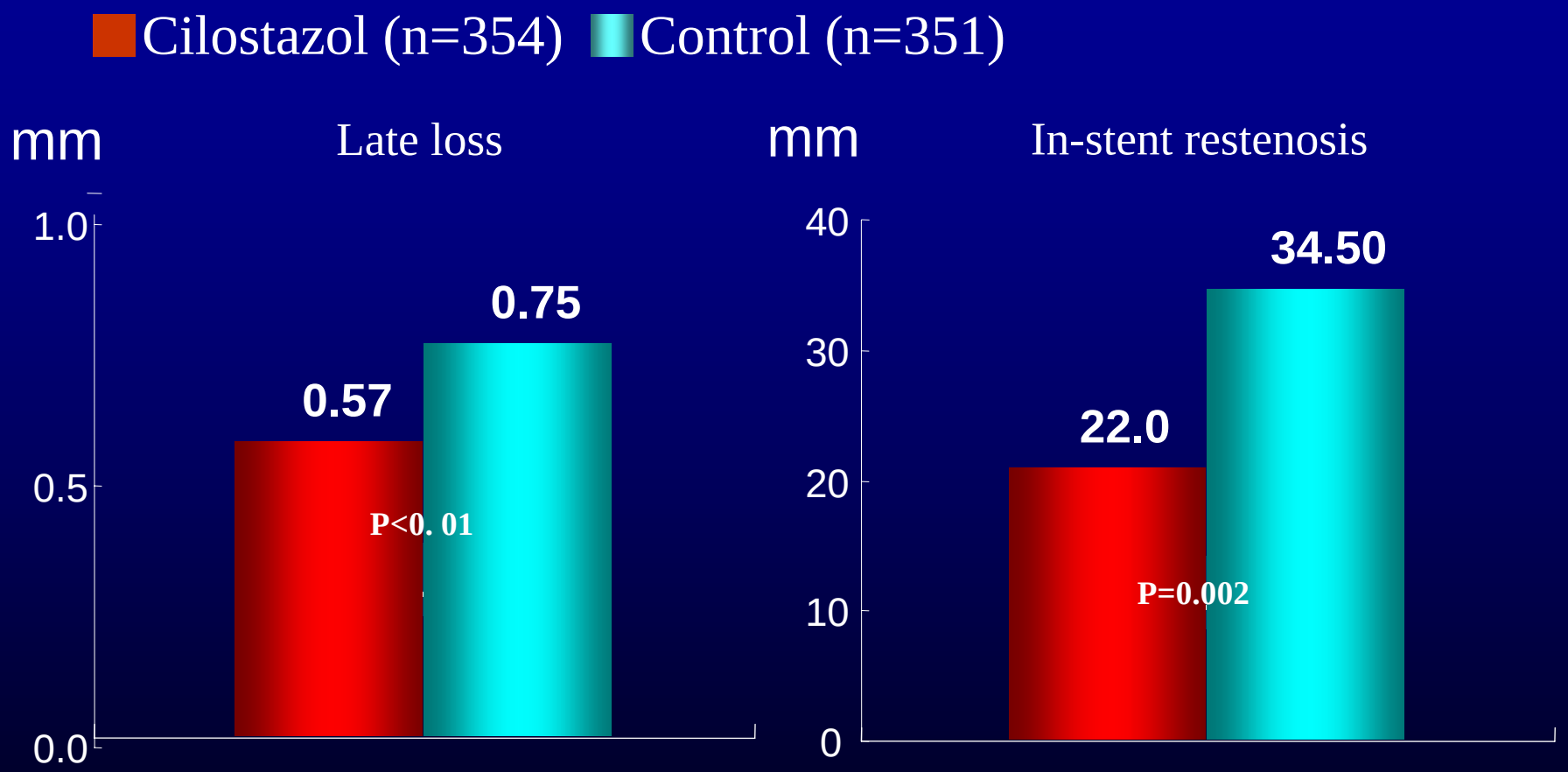
Effects of Cilostazol on Stent Thrombosis



Compared with the dual antiplatelet regimen, triple therapy was more effective in preventing thrombotic complications after BMS stenting without an increased risk of side effects.

Lee SW et al, J Am Coll Cardiol 2005;46:1833

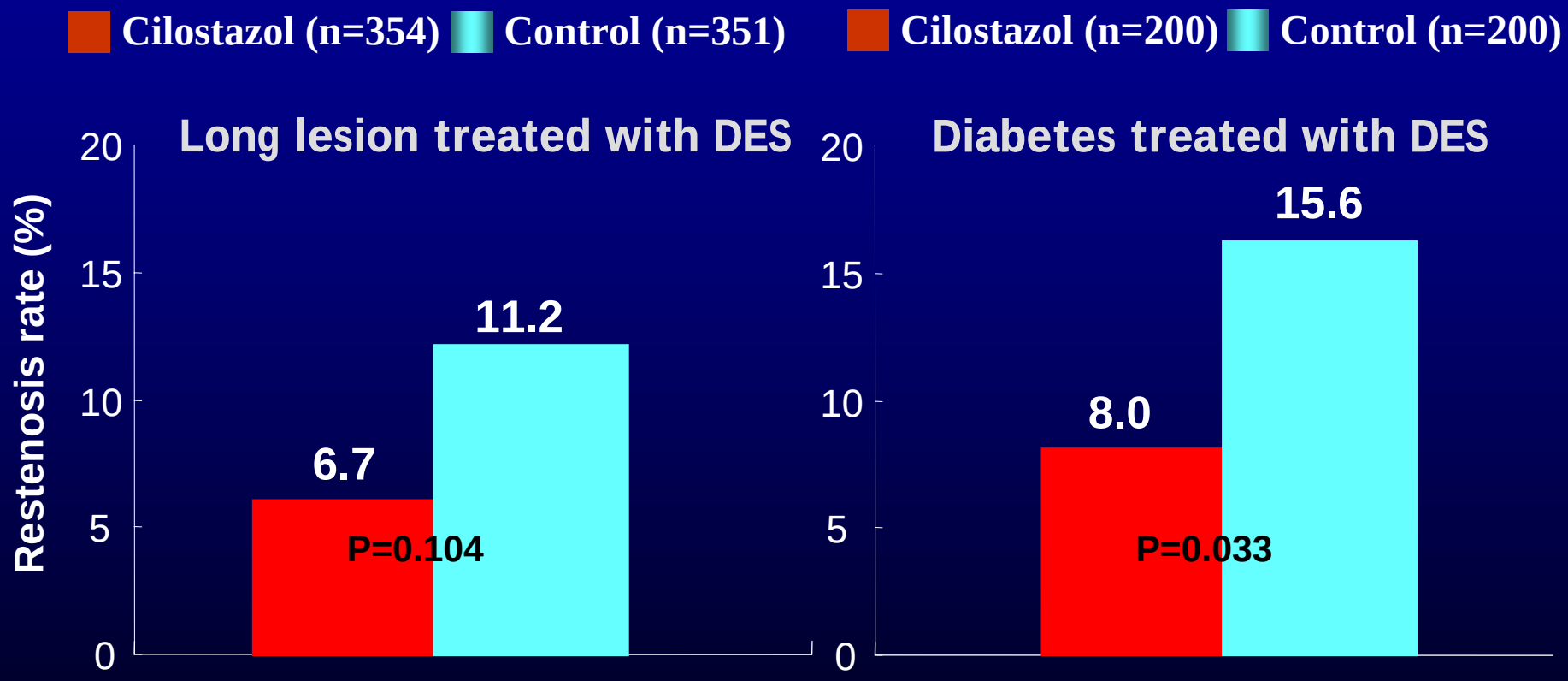
CREST Trial



Cilostazol taken orally after successful stenting significantly reduced the rate of restenosis.

Douglas JS, et al. Circulation.2005;112:2826-32

DECLARE - Long and Diabetes Study

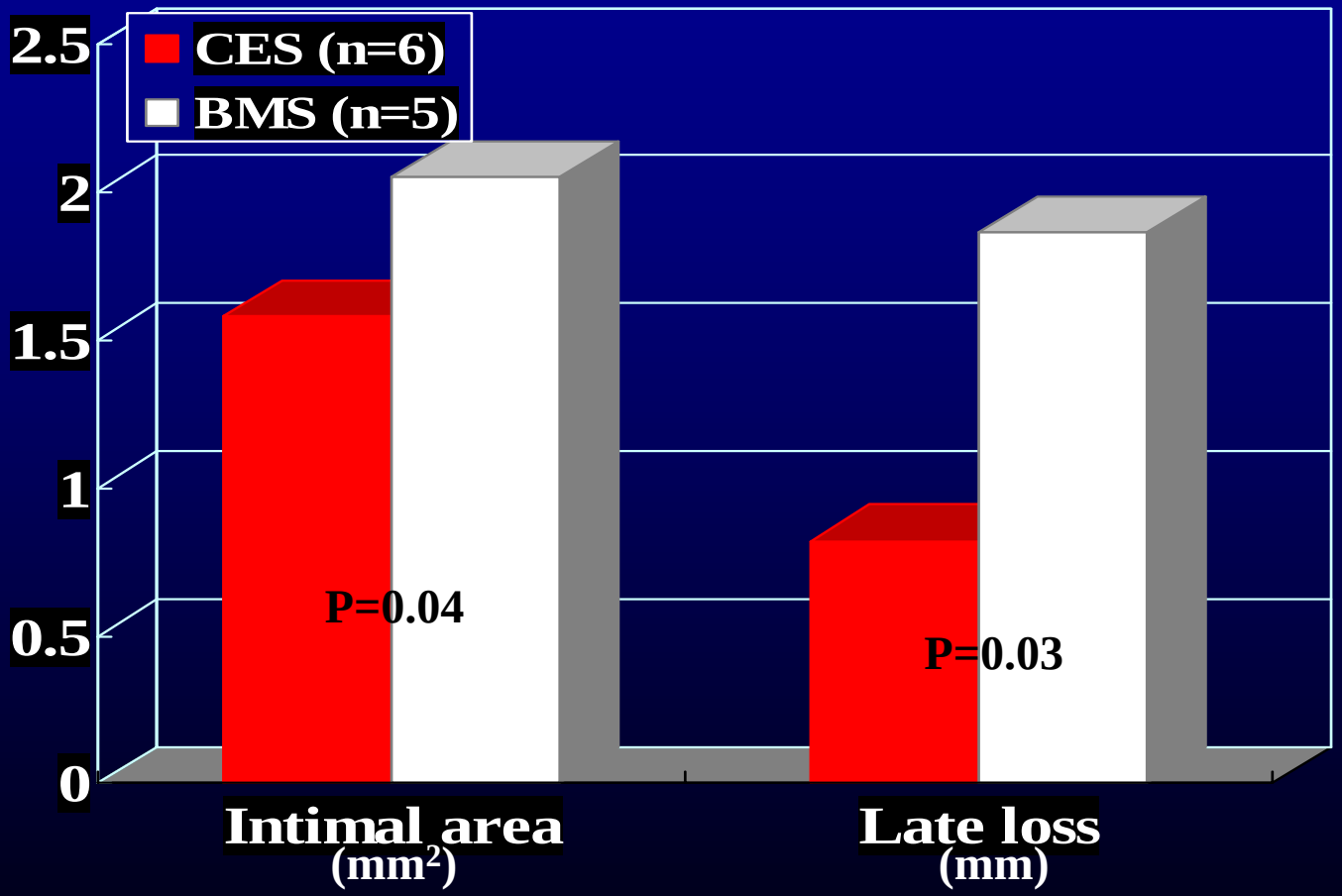


Cilostazol taken orally after DES implantation significantly reduced the rate of restenosis.

Lee SW, et al Am J Cardiol 2007;100:1103
J Am Coll Cardiol 2008;51:1181

Anti-restenotic Effect

Cilostazol-eluting Stent
in a Porcine Coronary Model



400 µg/18mm stent

Tsuchikane E, et al. J Invasive Cardiol 2007;19(3):109

The Ideal Combination?

Cilotax™ Stent

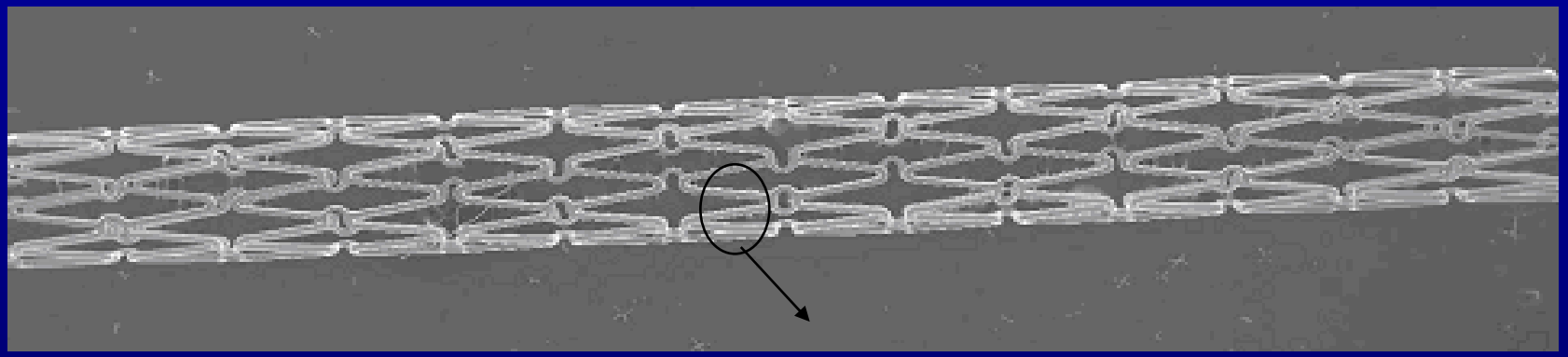
Dual-Drug DES

Potential Synergism with Paclitaxel

Cilostazol

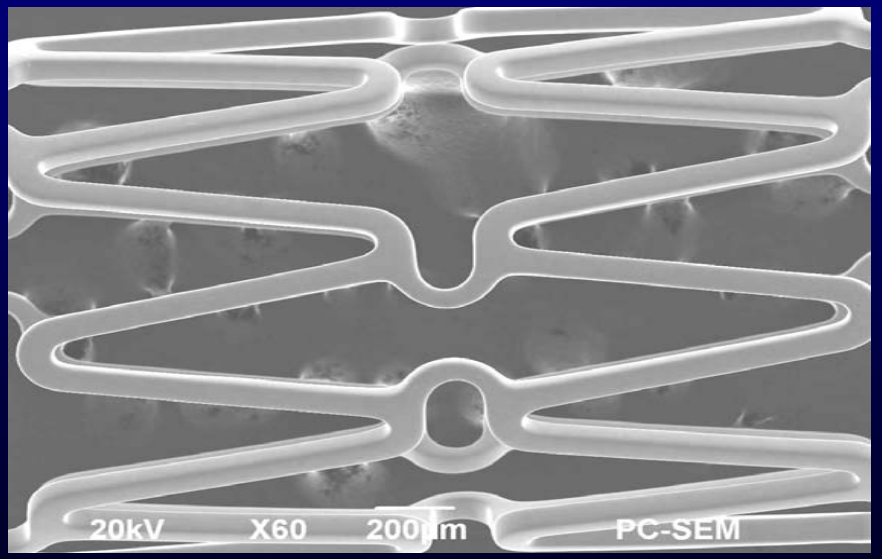
1. Anti-platelet effect
   stent thrombosis ↓
2. Anti-proliferative effect
   restenosis ↓

Stent Platform (RS Stent)

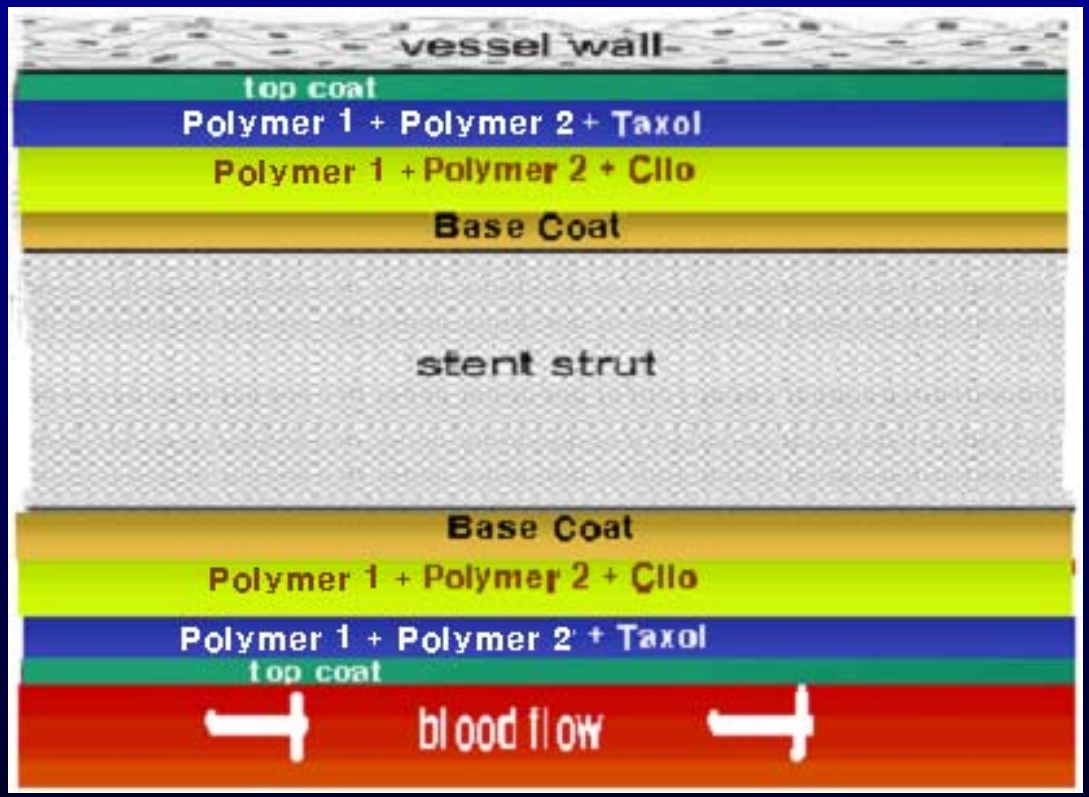


Alloy	L605 Cobalt Chromium
Strut Thickness	0.0035 inch

L605 cobalt chromium
- thinner
- stronger
- biocompatible

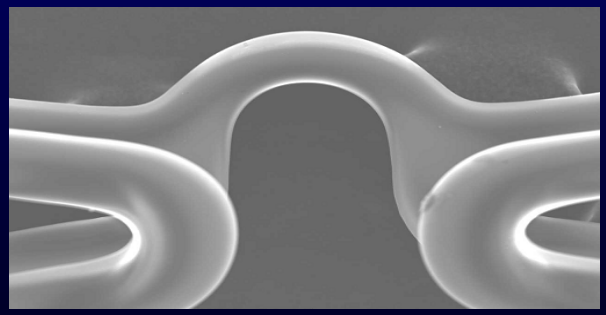


Polymer & Drugs

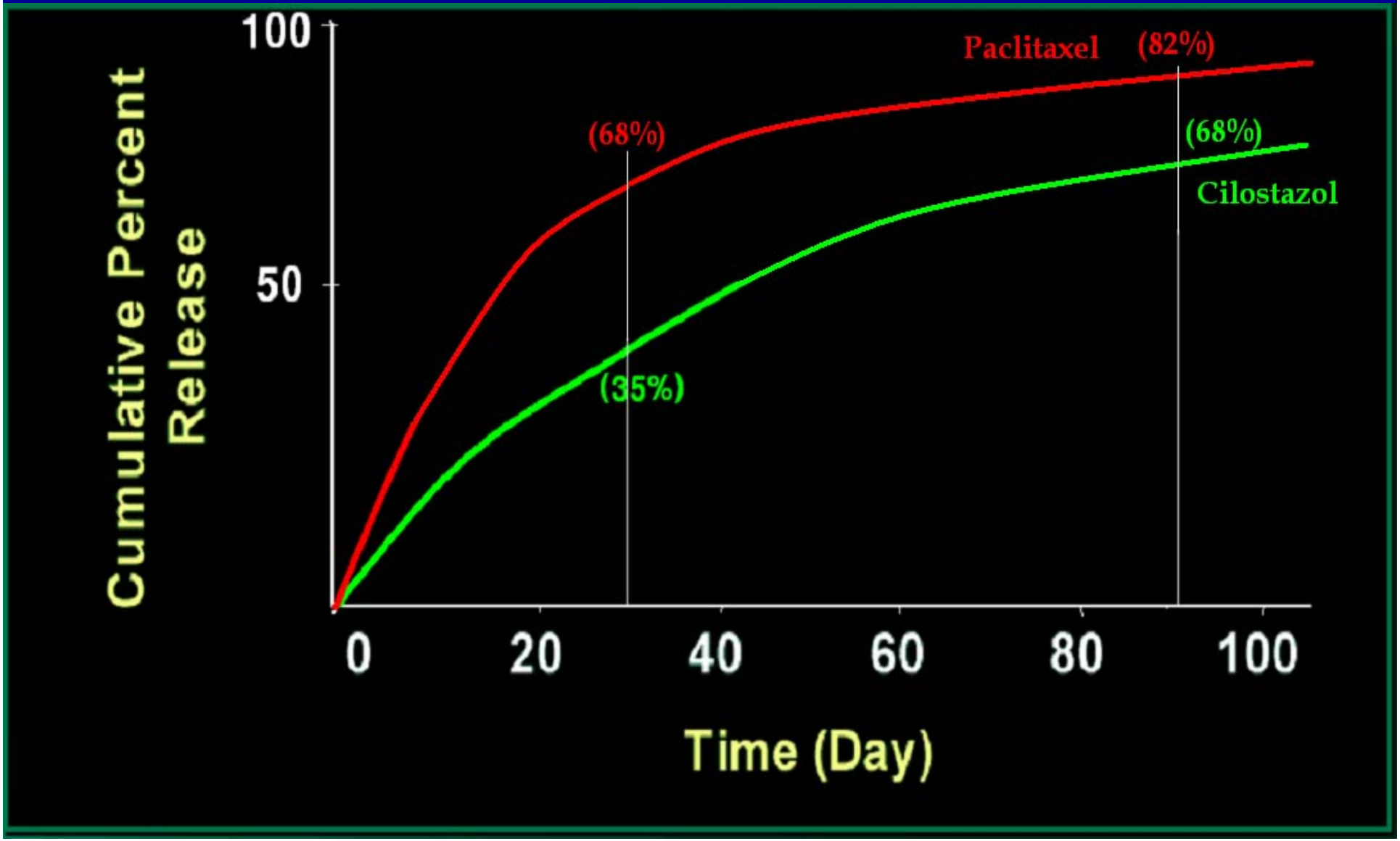


Polymer (1: 1 mixture)
- cellulose acetate butyrate (durable, biocompatible)
- resomer (bioabsorbable)
- coating thickness: ~ 8μm

Drugs
paclitaxel = 1μg/mm2
cilostazol = 6μg/mm2



Cilotax™ *In-Vitro* Drug Release Kinetics



Animal Study

Safety and Efficacy of the Cilotax™ Stent in a Porcine Coronary Model

Objectives

We tested whether the Cilotax™ stent system is safe & effective at preventing neointimal proliferation compared with BMS in a porcine model of restenosis.

Animal Preparation

- **Juvenile swine (25-30 kg), n=7**
- **Anesthesia:**
  - **- ketamine (15-20 mg/kg IM),**
  - **- xylazine(2 mg/kg IM)**
- **6F sheath via carotid or femoral artery**
- **Aspirin 100mg, plavix 37.5mg PO for 28 days**
- **Heparin 300 unit/kg intravenous injection**

Stent Implantation

- **Stents were implanted at LAD or LCX (RCA).**
  - **balloon injury using oversized balloon**
  - **stent size: 18 mm, 3.0/3.5**
  - **B/A ratio (~1.5), maximum pressure (~14 atm)**

Analysis

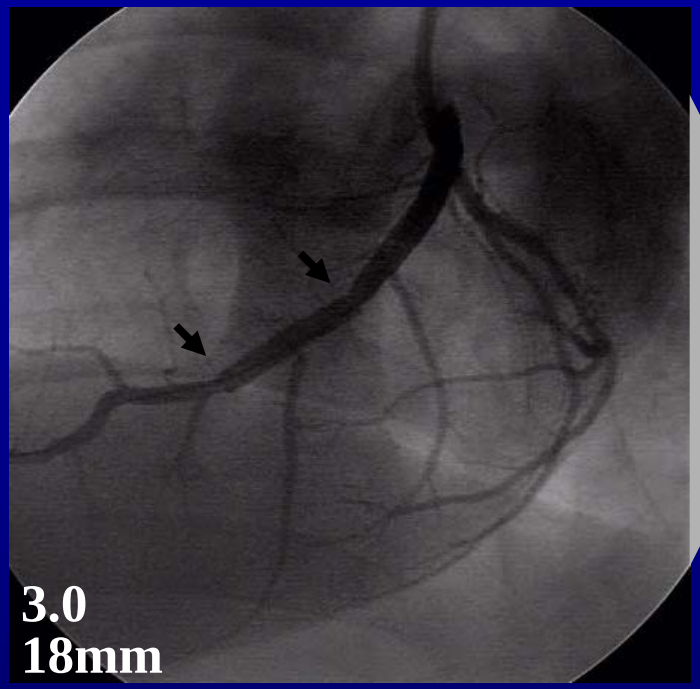
- **Angiography and IVUS:**
  - immediate post-stenting & 1 month follow-up
- **Histopathomorphometric study at 1 month:**
  - perfusion fixation using 10% buffered formalin
  - H&E, Carstair's fibrin content
  - Digital morphometry
- **Statistical analysis**
  - nonparametric Kendall's W test
  - nonparametric Wilcoxon/Kruskal-Wallis test
  - significance: $p<0.05$

Results

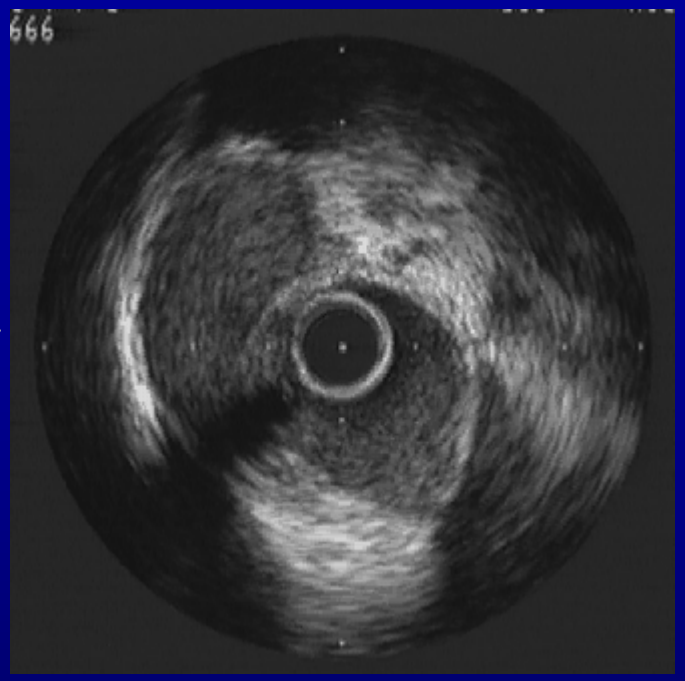
Systemic drug levels and outcomes during follow-up

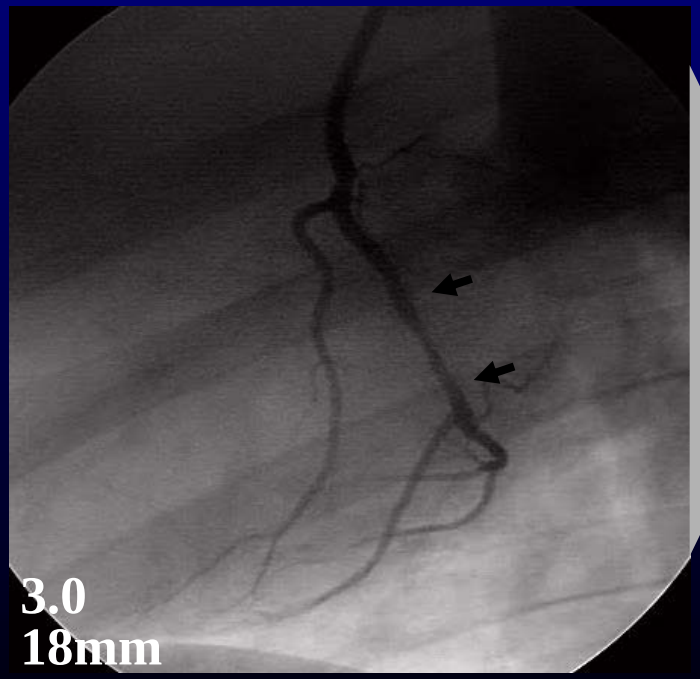
- **Cilostazol & taxol were not detectable systemically by HPLC method.**
- **There were no stent thrombosis or death during 1-month follow-up.**

Results

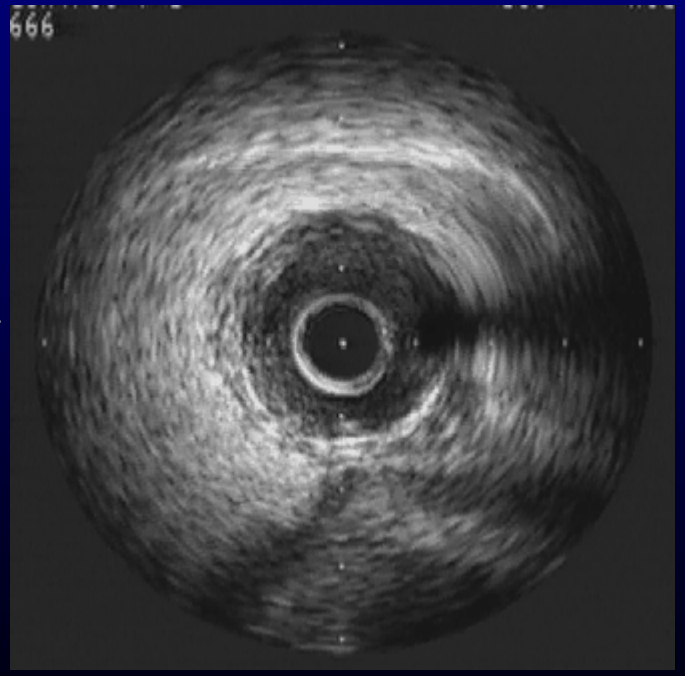


Cilotax





BMS



4 weeks
Follow-up

QCA Analysis (n=7)

	BMS	Cilotax	p-value
Reference diameter	2.51±0.27	2.67±0.12	0.174
MLD, post	2.75±0.27	2.74±0.14	0.943
MLD, follow-up	1.49±0.53	2.65±0.13	0.001
DS, post	-10.8±7.9	-13.4±8.2	0.540
DS, follow-up	39.9±16.6	2.8±2.8	0.001
Acute gain	0.57 ±0.28	0.39±0.20	0.173
Late loss	1.26±0.47	0.09±0.08	<0.001

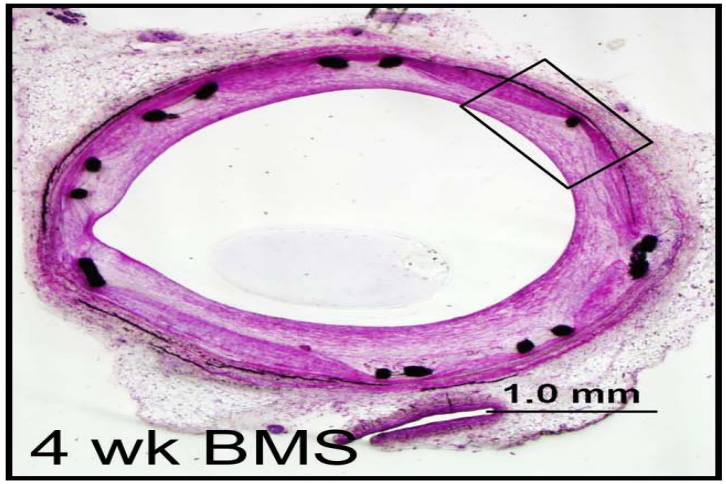
MLD: minimal lumen diameter, DS: diameter stenosis

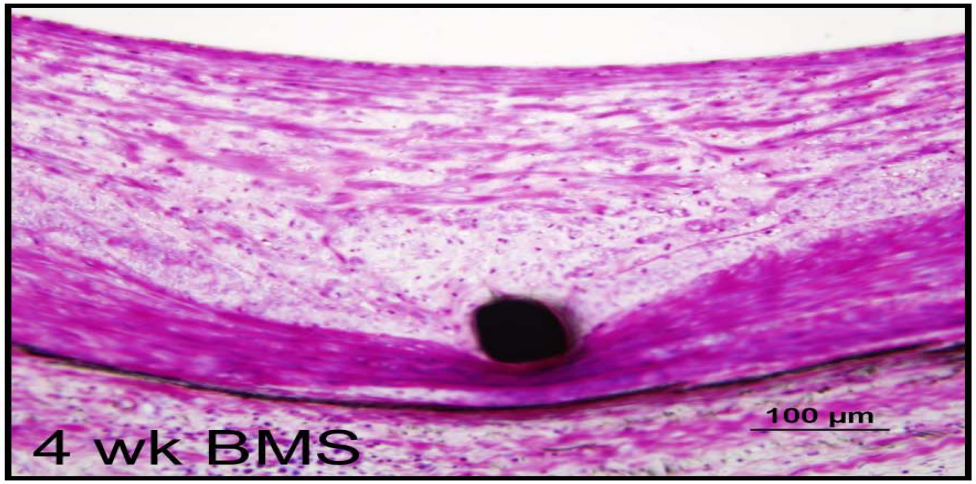
IVUS Analysis at Follow-Up (n=7)

	BMS	Cilotax	p-value
Proximal margin			
Vessel area, mm2	10.53±3.38	10.58±1.58	0.975
Lumen area, mm2	6.16±2.43	8.87±1.76	0.035
% area stenosis	40.1±21.1	15.9±12.2	0.022
Distal margin			
Vessel area, mm2	7.90±2.44	7.32±1.65	0.611
Lumen area, mm2	4.89±1.38	6.03±1.26	0.134
% area stenosis	35.3±15.3	17.1±6.2	0.020
Within the stent			
Lumen area, mm^2	4.30±1.85	7.19±1.58	0.009
% stent area stenosis	51.8±19.4	6.6±10.4	<0.001
Neointimal thickness, mm	0.75±0.28	0.09±0.10	<0.001
Neointimal area, mm^2	4.57±1.49	0.22±0.25	<0.001
Neointimal volume, mm^3	56.8±27.3	0.9±1.0	<0.001

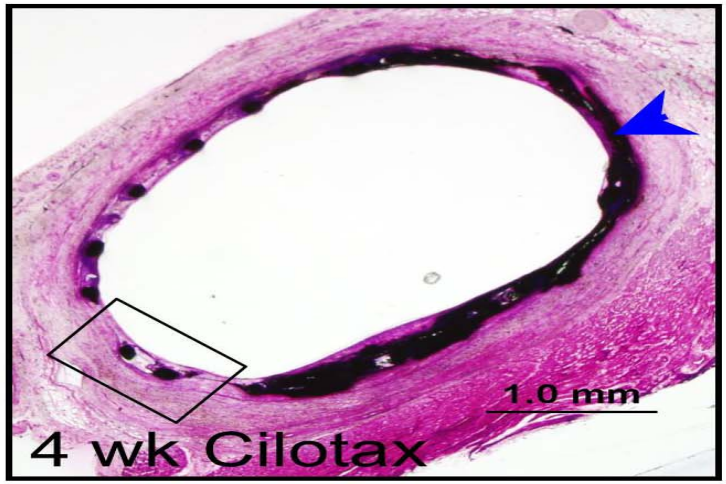
Histopathologic Examination

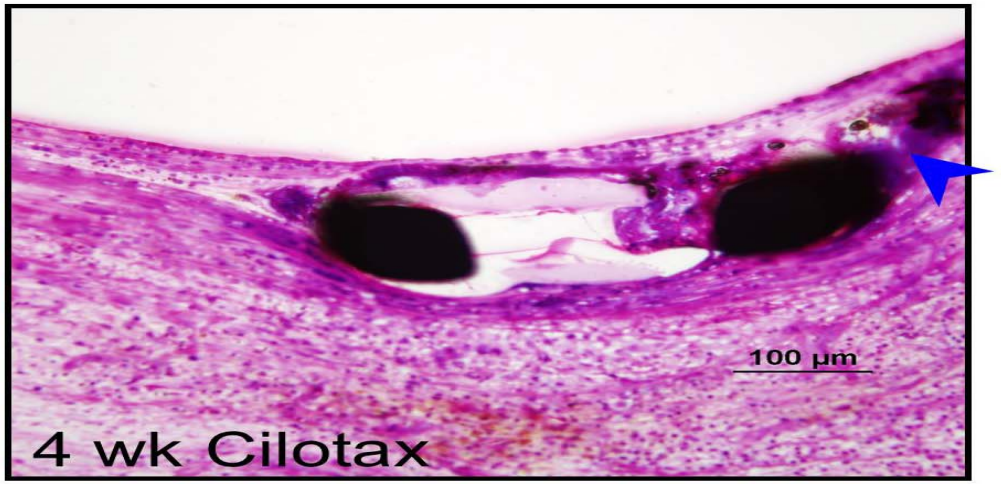
17571 BMS4 mid





17566 DES4 mid





Results

	BMS (n=3)	Cilotax™ stent (n=4)	P value
EEL area, mm^2	7.40 ± 2.50	7.17 ± 1.01	0.872
IEL area, mm^2	6.32 ± 2.17	5.82 ± 1.23	0.710
Stent area, mm^2	6.32 ± 2.17	5.53 ± 0.58	0.508
Lumen area, mm^2	3.80 ± 1.34	4.34 ± 0.66	0.504
Intimal area, mm^2	2.52 ± 0.98	1.48 ± 0.63	0.144
Medial area, mm^2	1.08 ± 0.33	1.35 ± 0.32	0.320
Stenosis, %	38.61 ± 5.35	24.91 ± 5.26	0.020
Intimal thickness, mm	0.39 ± 0.09	0.21 ± 0.04	0.019
Injury score	0.59 ± 0.39	0.33 ± 0.24	0.478

Vessel Healing

	BMS (n=3)	Cilotax™ stent (n=4)	P value
Fibrin, %	15.67 ± 17.2	97.85 ± 3.01	0.0002
Mean fibrin score	0.11 ± 0.19	2.83 ± 0.33	0.0262
Malapposition, %	0.00 ± 0.00	61.88 ± 23.6	0.0068
RBC, %	3.40 ± 5.88	35.43 ± 7.13	0.0015

Inflammatory Response

	BMS (n=3)	Cilotax™ stent (n=4)	P value
Intimal inflammation score	0.67 ± 0.67	2.67 ± 0.27	0.0323
Adventitial inflammation score,	1.44± 1.02	2.75 ± 0.50	0.0666
Giant cells, %	0.00 ± 0.00	0.00 ± 0.00	N/A

Conclusions

- **The Cilotax™ stent system was safe and effective in inhibiting neointima formation compared with BMS at 4 weeks in a porcine coronary model.**

- **Histologic analysis showed that the Cilotax™ stent induced more inflammatory response & delayed arterial healing than bare-metal stent.**

Clinical Study

Efficacy and Safety of the Cilotax™ Stent

Phase 1/2 Clinical Trial (Pilot Study)

Hypothesis

The co-drug formulation of cilostazol (6μg/mm2) plus paclitaxel (1μg/mm2) may attenuate the risk of stent thrombosis and potentially reduce the risk of restenosis as compared with paclitaxel alone.

Objectives

- **to assess safety and efficacy of the Cilotax™ stent in de novov native coronary lesions.**

- **to compare the performance of a dual DES with that of a standard paclitaxel-eluting stent.**

Study Design

- **Prospective randomized study**
  110 patients, 2 Korea centers (AMC &CMC)

- **Inclusion criteria:**
  - de novo lesion ≤ 20 mm in length
  - reference diameter ≥ 2.5 mm and ≤ 3.5 mm

- **Study devices:**
  - Cilotax (Cardiotec Co.): 3.0, 3.5 & 18 mm (23 mm)
  - Taxus (Boston Scientific Co.): 3.0, 3.5 & 20 (24 mm)

- **Repeat angiography and IVUS at 8 months**
  All patients to be followed clinically up to 12 months

Study Endpoints

- **Statistics**
  - a sample of 110 patients to detect a difference in the mean late loss of 0.2 mm between the two groups, assuming a standard deviation of 0.4 mm in each group & 80% power.

- **Primary endpoint**
  - in-segment late loss at 8 months (QCA)

  Secondary endpoint
  - stent thrombosis & MACE at 8 months
  - restenosis and TLR at 8 months
  - diameter stenosis at 8 months (QCA)
  - % in-stent volume obstruction at 8 months (IVUS)

Current Status

- **15 patients enrolled**
  - First patient: Feb 27, 2008
  - Enrolment complete: June 30, 2008

- **Study results expected in early spring 2009**