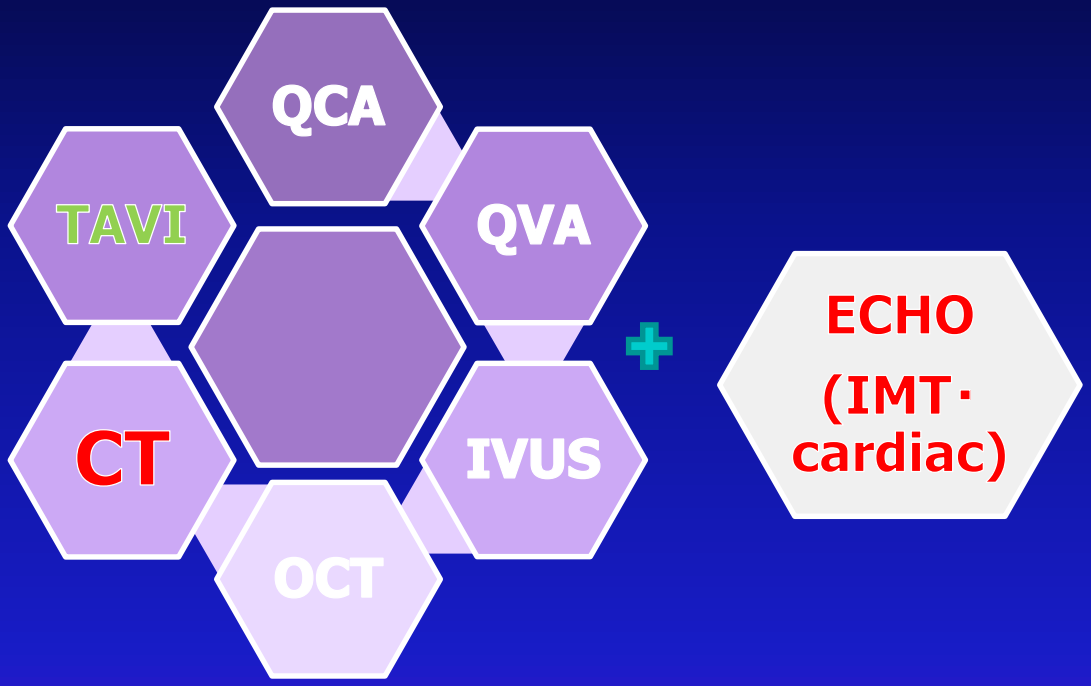
Experience of First in Human Study in Japan



Teikyo University Hospital
Cardiocore Japan
Ken Kozuma

History of Cardiocore Japan

- 2003/05 Cardiocore Japan Started operation
- 2006 Introduced QCU Analysis Software
- 2009 Expand Analysis Center (Present location)
  Introduced Image Server (Toshiba MS)
  Increased Analysis Machine
  (CAAS, QCA-CMS each 2 units)
  Introduced OCT Analysis Software
- 2010 Started Operation at Yokohama QCU Center
- 2011 Unify Database (Toshiba MS)
  Increase Analysis Machine (QCA-CMS 3units)
  Introduced QVA Analysis Software
- 2012 Approved ISO9001
- 2014 Started CTA analysis
- 2015 Started UCG (TTE) analysis

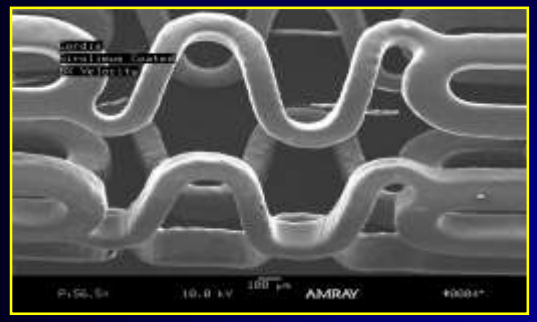
Evolution of PCI

	POBA	BMS	1st gen. DES	2nd gen. DES
Decade	1980s	1990s	2000s	2010s
Acute Success rate	70-85%	>95%	>95%	>95%
Restenosis	40-45%	20-30%	<10%	<10%
Early Thrombosis <30 days	3-5%	1-2%	0.3-2%	0.3-1%
Late Thrombosis >30 days	NA	<0.5%	0.3-2%	0.1-0.3%
Very Late Thrombosis (>1y)	NA	≈0%	0.3-2%	0-0.2%

Unresolved issues related to 2nd generation DES

- Efficacy issues
  - Late catch-up
  - Stent overlap (long stent)
  - Bifurcation (2 stent)
  - Hemodialysis, Diabetes
- Safety issues
  - Improved endothelialization and vasomotion
  - Prevent inflammation/ hypersensitivity reaction
  - Eliminate risk of very late stent thrombosis
  - DAPT duration
- Technical issues (CTO)

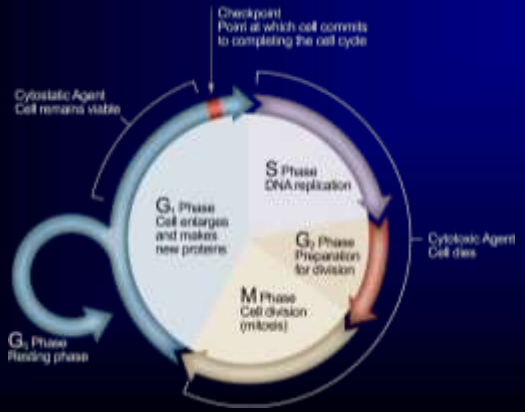
Components of DES



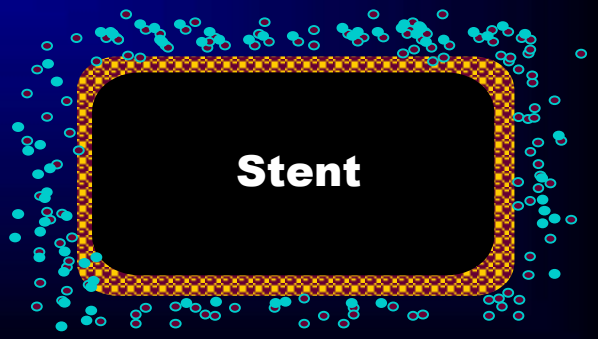
Platform

Drug-Eluting Stent

Drug



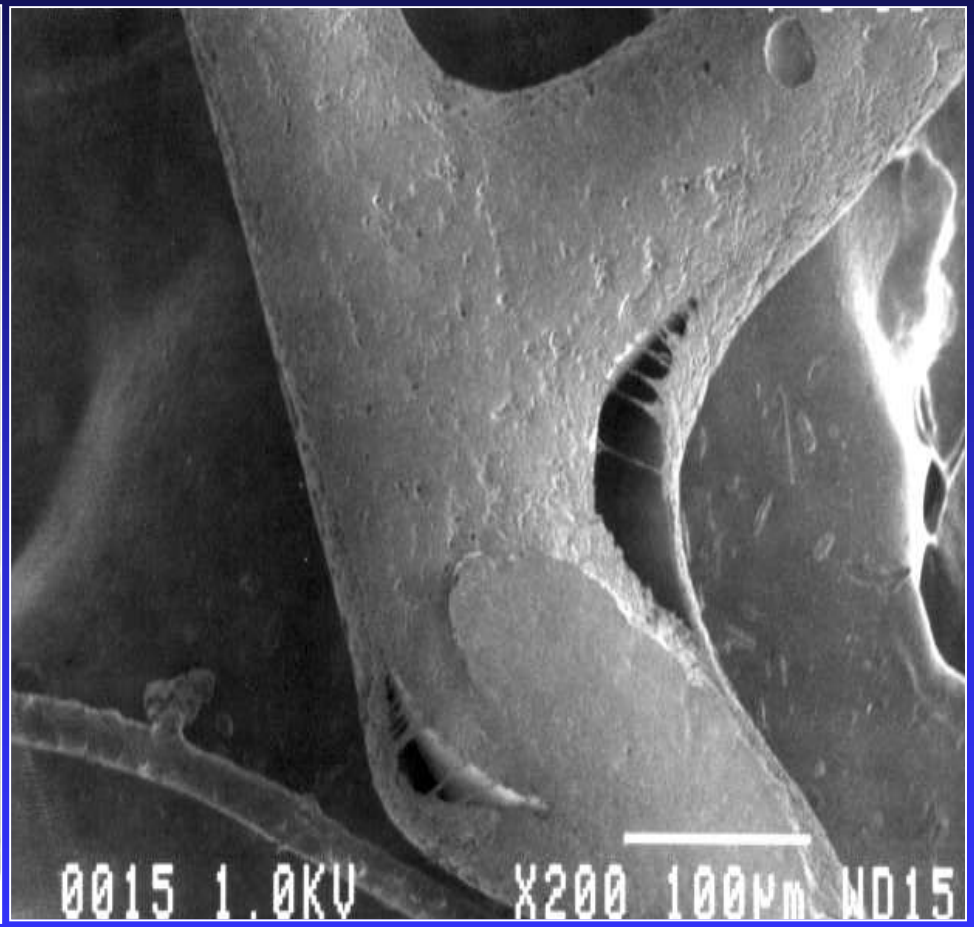
Carrier Matrix



Coating integrity

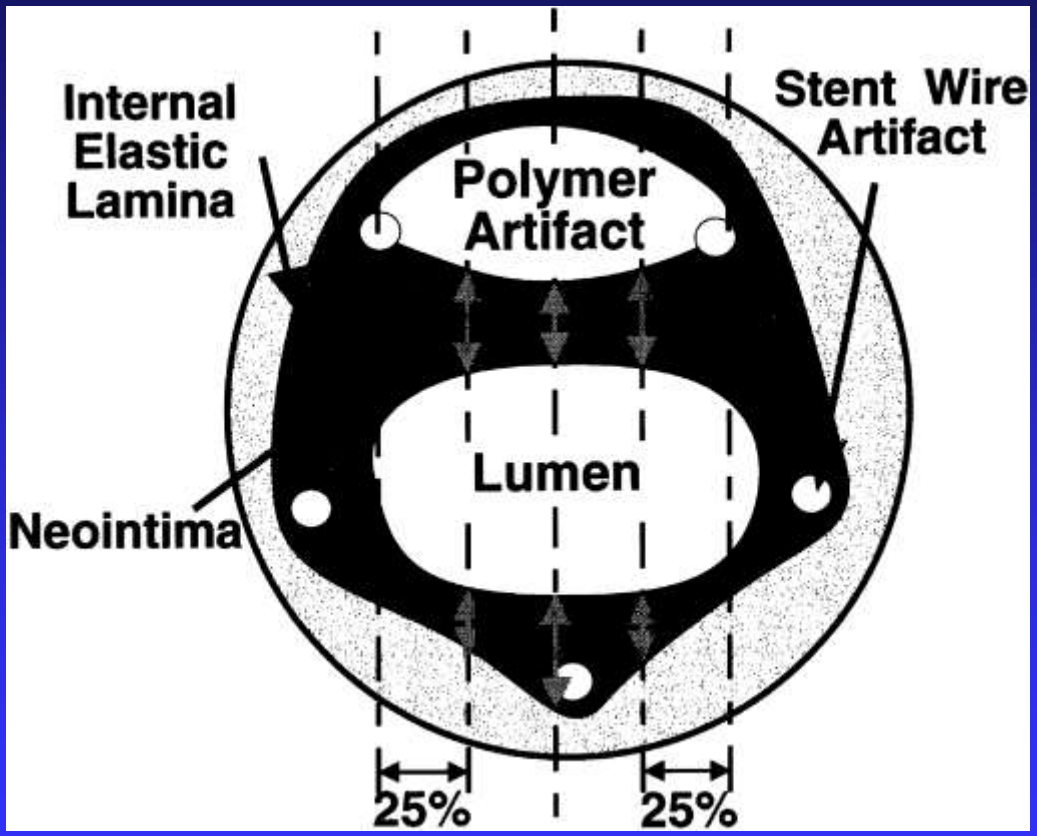
Effects of stent expansion

Effects of sterilization



Marked Inflammatory Sequelae to Implantation of Biodegradable and Nonbiodegradable Polymers in Porcine Coronary Arteries

- **Biodegradable polymers**
  - PGLA **(polyglycolic acid/polylactic acid)**
  - PCL **(polycaprolactone)**
  - PHBV **(polyhydroxybutyrate)**
  - POE **(polyorthoester)**
  - PEO/PBTP **(polyethyleneoxide)**
- **Nonbiodegradable polymers**
  - PUR **(polyurethane)**
  - SIL **(silicone)**
  - PETP **(polyethylene tetephthalate)**

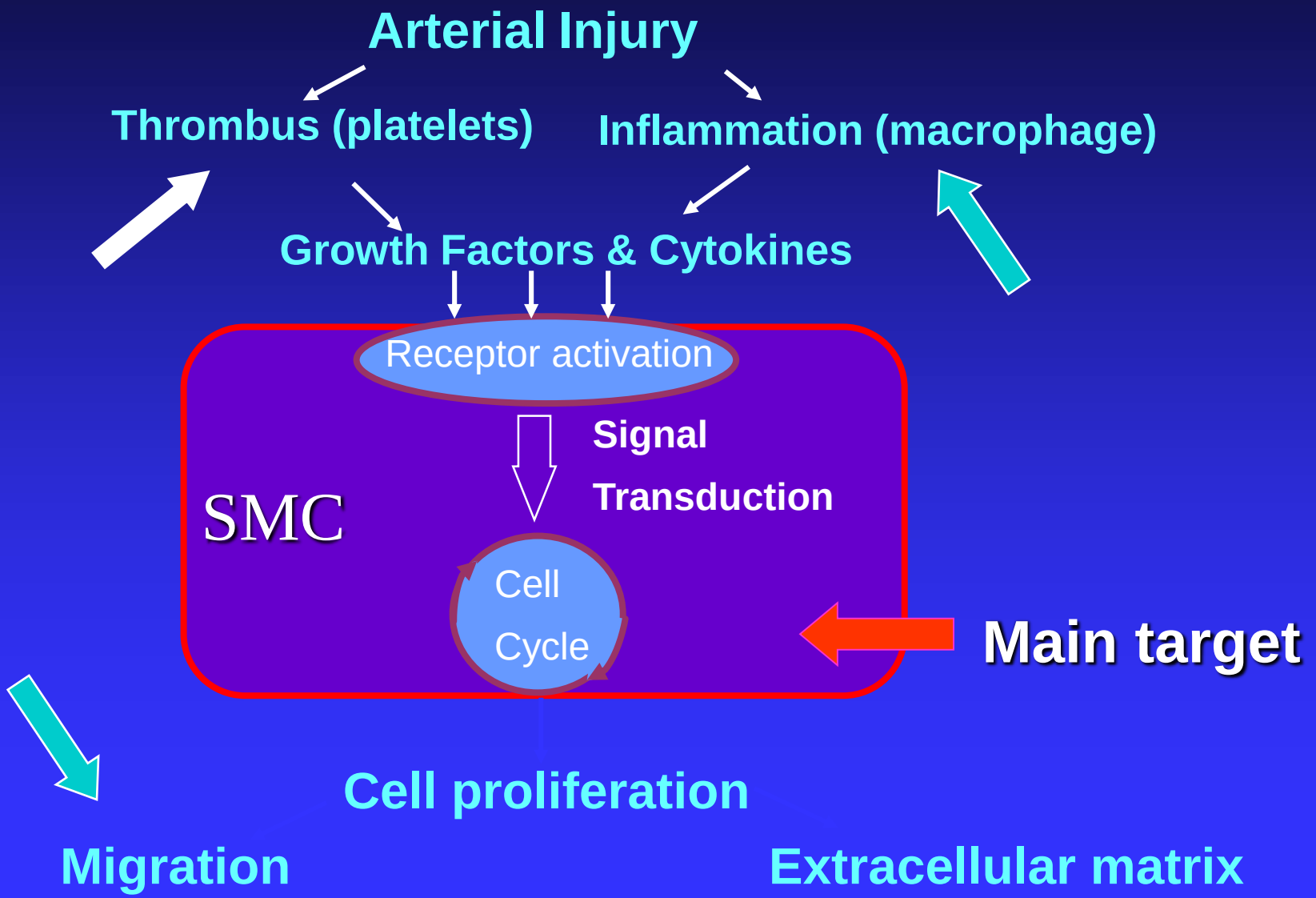


van der Giessen WJ et al. Circulation 1996; 94:1690

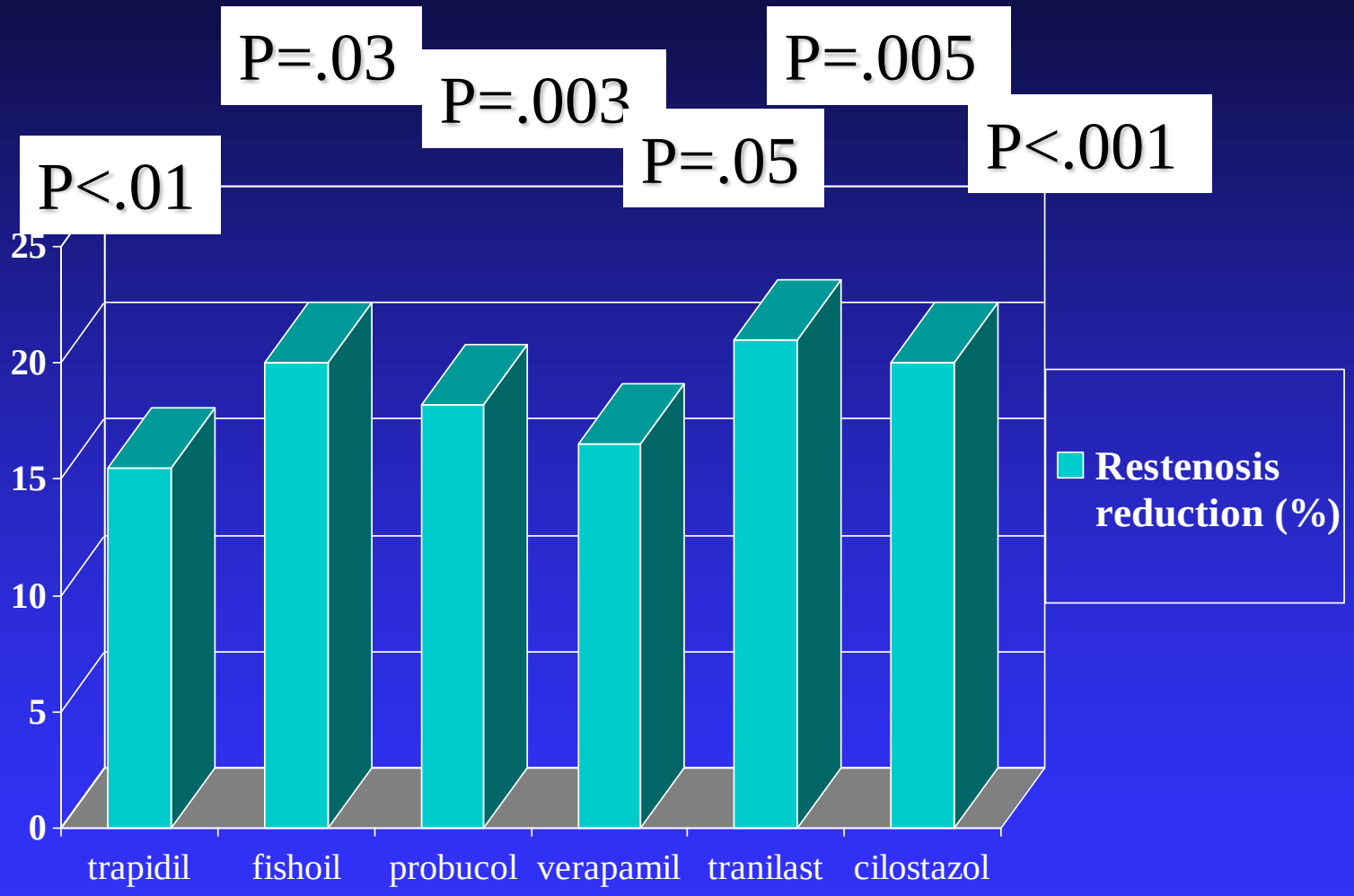
Japan Stent Technology
JF-03 (BMS) n=102

	In-segment	Proximal	In-stent	Distal
Late loss (mm)	0.47 ± 0.58	0.25 ± 0.48	0.69 ± 0.47	0.05 ± 0.42
Late loss index	0.42 ± 0.28	NA	NA	NA
Restenosis (%)	10.2	2.0	10.2	0.0

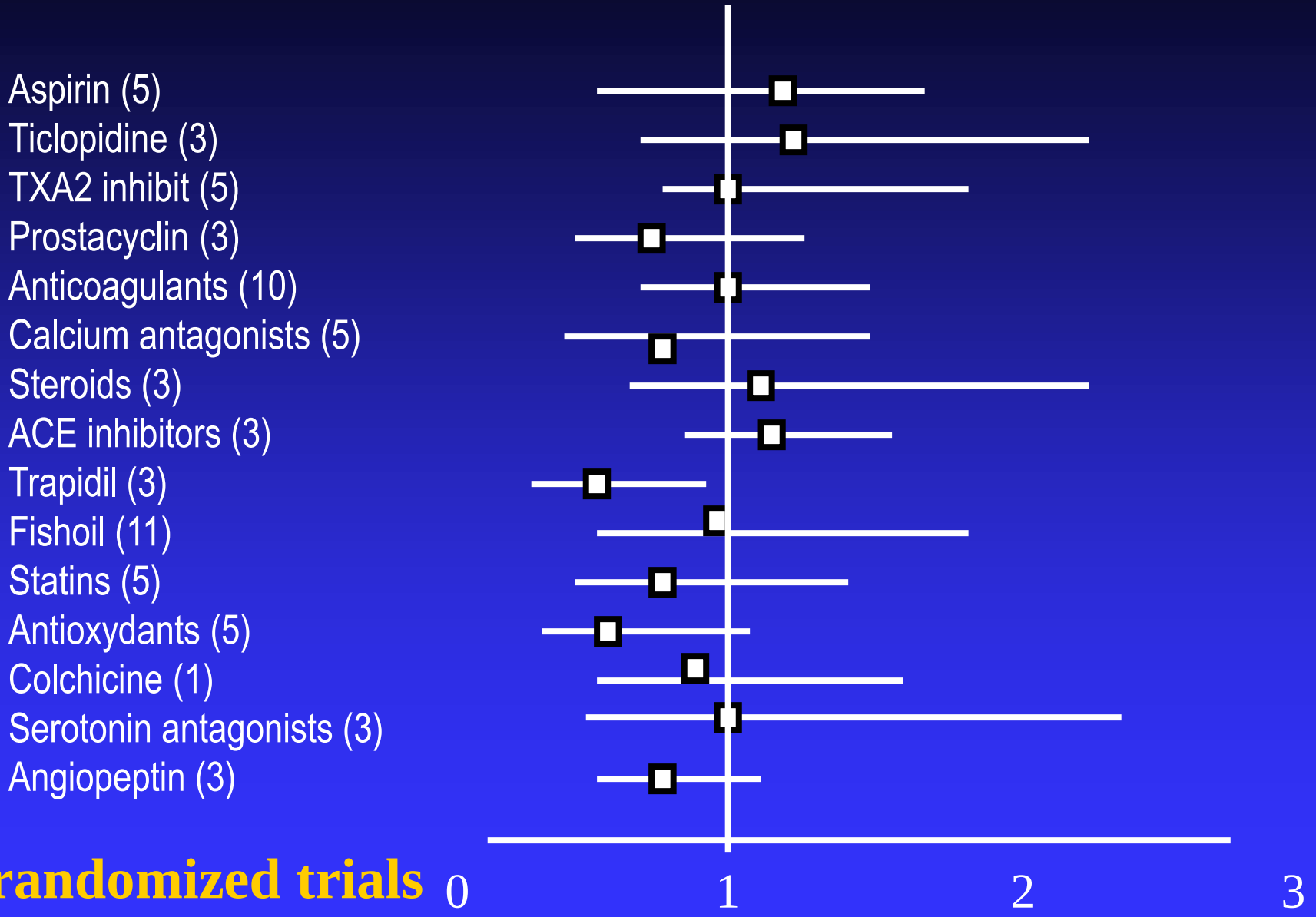
Target of Restenosis Inhibition by Drug eluting stent



DRUGS WORK!…


P=.03
P=.003
P=.005
P=.05
P<.001
P<.01
25
20
15
10
5
0
trapidil
fishoil
probucol
verapamil
tranilast
cilostazol
Restenosis reduction (%)

Anti-restenosis trials using drugs (Meta-analysis)



66 randomized trials

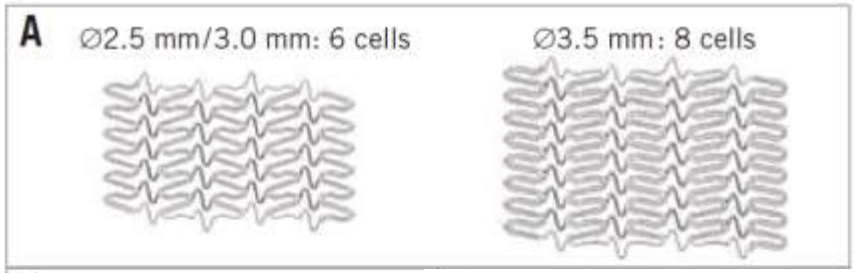
20,914 patients

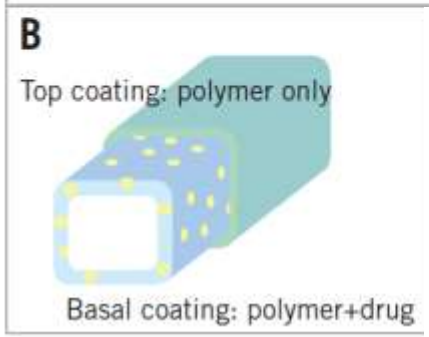
Drug for anti-restenosis

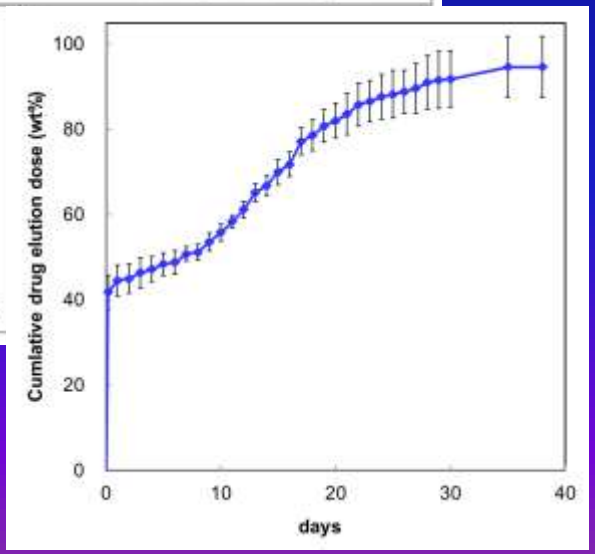
Anti-Inflammatory Immunomodulators	*Anti-Proliferative*	*Migration Inhibitors ECM-Modulators*	*Promote Healing & Re-Endothelialization*
Dexamethasone	QP-2, *Taxol*	Batimastat	BCP671
M-prednisolone	Actinomycin	Prolyl hydroxylase inhibitors	VEGF
Interferon γ-1b	Methothrexate	Halofuginone	Estradiols
Sirolimus	Angiopeptin	C-proteinase inhibitors	NO donors
Tacrolimus	Vincristine	Probucol	EPC antibodies
Everolimus	Mitomycine		Biorest
Biolimus	Statins		Advanced coatings
Mycophenolic acid	C MYC antisense		
Mizoribine	RestenASE		
Cyclosporine	2-chloro-deoxyadenosine		
Tranilast	PCNA Ribozyme		
	Cilostazol		

Biodegradable polymer-based, argatroban-eluting, cobalt-chromium stent (JF-04) for treatment of native coronary lesions: final results of the first-in-man study and lessons learned

Yoshihiro Morino[1]*, MD; Tetsuya Tobaru[2], MD; Satoshi Yasuda[3], MD; Kazuaki Kataoka[4], MD; Kengo Tanabe[5], MD; Atsushi Hirohata[6], MD; Ken Kozuma[7], MD; Takeshi Kimura[8], MD







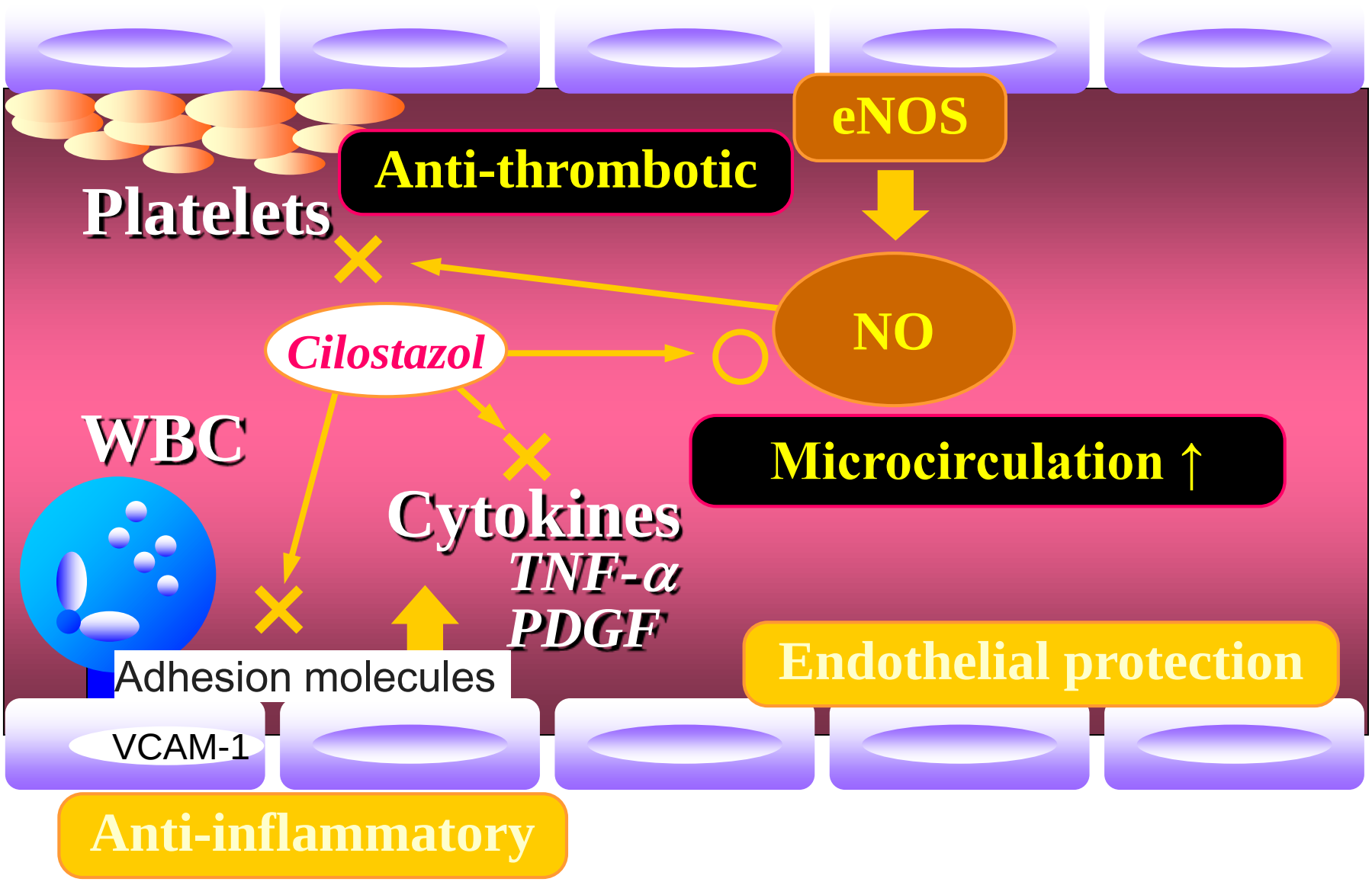
	JF-04	MOMO	
Platform	L605 cobalt-chromium, identical design		
Coating	biodegradable	durable	
	50:50 poly (DL-lactide-co-glycolide)	diamond-like carbon (DLC)	
Drug	argatroban	none	
Clinical study	first-in-man	first-in-man	pivotal
Countries	Japan	UK, Germany	Japan
Number of patients	31	40	99
In-stent late loss, mm	1.01±0.48	NA	0.69±0.47
In-segment late loss, mm	0.74±0.51	0.54±0.3	NA
Restenosis rate, %	29.0	12.5	10.5
Ischaemia-driven TVR, %	12.9	7.5	11.2

TVR: target vessel revascularisation

Cilostazol：Mechanism of action

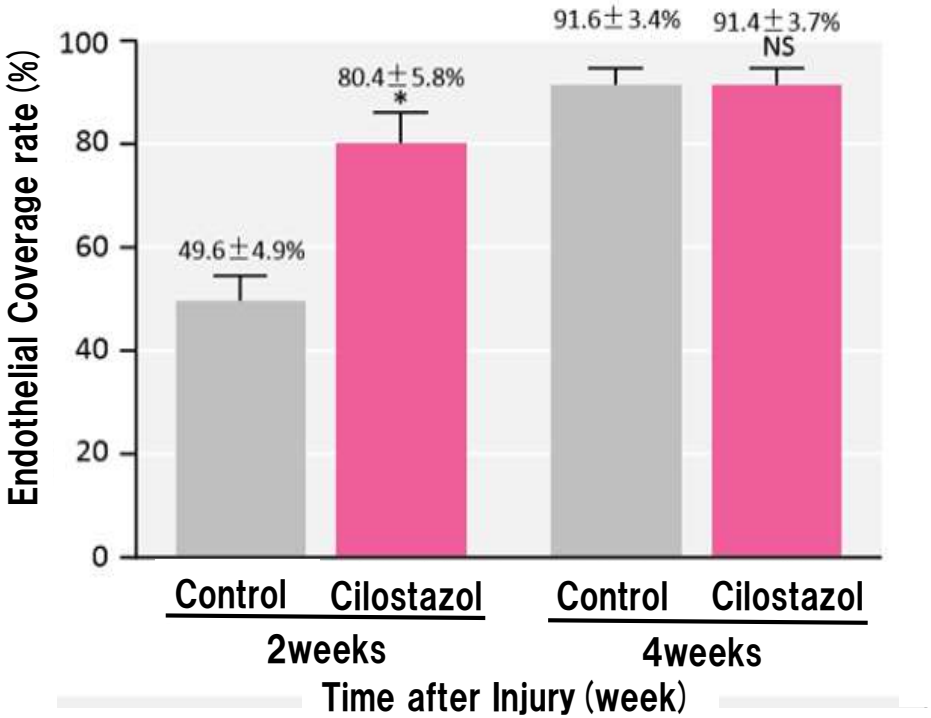
Target Cell	Efficacy
・Platelet	Anti-platelet effect
・Smooth muscle cell	Vasodilating effect Inhibition of proliferation
・Endothelial cell	Improvement of function Promote re-endothelialization

Effects of Cilostazol (PDE-III inhibitor)

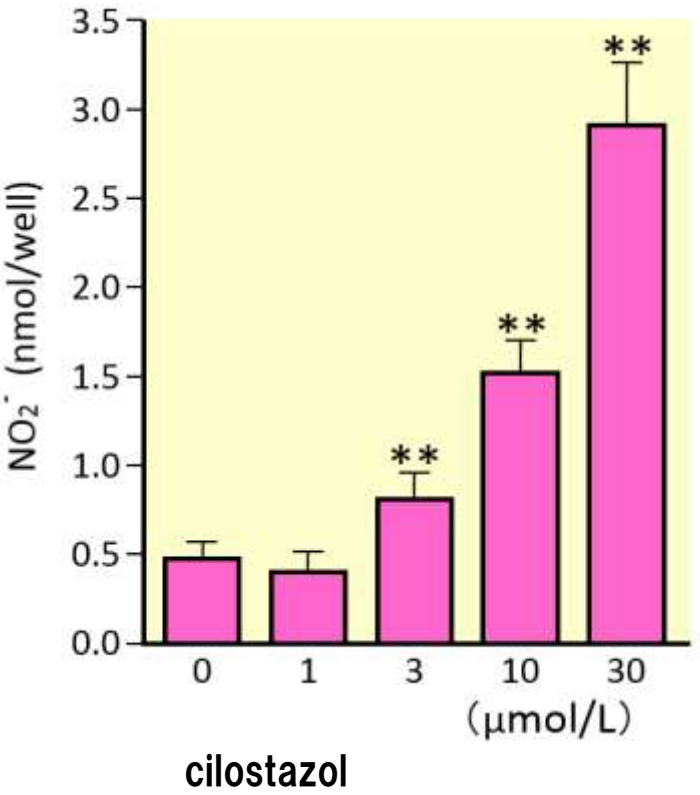


Effect of cilostazol for Endothelial cell

Re-endothelialization after balloon injury in rat carotid artery

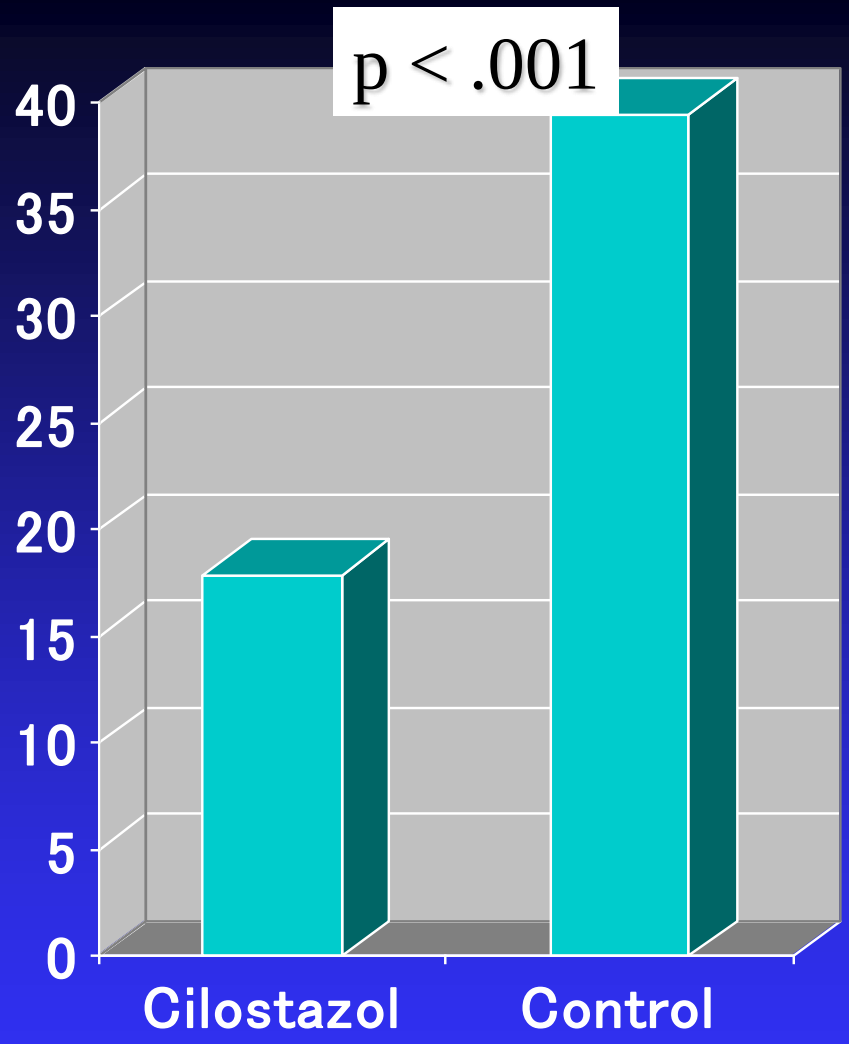


NO production in vitro (HAEC)



Cilostazol

- Cilostazol or Aspirin
- Anti-platelet drug
- Balloon angioplasty
- randomized
- n=252



Tsuchikane et al.,

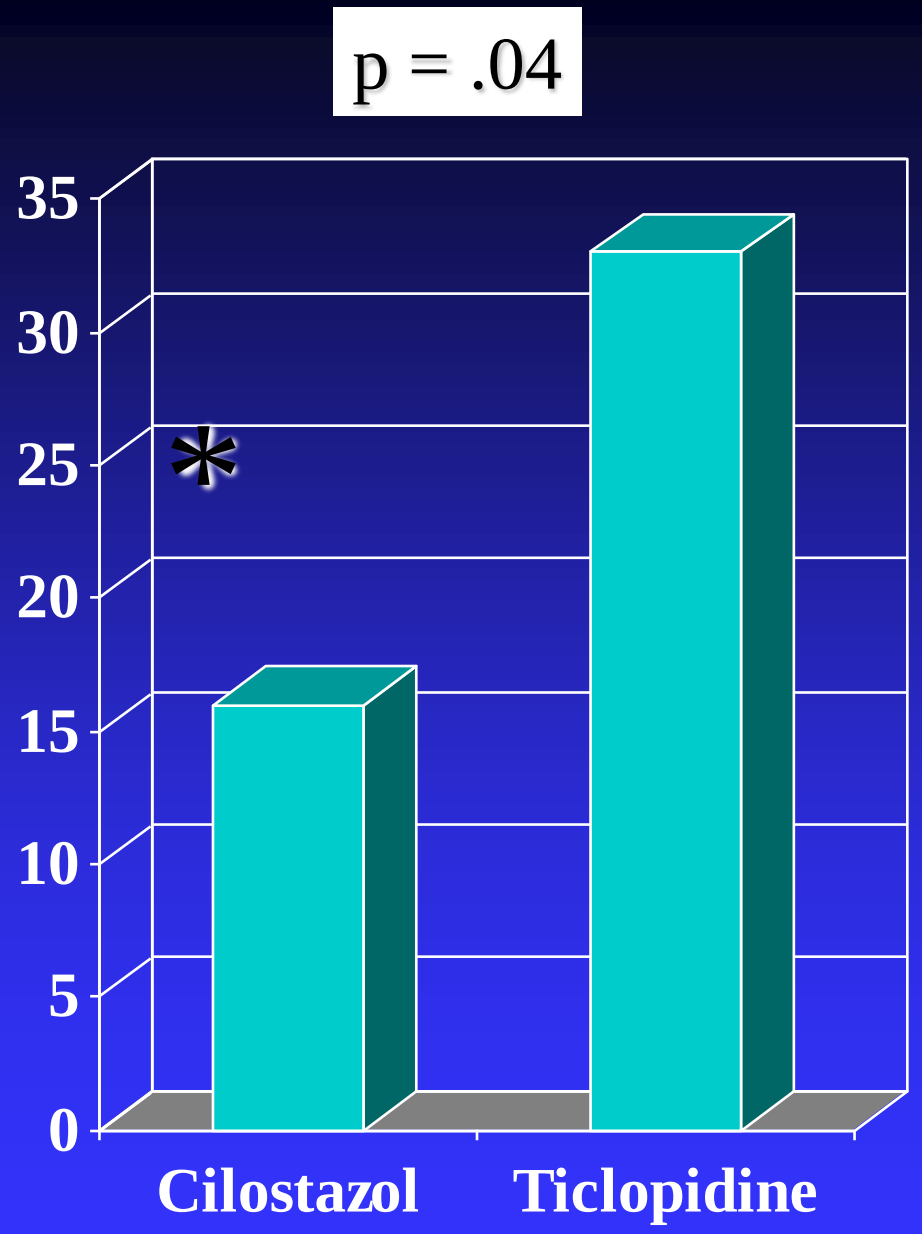
Circulation 1999

Cilostazol

- Cilostazol or Ticlopidine
- Anti-platelet drug
- Stenting
- randomized
- n=130

Kozuma et al.,

AHJ 2001



C R E S T

Cilostazol for RESTenosis Trial

John S. Douglas, Jr, David Holmes, Dean Kereiakes, Cindy L. Grines, Elizabeth Block, Karen Parker, Claudine Jurkovitz, Nancy Murrah, Jovonne Foster, Paul Kolm, John Mancini, William S. Weintraub

Emory University, Mayo Clinic, William Beaumont Hospital, Lindner Research Center, University of British Columbia

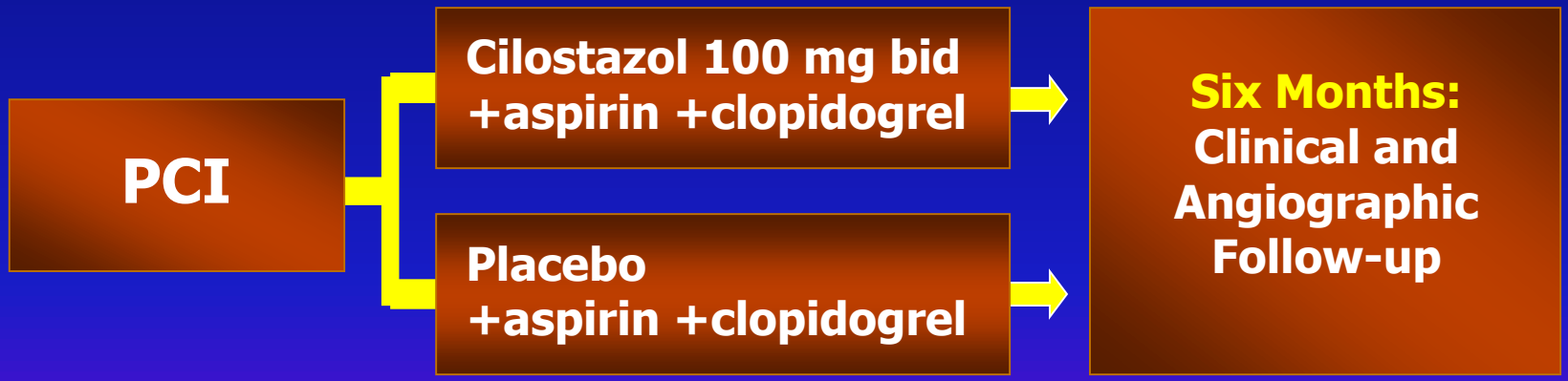
Douglas, John S. Jr. Cilostazol for Restenosis Trial (CREST); Late Breaking Clinical Trials from Plenary Session I and Interventional Cardiology, AHA, November 9,2003

C R E S T

Cilostazol
Restenosis Trial

Design

- Multicenter, randomized double blind clinical trial
- 705 patients at 19 sites

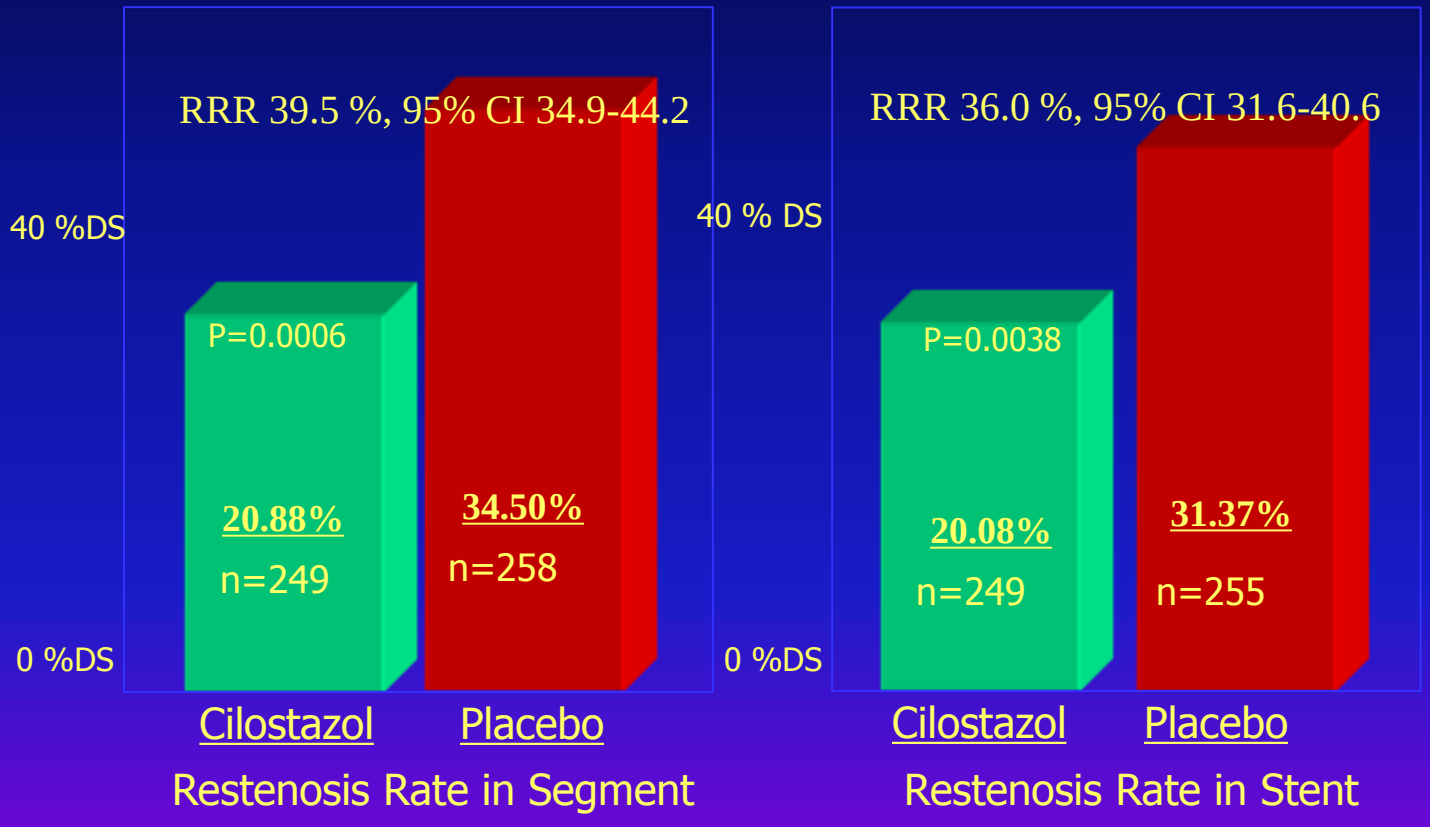


Douglas, John S. Jr. Cilostazol for Restenosis Trial (CREST); Late Breaking Clinical Trials from Plenary Session I and Interventional Cardiology, AHA, November 9,2003

C R E S T

Cilostazol
Restenosis Trial

Restenosis Rate



Douglas, John S. Jr. Cilostazol for Restenosis Trial (CREST); Late Breaking Clinical Trials from Plenary Session I and Interventional Cardiology, AHA, November 9,2003

Circulation 2005

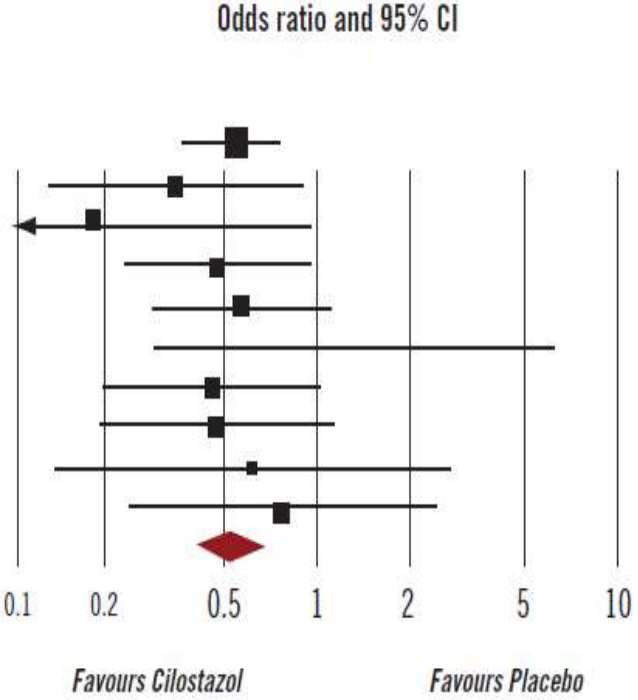
Efficacy of Cilostazol in reducing restenosis in patients undergoing contemporary stent based PCI: a meta-analysis of randomised controlled trials

Umesh Tamhane[1], MD; Pascal Meier[1], MD; Stanley Chetcuti[1], MD, FACC; Kang-Yin Chen[2], MD, PhD; Seung-Woon Rha[3], MD, PhD, FACC, FAHA; Michael P. Grossman[1], MD, FACC; Hitinder Gurm[1]*, MD, FACC

EuroIntervention 2009;5:384-393

Figure 3. The Forest plot of odds ratios of binary angiographic restenosis. Sizes of data markers are proportional to the weight of each study in the meta-analysis. Horizontal bars=95% CI.

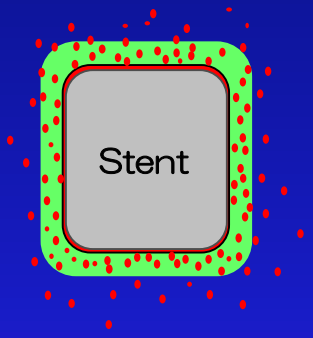
Study name	Stent type	Year	Statistics for each study				Restenosis / Total		Relative weight
			Odds ratio	Lower limit	Upper limit	p-Value	Cilostazol	Control	
CREST	BMS	2005	0.537	0.364	0.791	0.002	57 / 259	92 / 267	39.86
CHEN YD et al	BMS	2006	0.339	0.127	0.904	0.031	7 / 52	17 / 54	6.21
Min PK et al	BMS	2007	0.355	0.095	1.327	0.124	4 / 35	8 / 30	3.44
DECLARE-DIABETES	DES	2008	0.470	0.232	0.951	0.036	13 / 163	26 / 167	12.06
DECLARE–Long	DES	2007	0.565	0.282	1.132	0.107	14 / 210	23 / 205	12.41
Kim DH et al	DES	2008	1.333	0.284	6.260	0.715	4 / 55	3 / 54	2.50
CIDES	DES	2008	0.450	0.196	1.034	0.060	9 / 113	20 / 124	8.64
Lond-DES II	DES	2008	0.463	0.192	1.112	0.085	8 / 168	16 / 164	7.77
Hong SJ et al	DES	2008	0.600	0.133	2.700	0.506	3 / 39	5 / 41	2.65
Jeong JW et al	DES	2008	0.756	0.237	2.405	0.635	7 / 23	11 / 30	4.46
	Combined OR		0.517	0.405	0.660	0.000			



Components of CES-1

◆ シロスタゾール溶出ステント(CES-1)

【CES-1】



	Parts	Material
Stent	Platform	Cobalt Chromium L605（ASTM90）
Coating	Drug	Cilostazol：766μg/cm2 651μg/unit（3.0 x 18 mm）
	Polymer	PDLGA：766μg/cm2
Balloon	RXタイプ	PEBAX

Stent size：3.0 mm×18 mm

CES-1 FIM Design

Objective：Exploratory investigation of CES-1 for the treatment of de novo coronary lesions (Feasibility study)

De novo native coronary artery lesion
Reference diameter：2.75mm～3.25mm　lesion length＜15mm
Stent size：3.0mmx18mm　DAPT 6 months
Open label single arm registry

30 patients in 6 sites

Clinical Follow up

procedure　30day　6M　9M　1y　2y　3y　4y　5y

PK study

QCA/ OCT/OFDI

Primary Endpoint:　In-segment late loss at 9 months

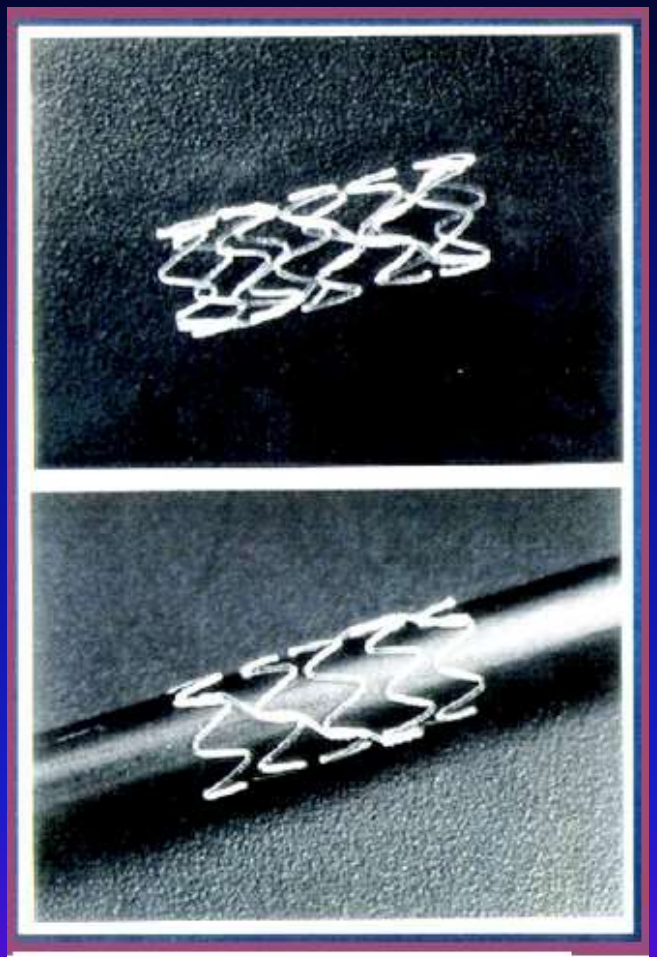
Secondary Endpoint：TLF, TVF, stent thrombosis, POCE

%DS (in-stent/in-segment)　& Binary restenosis rates (in-stent/in-segment)

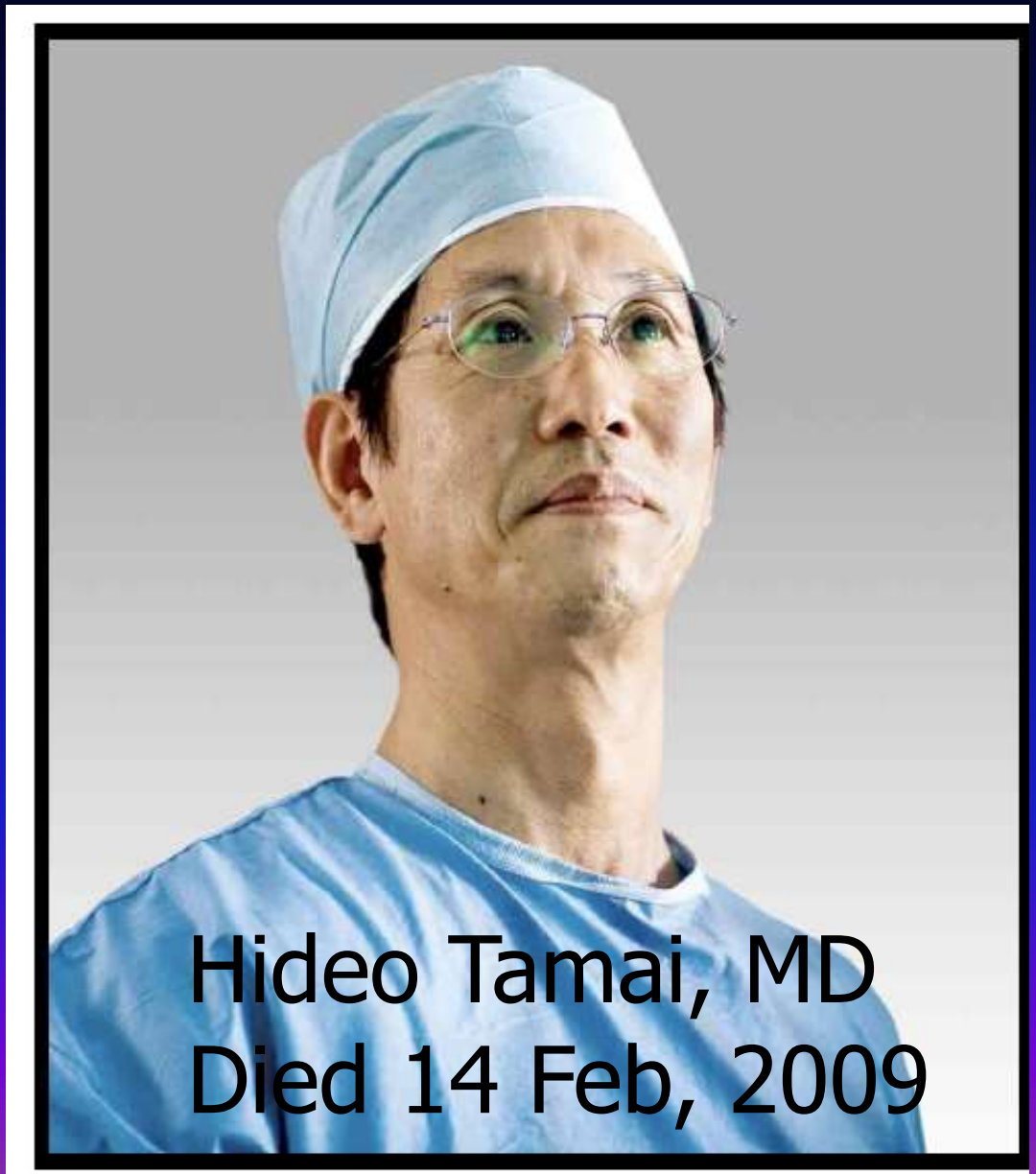
Neointimal volume, %Volume obstruction

ISA%、%Strut coverage

Igaki-Tamai Stent (2000)



Tamai et al, CCI 2001



Summary

- Although technologies of drug-eluting stents has matured, there still remain unresolved issues.
- For the innovation and further improvement of PCI, there is a chance to utilize Japanese original materials and technologies.