Nobori
Clinical Studies Up-dates

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Drug Eluting Stents

- **High benefit in preventing restenosis and improving quality of life**
- **The benefits outweigh potential risks**
- **All DES are not the same**
  - There are differences in:
    - platforms,
    - polymers,
    - drugs,
    - elution profiles

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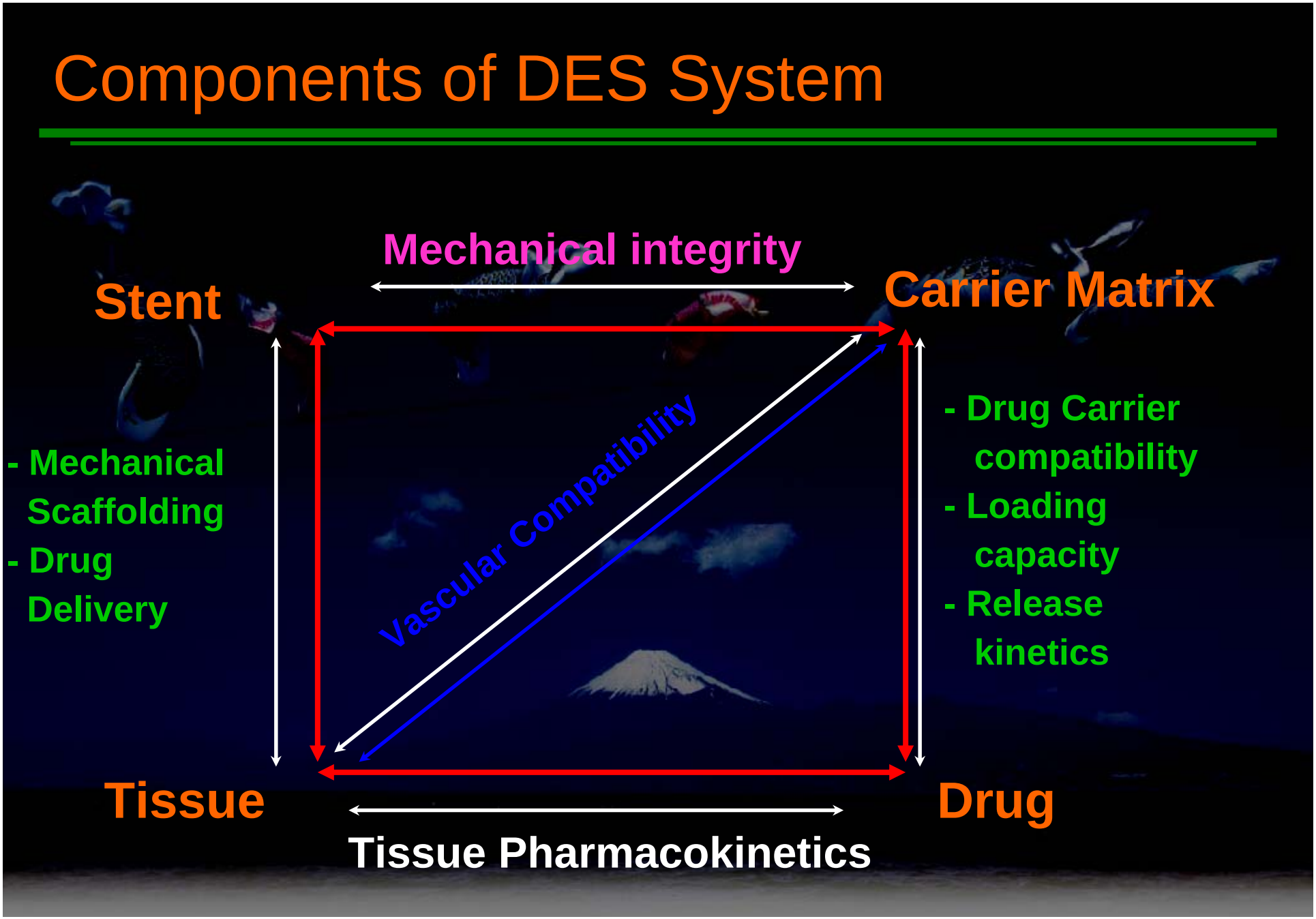
Components of DES System



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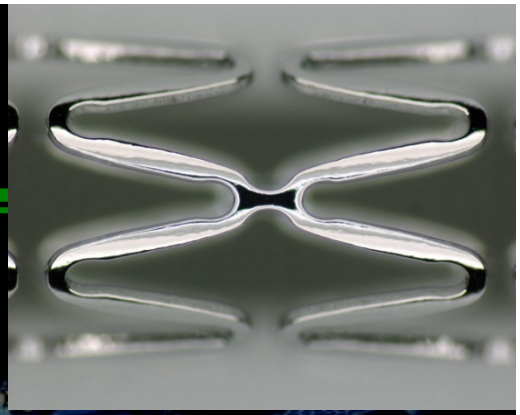
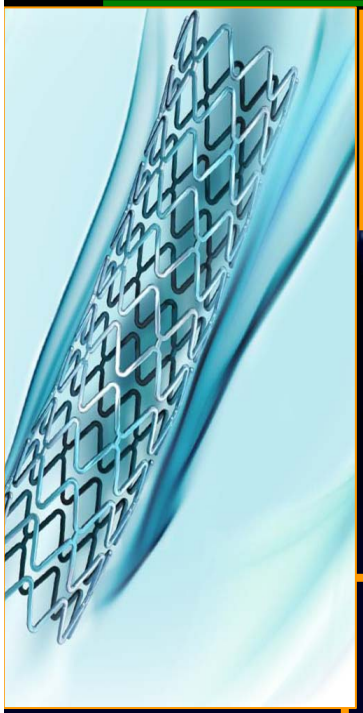
Nobori – The New Generation DES

Nobori DES components





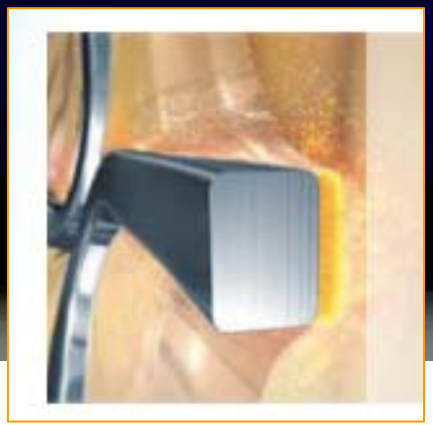
Highly Flexible BMS Platform
Easy Side Branch Access
Optimal Vessel Scaffolding
Uniform Drug Distribution

Polymer - PLA
Biodegradable

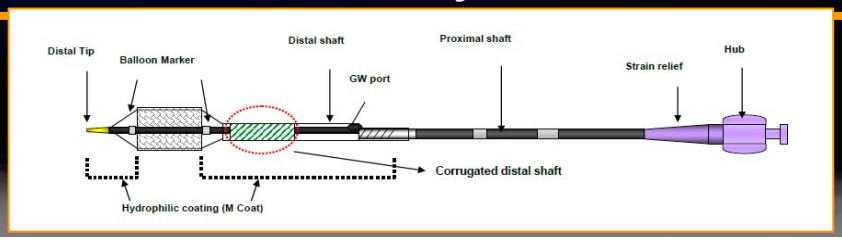
Nobori
DES

Drug – Biolimus A9
Highly Lipophilic
Antiproliferative
Low systemic level
Optimal release kinetics

Coating
Only abluminal for optimal endothelialization



Delivery Catheter
With Proprietary Hydrophilic Coating – for enhanced deliverability



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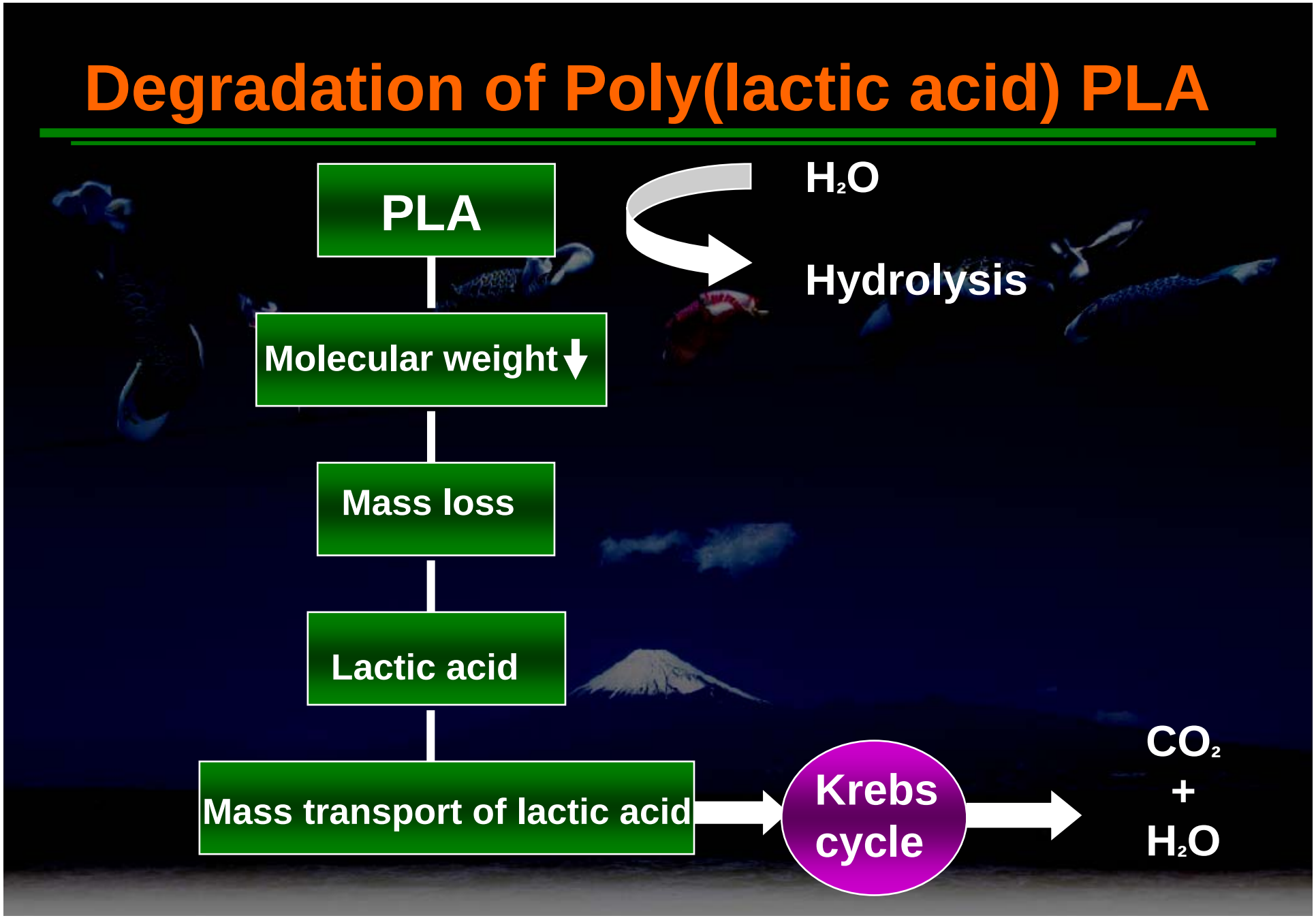
Degradation of Poly(lactic acid) PLA



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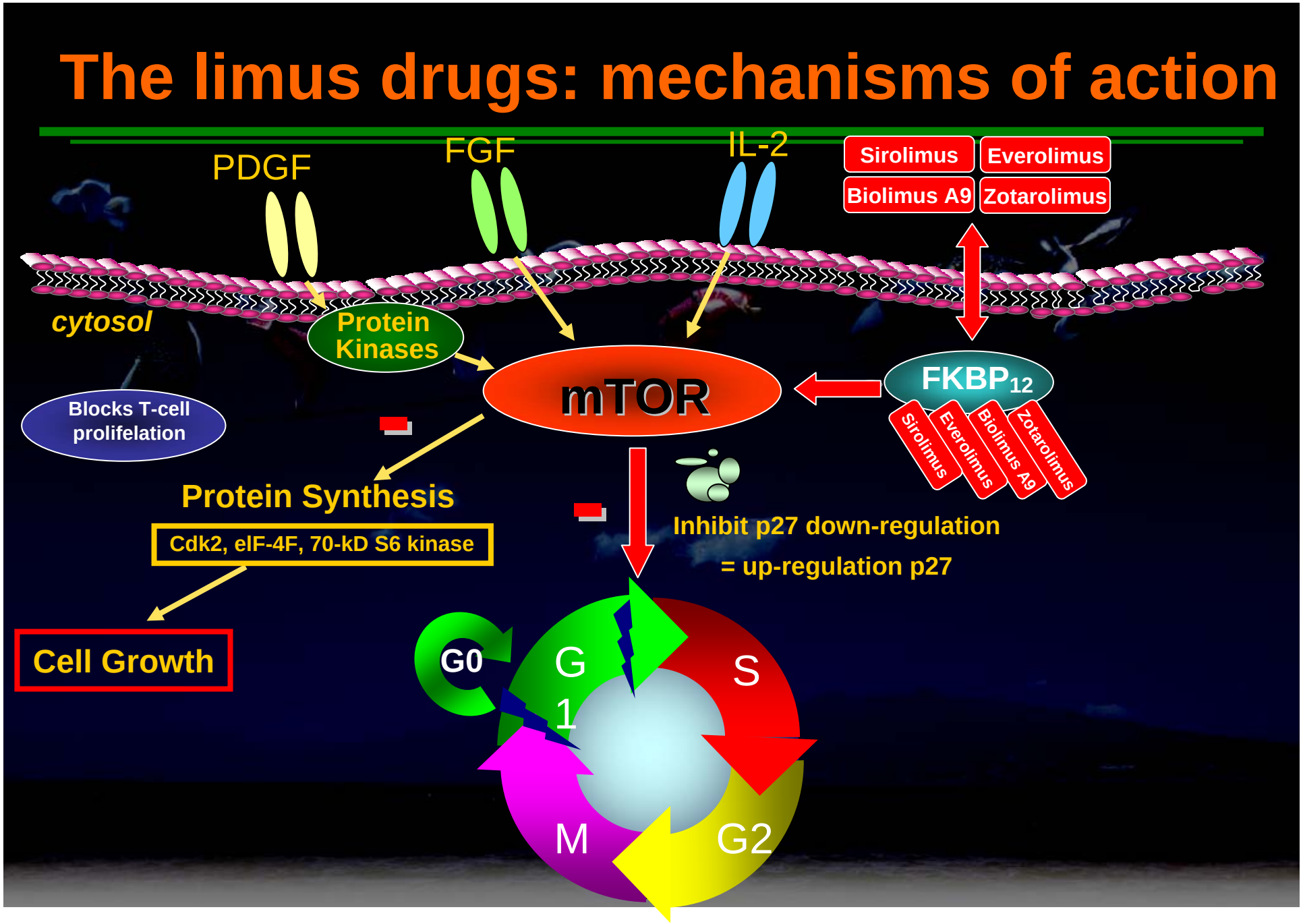
J.C. Middleton et al. Biomaterials 2000

The limus drugs: mechanisms of action



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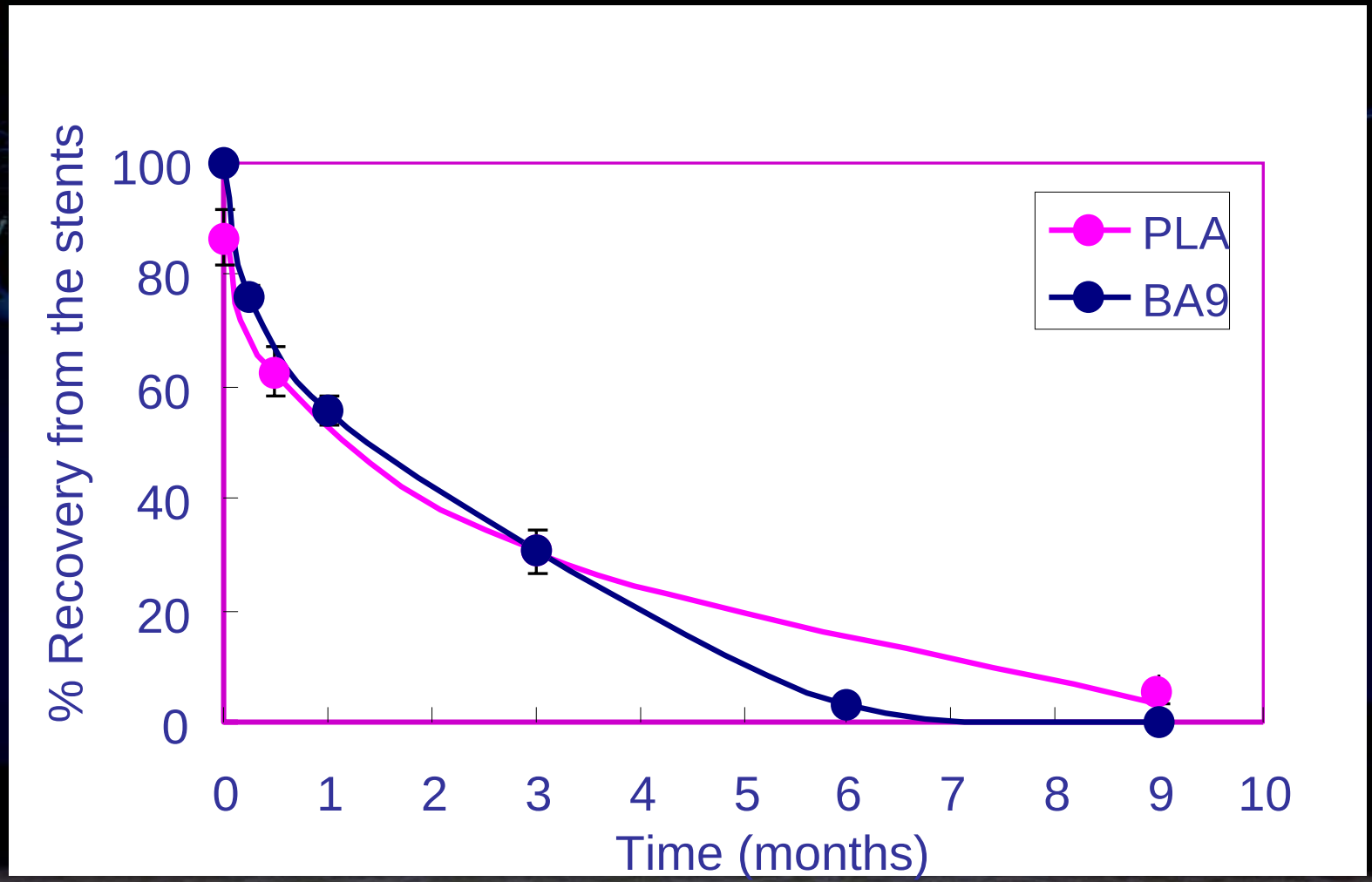
Nobori DES Drug Release vs Polymer Degradation



Design Hypothesis

- **Biodegradable polymer**
  - Controlled Drug release kinetics
  - Long term safety
- **Abluminal coating**
  - Optimal drug uptake – minimal systemic concentration
  - Enhanced endothelialization
- **Drug from limus family**
  - High efficacy

Design Supported by Extensive Clinical Programs

In all Nobori trials treatment of more than one vessel was allowed

NOBORI PK – 20 Patients	→	Confirmation of pharmacokinetics Nobori DES
NOBORI 1 – 363 patients	→	Nobori DES Randomized versus Taxus (surrogate endpoint-LL)
NOBORI CORE – 107 patients	→	Nobori DES similarity versus Cypher (surrogate endpoint-LL)
NOBORI CORE endothelial study 43 patients	→	Comparison endothelial function at 9 months Nobori vs Cypher
NOBORI Japan – 340 patients	→	Nobori DES Randomized versus Cypher (clinical endpoint-TVF)
NOBORI 2 – 3000 patients	→	Real life registry
COMPARE II 2700 patients	→	Randomized vs Xience V in all Comers population
COMPARE II STEMI 700 patients	→	Randomized vs Xience V in Patients with STEMI
SECURITY 4000 patients	→	Randomized 6 vs 12 m DAT New generation DES
BASKET PROVE 2300 patients	→	Randomized 3 arms study BMS vs Xience V vs Nobori

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NOBORI Pharmacokinetics Study

BA9 Blood Collection Time Points

Trial	Sample Size (n)	TIME POINTS													
		Pre-Procedure	Mins / Hours / Days / Months												
			2	15	30	1	2	3	8	24	48	72	7	28	3	6
Nobori PK Study	20	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓

Biochemistry/Haematology Blood Collection Time Points

* t=0 defined as deployment balloon inflation/ stent implantation

Pharmacokinetics

Maximum blood concentration of Biolimus A9 is 52 times LOWER than Sirolimus and 87 times lower than Everolimus

Systemic concentration of drugs (ng/mL) eluted from different DES

	Biolimus[1] A9	Sirolimus[2]	Everolimus[3]
Mean	0,020	0,80	NR
SD	0,007	0,37	NR
Minimum*	0,010	0,43	0,14
Maximum	0,032	1,66	2.79
n	20	19	37

NR= Not reported

1= Ostojic et al. CCI 2008
2=Vetrovec et al. CCI 2006
3=Wiemer et al. AHJ 2008

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NOBORI 1

2:1 randomization
Single blind - two vessel – staging allowed

De novo native coronary lesion
Vessel diameter: 2.5-3.5 mm
Lesion length: <25 mm
Predilatation required

Nobori stent
n = 85 phase 1
153 phase 2

PI: Dr B. Chevalier
N = 363 patients
29 sites
Europe, Asia, Australia

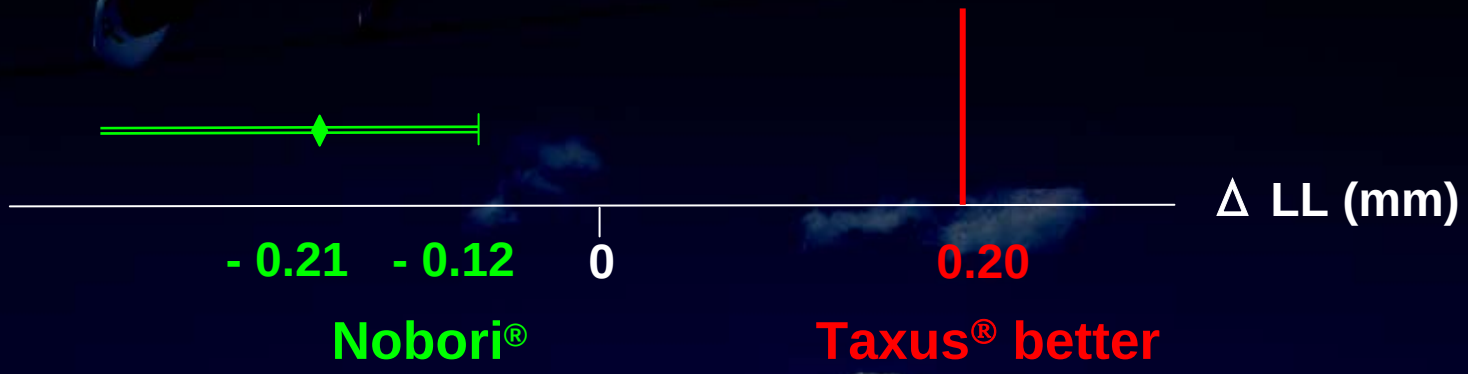
Control Taxus stent
n = 35 Express Ph 1
90 Liberte Ph 2

Primary endpoint: In-stent late lumen loss by QCA at 9 months
Secondary endpoints: MACE (Death, MI, TVR) TLR, TVF at 9 months and ABR at 9 months, Procedure, Lesion success, In-segment late loss
Drug therapy: ASA and clopidogrel 6 months


Nobori DES Efficacy

Primary Endpoint Result

- Assumed in-stent Late Loss (LL)
  - ✓ 0.39 mm for Taxus® / 0.34 mm Nobori
  - ✓ Assumed SD: 0.50 mm
- Delta non-inferiority margin: 0.20mm



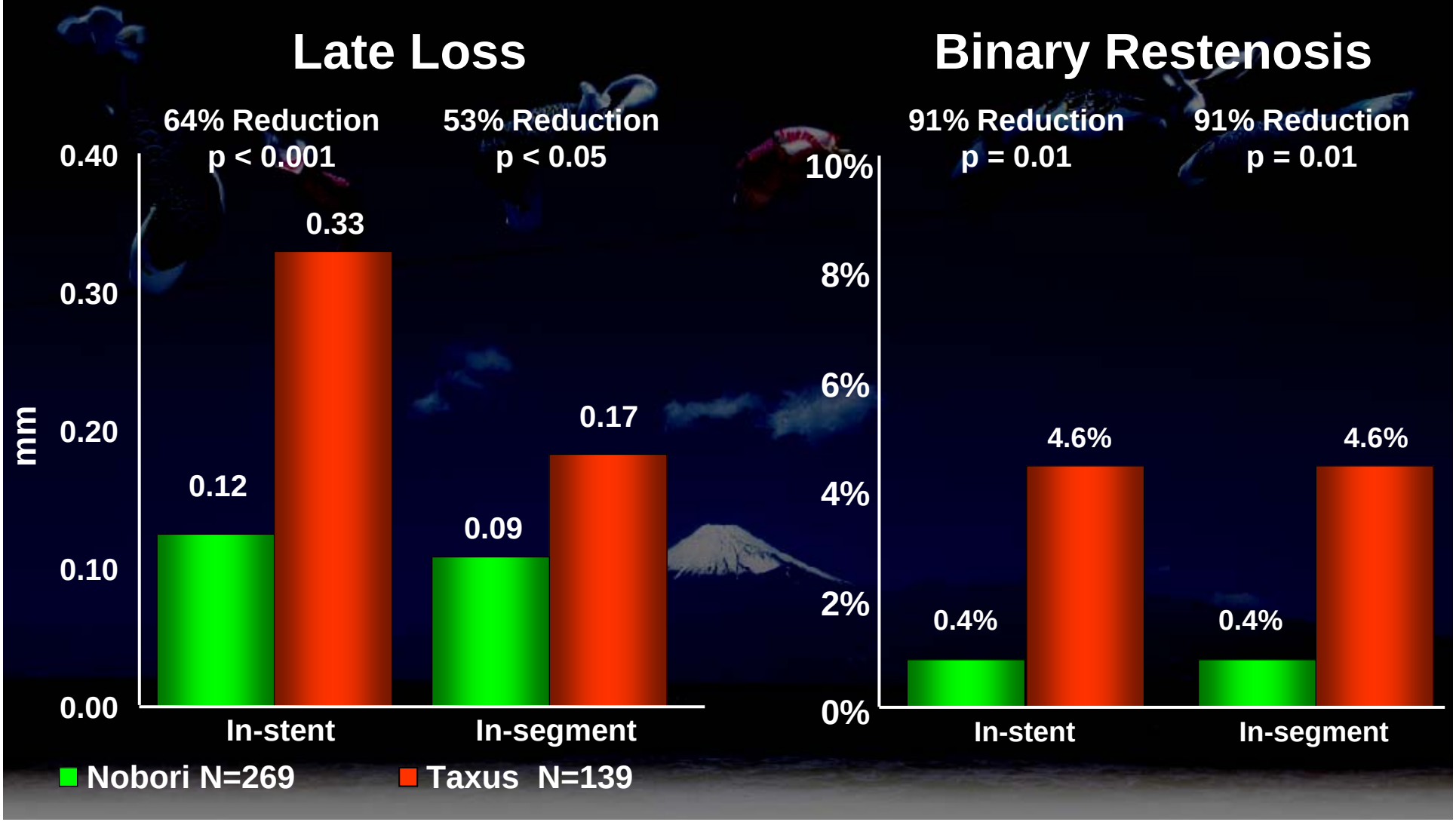
Late Loss result

- ✓ 0.33 ± 0.51 mm Taxus®
- ✓ 0.11 ± 0.30 mm Nobori

Result:
Nobori = NON-INFERIOR p<0.001
Nobori = SUPERIOR* p=0.001

*The SUPERIORITY was a secondary objective

Key Angiographic Results



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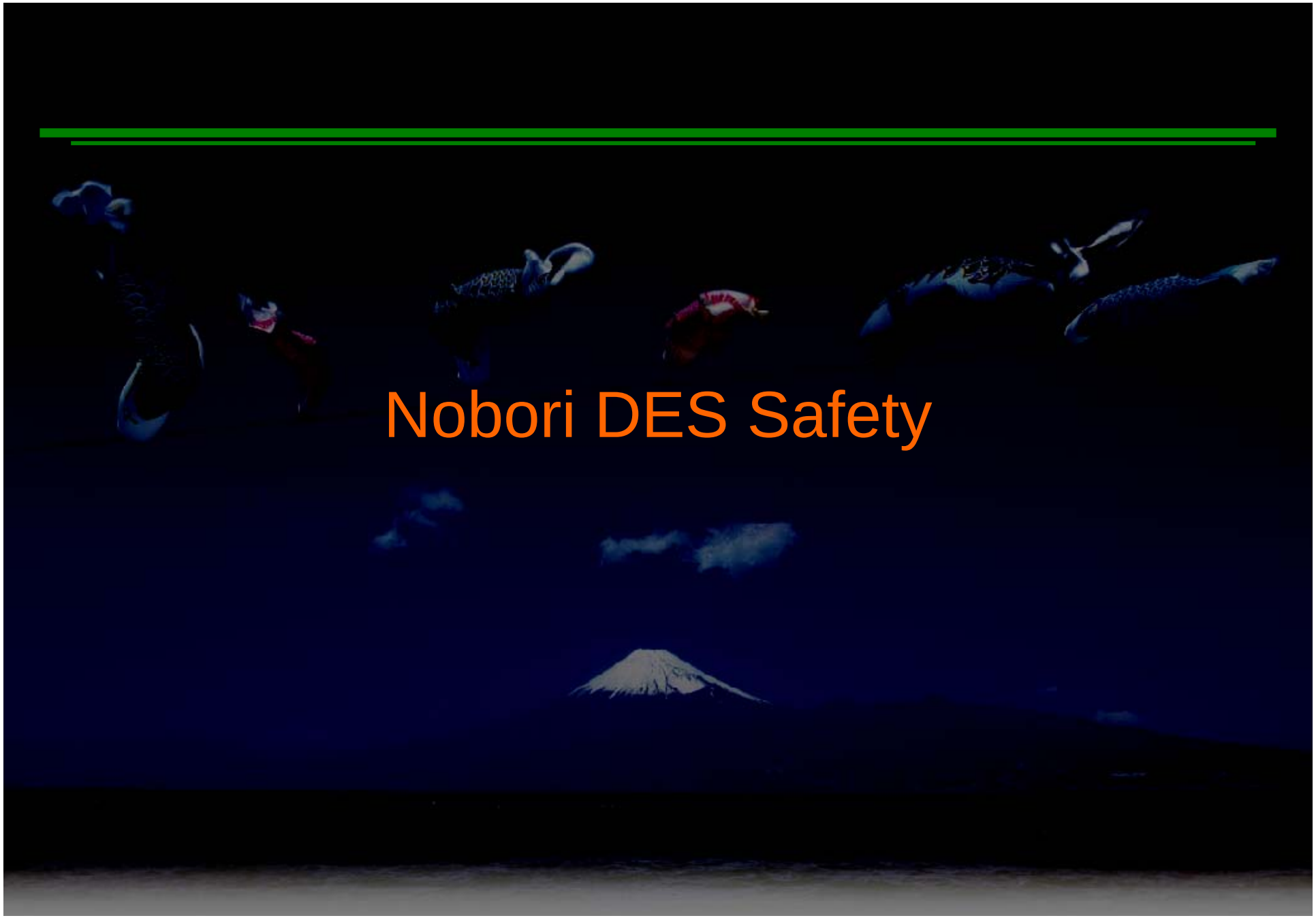
Intravascular Ultrasound Results

IVUS	Nobori N =101	Taxus N =53	P value
Volume obstruction (%)	**1.93±5.54**	**6.76±8.04**	**<0.001**
Neointimal hyperplasia (mm3)	**3.11±8.84**	**13.50±20.4**	**0.003**
Mean plaque area (mm2)	**0.15±0.48**	**0.52±0.64**	**<0.001**


Nobori DES Safety

Stent Thrombosis up to 2 years in NOBORI 1

Stent thrombosis Per Protocol

	Nobori Stent N=238	Taxus Stent N=125
Acute	0.0	2.4
Subacute	0.0	1.6
Late	0.0	0.8
Total up to 1 year	0.0	3.2
Total up to 2 years**	0.0	4.0

Definite and Probable Stent Thrombosis According to ARC*

	Nobori Stent N=238	Taxus Stent N=125
Early	0.0	1.6
Late	0.0	0.0
Very Late	0.0	0.8
Definite and probable	0.0	2.4
Total up to 2 years	0.0	2.4

Dual Antiplatelet **Two Years**

Nobori = 25%

Taxus = 23%

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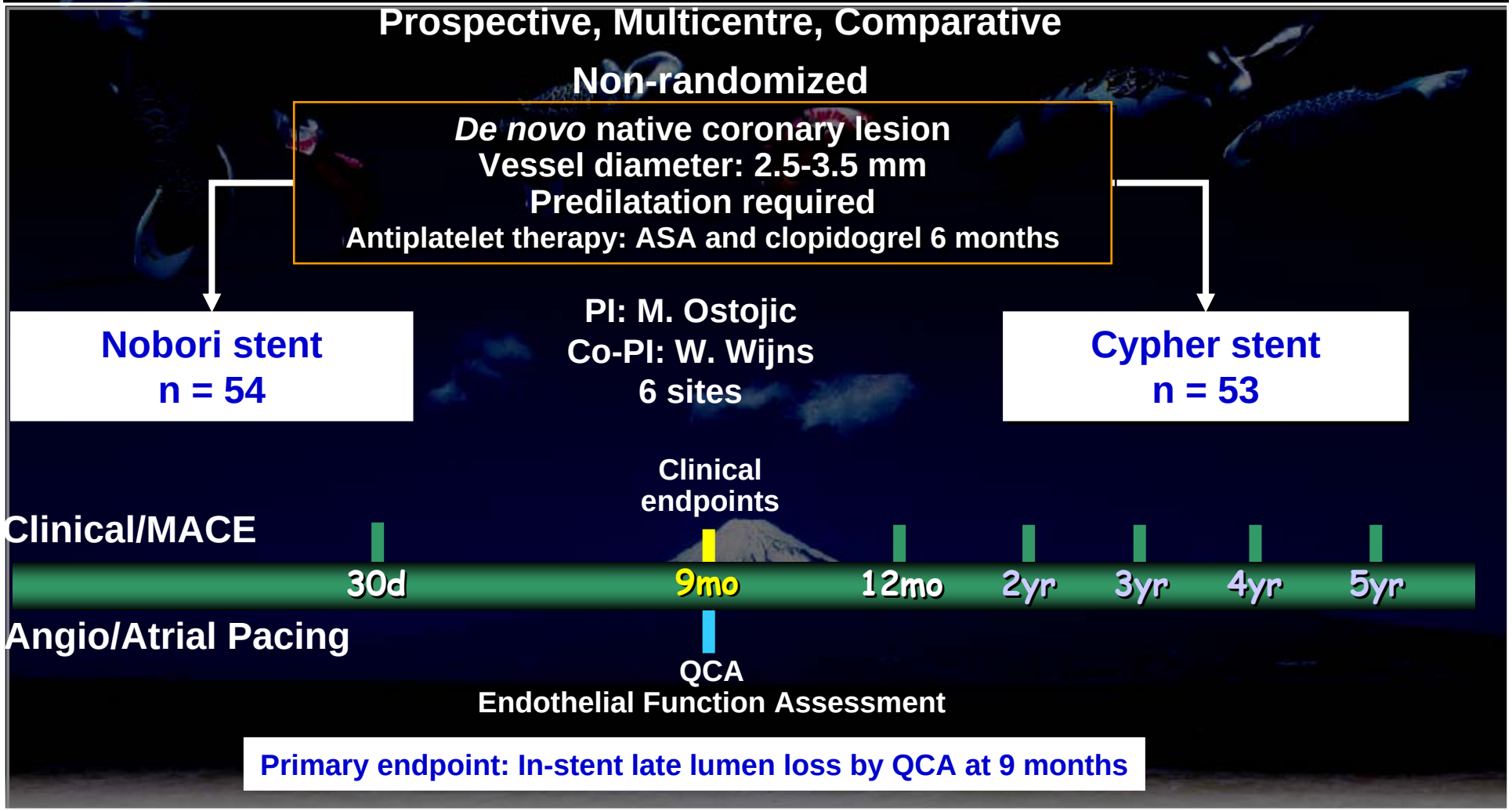
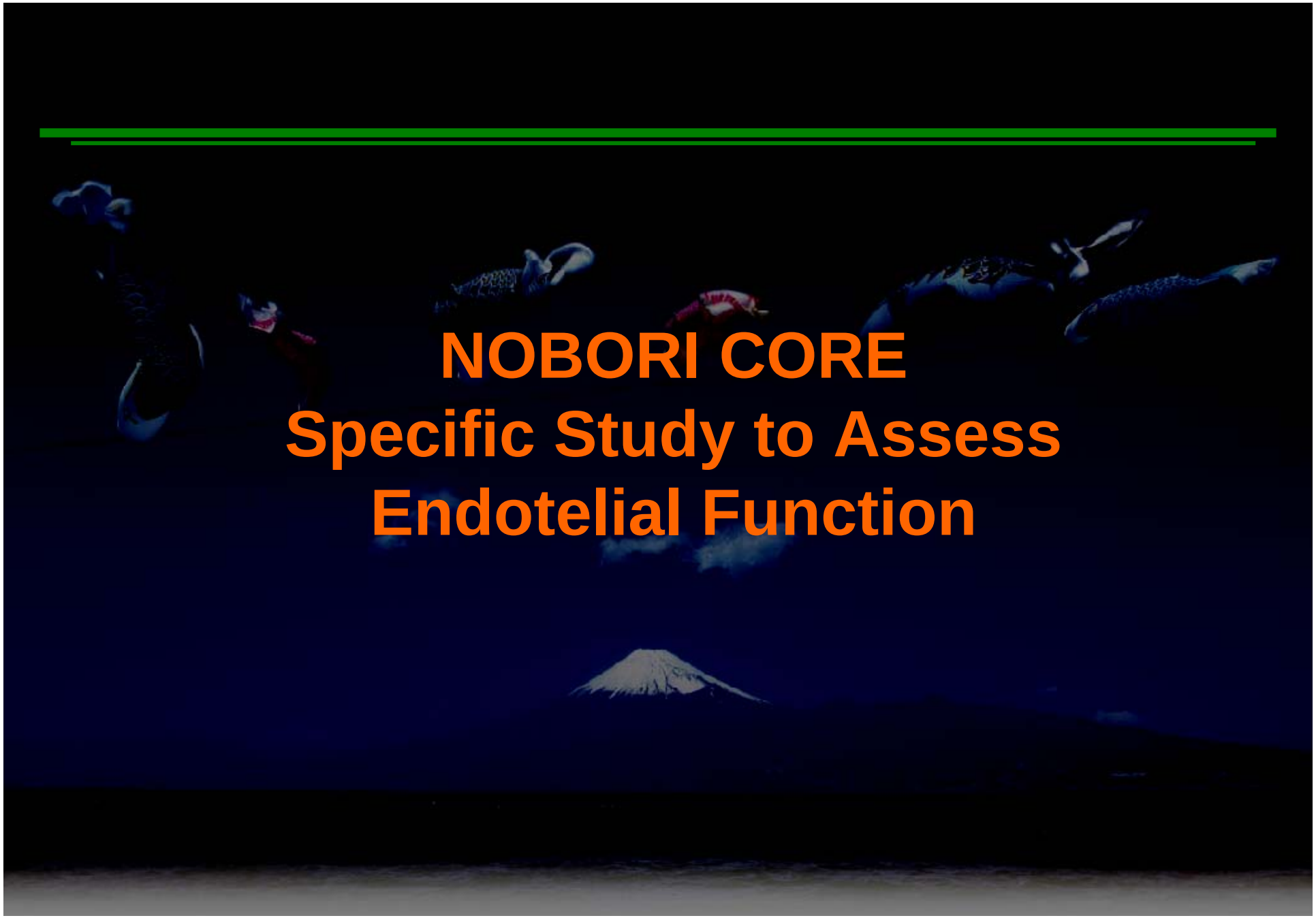
NOBORI CORE Study Design



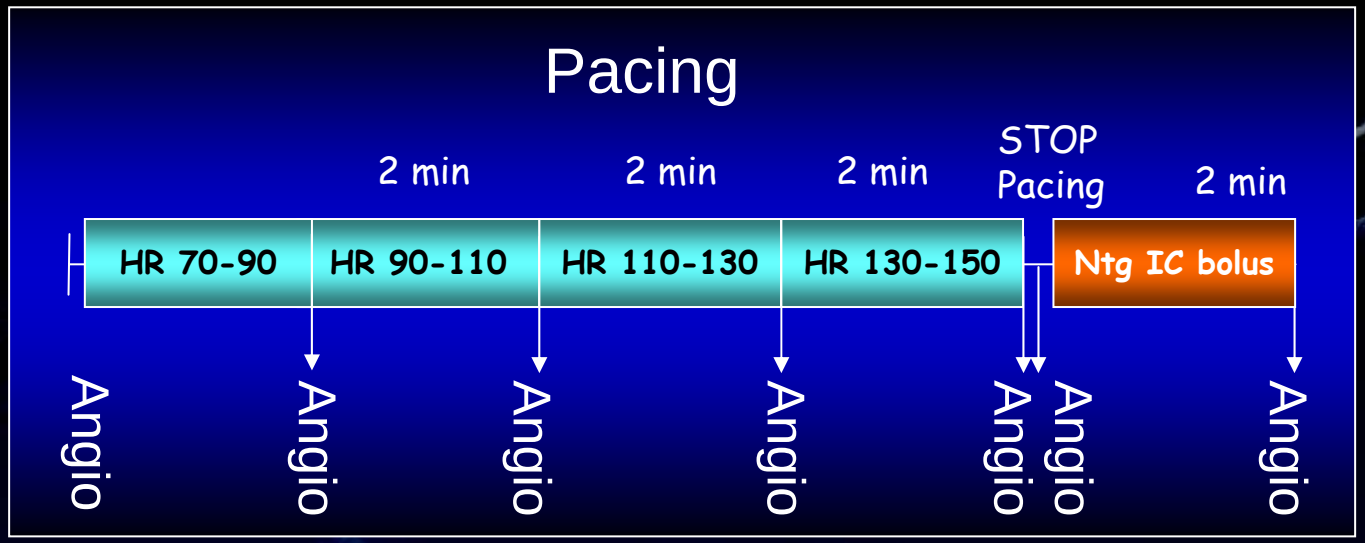
Secondary endpoints: Endothelial functionality, MACE (Death, MI, TVR) TLR, TVF at 9 months and restenosis at 9 months, Procedure, Lesion success

QCA Findings at 9 Months

	Nobori 72 Lesions	Cypher 74 Lesions	P Value
RVD (mm)	3.00 ± 0.36	2.84 ± 0.40	0.09
MLD – stent (mm)	2.59 ± 0.42	2.28 ± 0.49	<0.001
MLD – lesion (mm)	2.27 ± 0.48	2.13 ± 0.48	0.15
DS (%)	13 ± 10	20 ± 12	0.001
Late loss – stent (mm)	0.10 ± 0.26	0.12 ± 0.43	0.70
Late loss – lesion (mm)	0.12 ± 0.35	0.18 ± 0.40	0.43
Binary Restenosis %	1.7 (1/60)	4.2 (2/48)	0.18


NOBORI CORE
Specific Study to Assess
Endotelial Function

Protocol of atrial pacing for Endothelial Function Assessment



METHODS

1. Baseline conditions were established and angiography performed
2. Rapid Atrial pacing with 20 bpm higher than baseline for 2 min
3. Angiographic images acquisition followed by 2 minutes rest
4. Repeat procedure with increasing pacing rate by 20 bpm up to 150
5. Intra-arterial nitroglycerin injection
6. Angiographic image acquisition
7. Off line QCA analysis of proximal, in-stent, distal segments and reference vessel

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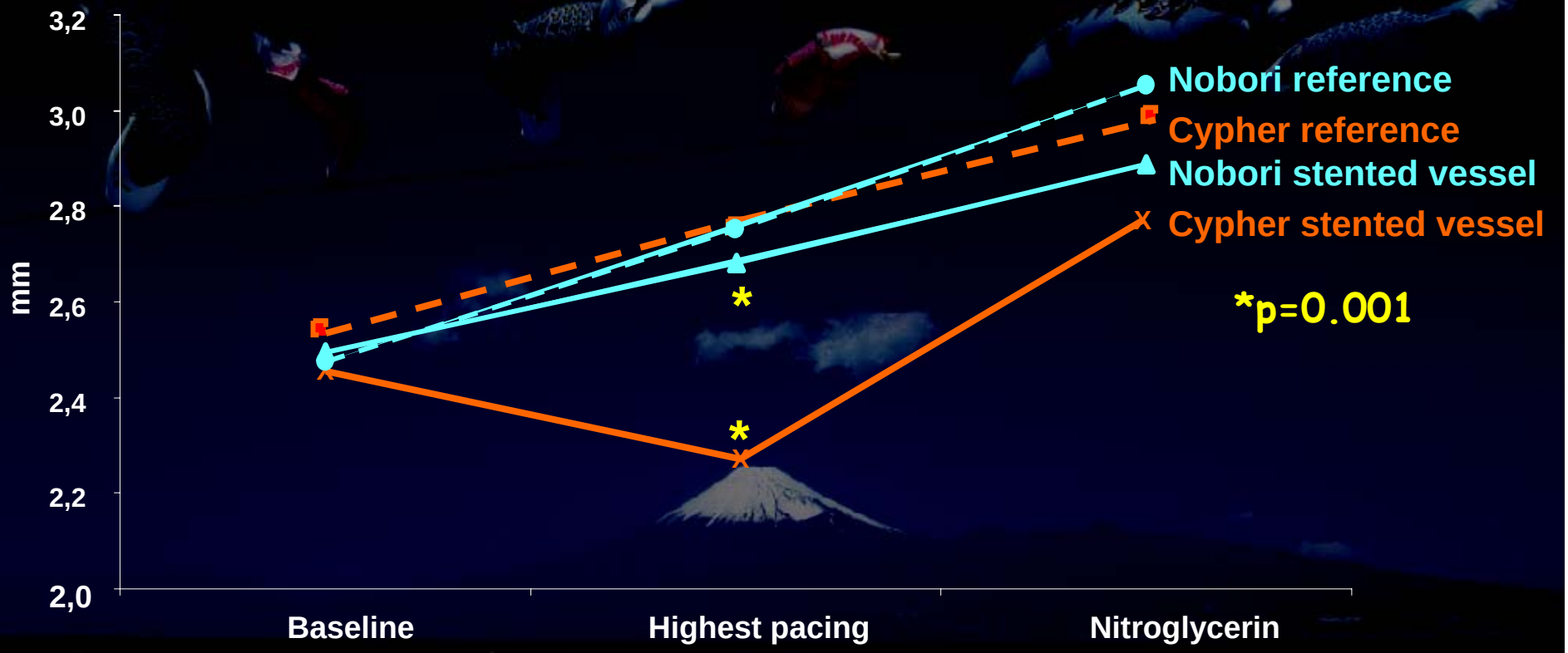
Preserved endothelial function after NOBORI DES implantation

Change in mean diameter in distal segments



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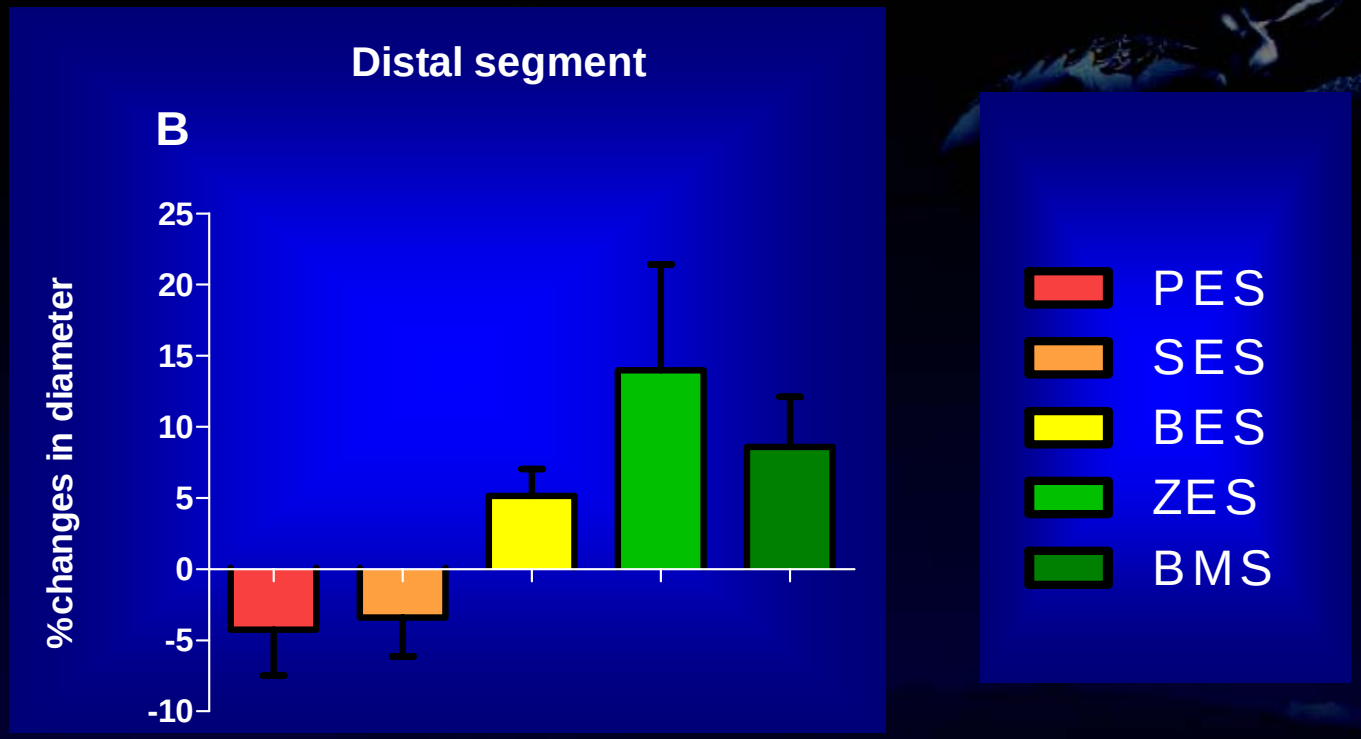
Different endothelium dependent vasomotion with different stents



- Paradoxycal vasoconstriction with first generation DES
- Normal vasodilatation with second generation DES and BMS

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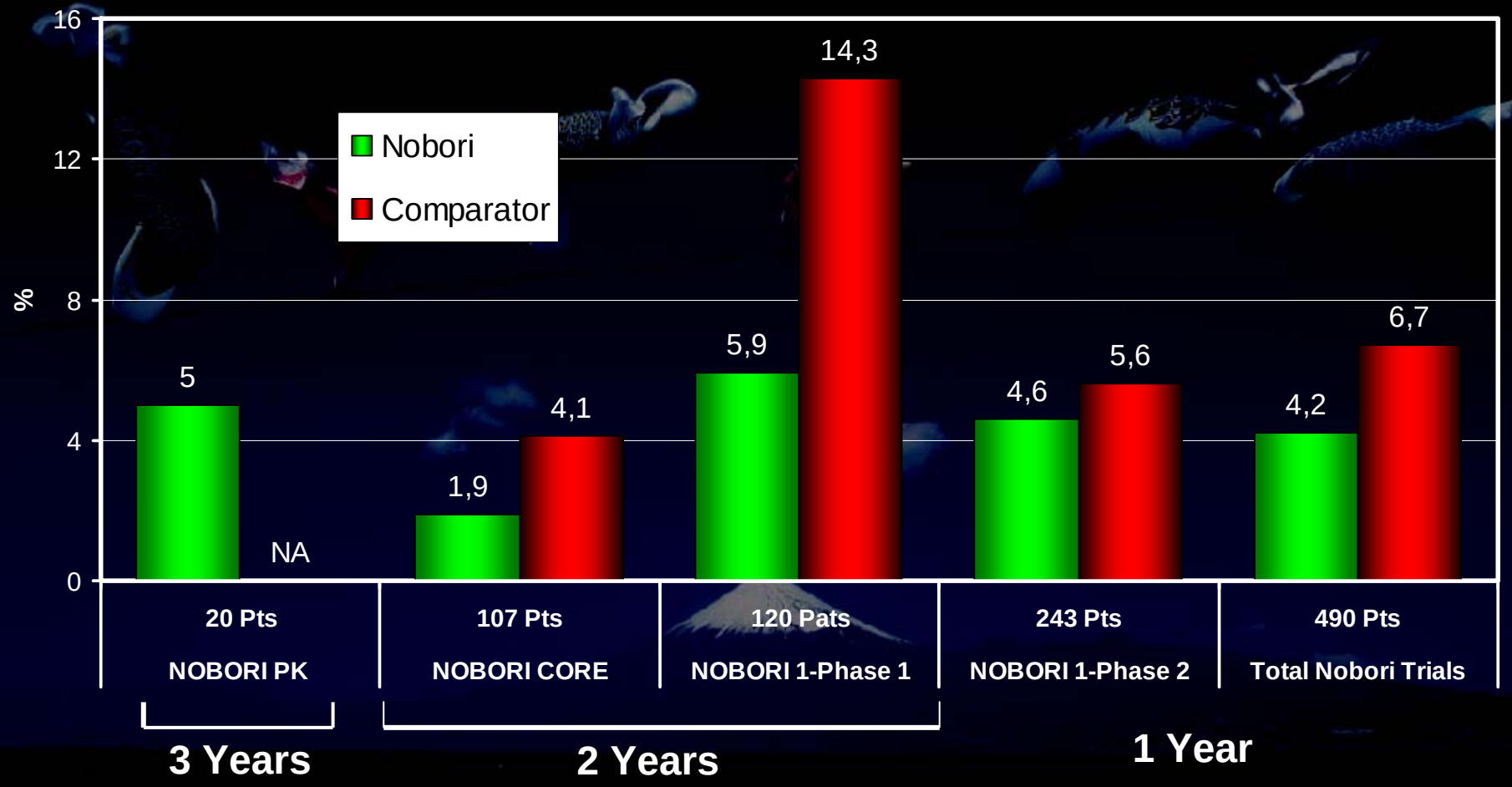
Hamilos et al, Circulation CI 2008

Possible Explanations

- **Possible explanations for different impact on endothelial function could be :**
  - Different Healing process and Endothelialization after stent implantation
  - Different Polymer
    - Permanent versus Biodegradable
  - Different Coating Method
    - Circumpherential versus Asymetric and Abluminal
  - Different Drug
    - Mechanism of action, dose, release kinetics
- **Clinical relevance of those findings is still undetermined and requires further, specifically designed studies**

NOBORI CLINICAL TRIALS
Summary

MACE Rate in NOBORI Trials – Sustained Low MACE Rate Over Time



MACE = Cardiac Death, Myocardial Infarction, Clinically Driven TLR

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Key Angiographic Findings in all NOBORI Trials

	NOBORI 1 Phase 1 N=120		NOBORI CORE N=107		NOBORI Phase 2 N=243	
	Nobori	Taxus	Nobori	Cypher	Nobori	Taxus
Follow-up	9 months		9 months		9 months	
Late loss mm	0.15±0.27	0.33±0.34	0.10±0.26	0.12±0.43	0.11±0.30	0.32±0.50
Diameter stenosis	14±8	19±10	13±10	20±12	14±8	21±15
Restenosis - stent	0.0%	0.0%	1.7%	6.3%	0.7%	6.2%
Restenosis - lesion	0.0%	0.0%	3.3%	6.3%	0.7%	6.2%
TLR	0.0%	2.9	0.0%	4.1%	0.0%	1.1%

TLR = Clinically driven target lesion revascularization

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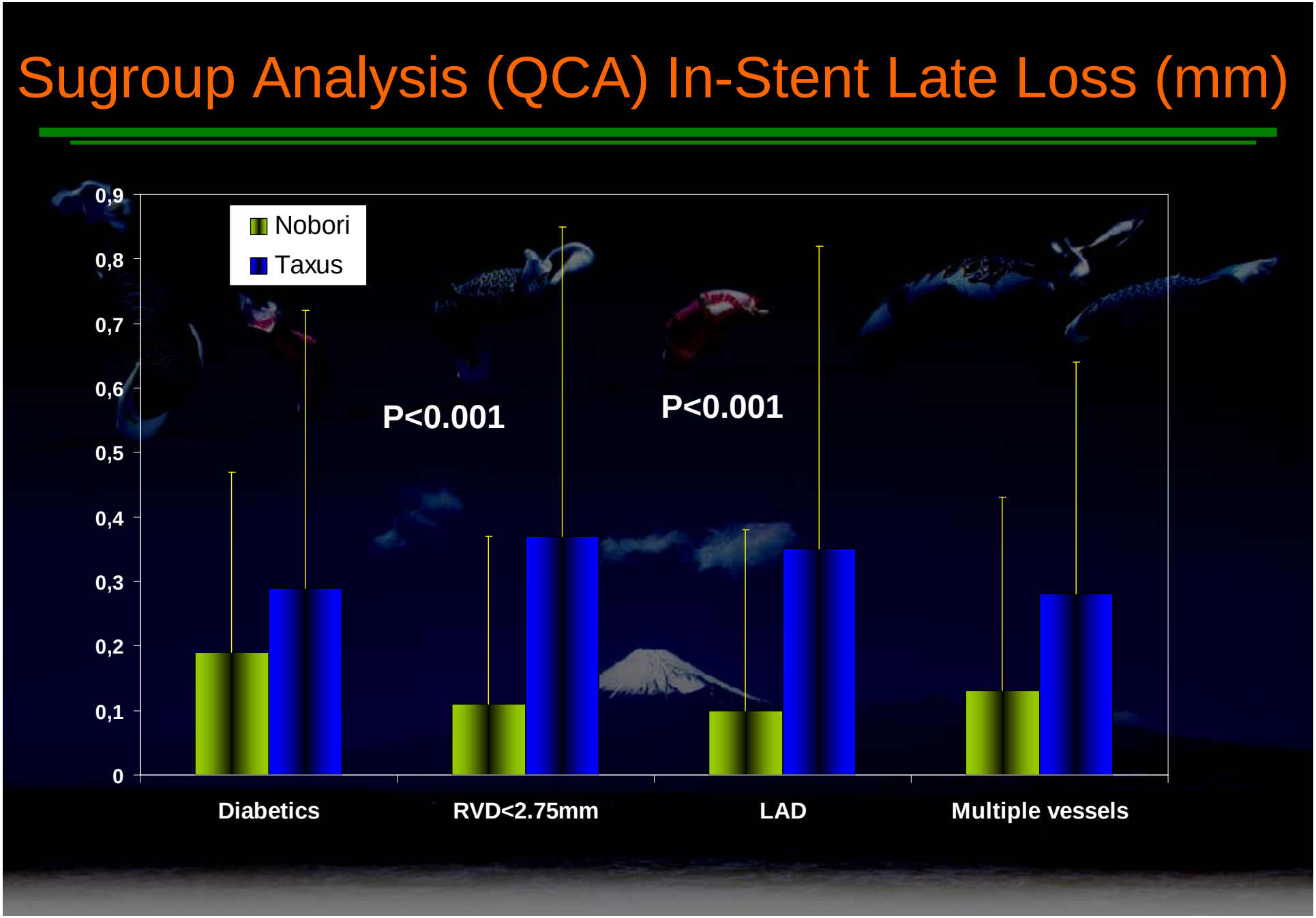
Sugroup Analysis (QCA) In-Stent Late Loss (mm)



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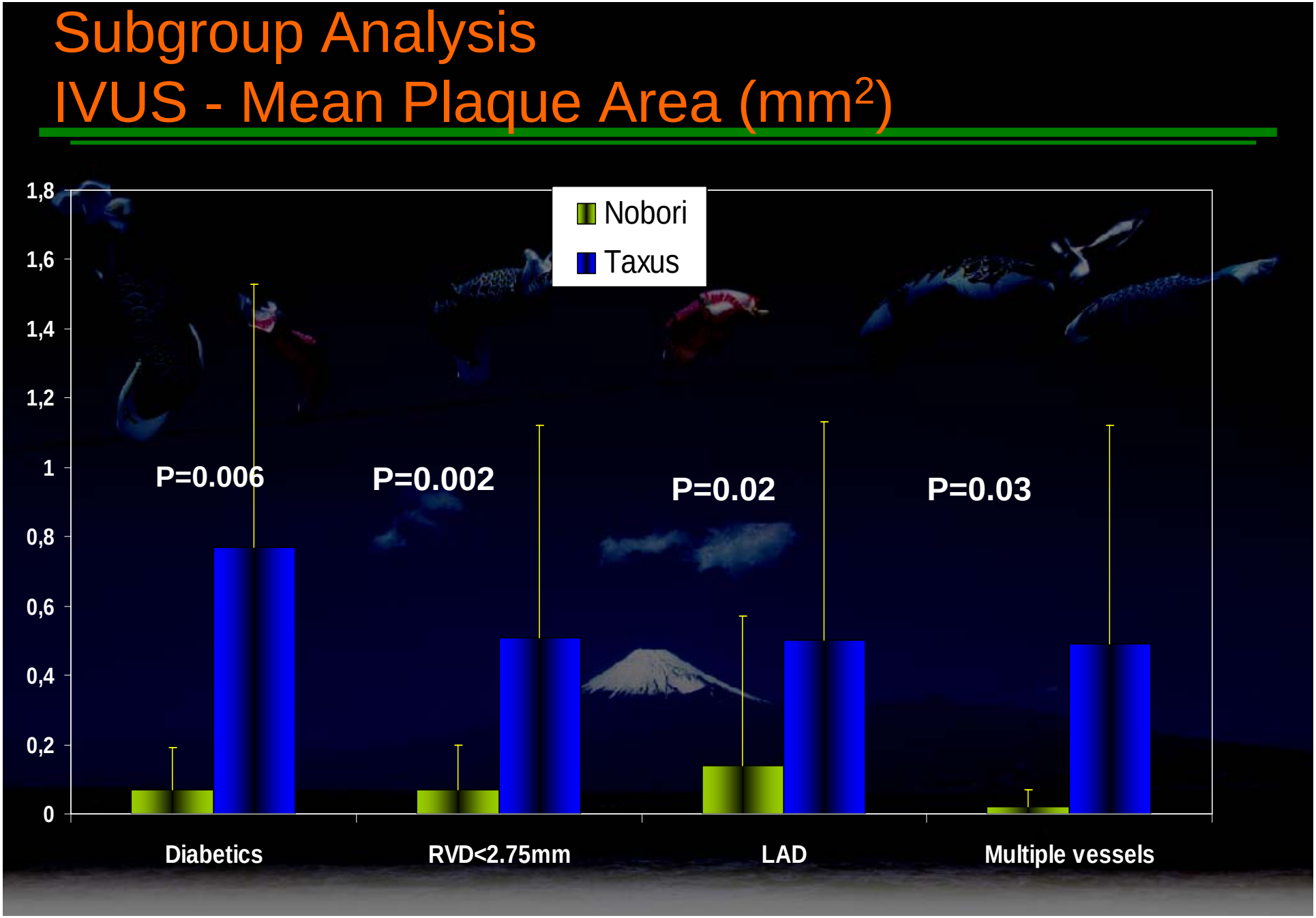
Subgroup Analysis
IVUS - Mean Plaque Area (mm^2)



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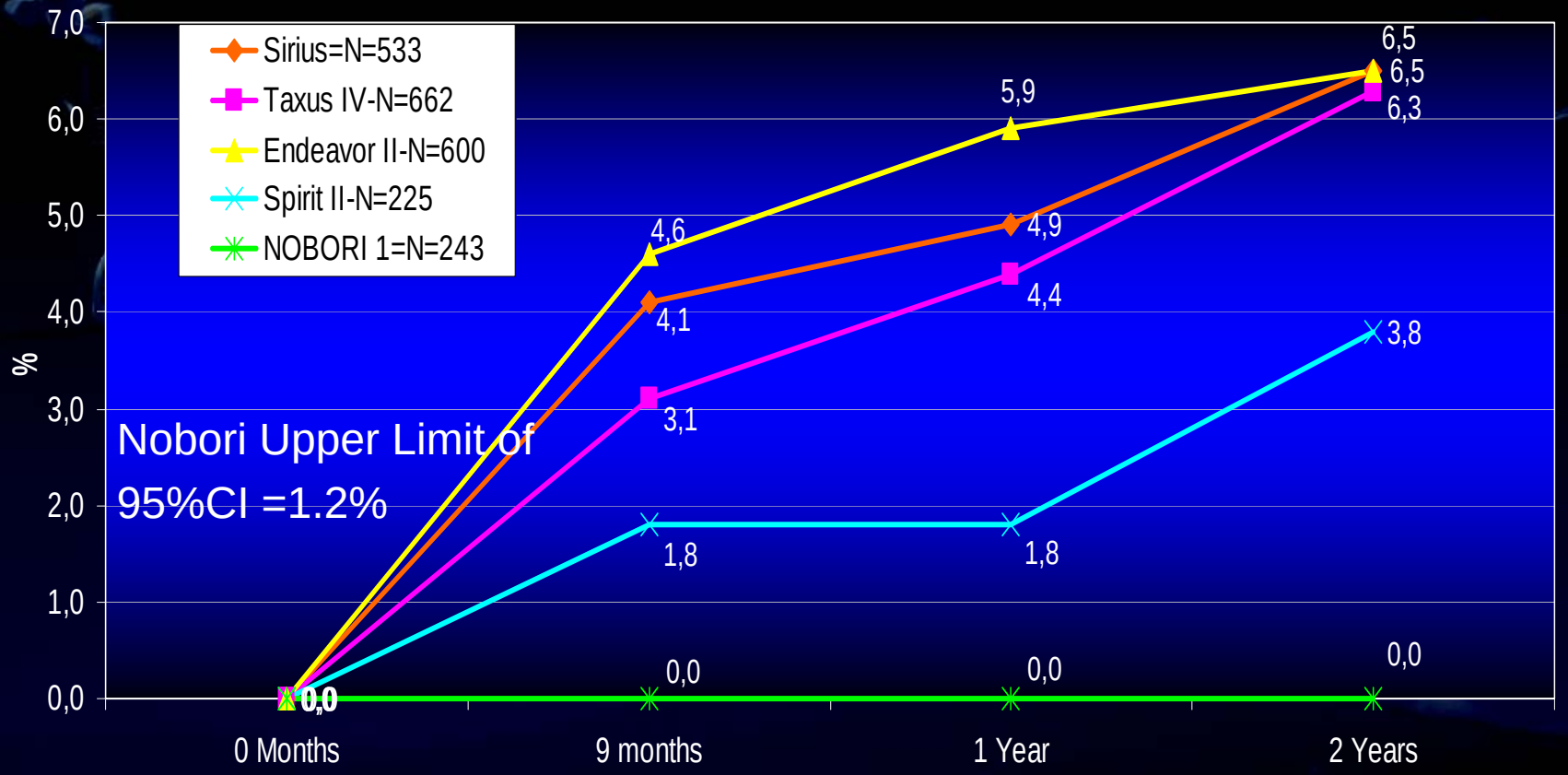
Hamilos et al JACC 2008
Hamilos et al Circulation CI 2008

DES Efficacy
Clinically Driven TLR Rate in DES Pivotal Trials



*Nobori 2 years N=85

Holmes et al Circulation 2004; Stone et al Circulation 2004; Leon – ACC 2004; Stone, TCT 2004; Fajadet, Circulation 2006; Fajadet PCR-2006; Chevalier et al; Eurointervention 2007; PCR 2008

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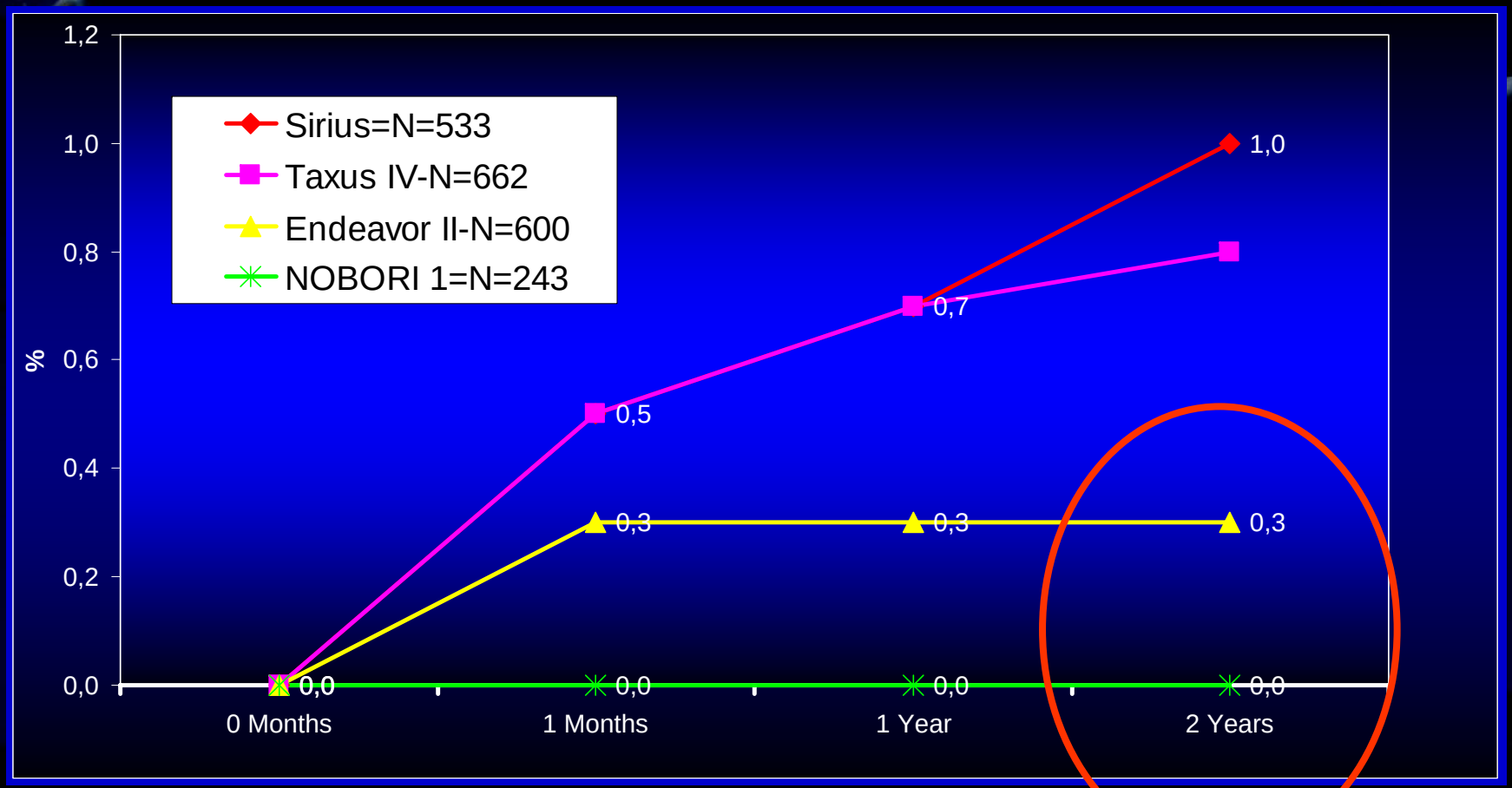
DES Safety
Stent Thrombosis in Pivotal Trials



Holmes et al Circulation 2004; Stone et al Circulation 2004; Leon – ACC 2004; Stone, TCT 2004; Fajadet, Circulation 2006; Fajadet PCR-2006; Chevalier et al; Eurointervention 2007; PCR 2008

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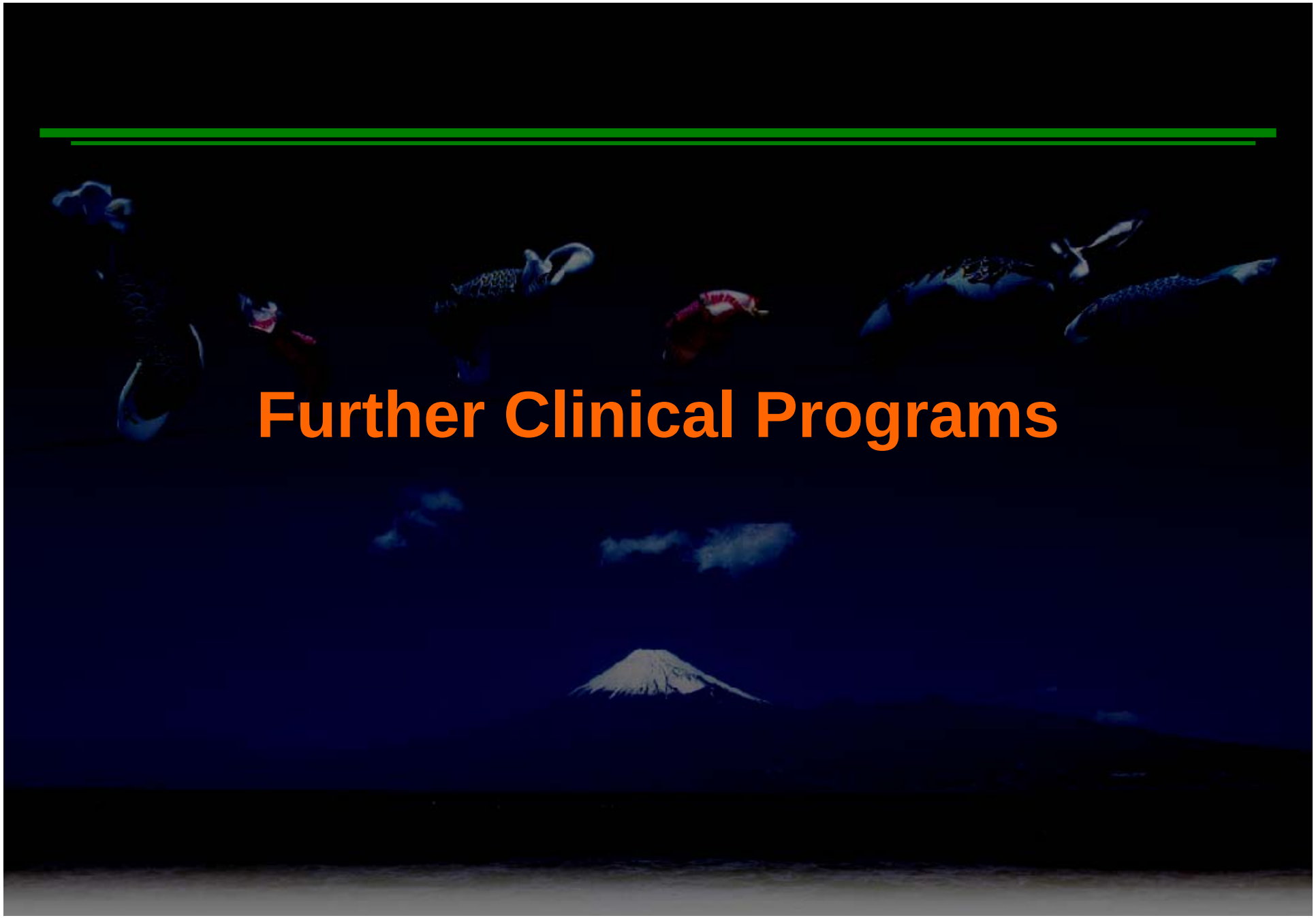
Further Clinical Programs

NOBORI 2 Study Design

Patients with Coronary Artery Disease
Vessel Diameters: ≥2. 5 - ≤3.5 mm
All consecutive patients treated with DES
3000 patients (150 centers Europe, Asia, Africa)

Group 1 Patients falling within inclusion criteria of pivotal DES trials	**Group 2** Patients outside inclusion criteria pivotal DES trials
Prespecified Subgroups	**Prespecified Subgroups**

Study Management
PI-G.B. Danzi
SC, EOC

Clinical Follow-Up

1m **6m** **12m** **2y** **3y** **4y** **5y**

Primary Endpoints: **Device oriented composite endpoint (Death, MI, TLR) at 12 months**

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Patients per Subgroups

Female, n (%)	674 (22.0)
Diabetics	885 (28.9)
Acute Myocardial Infarction	692 (25.4)
Small vessels (<2.7 mm)	1106 (32.0)
Long lesions (>24mm)	822 (26.8)
Overlapping	578 (18.8)
CTO	357 (11.6)
Bifurcation	558 (18.2)
Restenosis	232 (7.6)

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One patient could be assigned to more than one subgroup

Procedure Characteristics

	Total N=3072
Number of diseased vessels/patient (n)	1.8
Lesions per patient (n)	2.0
Lesion treated per patient (n)	1.40
Stents per patient (n)	1.7
RVD (mm ±SD)*	2.73 ±0.4
Lesion length (mm ±SD)*	18.2 ±10.3
Diameter Stenosis before (%)*	84 ± 13

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*Visual estimate QCA analysis not yet finaliazed

Procedure Characteristics

Values presented as percentage	Total N=3072 patients N=4.300 lesions
Pre-Dilatation	72.4
Post-dilatation	33.9
Side branch event	4.0
Dissection	2.5
Device success	98.8
Procedure success	98.7

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MACE Rate In-Hospital

All events ***	Total N=3072
Cardiac Death (N, %)	2 (0.06)
MI	30 (1.0)
TL CABG	0 (0.0)
TL Re-PCI	5 (0.2)
Bleeding and vascular complication	21 (0.7)
Events all	**37 (1.3)**

MACE = Cardiac death, MI, clinically driven TLR

****20% of the patients monitored on-site and 80% on-line**

*****Events are not yet adjudicated**

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MACE Rate Between Discharge and 1m FU

All events *	Total N=2666
Cardiac Death (N, %)	5 (0.2)
MI	4 (0.2)
TL CABG	2 (0.07)
Re-PCI	13 (0.5)
Total Events	**24 (0.9)**

Events are not yet adjudicated

20% of the patients monitored on-site and 80% on-line

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CONCLUSIONS - Nobori new generation DES

Nobori DES incorporates several innovative design characteristics which proved valuable through the results of clinical trials

Nobori stent showed non-inferiority vs Taxus and Cypher DES with respect to late loss, and other angiographic and IVUS parameters

Endothelial function showed better recovery in Nobori- than in Cypher or Taxus - treated vessels at 9m

⇒ could be related to drug, drug release kinetics, biodegradable polymer or abluminal coating

The clinical evidence available to date for Nobori stent shows excellent safety and efficacy confirmed by:

- **Very low rate of MACE, Restenosis and TLR**
- **No late stent thrombosis**

- **Long term follow-up results awaited to confirm current trends and to further explore the potential positive impact of biodegradable polymer on long term safety of this innovative DES**

- **Initial results of NOBORI 2 in 'real-life' setting tend to confirm preliminary findings**

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