

Summit TCT Asia Pacific

Future Horizons in Coronary Stenting

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**Where are we ?
Where do we want to go?**



TODAY - the Drug Eluting Stent

DES status quo

- Unanswered questions
- Future requirements

DES Efficacy

- Late loss and TLR

DES Safety

- Stent thrombosis
- Death and MI
- *Role of the endothelium*

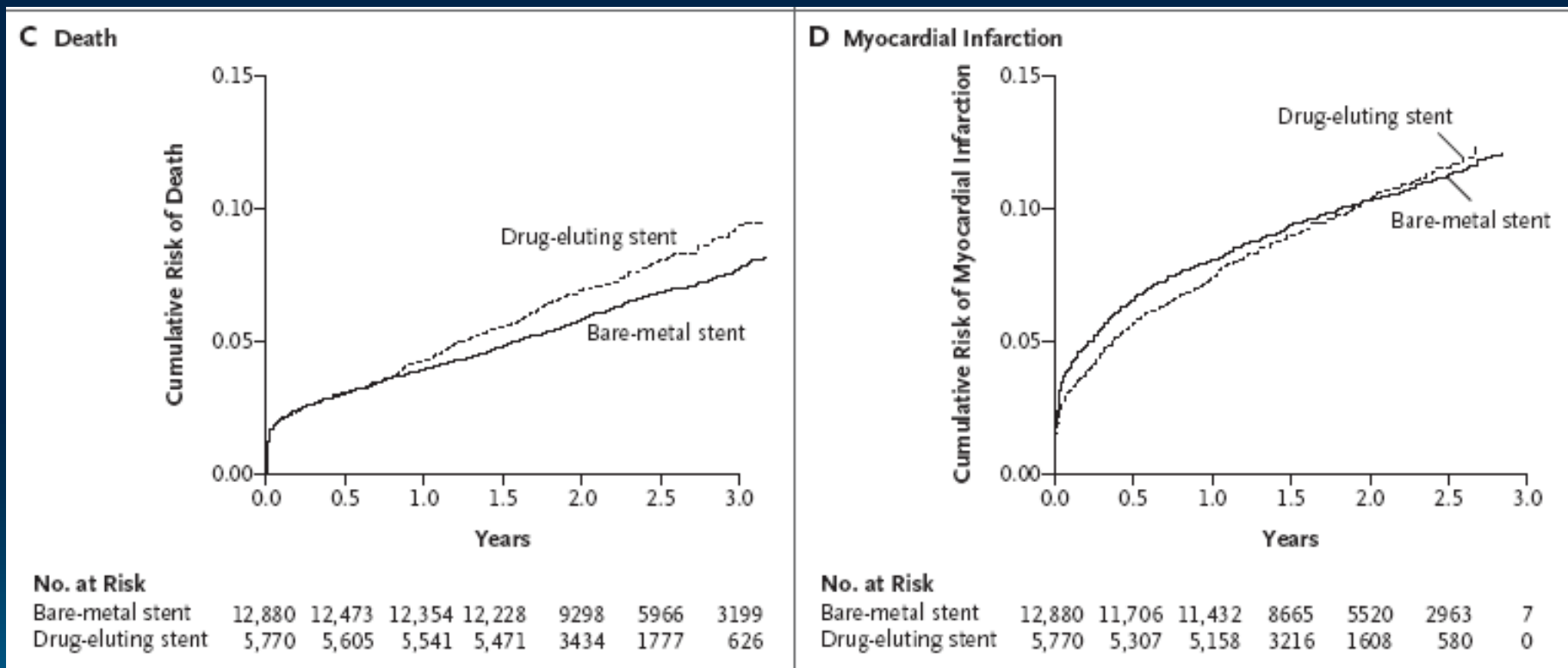


SCAAR REGISTRY DEATH AND MI

Estimated Cumulative Event Rates

Death

MI

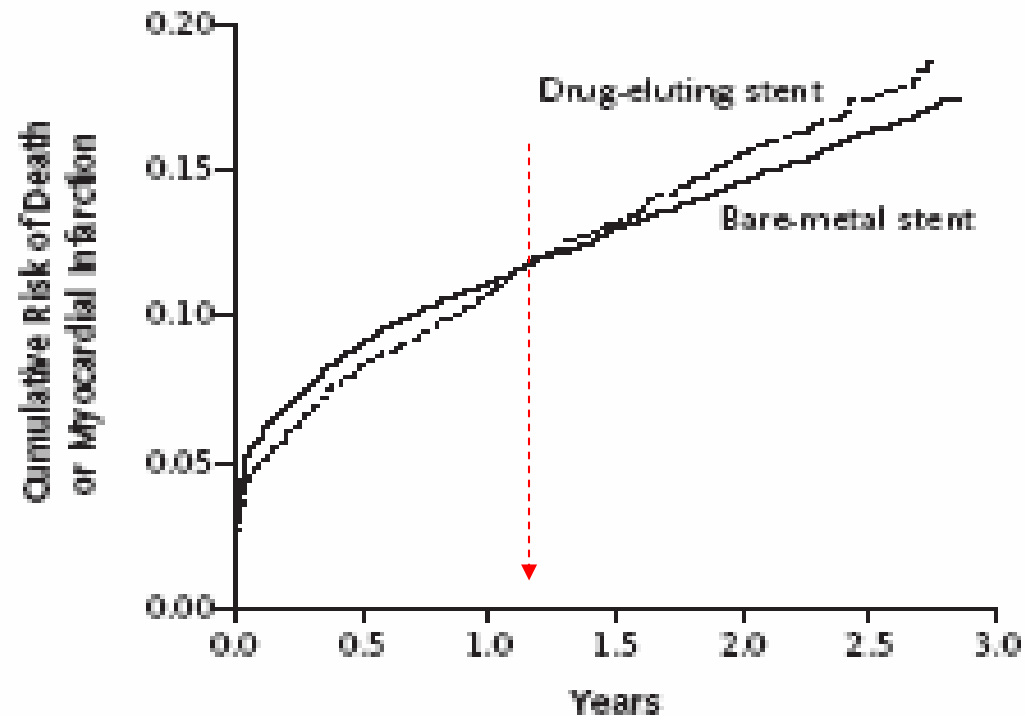


SCAAR REGISTRY DEATH AND MI

Estimated Cumulative Event Rates

Composite of Death and MI

B Adjusted Composite Event



No. at Risk

Bare-metal stent	12,880	11,706	11,432	8665	5520	2963	7
Drug-eluting stent	5,770	5,307	5,158	3216	1608	580	0

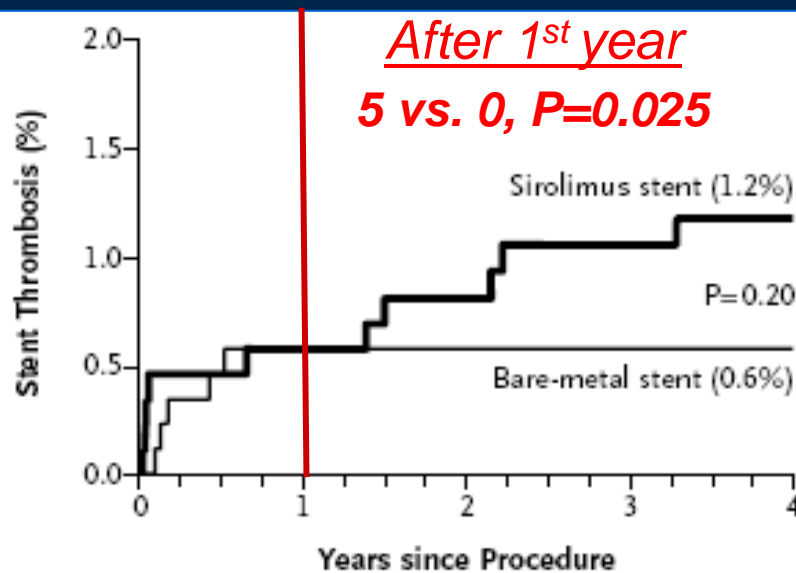


STENT THROMBOSIS - 3 YEARS – I

Meta-analysis of clinical trials

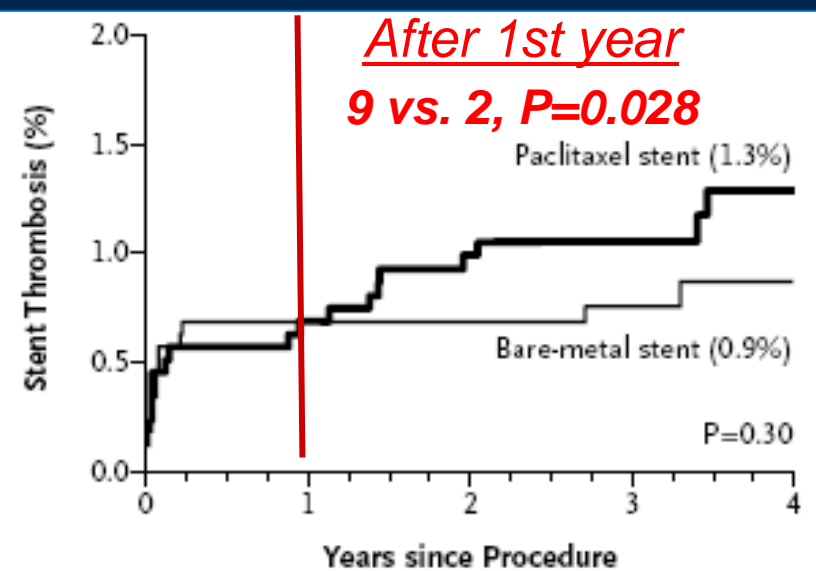
RAVEL, SIRIUS, E-SIRIUS, C-SIRIUS
(n=1,748)

TAXUS I, II, IV, V, VI
(n=3,506)



No. at Risk

Bare-metal stent	870	852	833	806	742
Sirolimus stent	878	854	826	795	732



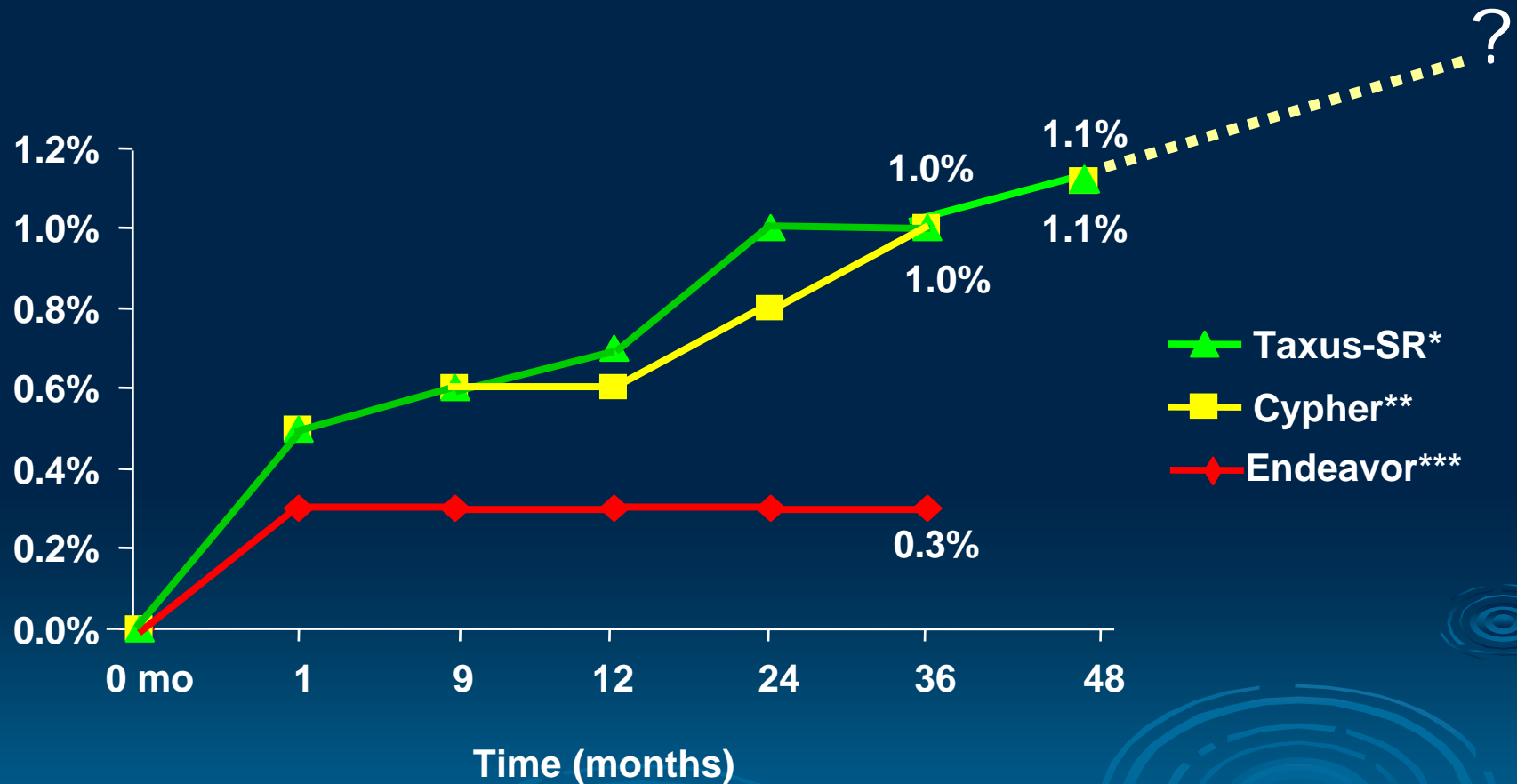
No. at Risk

Bare-metal stent	1756	1692	1579	1126	319
Paclitaxel stent	1753	1687	1561	1106	279

(2 - 4) YEARS	ENDEAVOR	BMS	SES	BMS	PES	BMS
CEC	0.3 %	1.2%	1.2%	0.6%	1.3%	0.8%
ARC (D +P)	0.6%	1.4%	1.5%	0.8%	1.8%	1.1%
ARC (D+P+P)	1.0%	3.3%	3.6%	3.3%	3.5%	3.6%

STENT THROMBOSIS RATES WITH DES

Pre-specified HCRI CEC Defined Stent Thrombosis



* TAXUS I, II SR, IV, V 1338 out to 3 years; 1217 to 4 years; 1.1% = 16 events / 1400 pts enrolled

** RAVEL, SIRIUS, E-SIRIUS, C-SIRIUS; 741 pts to 4 years; 1.1% = 10 events / 878 pts enrolled

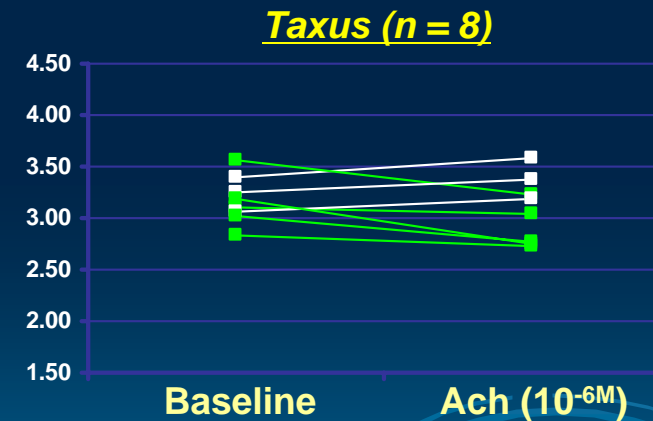
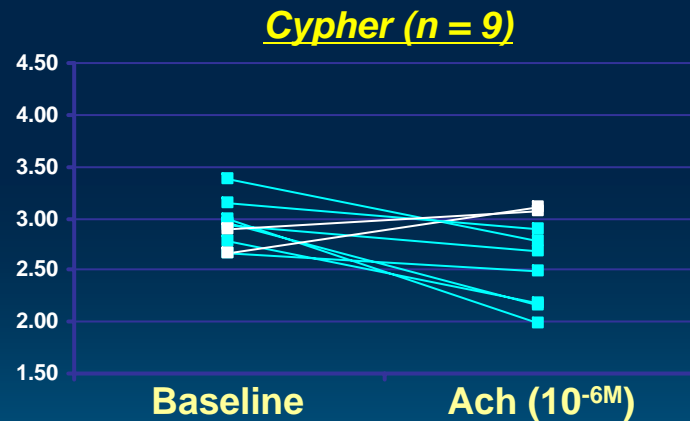
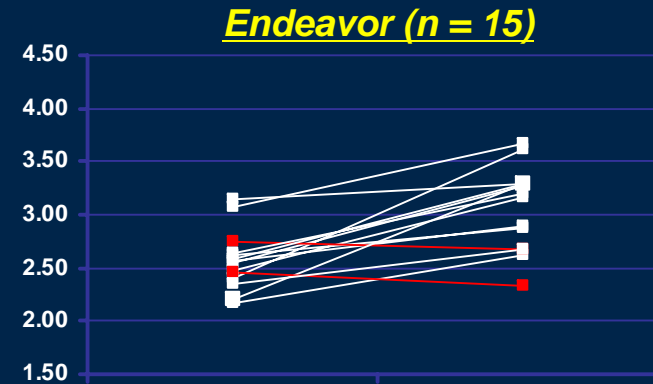
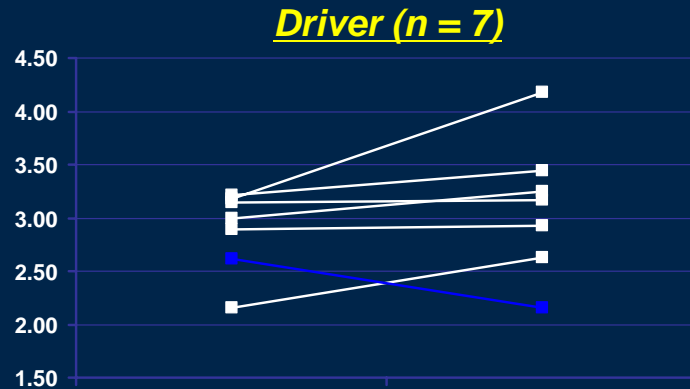
*** E-I, II, IICA, III 1206 pts out to 2 years; 690 patients out to 3 years; 0.3% = 4 events / 1316 pts enrolled

Clinical results are not suitable for comparison



DES - ENDOTHELIAL FUNCTION

ACH Challenge 28 Days After Stenting



- Cypher and Taxus constrict in response to acetylcholine (ACH)
 - Suggesting EC dysfunction.
- Endeavor and Driver show normal vasodilation in response to ACH
 - Suggesting normal EC function



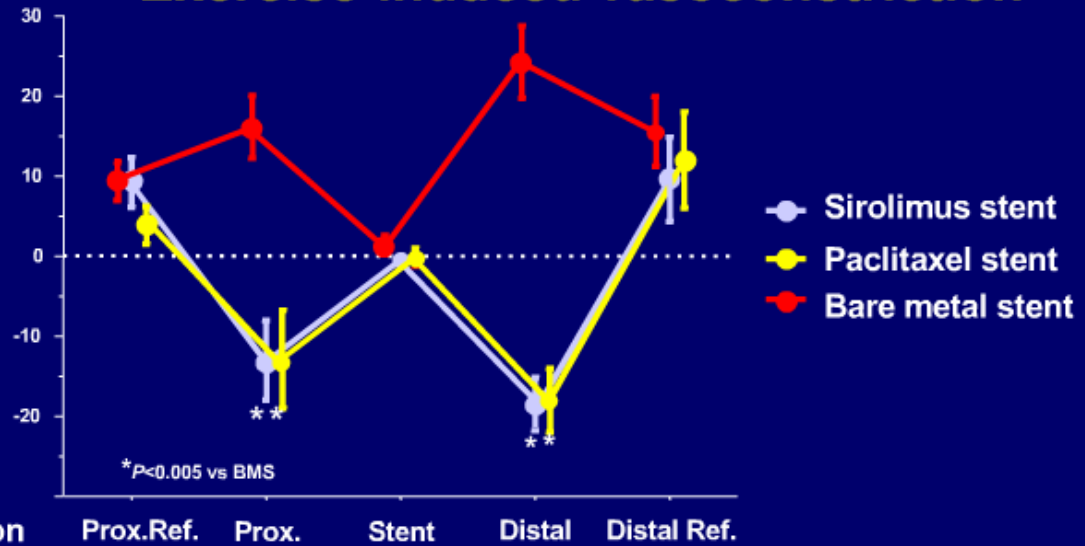
Endothelial Function

Sirolimus-Eluting Stents Associated With Paradoxical Coronary Vasoconstriction

Togni M et al.
J Am Coll Cardiol 2005, 46:231-6

Vasodilation
 ↑
 PERCENT CHANGE (%)
 ↓
 Vasoconstriction

Exercise-induced vasoconstriction

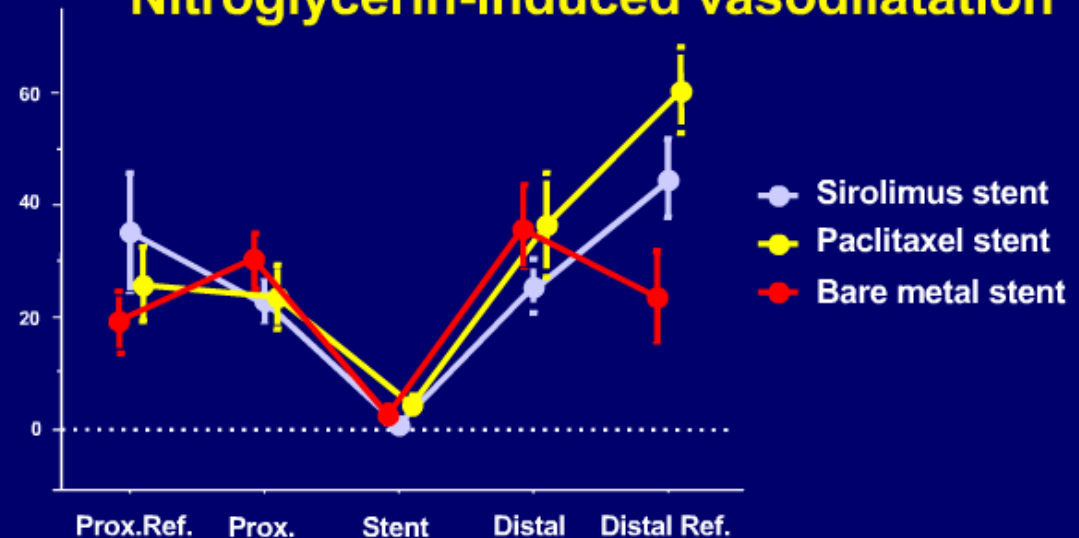


Paclitaxel-Eluting Stents Associated With Paradoxical Coronary Vasoconstriction

Togni M et al., submitted

PERCENT CHANGE (%)

Nitroglycerin-induced vasodilatation



ENDOTHELIAL INJURY AND HEALING

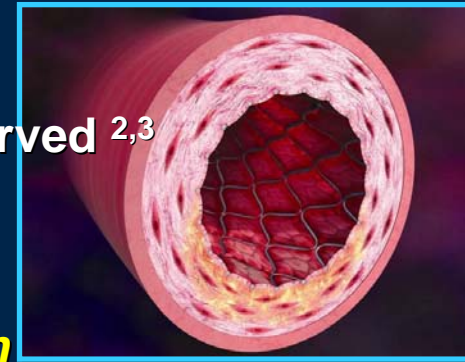
POST-STENT IMPLANTATION

- **Endothelial denudation** ¹

- Small area – little to no intimal hyperplasia observed ^{2,3}

- Large area

- Focal fibrin deposition + **thrombus formation**
- **Inflammation**
- **Activation of SMCs**



- Severe and deeper injury results in delayed re-endothelialisation ⁴

- **Subsequent arterial healing process begins immediately** ^{1,5}

- Eventually is essential for restoring normal arterial function
- In around 15 - 20 % of patients this normal process is exaggerated resulting in re-stenosis


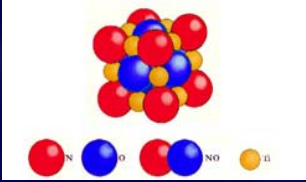


Which way to go ?

- Another metal?
- Another drug?
- Another mechanism?
- Another idea?



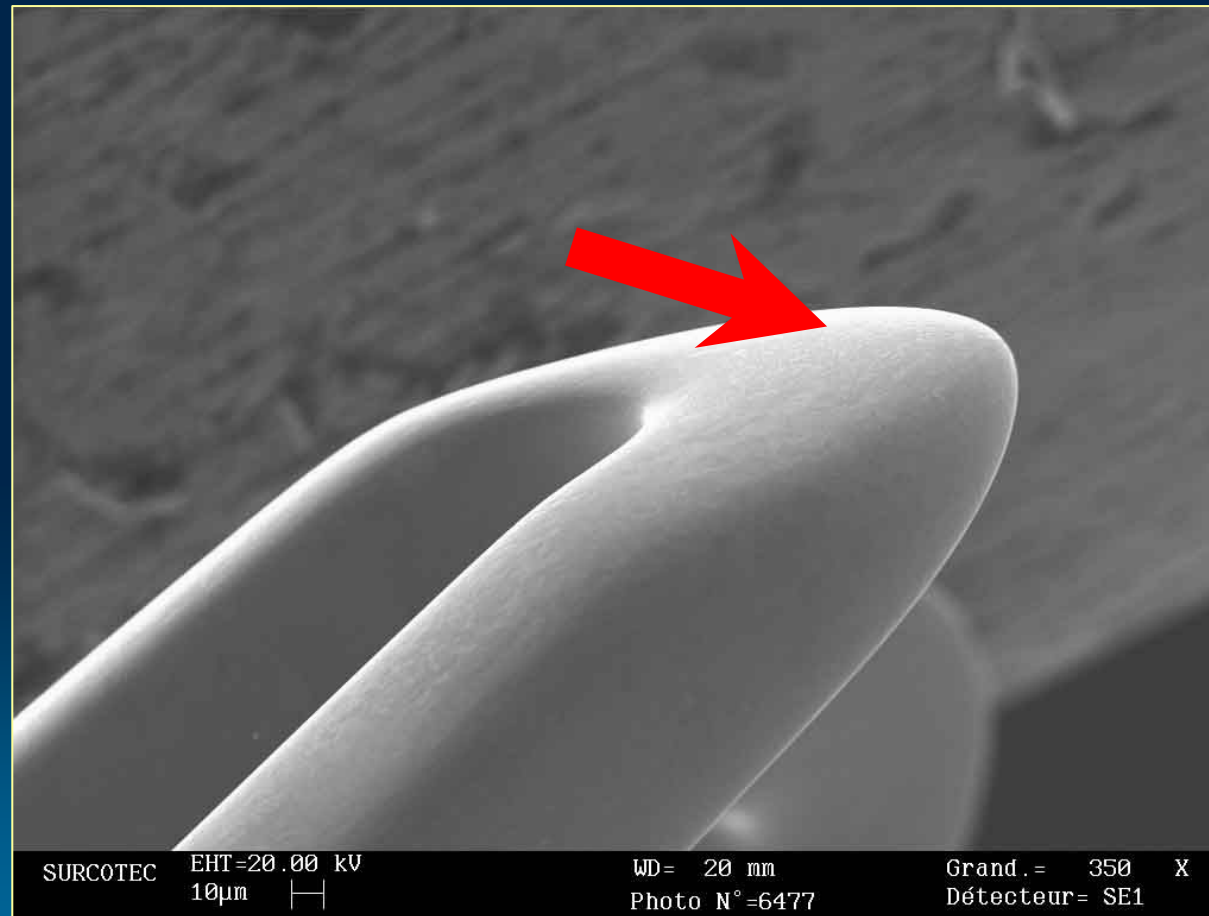
TITAN2[®] Bio-Active-Stent by HEXACATH

STENT GEOMETRY	HELICOIDAL DESIGN 
MATERIAL	316L
COATING	TITANIUM NITRIDE OXIDE BIO ACTIVE COATING 
VARIABLE STRUT THICKNESS	FROM 70 TO 90 MICRONS

TITAN2 DESIGN

TITAN2

Unique Wedge Profile maximises the stent crossability



HEXACATH PROPRIETARY CONCEPT

FUNDAMENTAL STUDIES

TITANIUM OXIDE FILMS SUPERIORITY

1. Titanium oxides minimize red blood cells damages
2. Titaniums oxides minimize platelet aggregation
3. Titanium oxides minimize fibrin growth
4. Titanium oxides promote re-endothelialization



- Just started :a comparison between Taxus and Titanium Stent in diabetic patients

A prospective randomized multicenter (Benelux) study
Coordinating Center Catharina Hospital Eindhoven



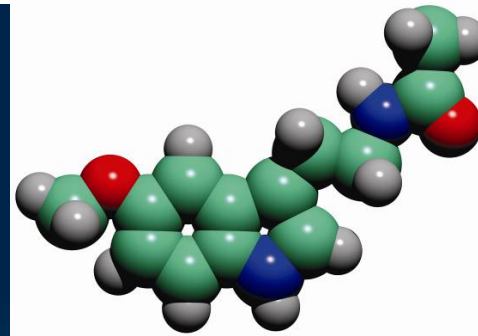
MELISSA

Non-Toxic and safe next generation through vessel healing



- **Drug: Melatonin**

- Nitric Oxide preserving
 - Anti-inflammatory
 - Strong anti-oxidant

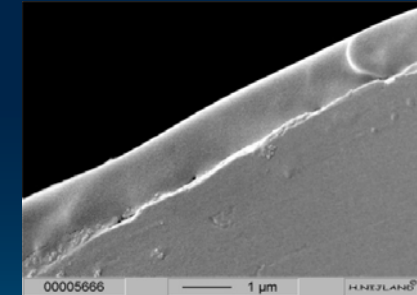


- **Drug carrier: PEA**

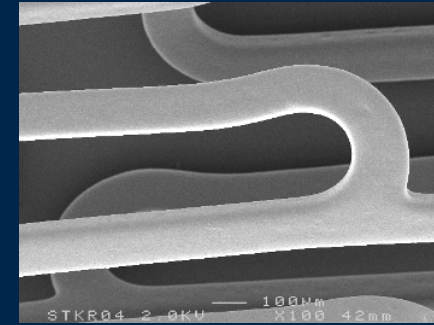
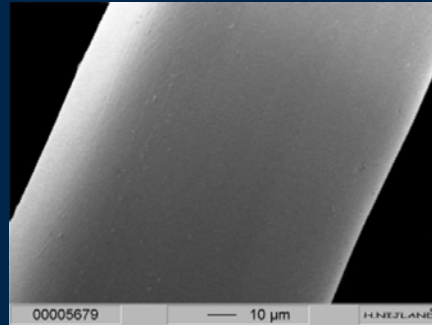
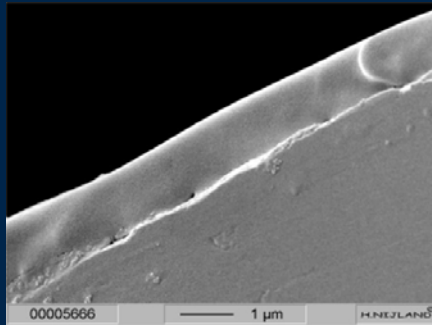
- Fully bio-degradable and bio-absorbable coating

- **Platform:**

- Blue Medical XTRM FIT Coronary Stent System



PEA bio-degradable coating

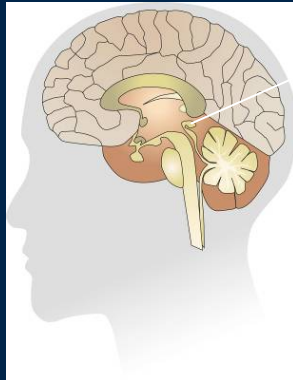


- PEA is based on natural amino- and fatty acids, which means it is fully biocompatible and non-toxic and **non-inflammatory**. Therefore it is not necessary to overcome toxicity and inflammatory responses of the coating.
- The active compounds are released through the bio-absorption of the delivery layers ensuring all drugs and coating is gone after 60 days; **NO LATE TROMBIS RISK FACTORS**
- Human data of the coating (Noblesse Study) indicated efficacy and safety (late loss at 24months FU: 0.69)



Melatonin

(N-acetyl-5-methoxytryptamine)

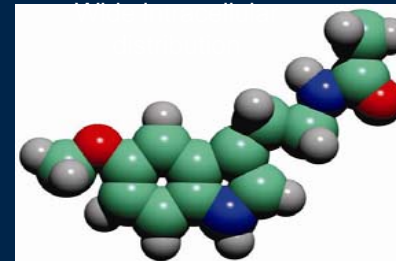


Pineal gland

Stimulates
antioxidative
enzymes

Detoxifies oxygen-based
radicals/reactive species

Detoxifies oxygen-based
radicals/reactive species



Inhibits
pro-oxidative
enzyme

Reduces
NF-KB binding
to DNA

Reduces
pro-inflammatory
cytokines
Reduces adhesion
molecules

Crosses all
morphophysiological
barriers

Stabilizes cellular
membranes

Increases efficiency of
oxidative phosphorylation

- A human hormone produced in the pineal gland, mainly to control the biological clock and 24h rhythm
- Known for several beneficial effects on cardiovascular disease
- Extensive animal and cell biology data prove **strong reduction** of proliferation **without any cell death**

- Bio-compatible
- No toxic dose
- Anti-cancer effect
- Strong antioxidant
- Inhibition of NO tolerance
- Cardio protective
- Suppresses formation of cholesterol
- Reduces blood pressure



MELISSA

Human Trial

Human trials:

- Melissa I: 45 patients (Catharina Hospital Eindhoven)
Now enrolling!!
- Melissa II: 150 patients, enrollment 2007-2008

Trial designs:

- Multi-center, prospective, non-randomized
- IVUS inclusion
- IVUS and Angiographic Follow-up at 6 months
- 30, 60 and 360 days clinical follow-up
- Primary endpoint late loss at 6 months
- Secondary endpoints, Binary restenosis at 6 months, MACE at 6 months



A New Paradigm for the Prevention of Restenosis?

“As cardiologists, vascular biologists, and physicians, we must now consider an alternative to the “antitumor” approach to restenosis prevention and seek to restore the normal biology of the vessel wall rather than perpetuate its disruption.”

D.W. Losordo, et al.
Circulation 2003;107;2635-7.



A New Paradigm for the Prevention of Restenosis?

Rather than intervening locally using cytotoxic or cytostatic pharmacological compounds to prevent specific events which contribute to the occurrence of an over-exuberant healing response (DES).

.....promote the establishment of a functional endothelial monolayer and thereby provide the endogenous modulators necessary for efficient healing (EPC).



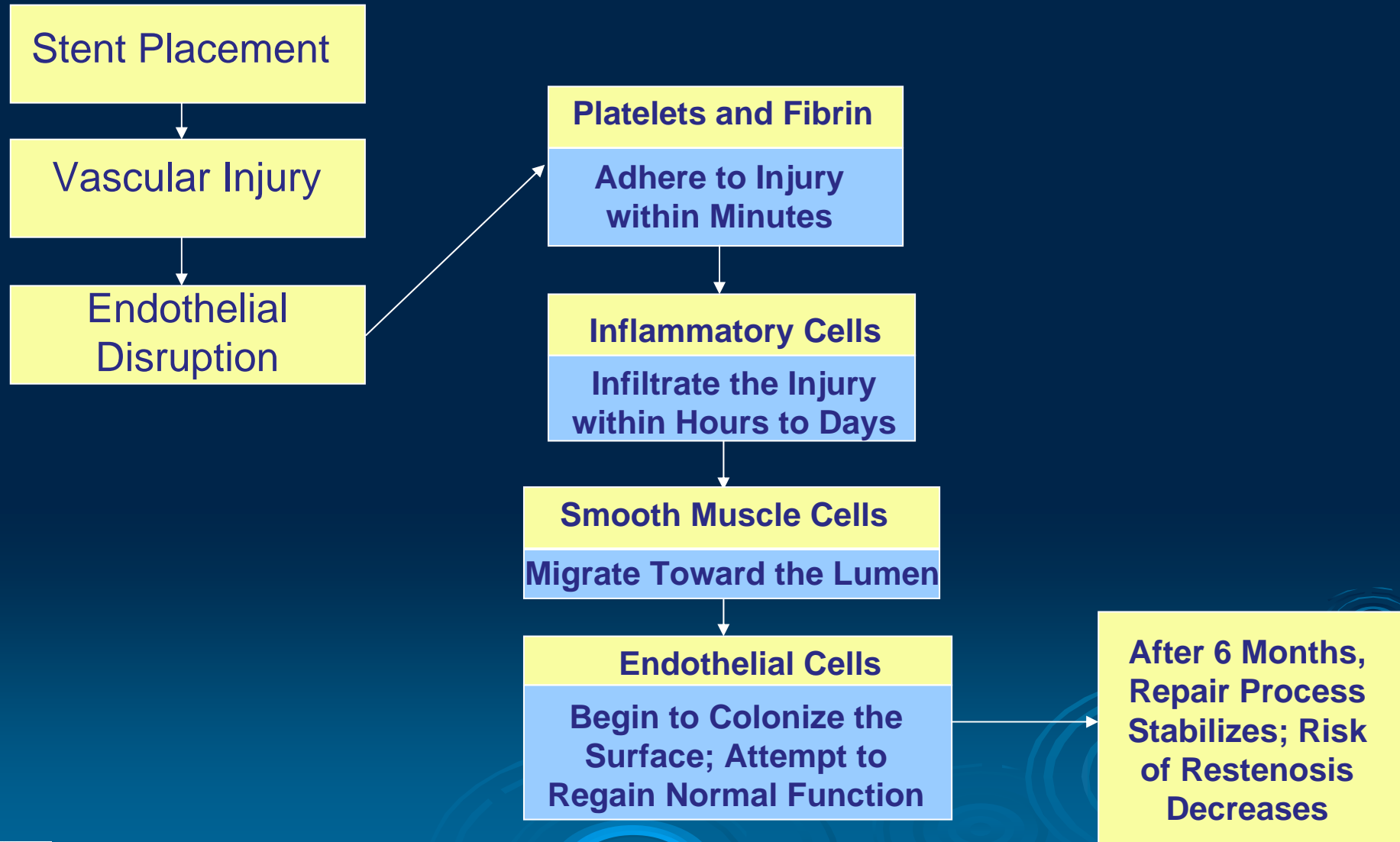
Background

- “Pro-healing” approach to the treatment of vascular stenoses is favored over cytotoxic or cytostatic local or systemic pharmacological therapies
- The central role of the vascular endothelium to maintain quiescence of the underlying media and adventitia is well recognized
- Rapid endothelialization of stainless steel stents with a functional endothelium will prevent stent thrombosis and reduce restenosis



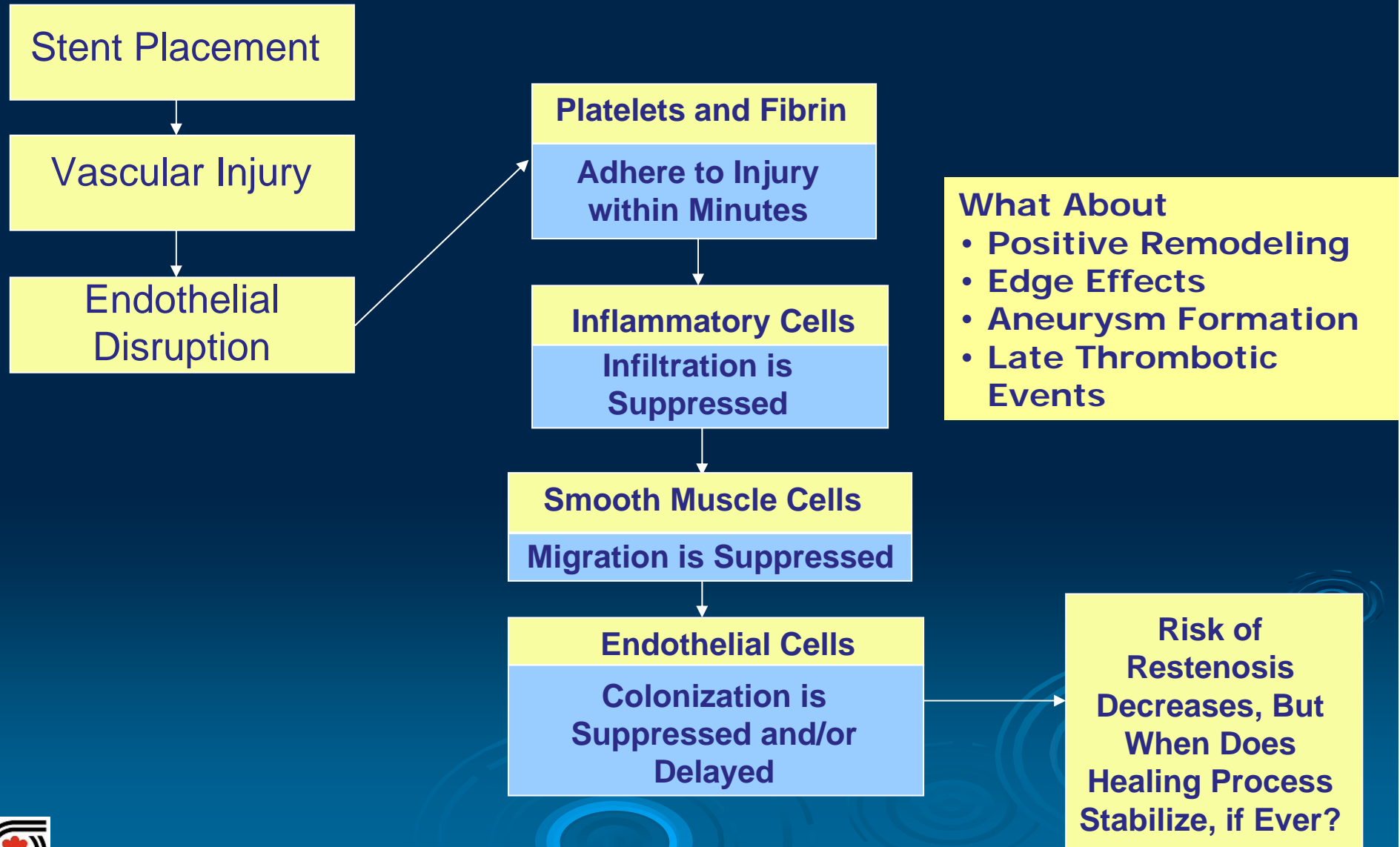
Bare Metal Stent

Response to Injury Model



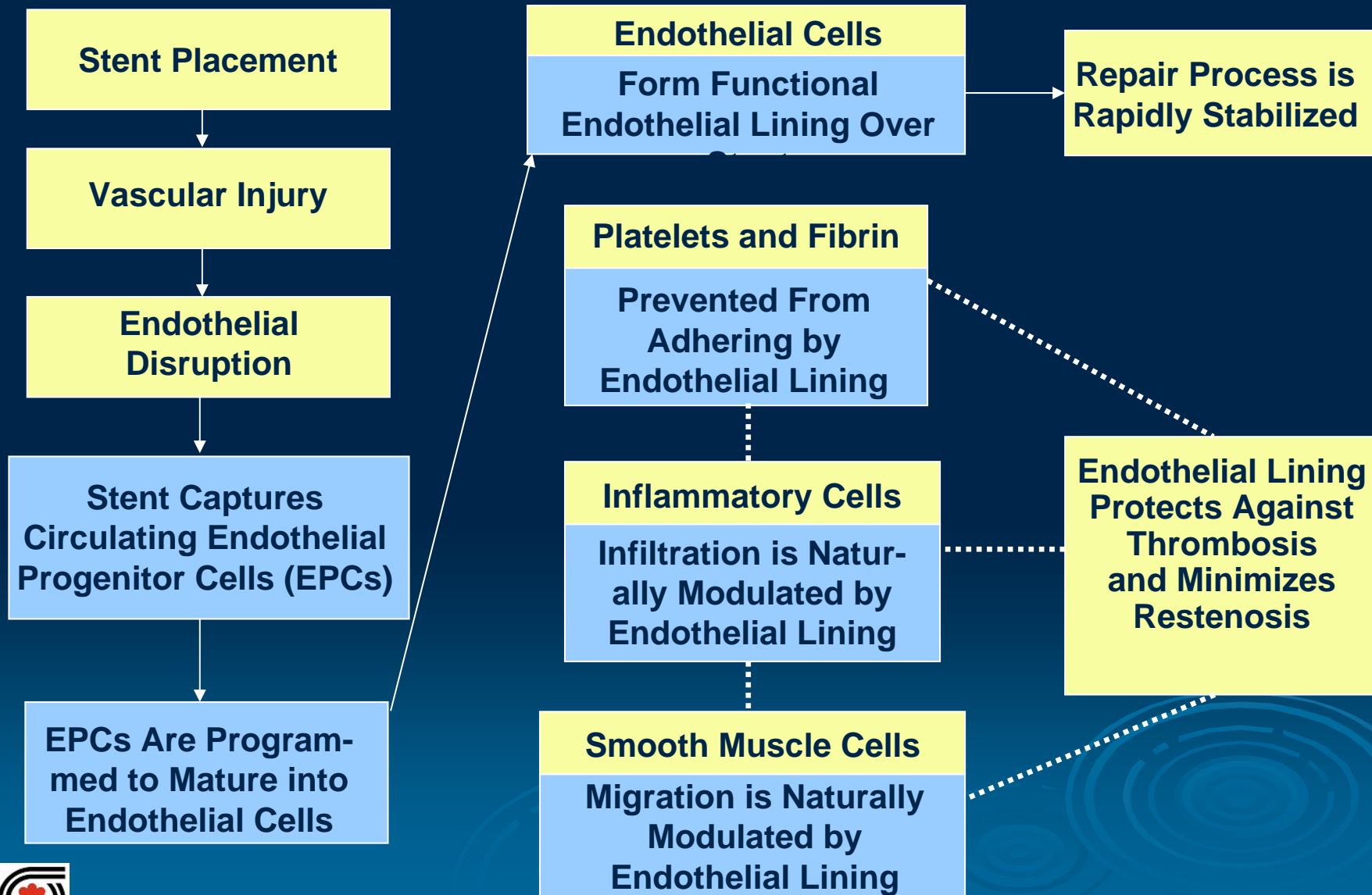
Drug Eluting Stents . . .

New Solutions Create New Problems

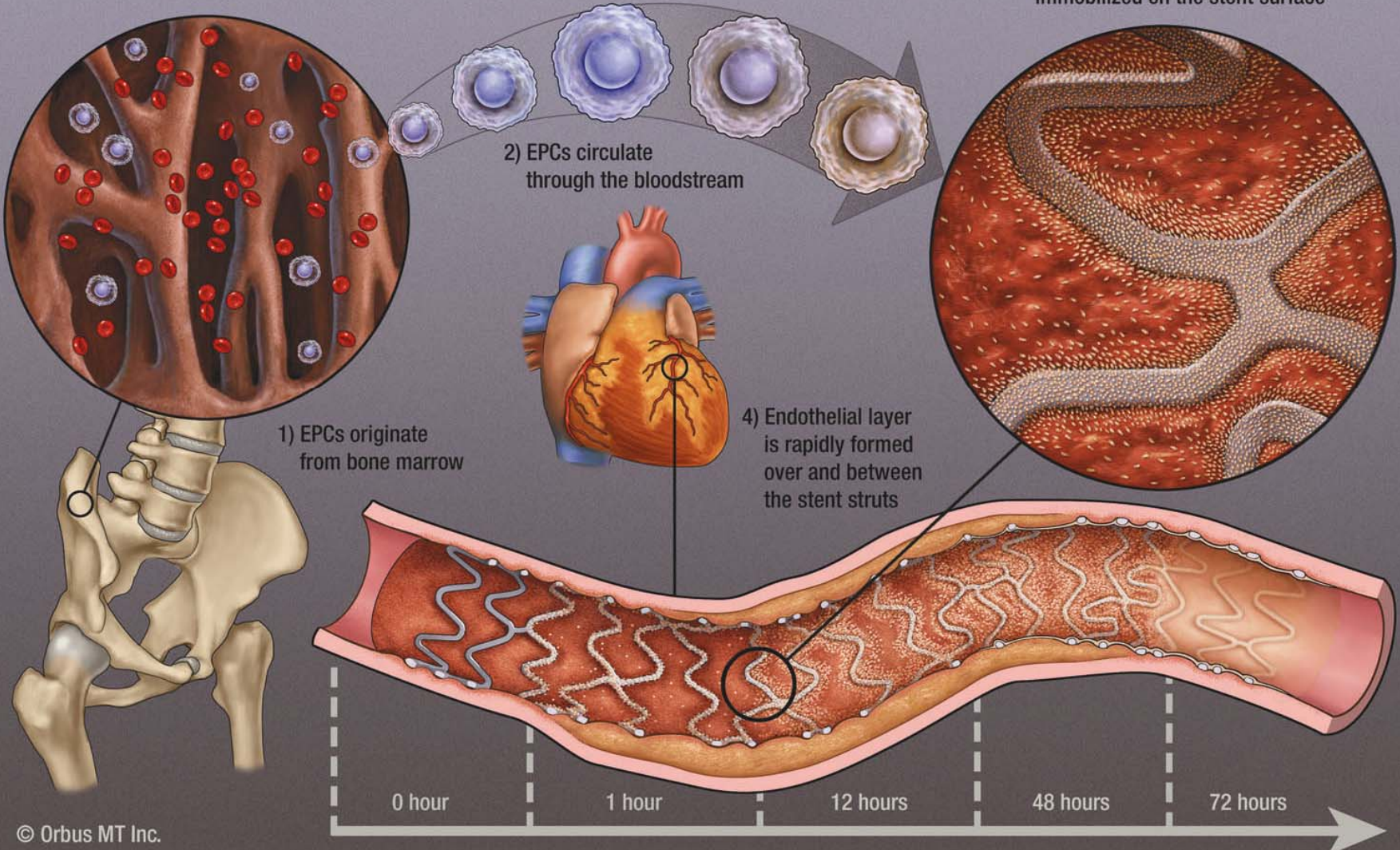


Genous Bio-engineered Restent

A Pro Healing Approach



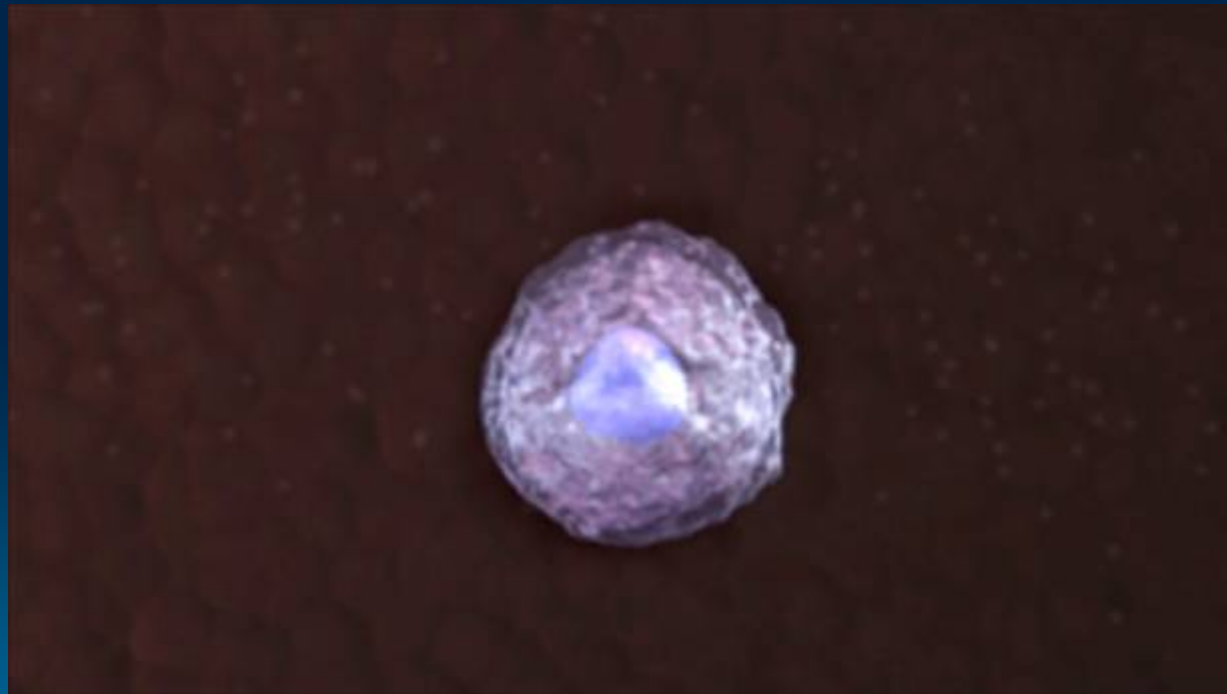
GENOUS: the Role of Endothelial Progenitor Cells (EPCs)



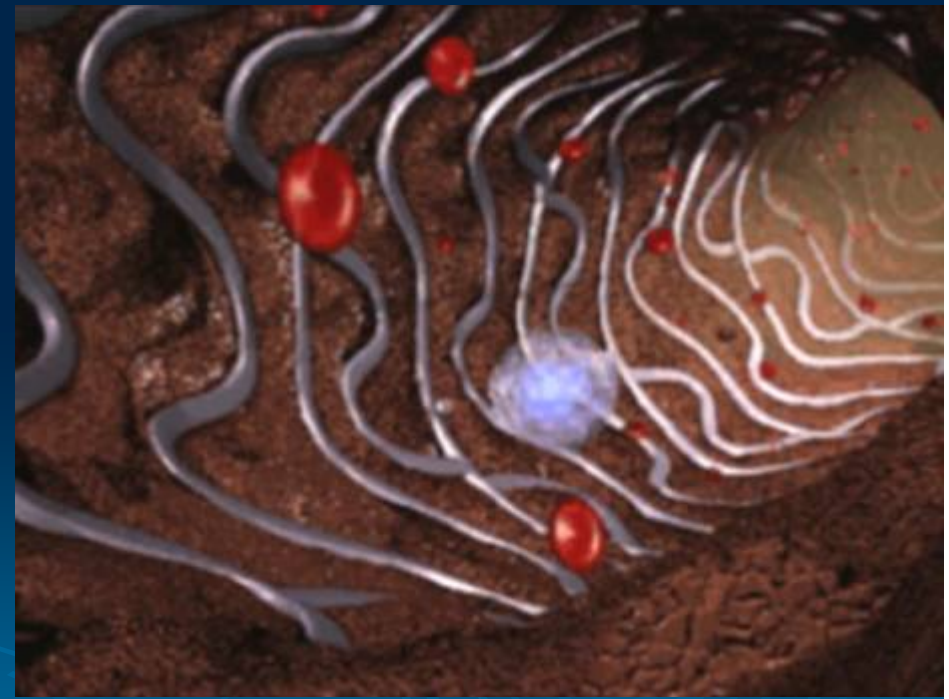
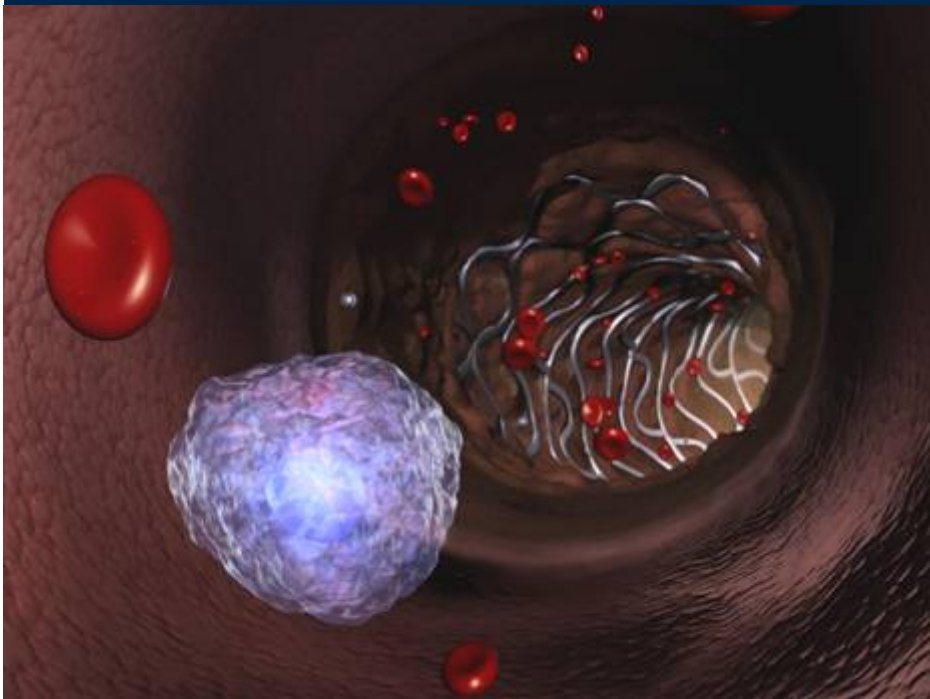
© Orbus MT Inc.



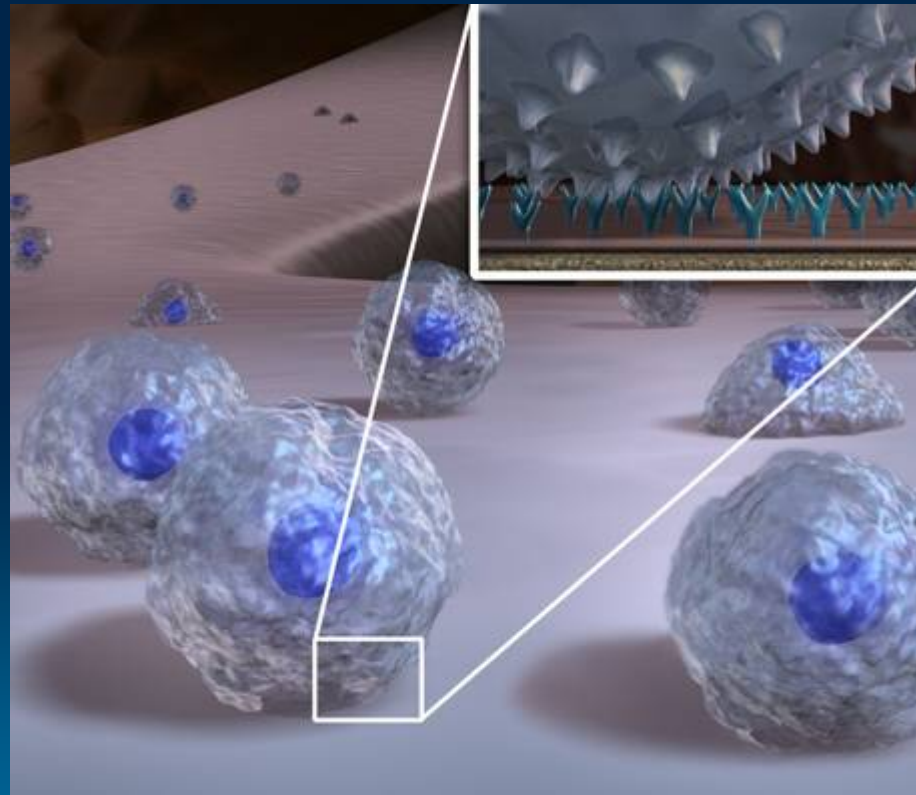
Bone marrow derived EPCs
are part of the circulating blood cell population.



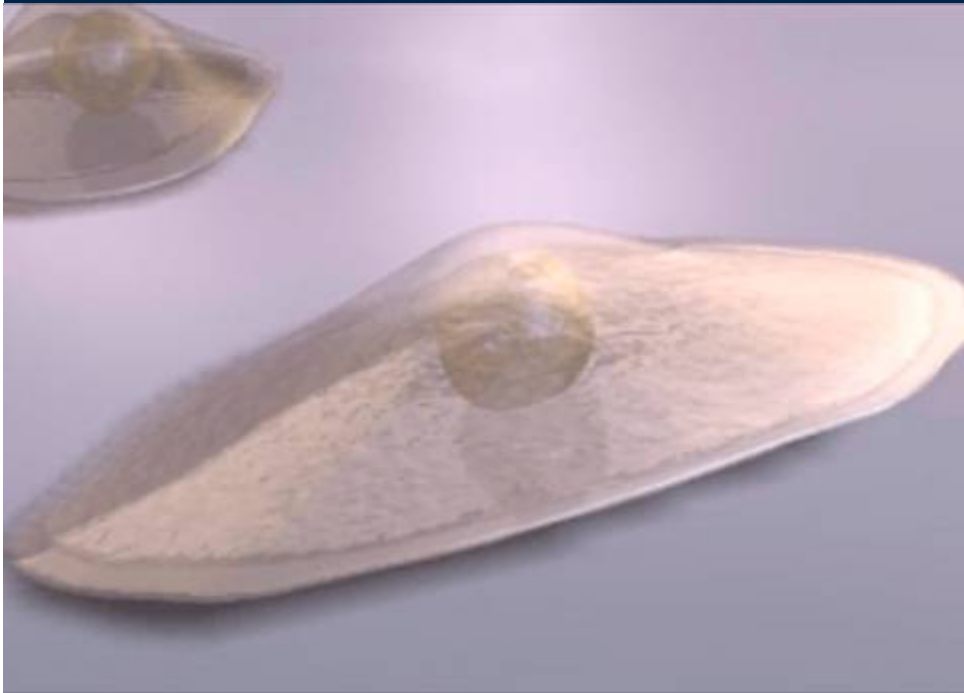
EPCs are an integral part of repairing the disrupted endothelium and injury to the vascular wall.



Antibodies specific to EPCs are immobilized on the stent surface and capture circulating EPCs.



Once captured onto the surface of the stent, EPCs flatten out and mature into endothelial cells.



No restenosis
No late thrombosis
Maybe no stent at all?



Advantages of a Bioabsorbable Non-polymer Based Stent

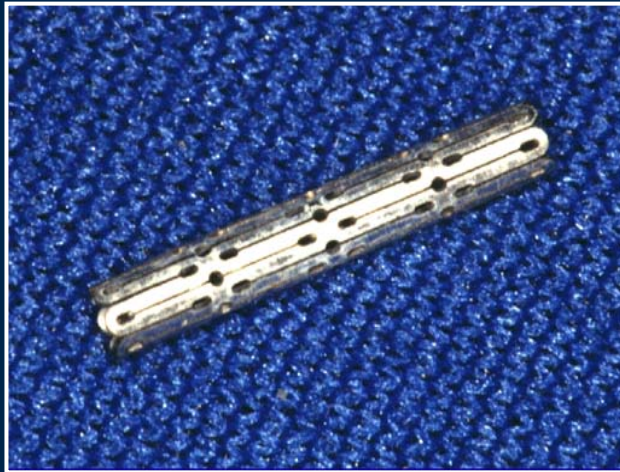
- Provides metal stent scaffolding and radial strength properties
- Leaves no stent behind (no chronic inflammation, no long-term impact on local vasomotion)
- No “Full metal jacket” → easier surgical bypass connection
- No Stent Thrombosis
- No Need for Prolonged antiplatelet therapy
- MRI / CT compatibility → provides non-invasive F/U



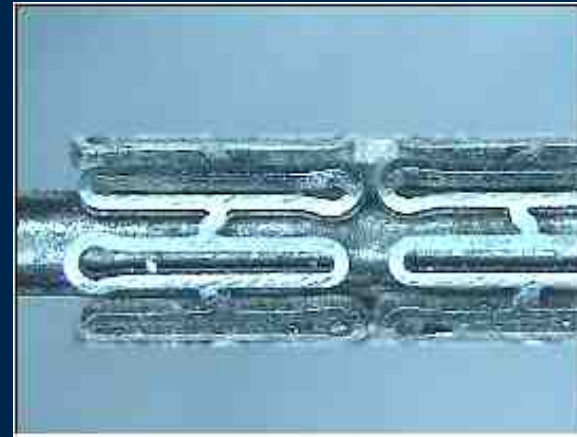
Technology

Design & Surface

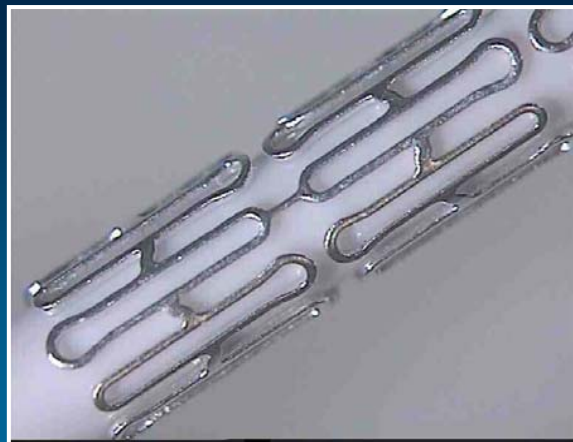
Adaptation of the Stent Design



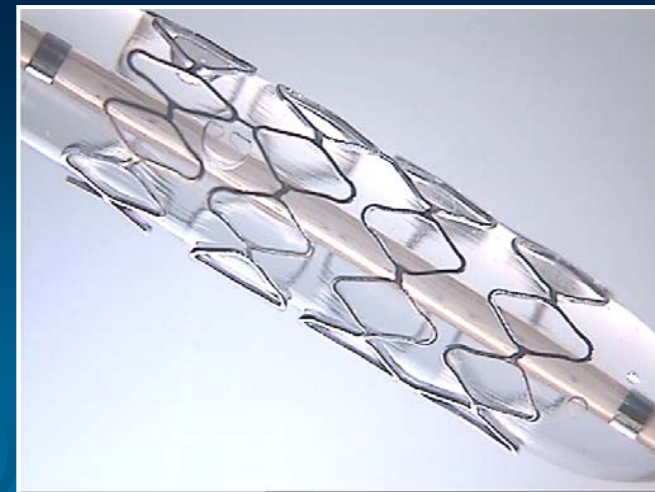
1st Animal Study



2nd & 3rd Animal Study

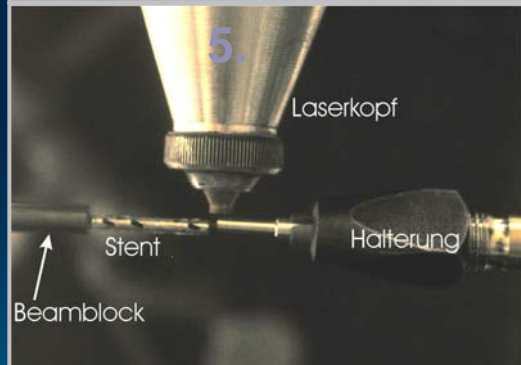
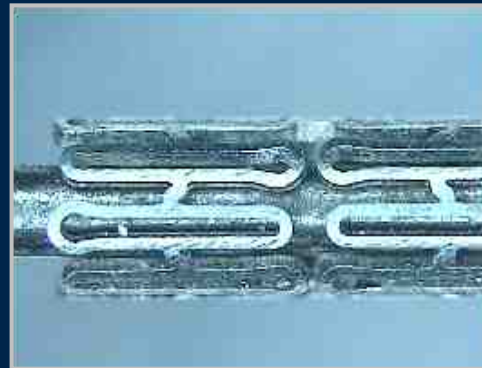
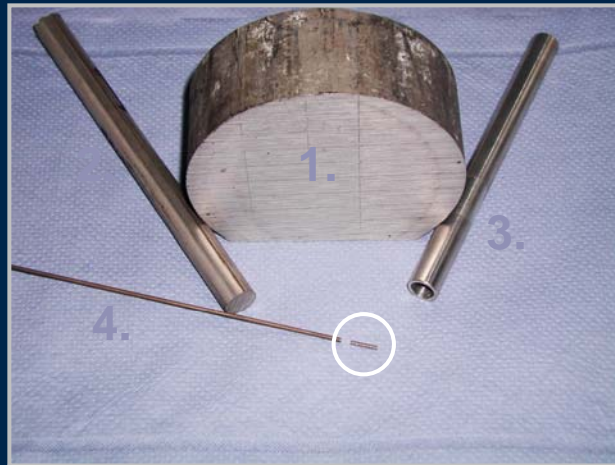


4th Animal Study

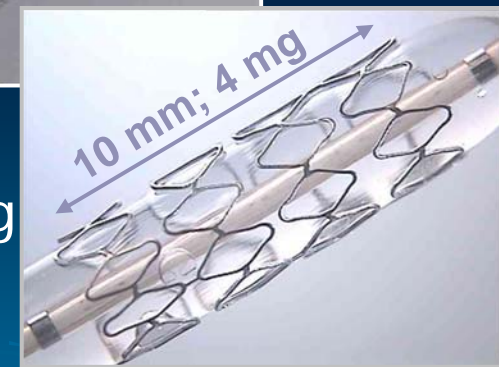
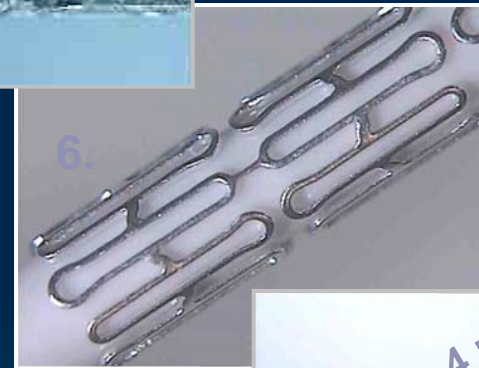


Technology

Design & Surface



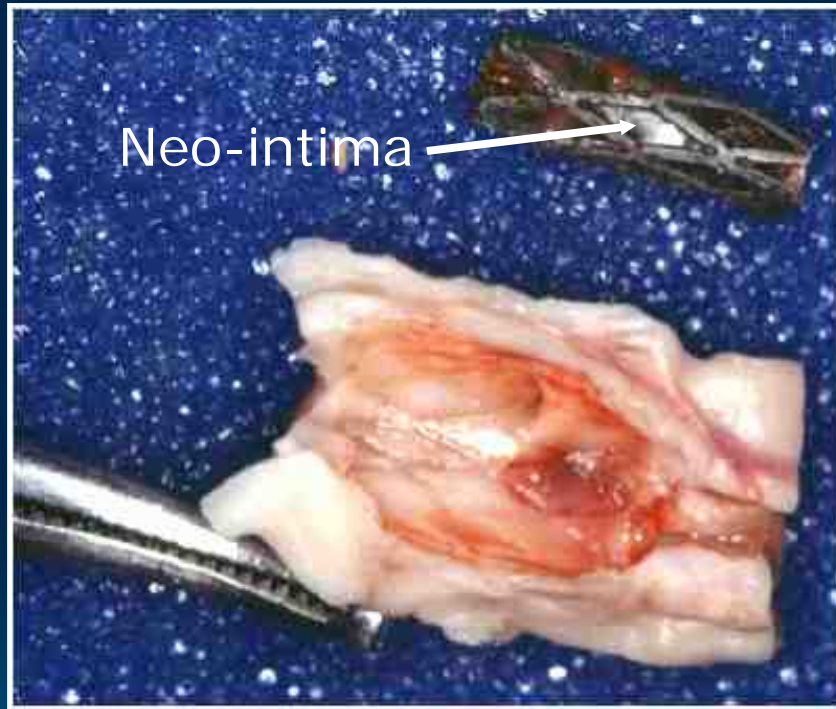
1. Casting
2. Extrusion
3. Drilling
4. Drawing
5. Laser Beam Cutting
6. Electro Polishing



Animal Study I

First Steps

Organized Neointimal Growth



Complete coverage
after 10 days !

Alloy 1 in domestic pig RCA after 10 d.



Clinical Results

BEST-BTK study

First in Man experience with the Biotronik absorbable metal Stent Below The Knee

Demographics:

- Number of patients 20 (Average age 76 yrs)
- CLI status:
 - Rutherford Class 4: 9 (45%)
 - Rutherford Class 5: 11 (55%)

Lesion characteristics:

- Lesion length: 11 mm (range: 2–20 mm)
- Average vessel diameter: 2.7 mm (range: 2.5–3 mm)
- Mean diameter stenosis: 84% (range: 75 – 95%)
- Calcified lesions: 14 (70%)



Clinical Results

PROGRESS-AMS

	In Hospital	30 day	4 months
MACE (Cardiac death, nonfatal MI, ischemia driven TLR)	0	0	15 (23.8%)
Death	0	0	0
Q-wave MI	0	0	0
Non Q wave MI	0	0	0
Ischemic Driven TLR	0	0	15 (23.8%)



Clinical Results

PROGRESS-AMS

Conclusions:

High technical and procedural success

- No death, no MI, no stent thrombosis
- The study met the primary endpoint (MACE <30%)

The Absorbable Metal Stent (AMS):

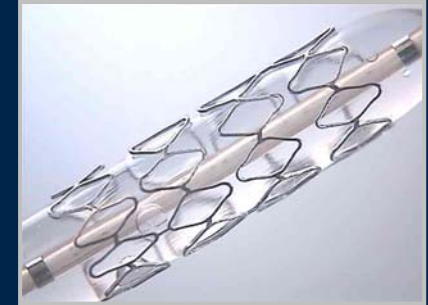
- The AMS technology platform is proven
- Is MRI / CT compatible
- Absorption was detected with IVUS during FU

- In Press :Lancet 2007



Where are we today?

Status of AMS 2007



- Safe in human coronaries
- Safe in peripheral arteries (tibial)
- Absorbed as intended < 90 days
- No distal embolization, No inflammation
- Fully compatible with CT or MRI angiography
- Restenosis mainly due to early recoil and neointima formation
- New Generations AMS under preclinical testing



Conclusions

However...

... efficacy of current AMS is not yet matching our expectations,

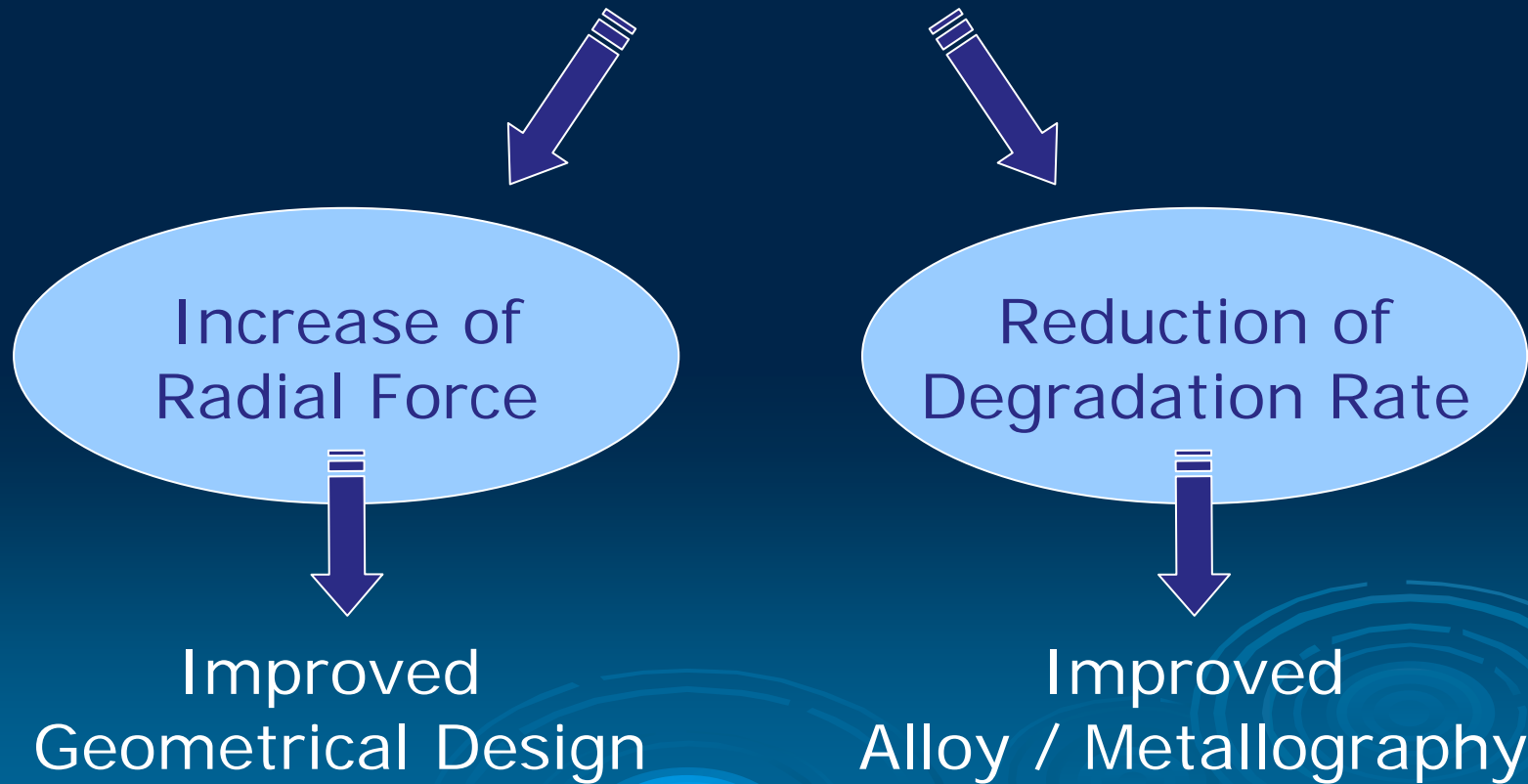
because...

... it is not comparable to state of the art systems like DES.

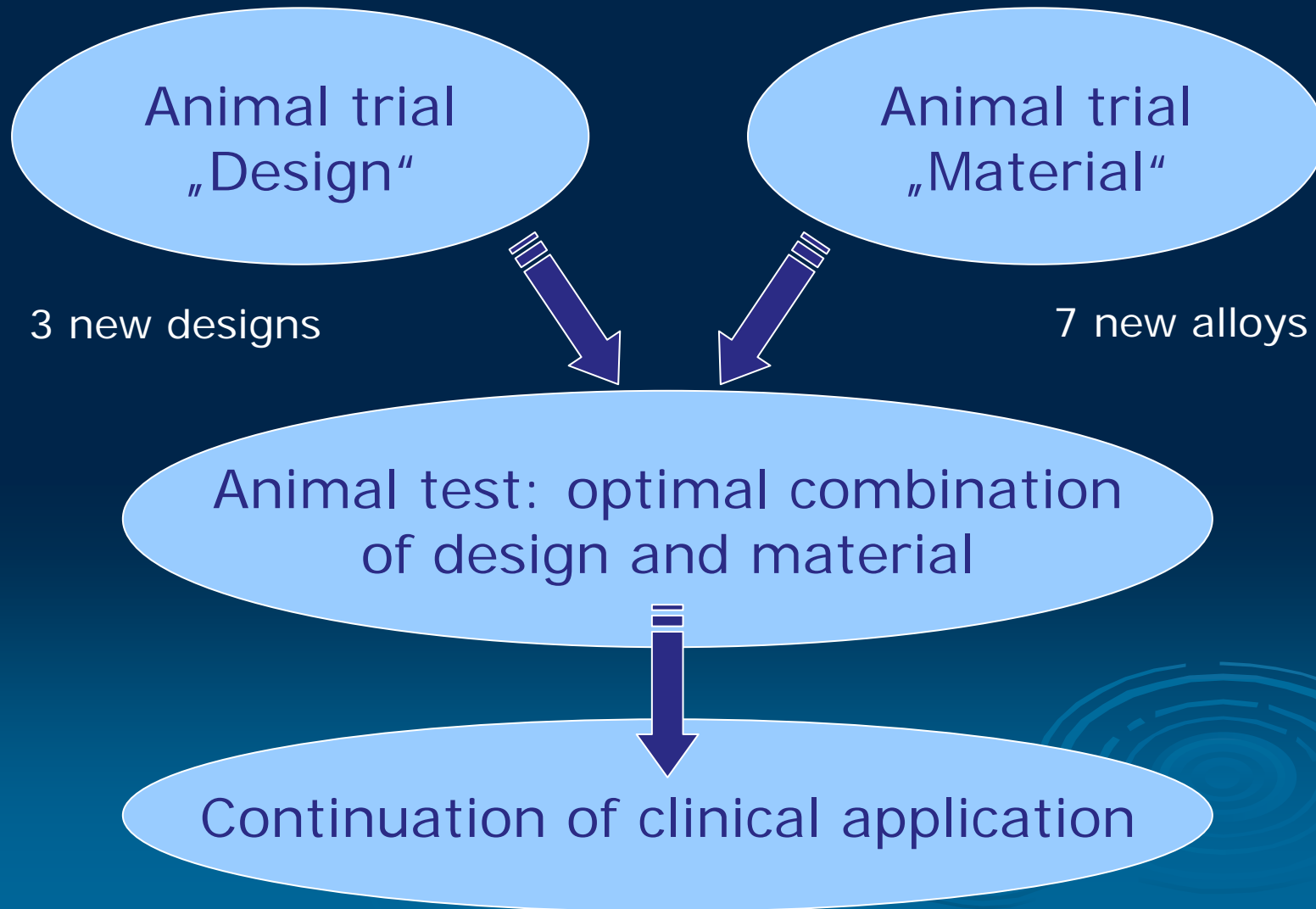


How to improve AMS 1?

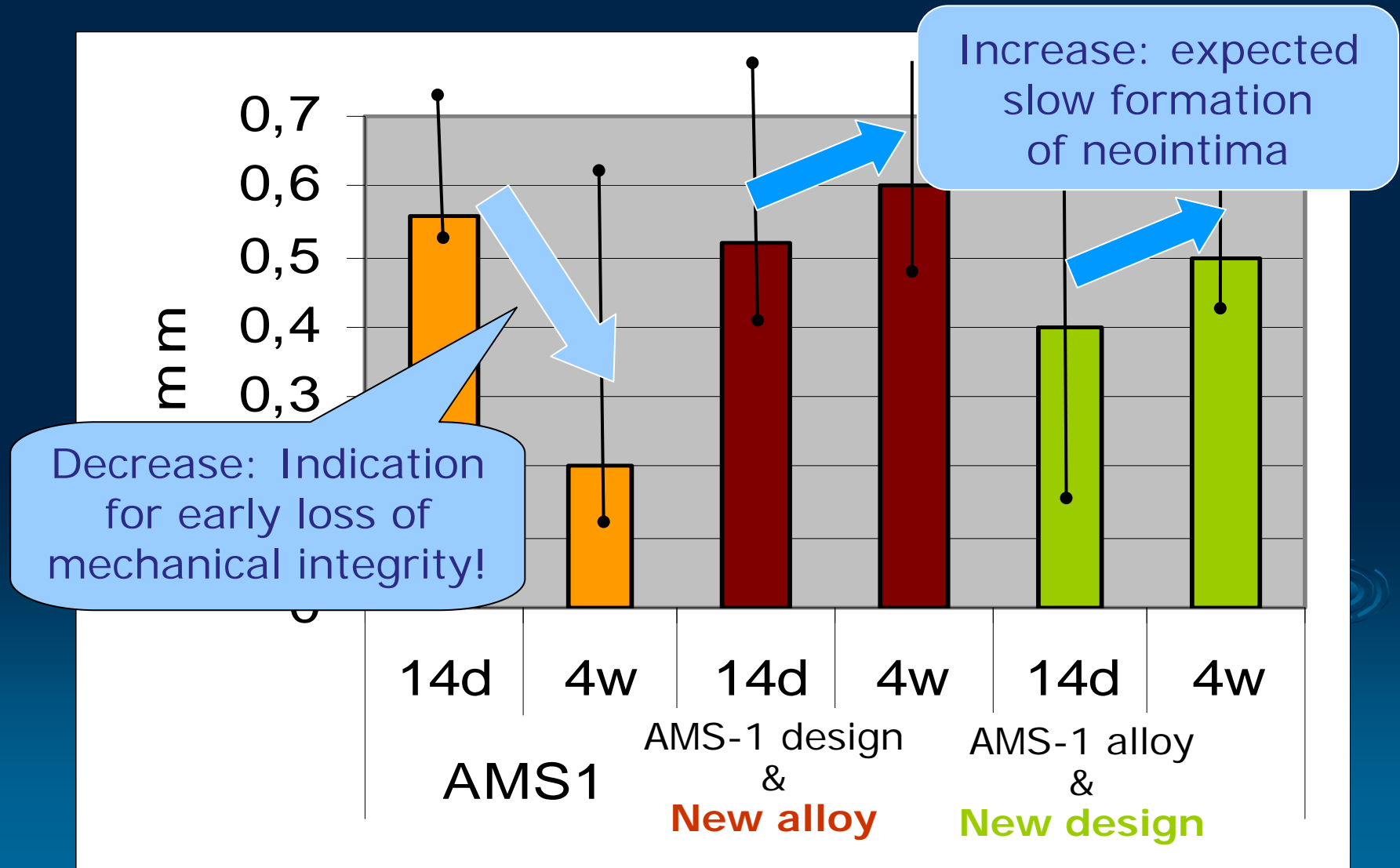
Optimization of mechanical stability



In vivo evaluation of AMS 2

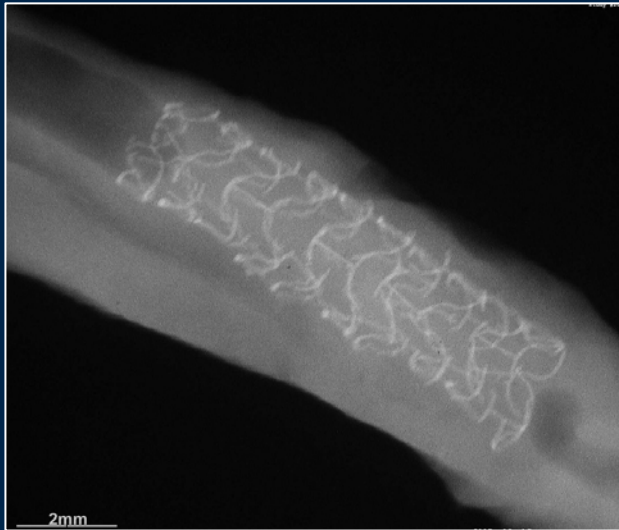


Late Lumen Loss [mm] in domestic pig

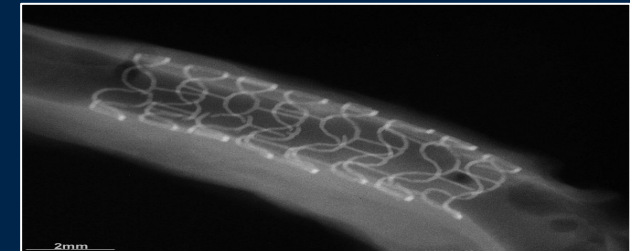


Stent Structure after 4 Weeks

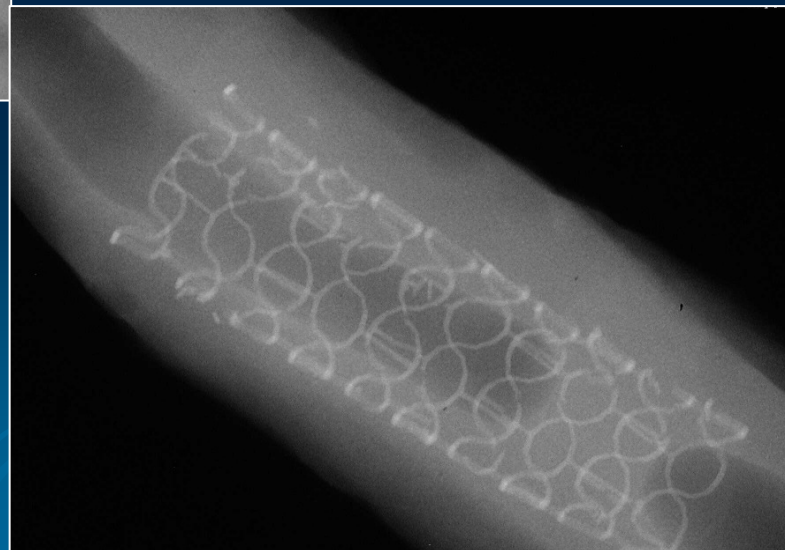
AMS 1



AMS1 Alloy & New design



AMS1 Design & New alloy



Summary

- Prolongation of mechanical integrity is useful
- New Mg alloy / design modification
- Ensure independent longer stability
- Combination of both is currently under animal investigation



Current Status

AMS 2 – Clinical strategy

Animal
Trial results
Improved
alloy + design

Coronary
Human
FIM

Peripheral
Human
FIM

PERIPHERAL



Conclusion

- For the future multiple options to improve P.C.I results
- Minimizing vessel wall damage ,controlling inflammatory and proliferative reactions can be achieved by the combination of new stent designs and new drugs
- Absorbable stents (most likely in combination with one or more drugs) seems a very logical approach but is a technical challenge.

