American Heart Association®

Fighting Heart Disease and Stroke

Eluting stents

The beginning of the end and the end of the beginning

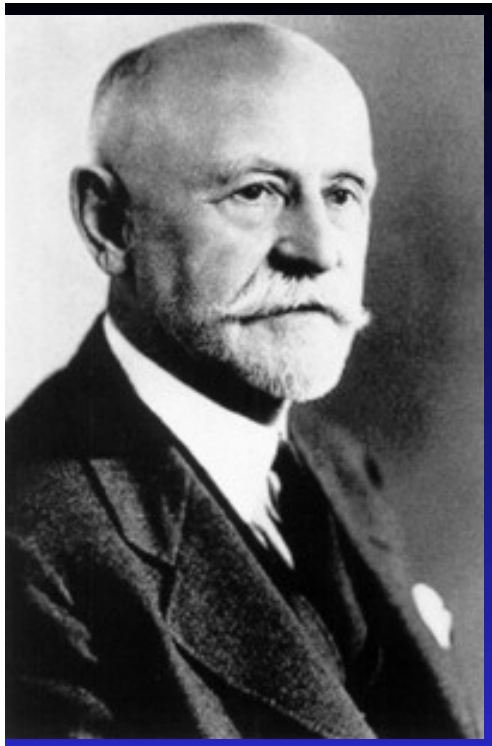
Patrick Washington Serruys, MD, PhD

Professor of medicine at the Erasmus University (EMC)

Head of the department of interventional cardiology at the Thoraxcenter

James B. Herrick lecture

Chicago



When I learned that I would receive this prestigious award…

I went to read James Bryan Herrick's old papers (difficult to obtain from the university library)

I became fascinated by the actuality of a paper written almost a century ago in the Transactions of the association of American Physicians: "Concerning thrombosis of the coronary arteries"

I was also charmed by the fact that he earned his Bachelor of Arts degree before getting his medical education.

I felt some sympathy for this great man…having myself studied philosophy before getting engaged in medicine.

The Title of my talk may seem cryptic…but was inspired by a quotation of Sir Winston Churchill, in a speech in November 1942 in an early, but critical phase of the World War II: “Now this is not the end. It is not even the beginning of the end. But it is, perhaps, the end of the beginning.”

I’ll try to convince you that we have seen the beginning of the end of a surgical era in coronary revascularization and that we are perhaps going to see the end of the first generation of drug-eluting stent and the beginning of the second and third generation of drug-eluting stent.

Overview of this lecture

Part I

The rosy prophecy and the beginning of the end

Part II

The DES journey from the rosy prophecy to harsh reality

Part III

Perspective and future expectations

Overview of this lecture

Part I

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Perspective and future expectations

The Rosy period

FIM: FIRST IN MAN

Rapamycin experience:

15 patients (Sao Paulo, E. Sousa) ; fast release

4 months follow-up ⟶ No restenosis, no TVR*

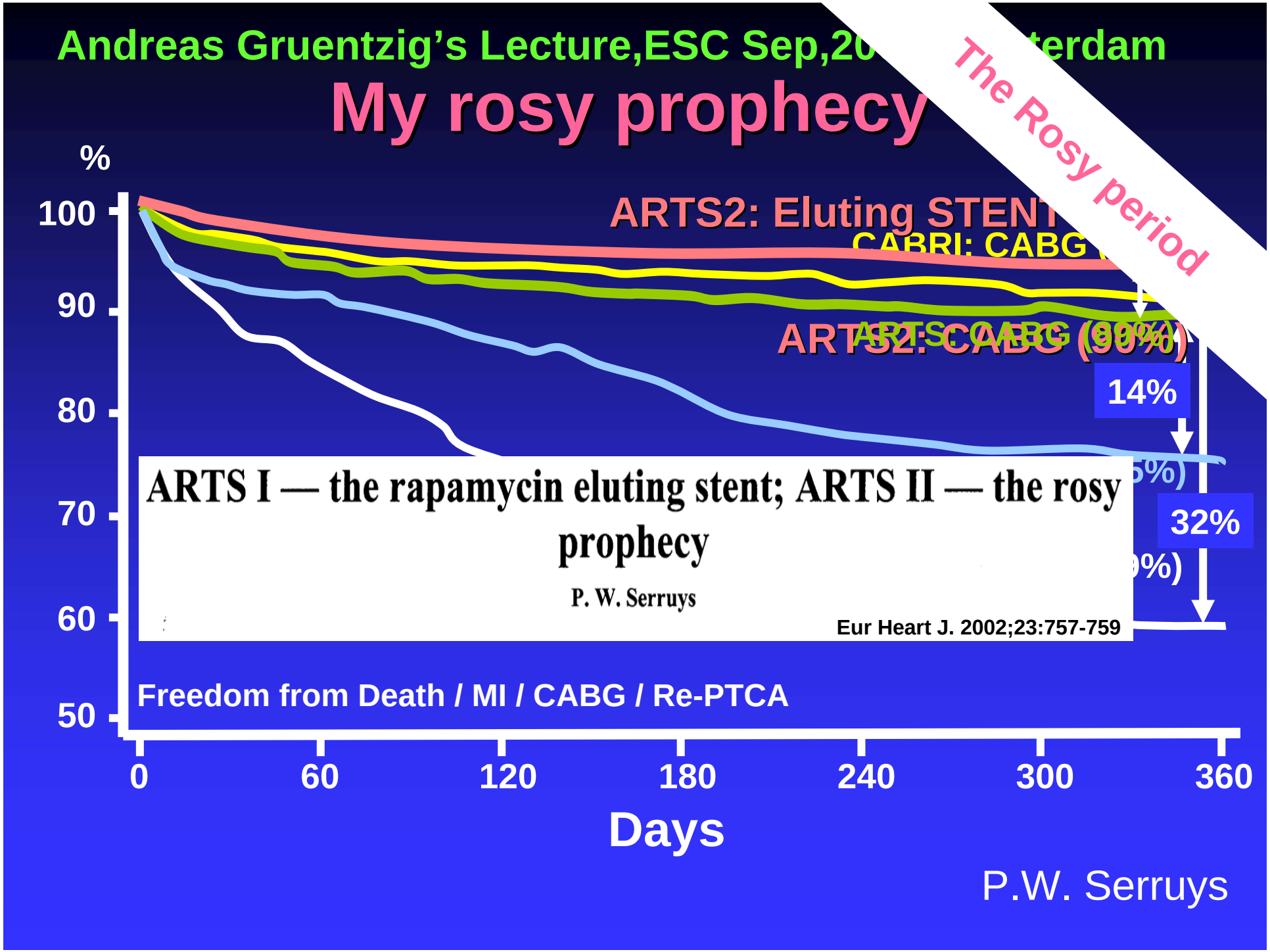
15 patients (Sao Paulo, E. Sousa) ; slow release

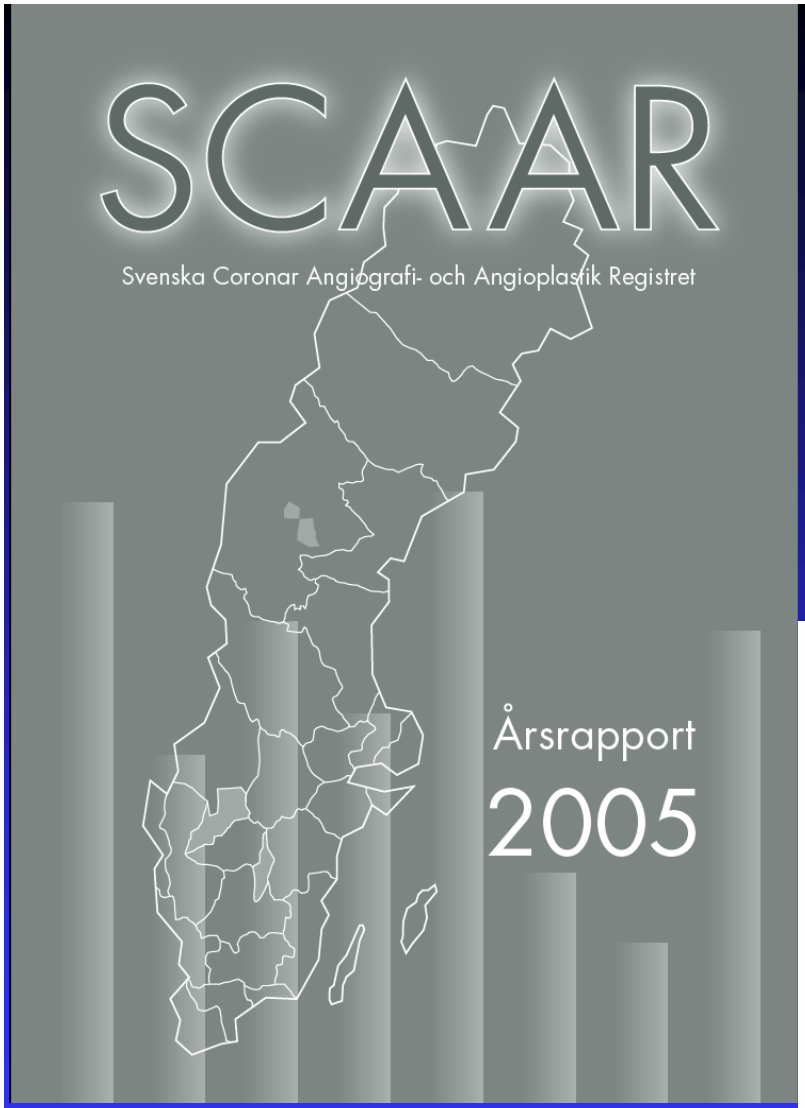
4 months follow-up ⟶ No restenosis*, no TVR*

15 patients (Rotterdam, PW. Serruys); slow release

6 months follow-up ⟶ No restenosis, no TVR

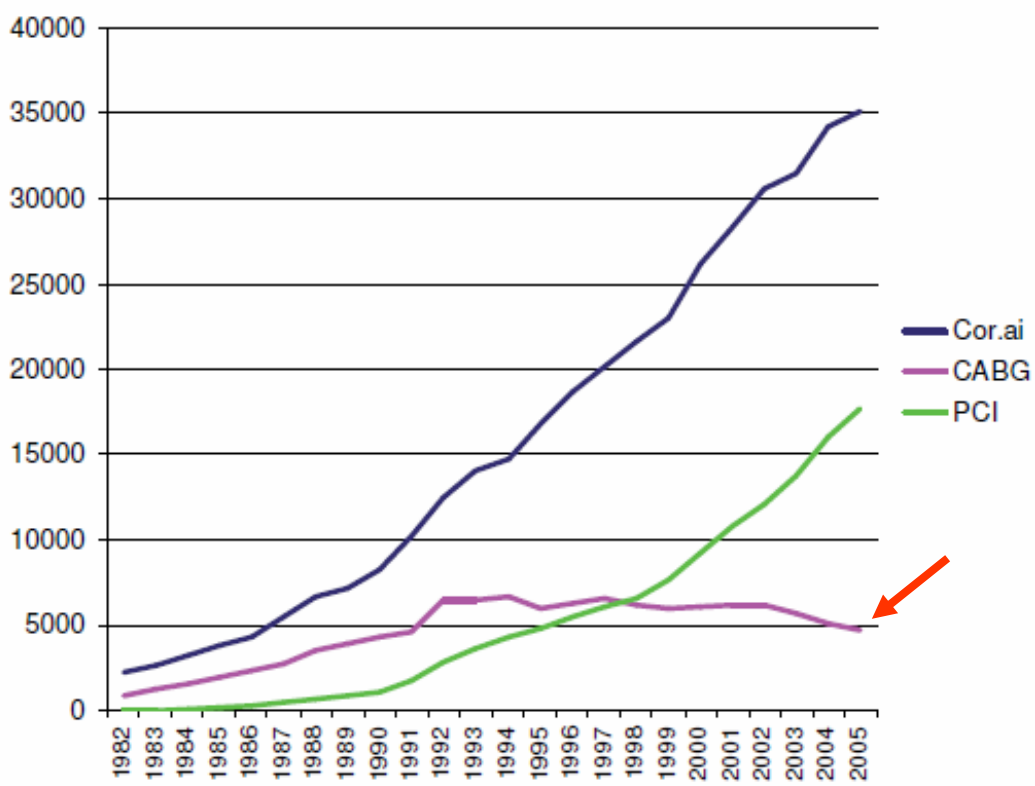
Don't wake me up,don't pinch me,let me keep dreaming


Andreas Gruentzig's Lecture,ESC Sep,20 terdam
My rosy prophecy
The Rosy period
%
100
90
80
70
60
50
ARTS2: Eluting STENT
CABRI: CABG
ARTS2: CABG (90%)
14%
32%
ARTS I — the rapamycin eluting stent; ARTS II — the rosy prophecy
P. W. Serruys
Eur Heart J. 2002;23:757-759
Freedom from Death / MI / CABG / Re-PTCA
0
60
120
180
240
300
360
Days
P.W. Serruys

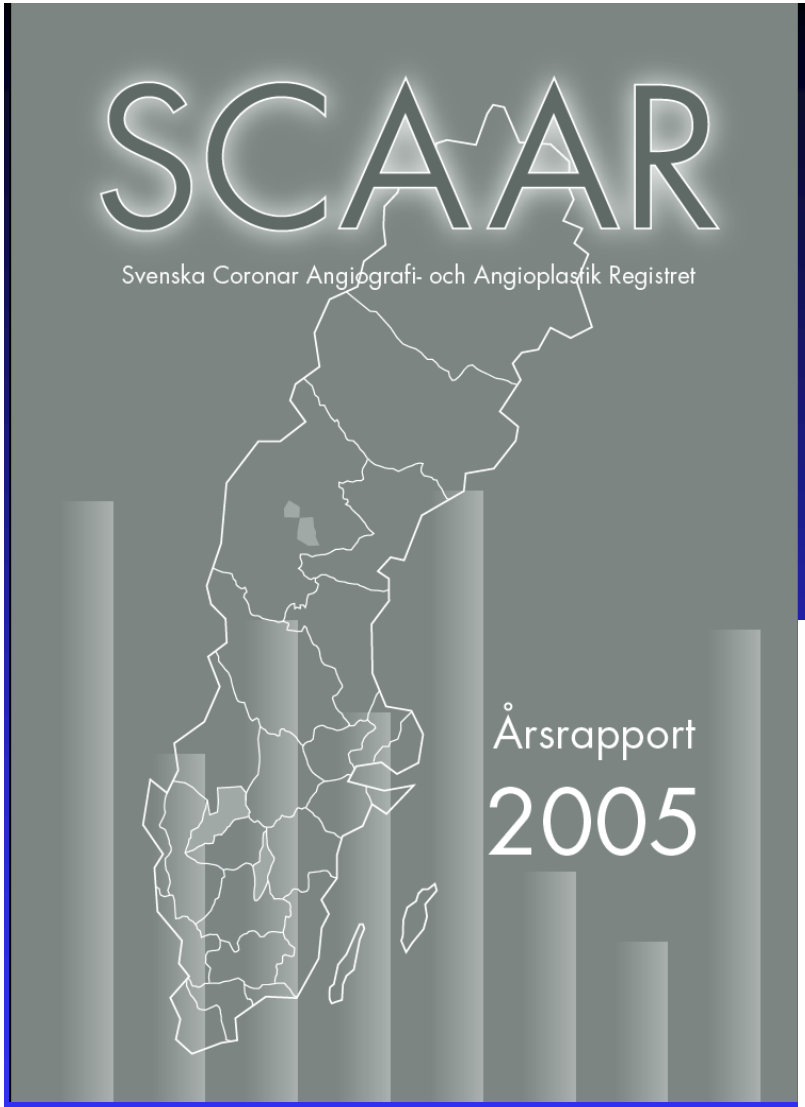


This is the last governmental report of Sweden on use of

1. **coronary angiography (Cor.ai),**
2. **bypass surgery (CABG)**
3. **percutaneous coronary intervention (PCI)**



The beginning of the end…



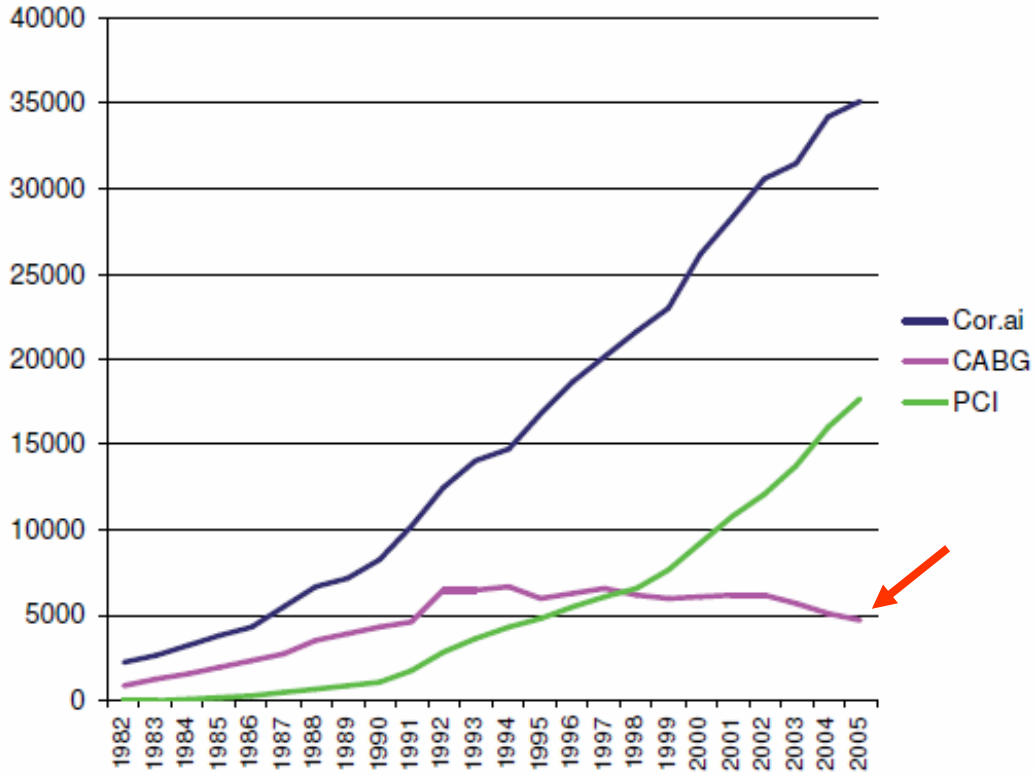
The beginning of the end…

During debates my friend-surgeons usually misquote me by telling the audience that I once said:

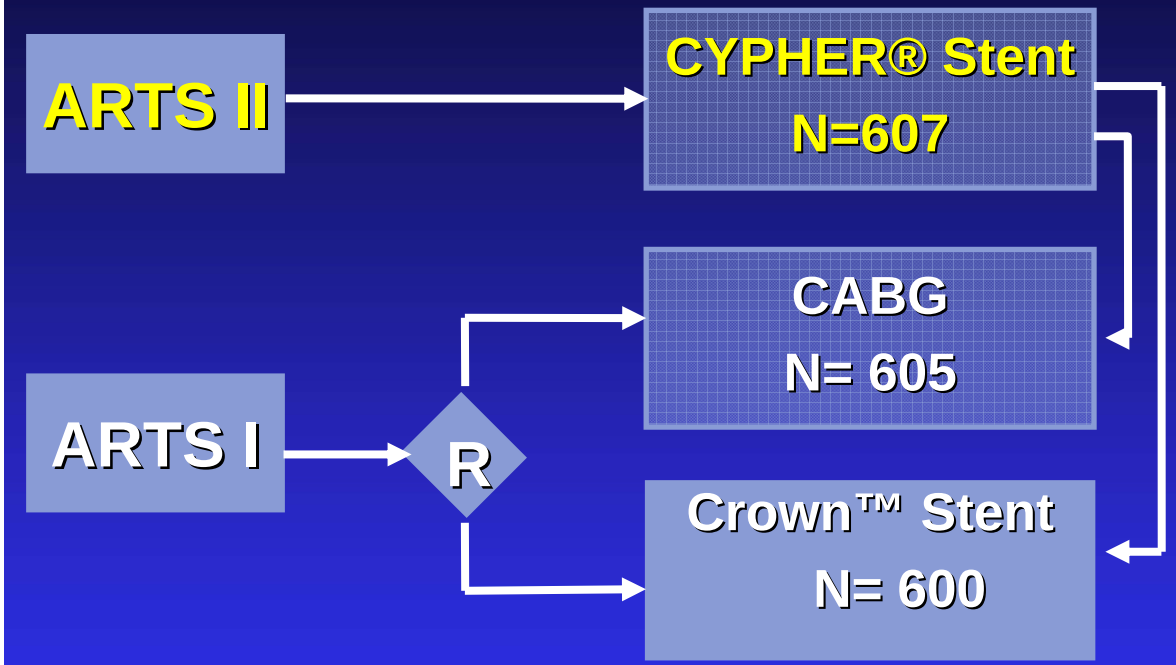
“Surgical coronary revascularization will disappear”

What I really said was the following:

“The question is not whether surgical coronary revascularization will disappear but when? ”



ARTS II – Study design



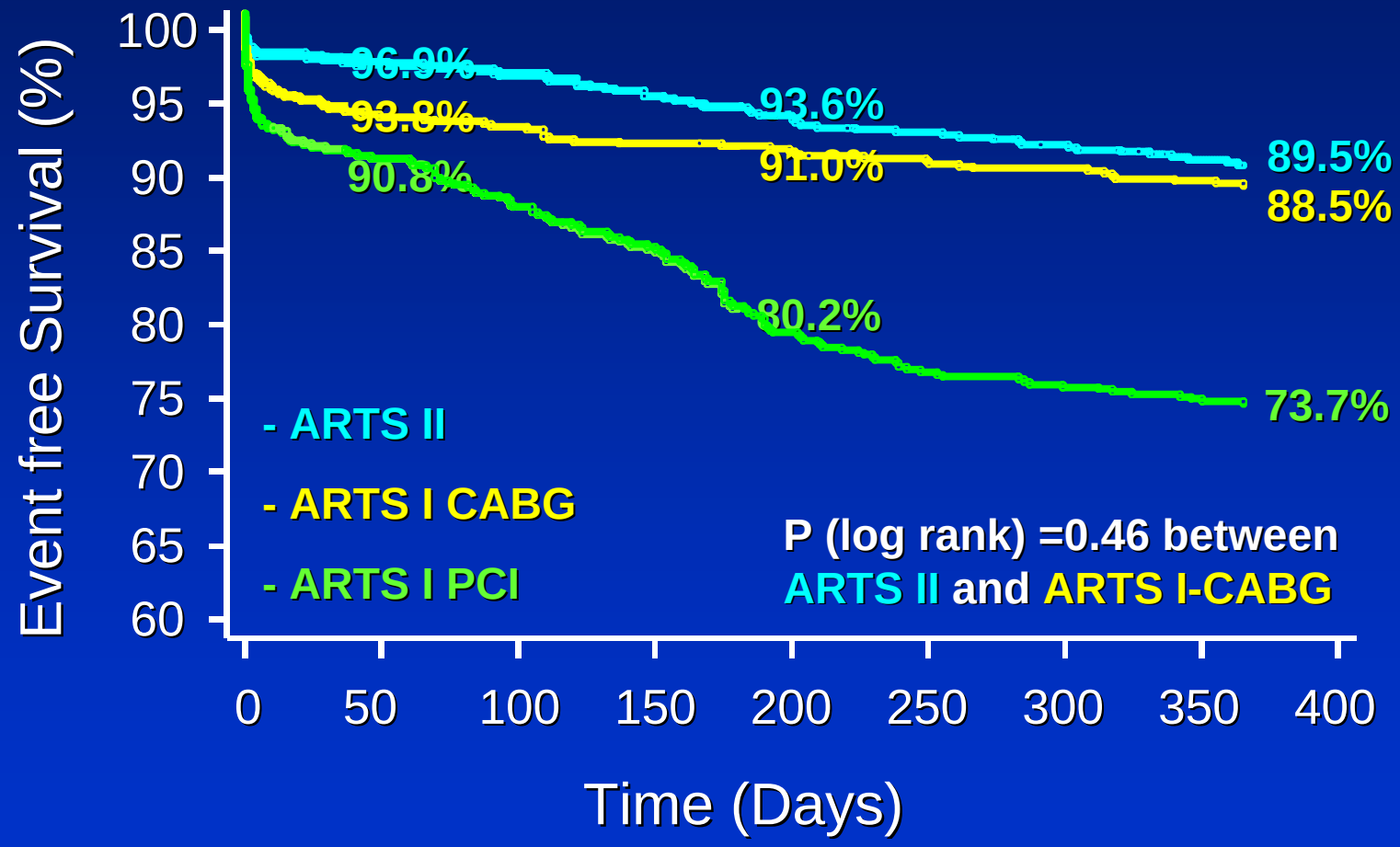
3VD treatment: 54%
2VD treatment: 48%
73 mm stent length

3VD treatment: 27%
2VD treatment: 69%
48 mm stent length

- **Primary endpoint:** **Major adverse cardiac and cerebrovascular events (MACCE) free survival at 1 year.**
- **Same inclusion / exclusion criteria as in ARTS I**
- **Same MACCE definition as in ARTS I**

Serruys PW et al; EuroInterv 2005; 1: 147-56

ARTS II - MACCE up to 1 year

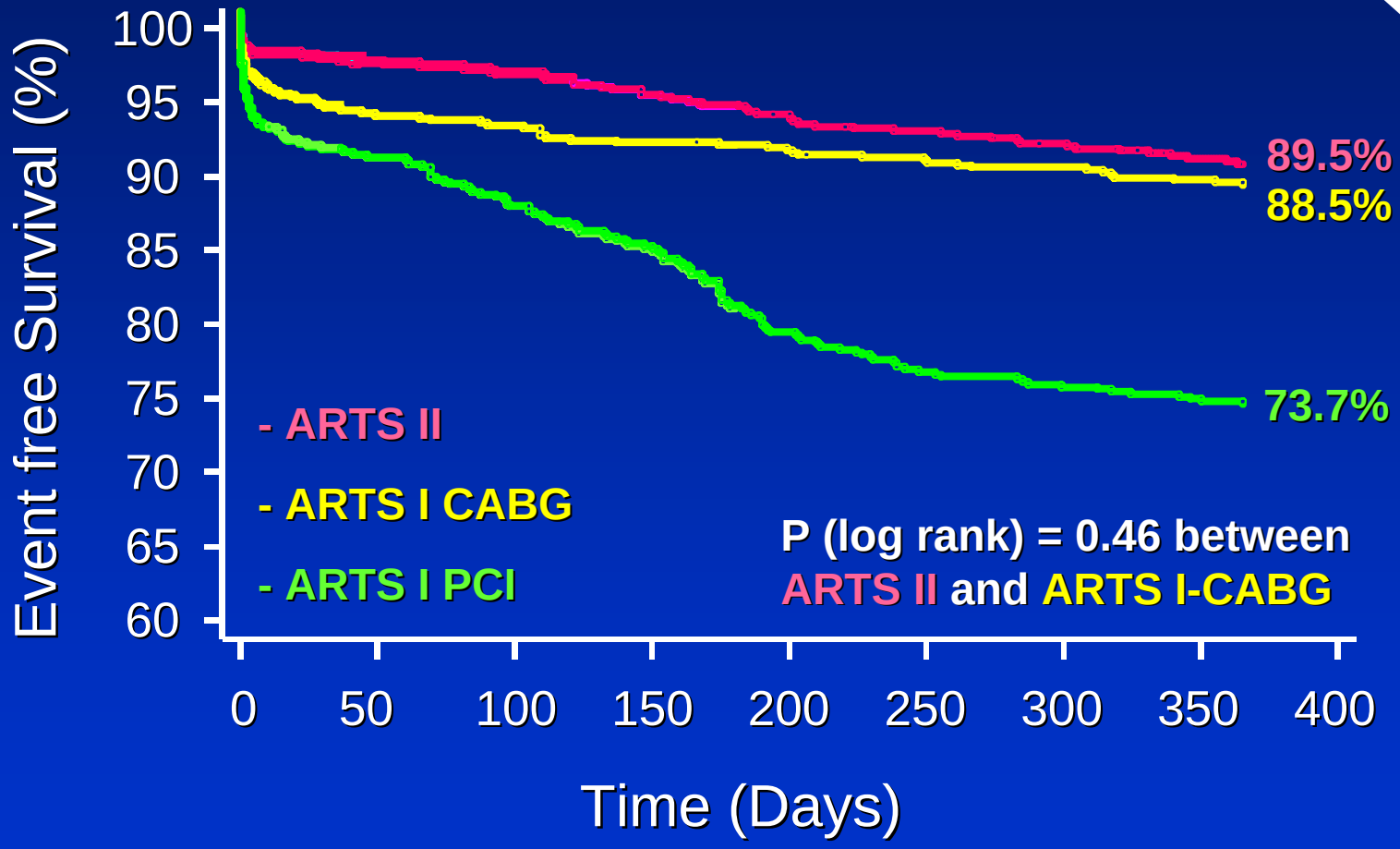


Serruys PW et al; EuroInterv 2005; 1: 147-56

ARTS II - MACCE up to 1 year

The Rosy period

The rosy prophecy came true !!!



Serruys PW et al; EuroInterv 2005; 1: 147-56

ARTS II (recruitment completed in November 2003) 3-year follow-up

Hierarchical MACCE at 3 years			
	Cypher (%)	BMS (%)	CABG (%)
Death	3.1	4.2	4.3
Death/MI	6.6	10.5	8.8
Death/CVA/MI	8.4	13.3	11.0
Revascularisation	11.3	21.4	5.1
MACCE	19.8	34.7	16.1

Preview of non-adjudicated events, to be presented at ACC

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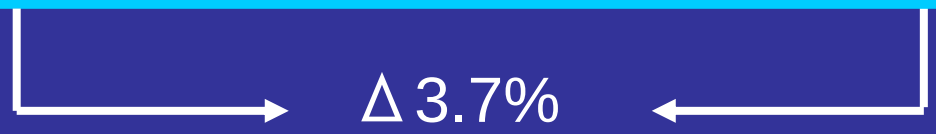


In November 2003 we started to design the next randomized trial…

Design of a new generation of randomized trial comparing percutaneous revascularization with DES and surgery for main stem and 3 vessel disease

concept

Syntax Chronology

realization

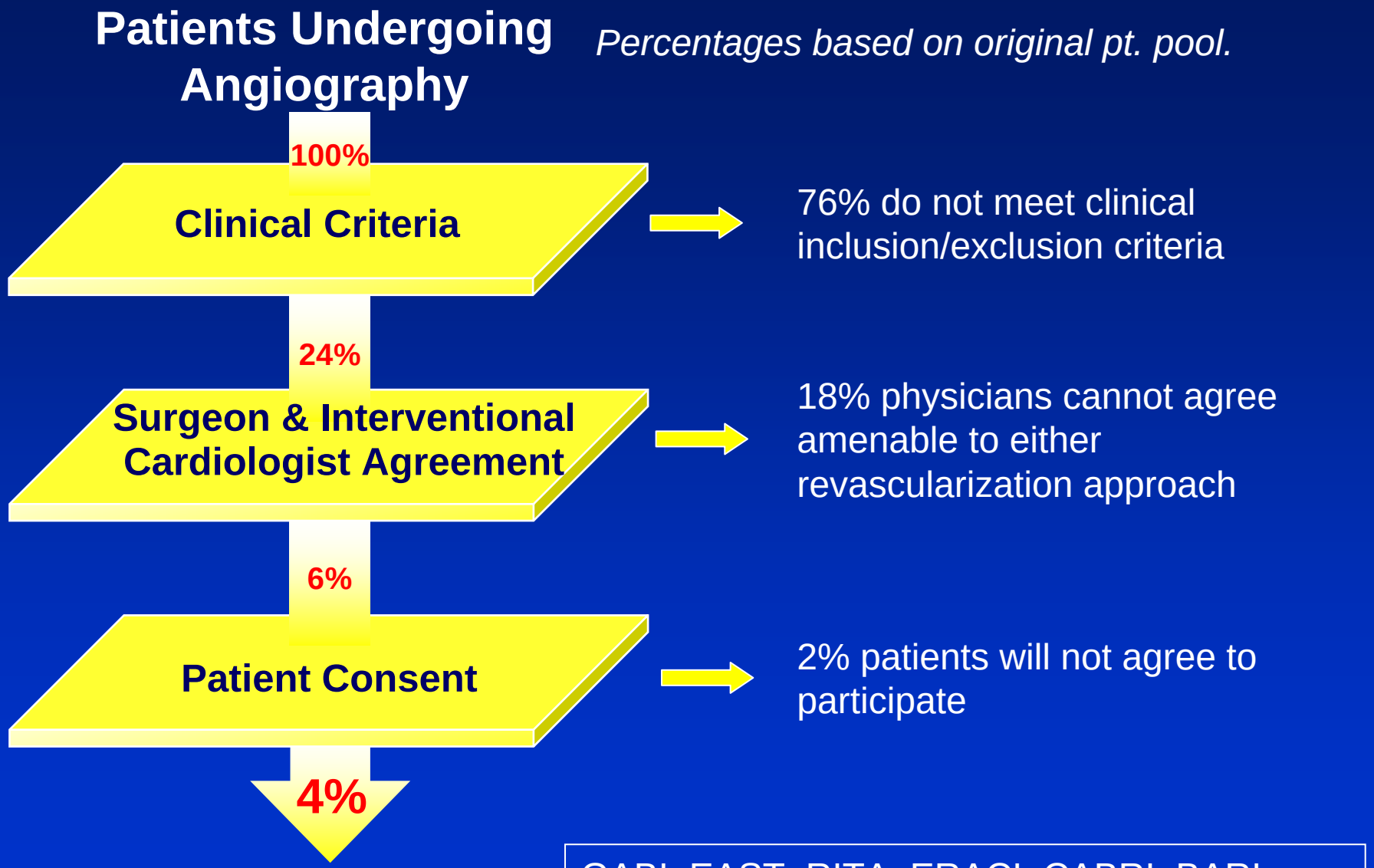
Statement made by Friedrich Mohr, professor of surgery in Leipzig during the Frankfurt kick-off meeting on February 21st 2004

Friedrich Mohr

"I fully disagree! These trials represent biased patient selection and it does not reflect the current practice in surgery!"

Therefore we need to study all-comers!

Trials studied highly selected patients



Syntax Overall Study Goal

For patients with 3VD or LM disease

1) to define the patient to be treated by CABG

2) to define the patients to be treated by PCI

all comer study
instead of highly selected patient population

consensus physician agreement (surgeon & cardiologist)
instead of inclusion & exclusion criteria

nested registry to define patient characteristics and outcomes
of patients amenable only to either CABG or PCI

SYNTAX: Study Design

All Pa… with 3VD / LM

Heart T… …tionalist)

1653 pts randomized

amenable for both treatments options

amenable for one treatment approach

Randomized Arm

***N=1800* (1:1)**

TAXUS *vs* CABG

- reasonable doubt
- follow-up: 30d, 6m, 1-5 yrs
- **Goal: to define the most appropriate treatment through randomized trial methods**

Two Registry Arms

CABG	***PCI***
2750 captured (750 followed)	***All captured and followed***

- consensus exists that only one treatment option (CABG vs PCI) is appropriate
- **Goal: to profile larger pool of non randomizable patients and their subsequent outcomes**

FREEDOM: Study Design

460 pts
enrolled

Diabetes Mellitus with 2-3VD

surgeon and interventionalist

amenable for both treatments options

amenable for one treatment approach

Randomized Arm
N=2400 (1:1)

DES *vs* CABG

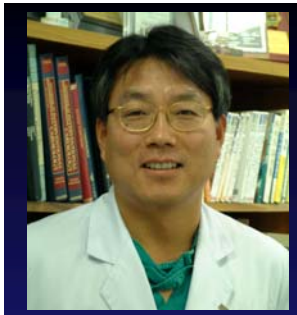
- follow-up: 30d, 6m, 1-5 yrs
- Goal: to define the most appropriate treatment ***for diabetic patients*** through randomized trial methods

Two Registry Arms
N=2000

CABG
All captured and followed

PCI
All captured and followed

- consensus exists that only one treatment option (CABG vs PCI) is appropriate
- Goal: ***to compare outcomes with randomized group***



COMBAT Randomized Trial

*COM*parison of *B*ypass surgery and *A*ngioplas*T*y using sirolimus eluting stent in patients with left main coronary

Left main disease with or without MVD

amenable for both treatments options

amenable for one treatment approach

Randomized Arm
N=1730 (1:1)

PCI with Cypher *VS* CABG

Three Registry Arms
N=1000

CABG
All captured and followed

PCI
All captured and followed

Primary Endpoint: 2-year death, MI and stroke

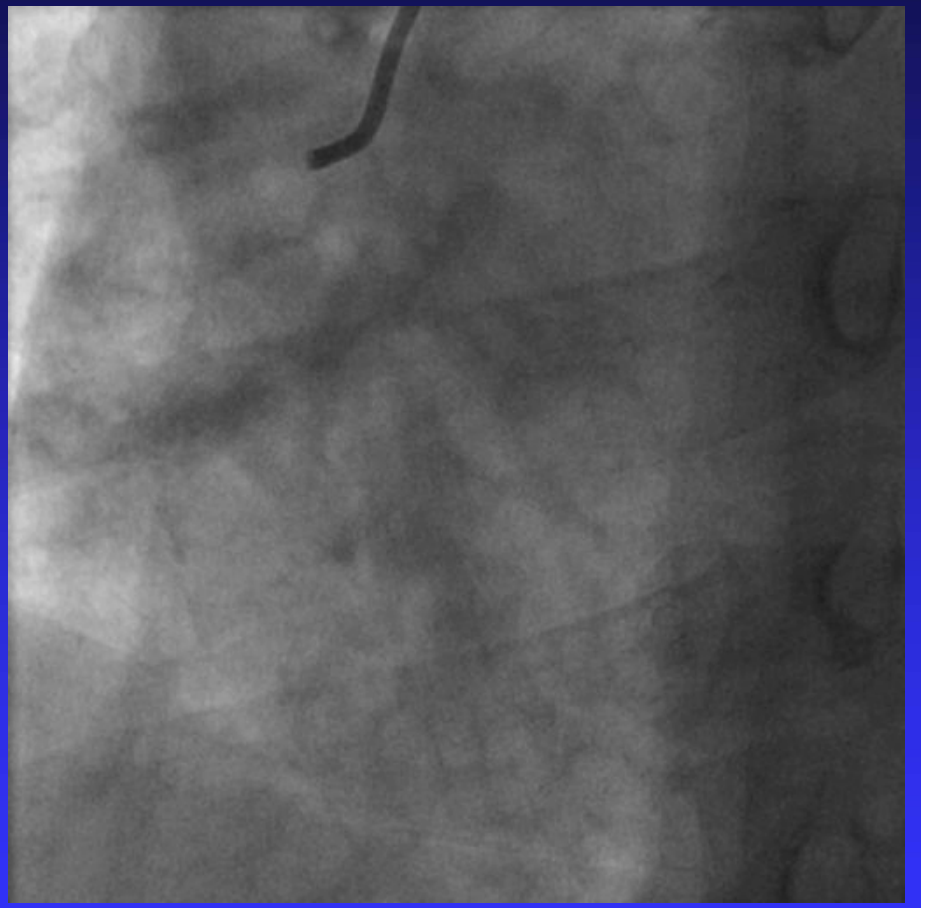
Secondary Endpoint: 6-month QCA; 2-year, 5-year TLR, MACE

Are their still cases with left main lesion that we could not technically treat with PCI ?

- **Patient:** 66 years old pt with no previous medical history
- **Coronary Risk Factors:** Smoking
- Admitted to a peripheral hospital because of acute heart failure and evidence of semi-recent anterior MI (LDH ↑)
- **Medication:** aspirin 100mg, clopidogrel 75mg, atorvastatine 40mg, ramipril, carvedilol, furosemide, heparine iv

SYNTAX SCORE

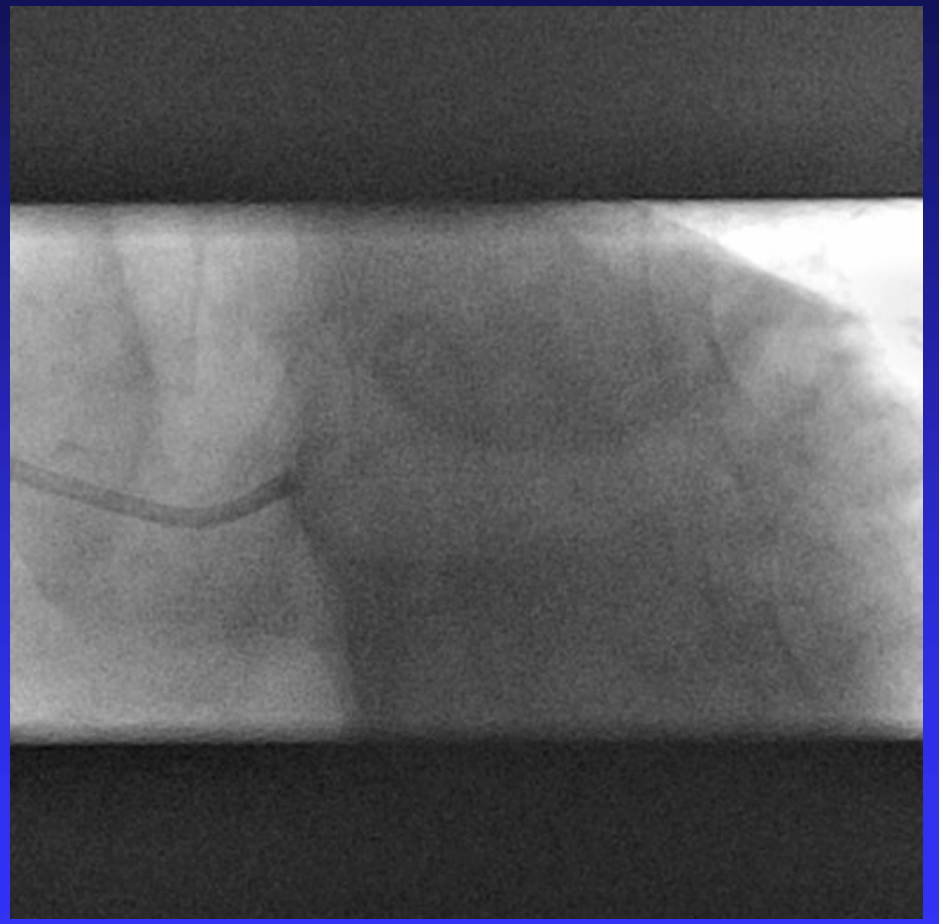
Lesion 1	
Segment 1 (1x5)	5
Age of total occlusion unknown	1
Bridging	1
First Segment Visualized (seg 2)	0
+ side branches<1.5mm	1
Length >20	1
Sub total lesion 1 Score	*9*



G. Sianos, M.-A. Morel, A.Pieter Kappetein, M.-C. Morice, A. Colombo, K. Dawkins, M.van den Brand, N. Van Dyck, M. E. Russell, P. W. Serruys EuroIntervention 2005;1:219-227

SYNTAX SCORE

Lesion 2	
Segment 5 (5x2)	**10**
Segment 11 (1.5x2)	**3**
Trifurcation ***(2 diseased seg. Involved)***	**4**
SevereTortuosity	**2**
Sub total lesion 2 Score	***19***



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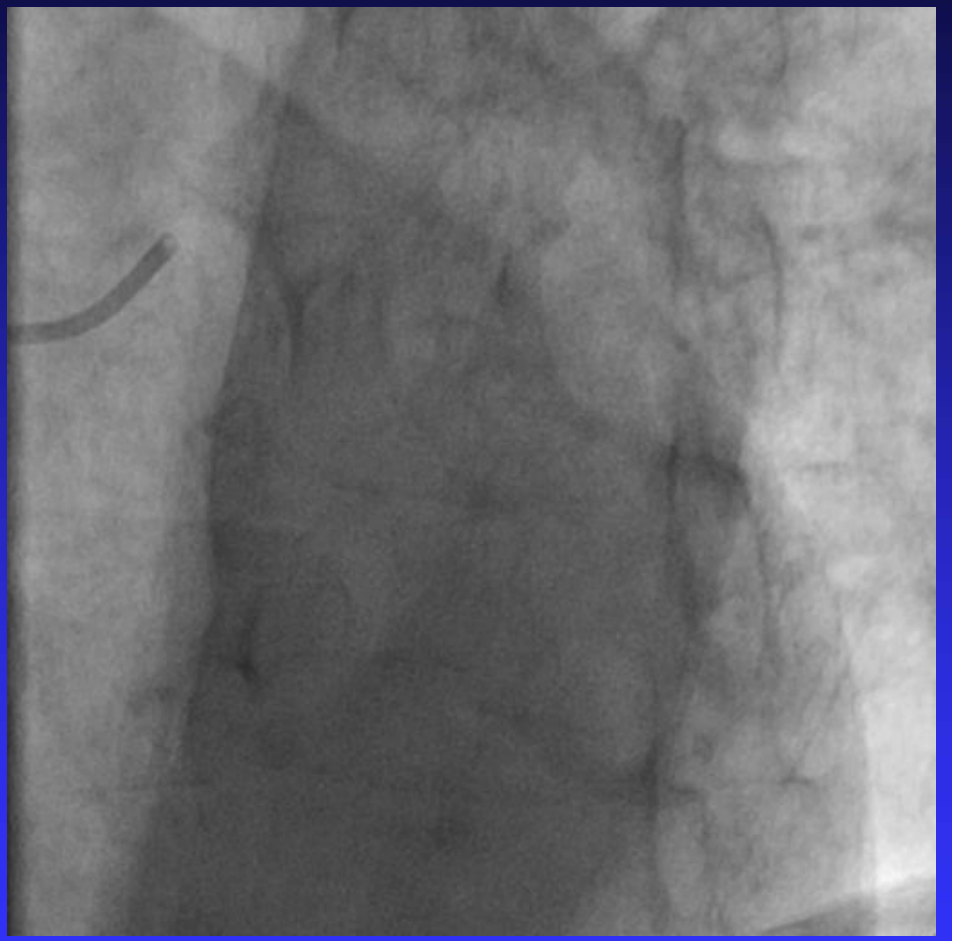
SYNTAX SCORE

Lesion 3	
Segment 7 (2.5x2)	
Sub total lesion 3 Sc	*5*
Lesion 4	
Seg (0.5x2)	1
re Tortuosity	*2*
Sub total lesion 4 Score	3

Total Syntax Score 36



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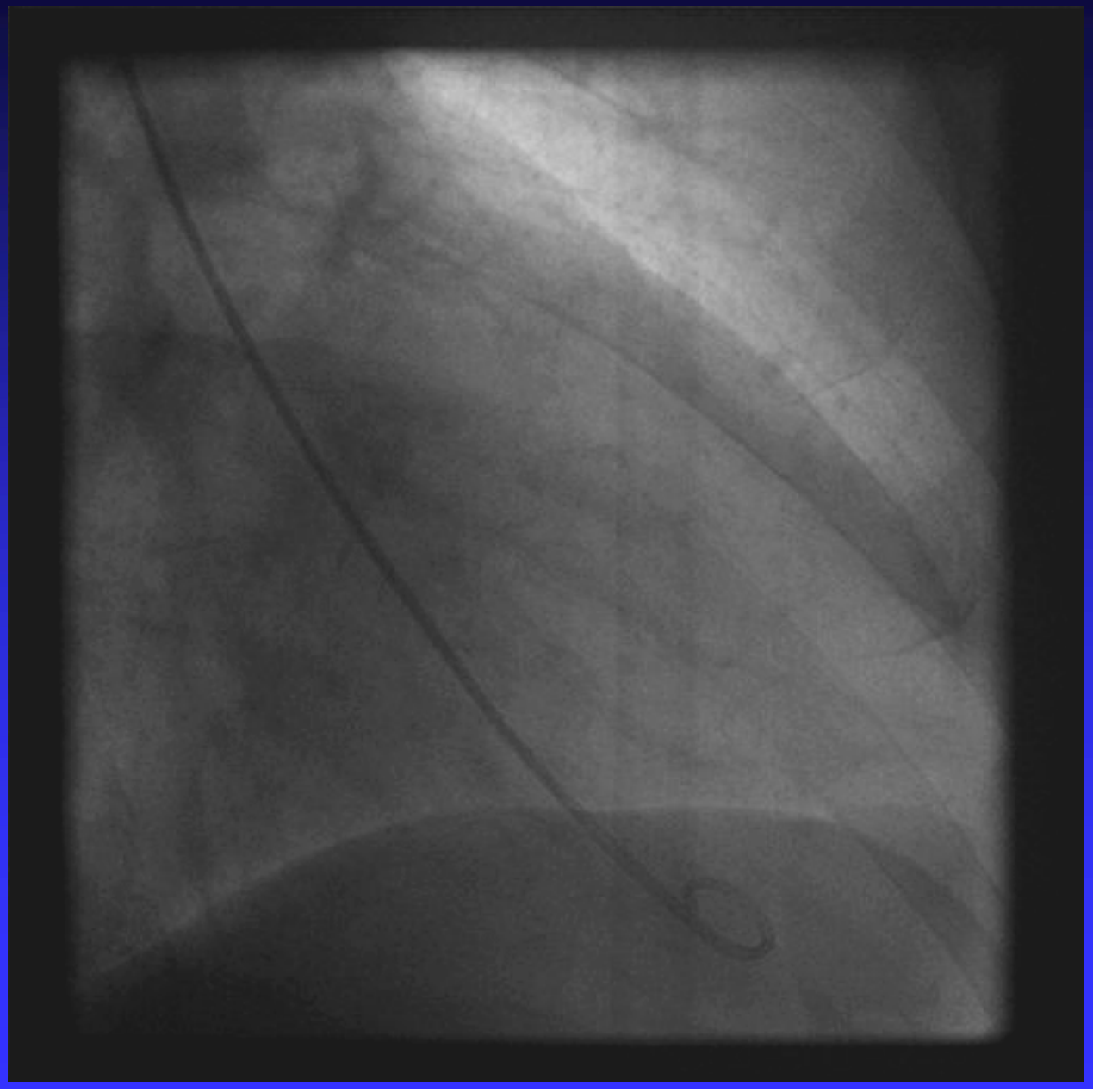
Left Ventriculogram



EUROSCORE

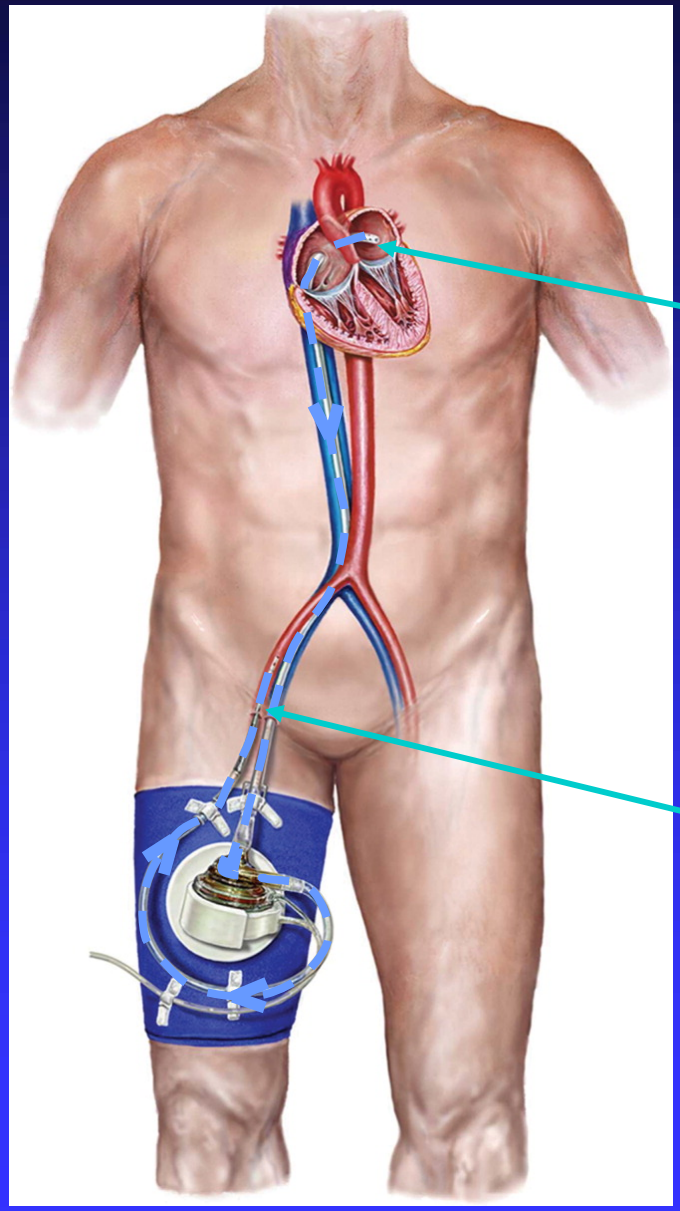
Cardiac – related factors			Operati		factors
Unstable angina	Yes	2	ted CABG	No	0
LV function			Emergency	No	0
Rec	Yes	2	Surgery on thoracic aorta	No	0
Pulmonary hypertension	No	0	Post infarct septal rupture	No	0

Total EuroScore = 9

Logistic Euroscore = 11.42%

Surgery or PCI?

The surgeon asked us to treat the patient percutaneously… and we did it, but with the hemodynamic support of percutaneous left ventricular assist device

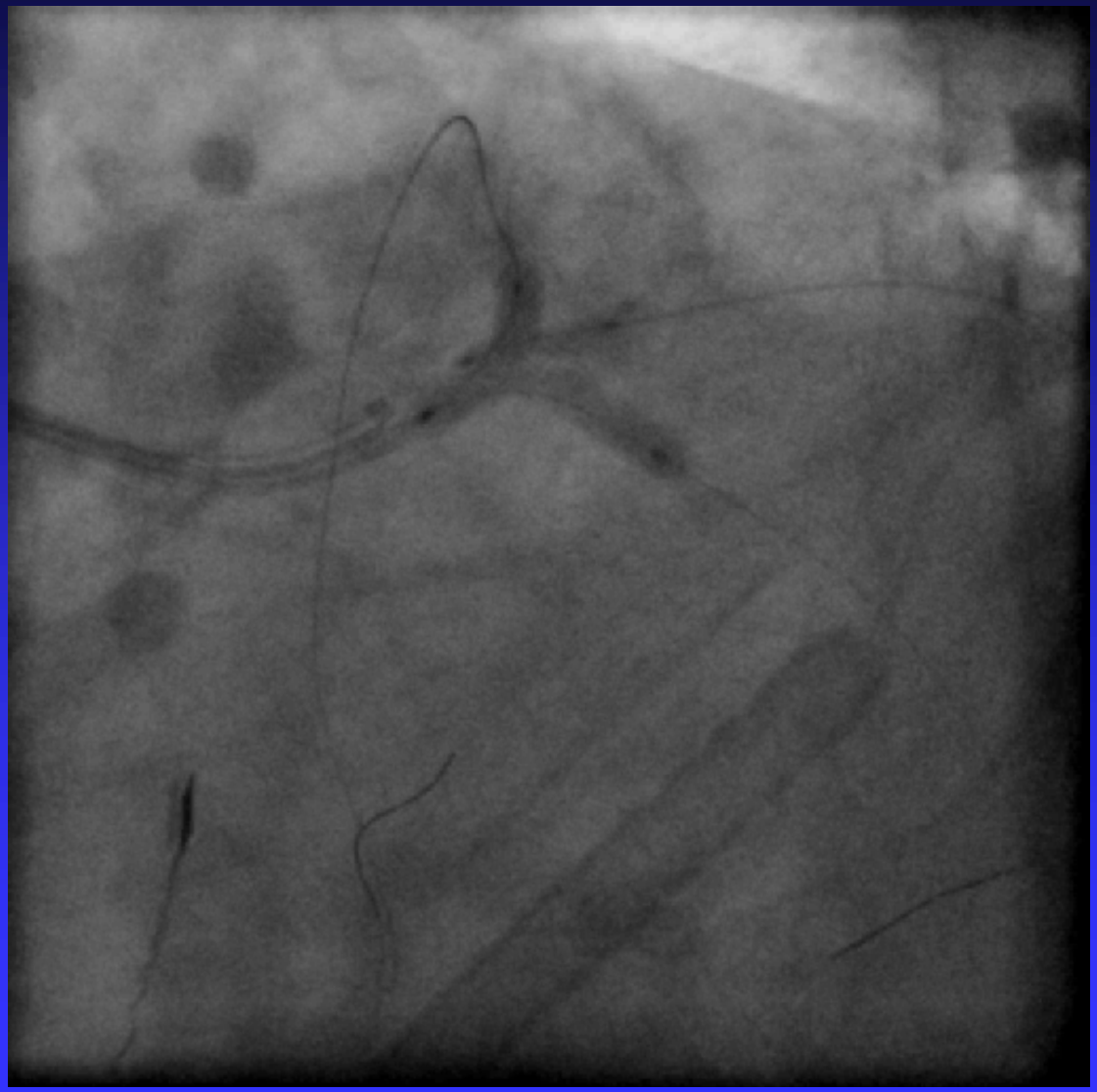


Removes oxygenated blood from the

left atrium via a transseptal cannula

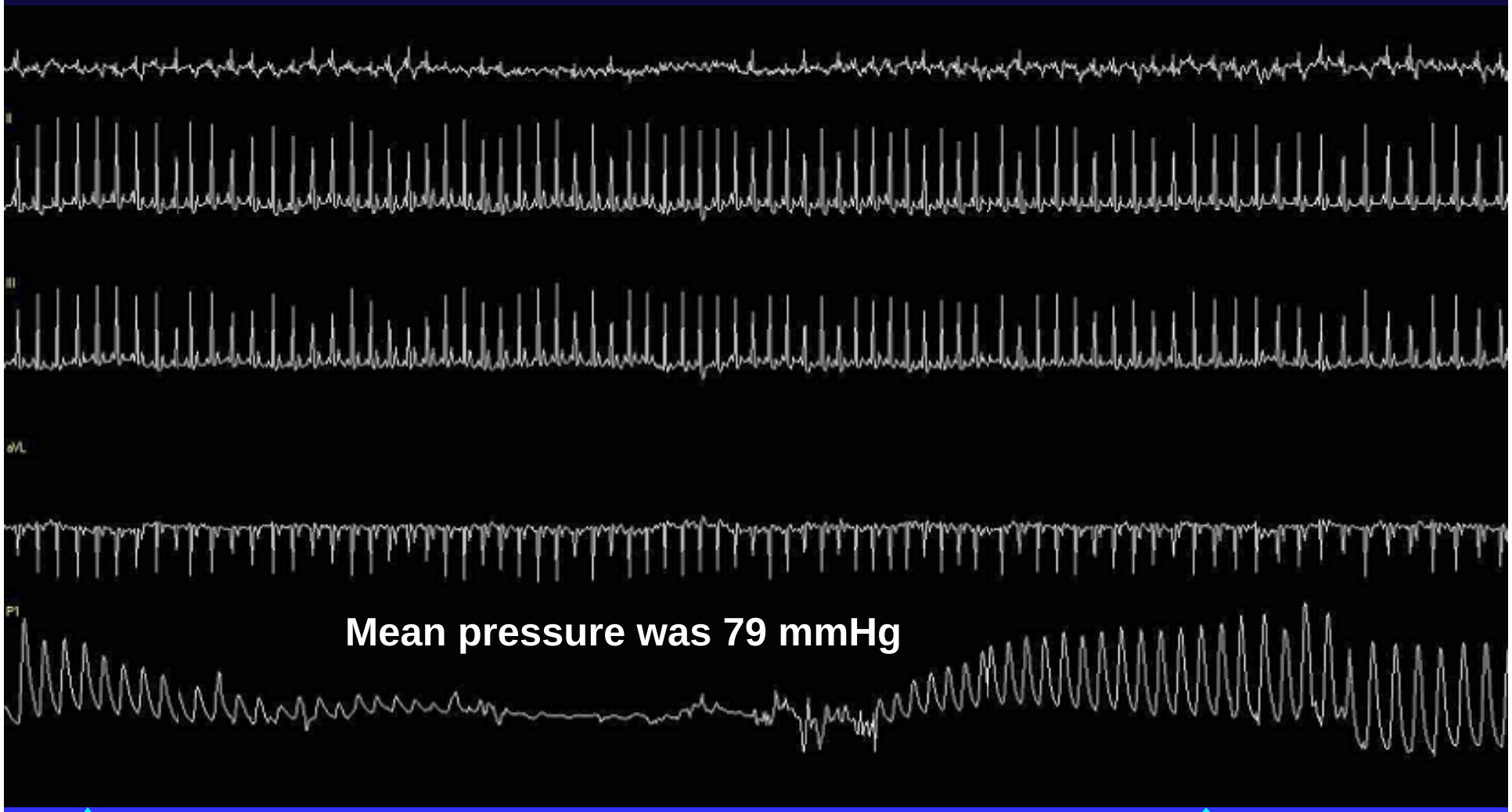
into the femoral artery

Simultaneous triple-balloon dilatation in the LM during one of the phase of the treatment



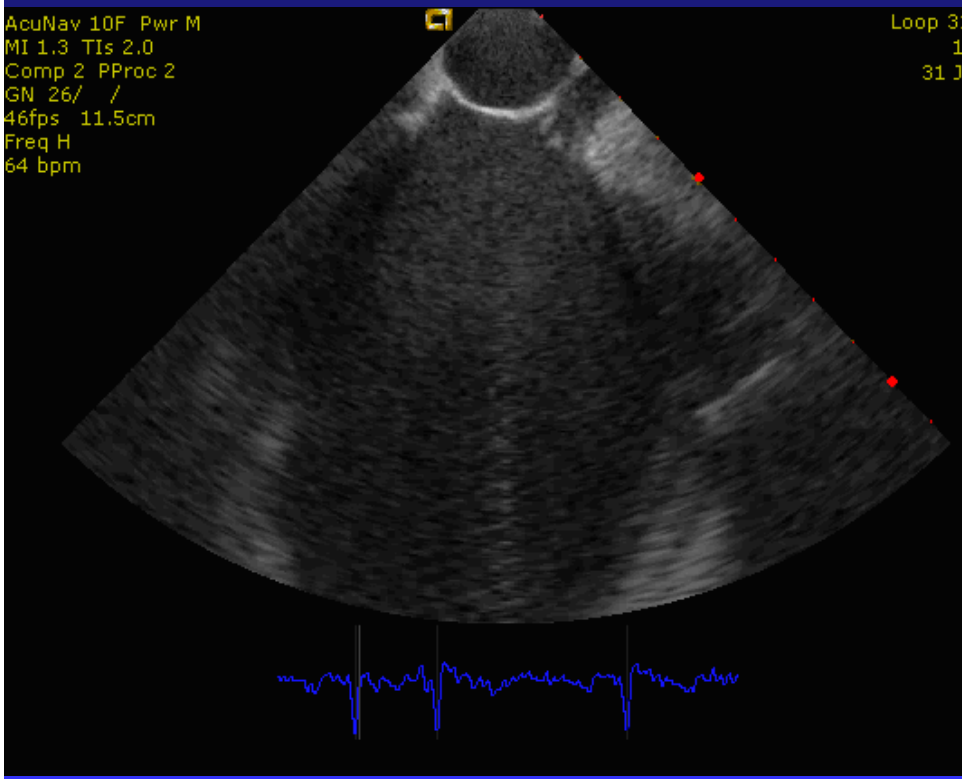
Spider View

Hemodynamic support by the left ventricular assist device during occlusion of the left main stem coronary artery



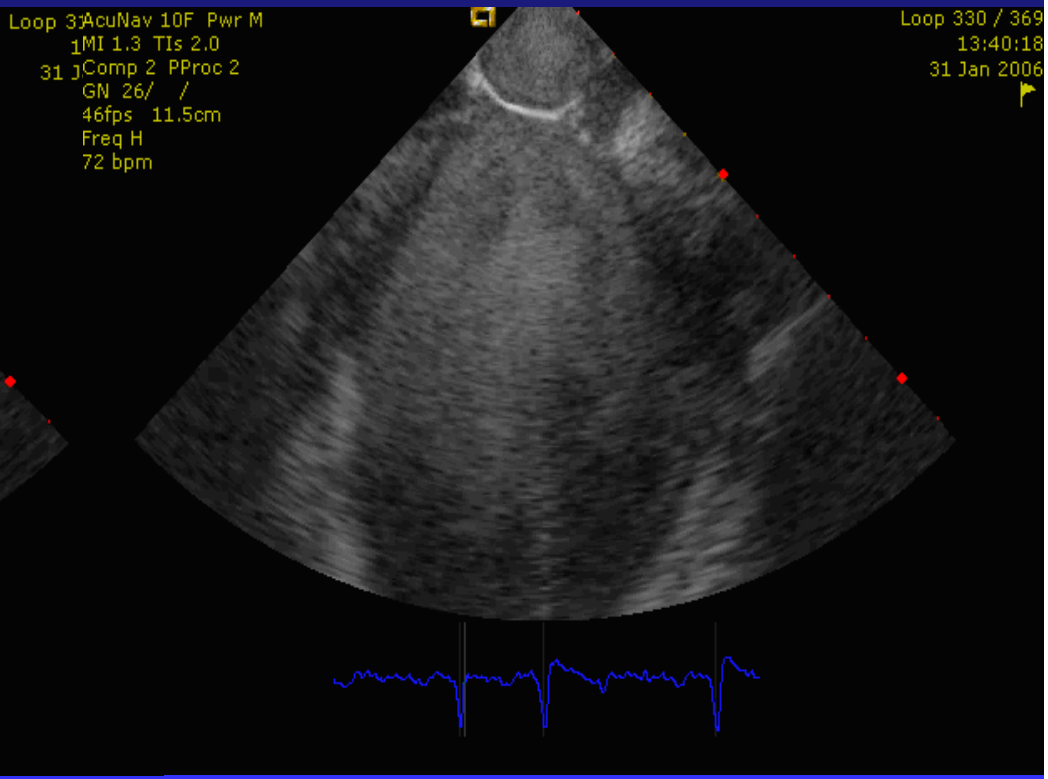
LV during gradual TANDEMHEART™ Function

Opening aortic valve



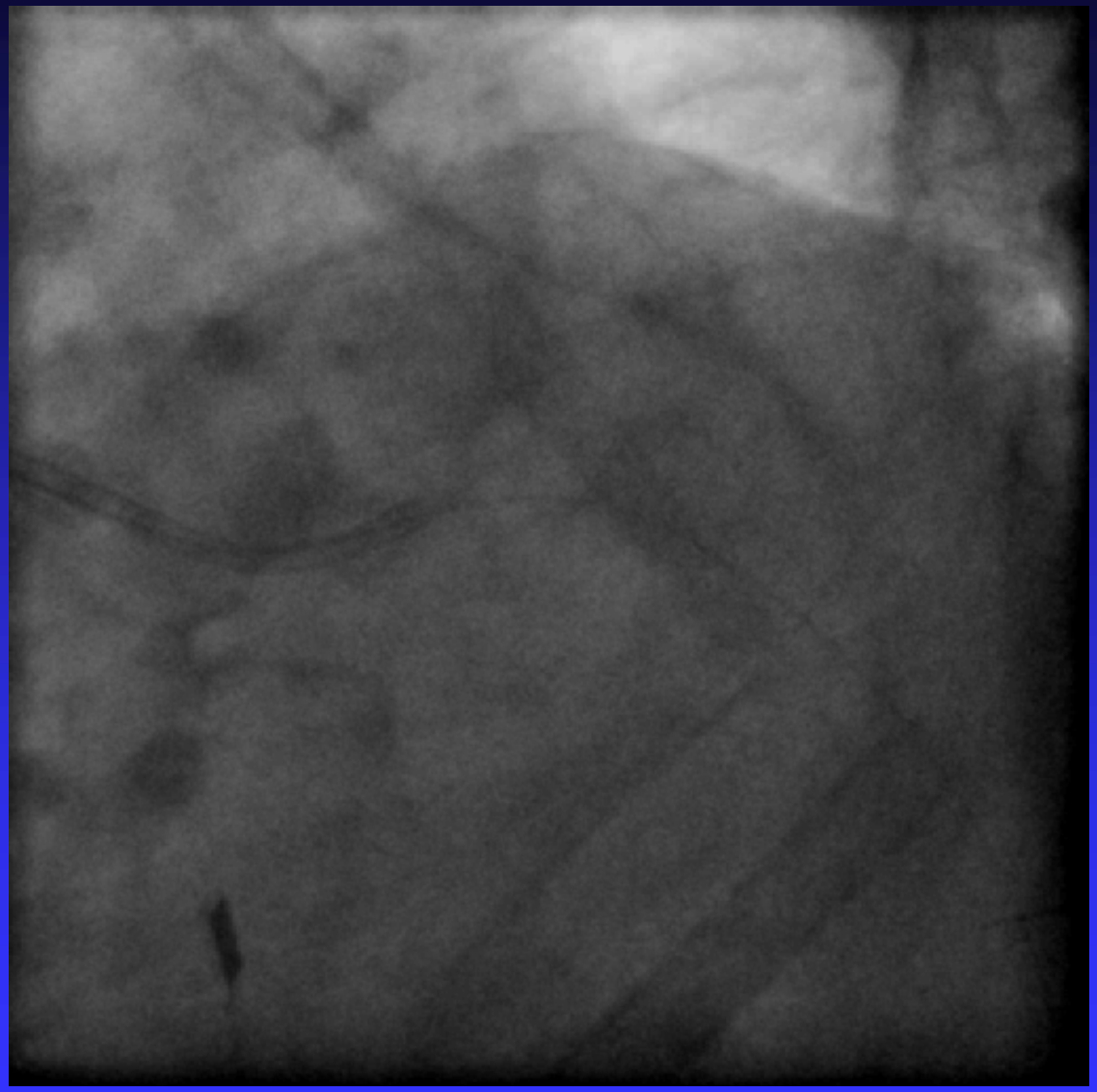
TANDEMHEART™ off

Aortic valve remaining closed



TANDEMHEART™ on

Final result



Spider View

LCX mid

3.0 x 12 mm

Left main- LCX ostium

3.5 x 20 mm

LAD mid

3.0 x 16 mm

LAD ostium

3.5 x 16 mm

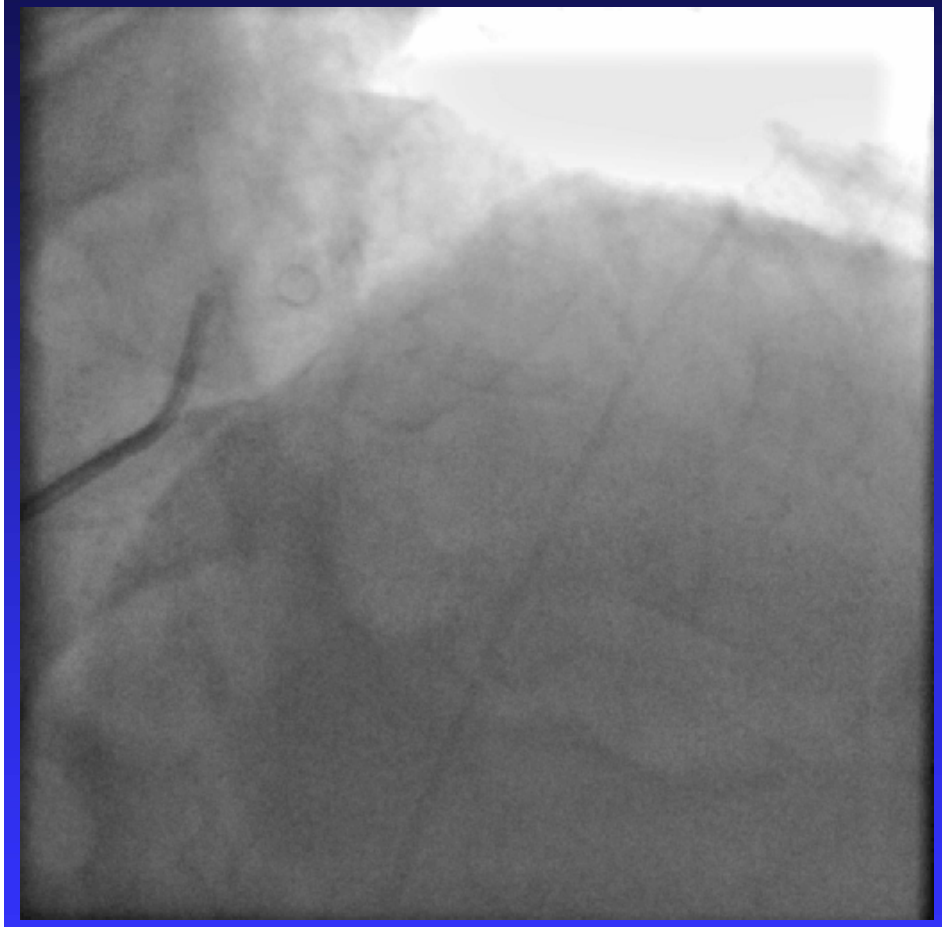
Intermediate ostium

2.5 x 12 mm

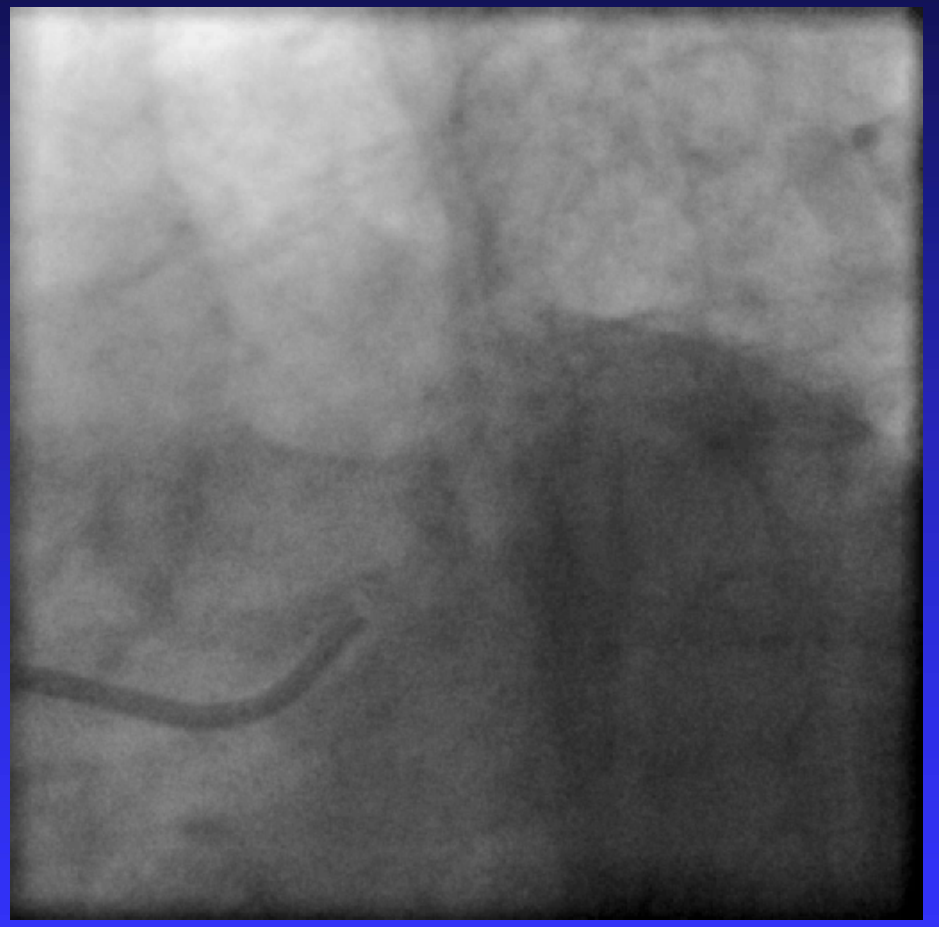
Total stent number: 5

Total stent length: 76 mm

Follow-up Angiogram (at 9 months)

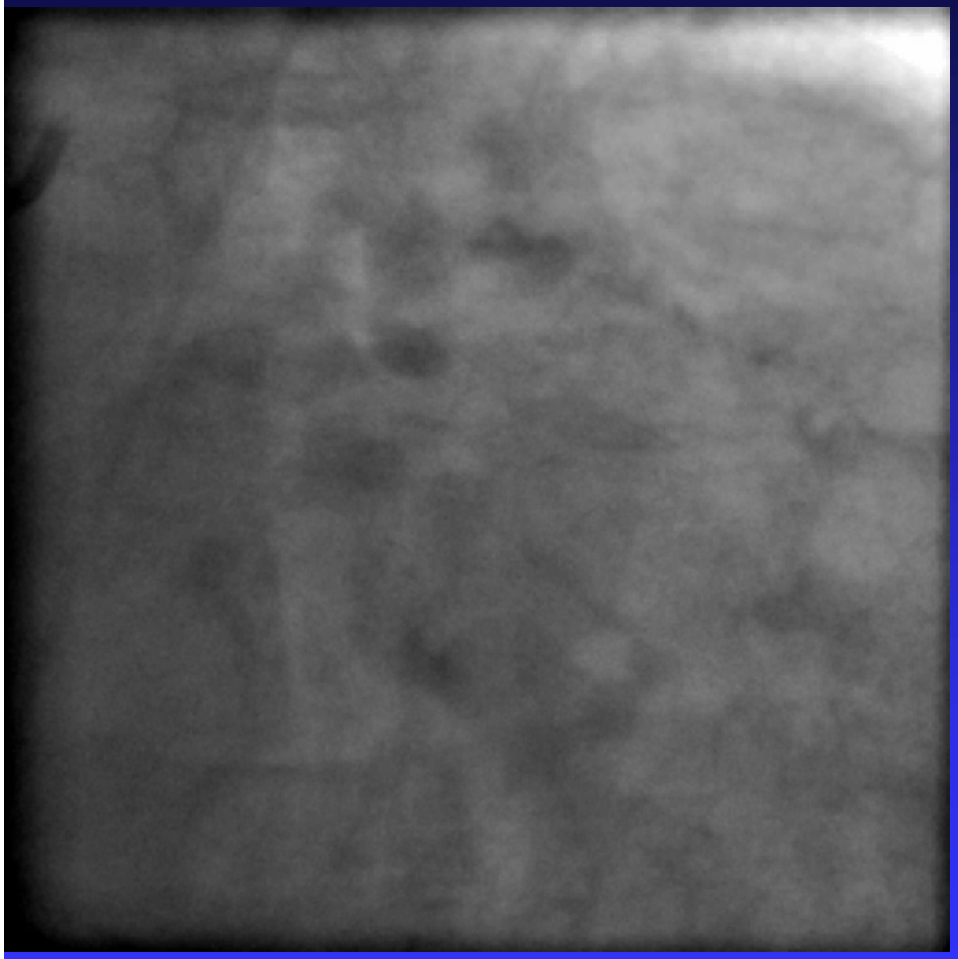


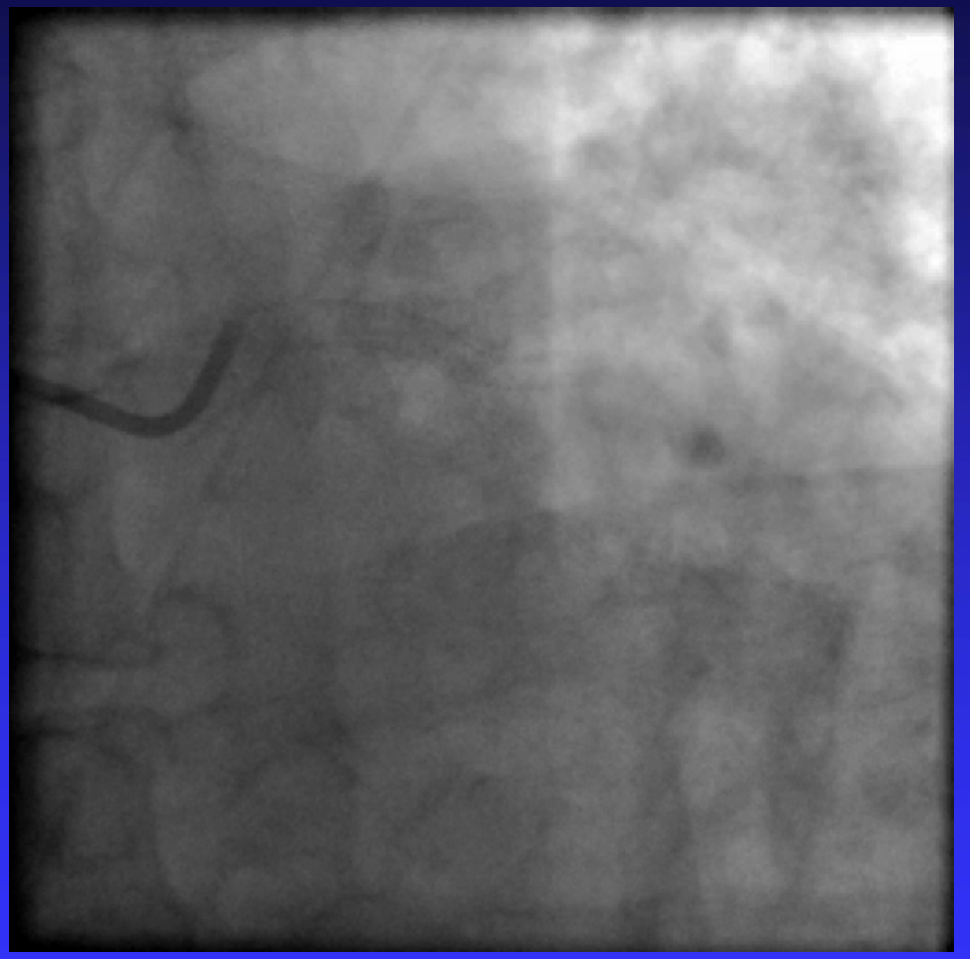
RSO View



Spider View

Follow-up Angiogram (9 motnhs)

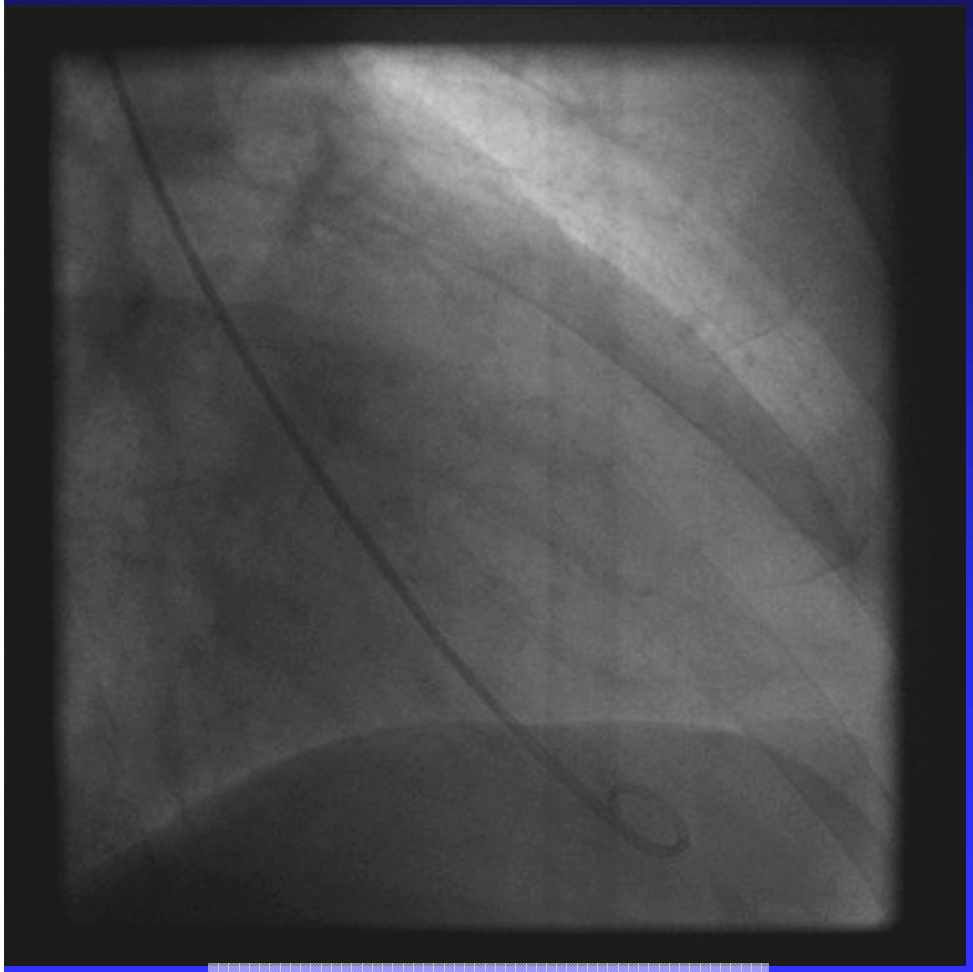




RIO View

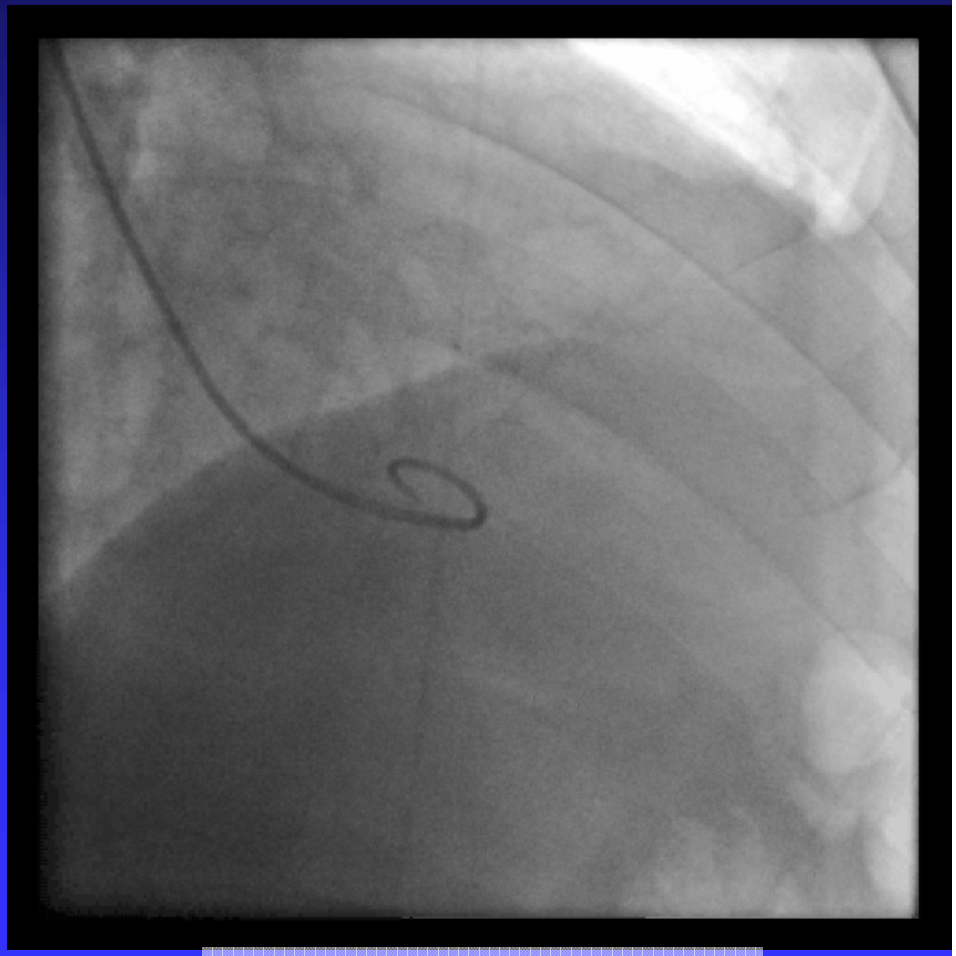
Follow-up (9 months) Ventriculogram

Before PCI



EF: 25.9%

Follow-up



EF: 54.6%

RAO View

Overview of this lecture

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The rosy prophecy and the beginning of the end

Part II

The DES journey from the rosy prophecy to harsh reality

Part III

Perspective and future expectations

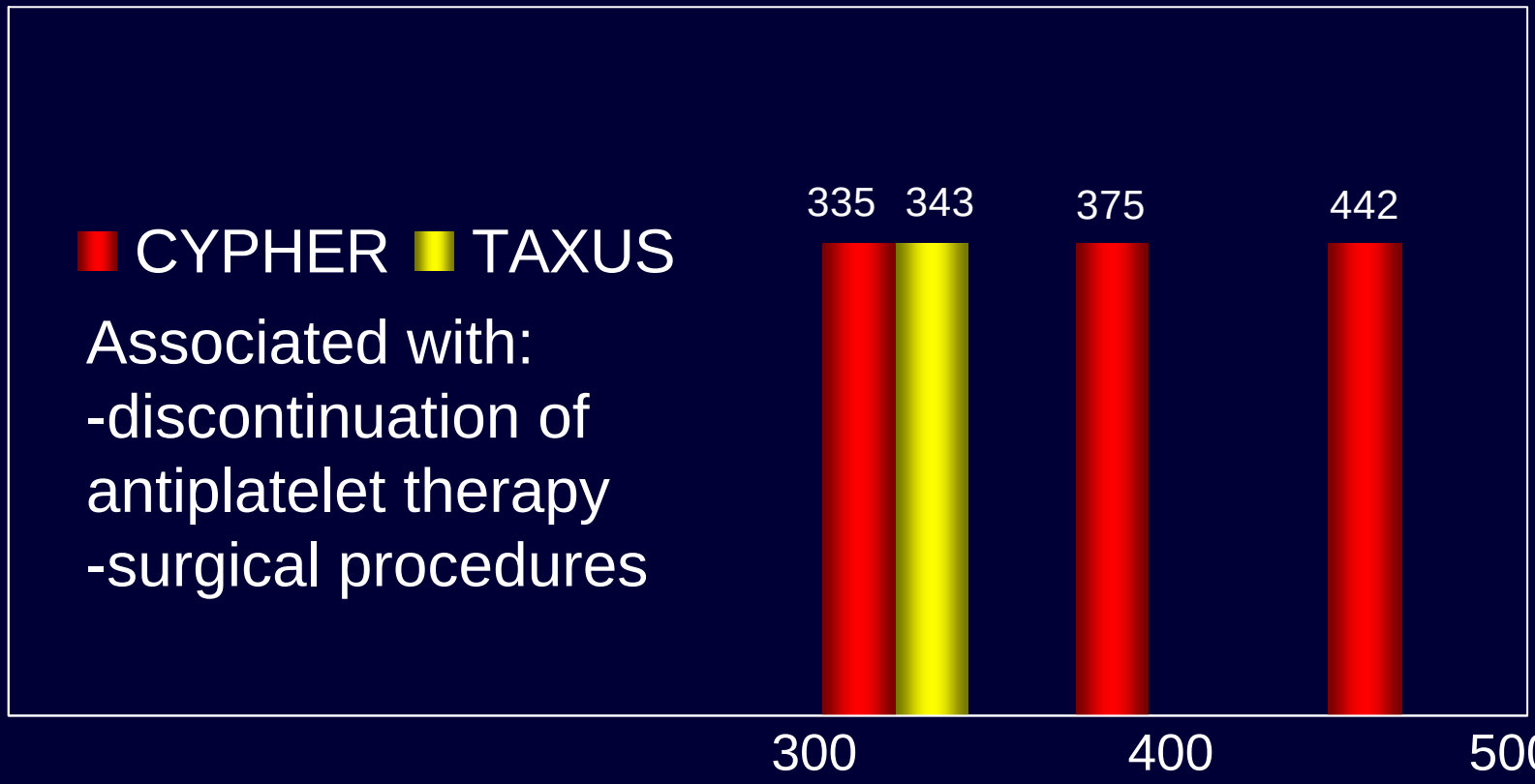
Late Stent Thrombo

The Black period

McFadden E et al. *Lancet* 2004;364:1519

Late thrombosis in drug-eluting coronary stents after discontinuation of antiplatelet therapy

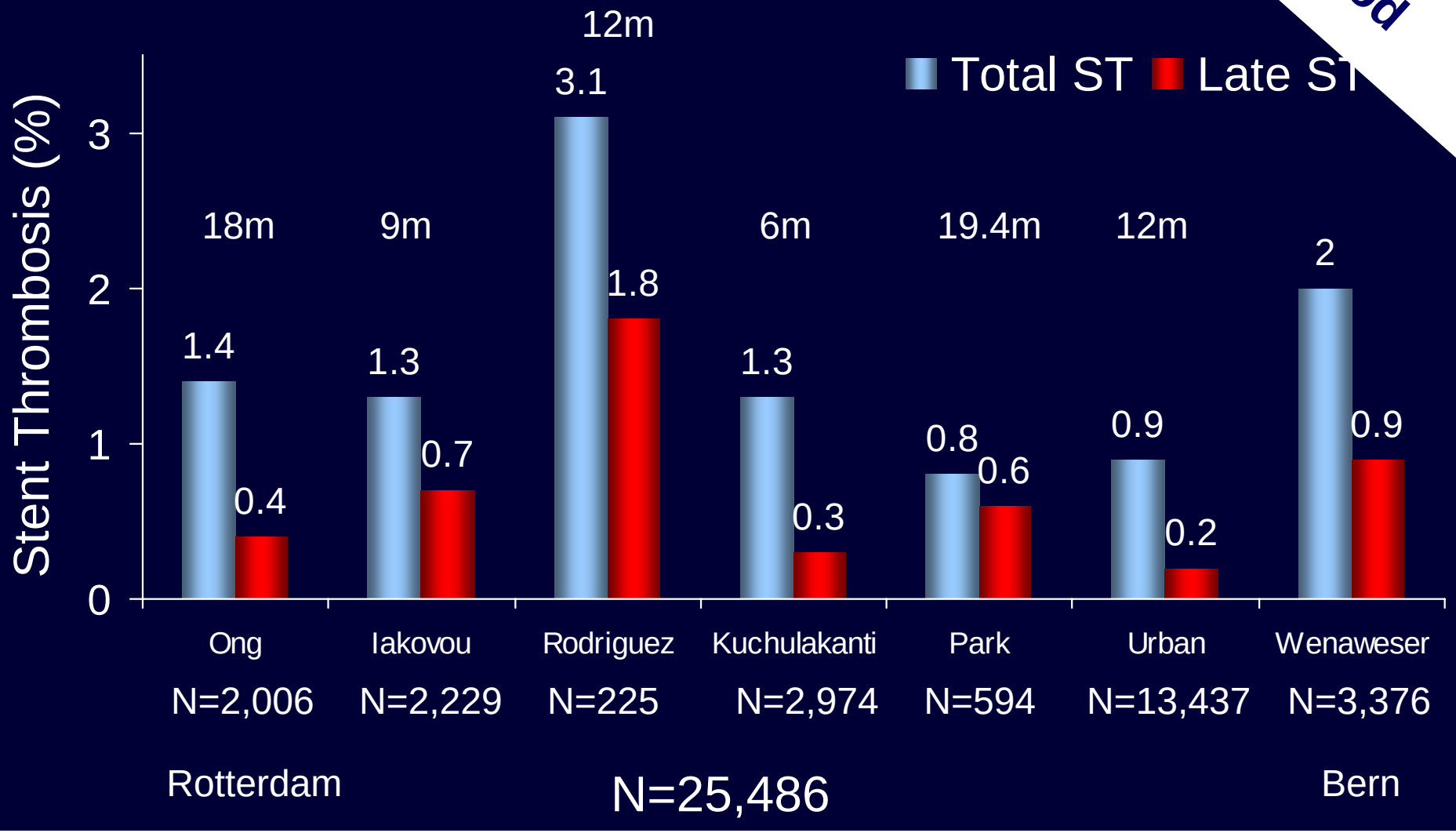
Eugène P McFadden, Eugenio Stabile, Evelyn Regar, Edouard Cheneau, Andrew T L Ong, Timothy Kinnaird, William O Suddath, Neil J Weissman, Rebecca Torguson, Kenneth M Kent, August D Pichard, Lowell F Satler, Ron Waksman, Patrick W Serruys



Associated with:
-discontinuation of antiplatelet therapy
-surgical procedures

Incidence of Late Stent Th osis
Drug-Eluting Stents

The Black period



ESC firestorm: Issue #1 very late sten[illegible]mbosis with drug-eluting stents

"Our Black Tuesday"

TUESDAY

ESC Congress News

EUROPEAN SOCIETY OF CARDIOLOGY®

WORLD HEART FEDERATION®

World Congress of Cardiology 2006

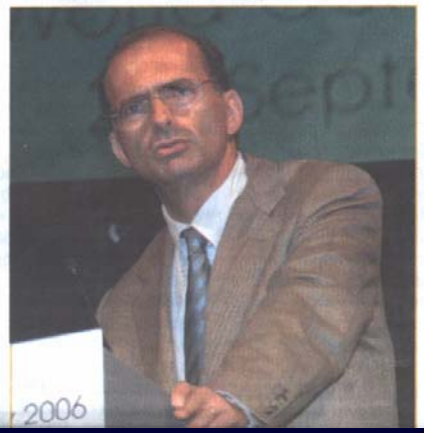
The unique meeting of the European Society of Cardiology Congress 2006 and the World Heart Federation's XVth World Congress of Cardiology

Do drug-eluting stents increase deaths?

TWO SEPARATE, independent meta-analyses, presented in Hot Line session I, suggest drug-eluting stents (DES) may increase death, Q-wave myocardial infarction (clinical surrogates of in-stent thrombosis) and cancer deaths, bringing the long-term safety of DES firmly into the spotlight. Discussant Salim Yusuf (McMaster University, Canada) hailed the data as one of the most important presentations to come out of this year's meeting.

"Six million people in the world have been implanted with DES, yet their long-term safety and efficacy is unknown," said Yusuf. "I've a feeling the data we're seeing today is only the tip of the iceberg. We need to encourage more public access to the data."

Presenter, Edoardo Camenzind (Geneva,

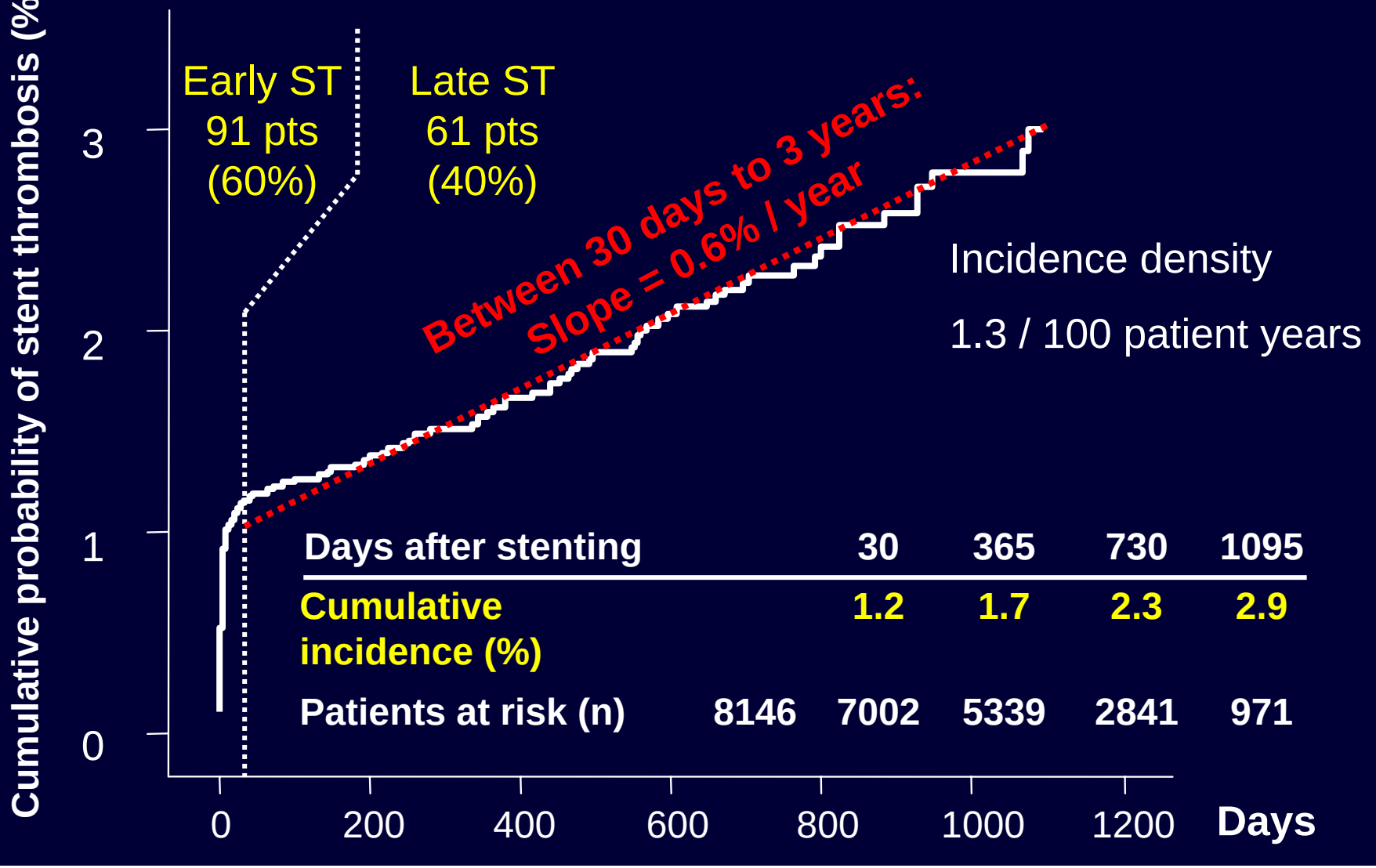


obtain this data from the manufacturer," said Nordmann. He speculated that the increase in cancer might be due to a rapid impairment of the immune system.

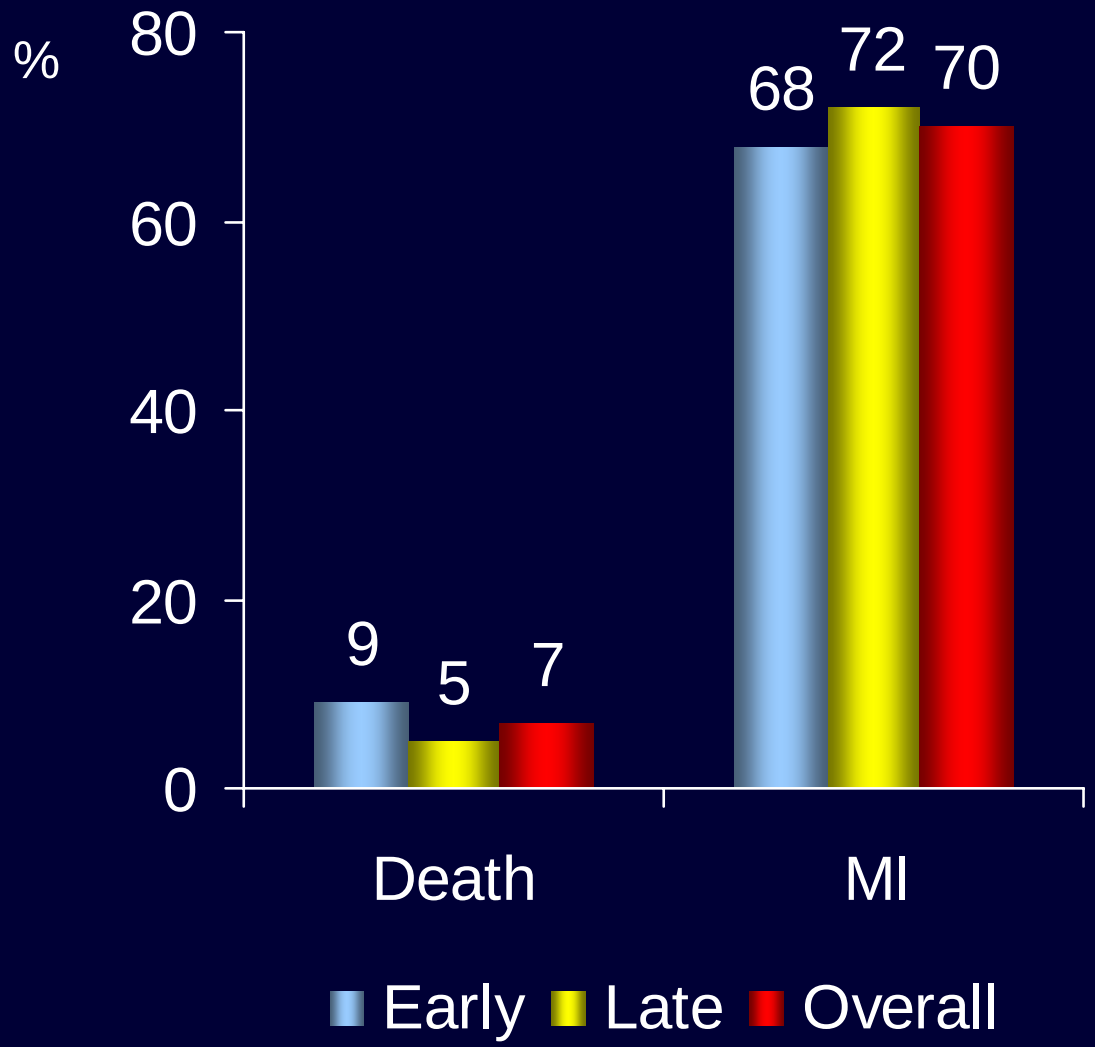
Yusuf widened the debate to include percutaneous coronary intervention (PCI). "The overuse of PCI is an insidious change in the culture of cardiology that needs to be reversed," he said. The use of PCI was established in MI, high-risk unstable angina and cardiogenic shock. However, its use in stable disease was a totally different question.

"There's no beneficial influence on mortality – PCI does nothing to prevent heart attack. All we are doing is providing short-term relief of chest pain. It's not re-stenosis that kills but the thousands of lesions you can't see. Stable

Angiographic DES Stent Thrombosis: Bern - Rotterdam Cohort Study: N = 8146 pts (Lancet in-press)



In-hospital death and MI in stent thrombosis patients



The NEW ENGLAND JOURNAL of MEDICINE

Perspective

NOVEMBER 9, 2006

Trading Restenosis for Thrombosis? New Questions about Drug-Eluting Stents

Miriam Shuchman, M.D.

In September, at the World Cardiology Congress in Barcelona, Donald Baim, a cardiologist who is the new chief medical and scientific officer of Boston Scientific, was talking to a reporter when he mentioned disturbing new findings regarding the risk of late thrombosis associated with drug-eluting coronary stents. The revelation fueled a newly ignited controversy. Lauded as a means of preventing restenosis, drug-eluting stents have been implanted in nearly 6 million patients worldwide since they were introduced 3 years ago. The Food and Drug Administration (FDA) responded to the controversy by issuing a statement that drug-eluting stents are "safe and effective when used for the FDA-approved indications," which involve discrete and relatively short lesions (up to 28 mm in the case of one approved stent and up to 30 mm in the other) in relatively small, native blood vessels (2.5 to 3.5 or 3.75 mm in diameter), but drug-eluting stents are also widely used on an off-label basis for longer lesions, larger vessels, and multivessel lesions. The FDA plans to discuss questions about the safety of drug-eluting stents at an open meeting of its Circulatory System Devices Advisory Panel on December 7 and 8, 2006, to be attended by physicians, scientists, and the two leaders — and fierce rivals — in the $5.5 billion stent industry, Boston Scientific and Johnson & Johnson.

In approving drug-eluting stents, the FDA obliged manufacturers to track all subjects in their pivotal clinical trials for 5 years, and it was Boston Scientific's review of the data on its paclitaxel-eluting Taxus stent to which Baim was alluding. Four years of data on nearly 3500 patients randomly assigned to receive the Taxus stent or a bare-metal stent showed that the risk of thrombus formation more than 6 months after stent placement was significantly higher in the Taxus group. The difference in risk increased by about 0.2% per year, so that 3 years after stent placement, patients with the Taxus stent had a risk that was about 0.5% higher than that of their counterparts with the bare-metal stent. In early August, the FDA met with Boston Scientific to review these findings.

Concerned about the risks of myocardial infarction and death associated with stent thrombosis, the FDA also met with Johnson & Johnson to discuss that company's data. Dennis Donohoe, vice president of clinical and regulatory affairs at Cordis Corporation, the division that makes Johnson &

Shuchman M. NEJM 2006:355: 1949-52

Assistant Professor of Psychiatry and free-lance journalist

ESC firestorm: Issue #2 death a

The Black period

TUESDAY

ESC Congress News

EUROPEAN SOCIETY OF CARDIOLOGY®

WORLD HEART FEDERATION®

World Congress of Cardiology 2006

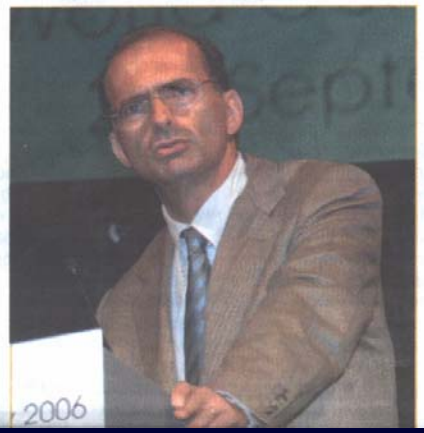
The unique meeting of the European Society of Cardiology Congress 2006 and the World Heart Federation's XVth World Congress of Cardiology

Do drug-eluting stents increase deaths?

TWO SEPARATE, independent meta-analyses, presented in Hot Line session I, suggest drug-eluting stents (DES) may increase death, Q-wave myocardial infarction (clinical surrogates of in-stent thrombosis) and cancer deaths, bringing the long-term safety of DES firmly into the spotlight. Discussant Salim Yusuf (McMaster University, Canada) hailed the data as one of the most important presentations to come out of this year's meeting.

"Six million people in the world have been implanted with DES, yet their long-term safety and efficacy is unknown," said Yusuf. "I've a feeling the data we're seeing today is only the tip of the iceberg. We need to encourage more public access to the data."

Presenter, Edoardo Camenzind (Geneva,



obtain this data from the manufacturer," said Nordmann. He speculated that the increase in cancer might be due to a rapid impairment of the immune system.

Yusuf widened the debate to include percutaneous coronary intervention (PCI). "The overuse of PCI is an insidious change in the culture of cardiology that needs to be reversed," he said. The use of PCI was established in MI, high-risk unstable angina and cardiogenic shock. However, its use in stable disease was a totally different question.

"There's no beneficial influence on mortality – PCI does nothing to prevent heart attack. All we are doing is providing short-term relief of chest pain. It's not re-stenosis that kills but the thousands of lesions you can't see. Stable

MACE rates indivi dat led dat
HCR Cardia nzi

RAVEL, SIR			
E-SIRIUS, C-			
D			0.13
	11.4%	10.1%	0.40

Although not completely correct from a methodological point of view, the Camenzind's report at ESC became a wake up call for everybody (device industry, PI's, CRO's and FDA)

endent physician-directed meta-analysis

versus

Indepe ident physician-assessed patient level meta-analysis

Fortunately, prior to ESC the people listed on this slide met in Washington (March 2006) and in Dublin (June 2006) to re-define the clinical endpoints of coronary stent trials and created the…

Academic Research Consortium (ARC)

ARC Co-Chairs

- **Don Cutlip, MD, Harvard and HCRI**
- **Patrick Serruys, MD PhD, Thoraxcenter, Rotterdam and Cardialysis**

Other Participants

- **Interventional Cardiologists**
- **Representatives from FDA**
- **Academic CROs (Cardialysis, HCRI, DCRI, CRF)**
- **Representatives from major stent manufacturers**

ARC Proposed Standard Definitions for stent thrombosis

- **Definite/Confirmed**
  - Acute coronary syndrome AND
  - [Angiographic confirmation of thrombus or occlusion
    OR
  - Pathologic confirmation of acute thrombosis]
- **Probable**
  - Unexplained death within 30 days
  - Target vessel MI without angiographic confirmation of thrombosis or other identified culprit lesion
- **Possible**
  - Unexplained death after 30 days

NOTE: Patients who have a TLR prior to a thrombosis are included by this set of definitions, as opposed to the “Per Protocol” definition

Rationale for ARC Definitions* for DES Endpoints

Concerns

- Variability in definitions of key clinical endpoints across DES Trials
- Inappropriate comparisons and conclusions based on different definitions
- Potential to bias results by choosing definitions most favorable to those conducting analyses

Objectives

- Standardization of definitions
- Consensus on the new standard
- Consistency for reporting
- Transparency of data

* Previously referred to as the “Dublin Definition”

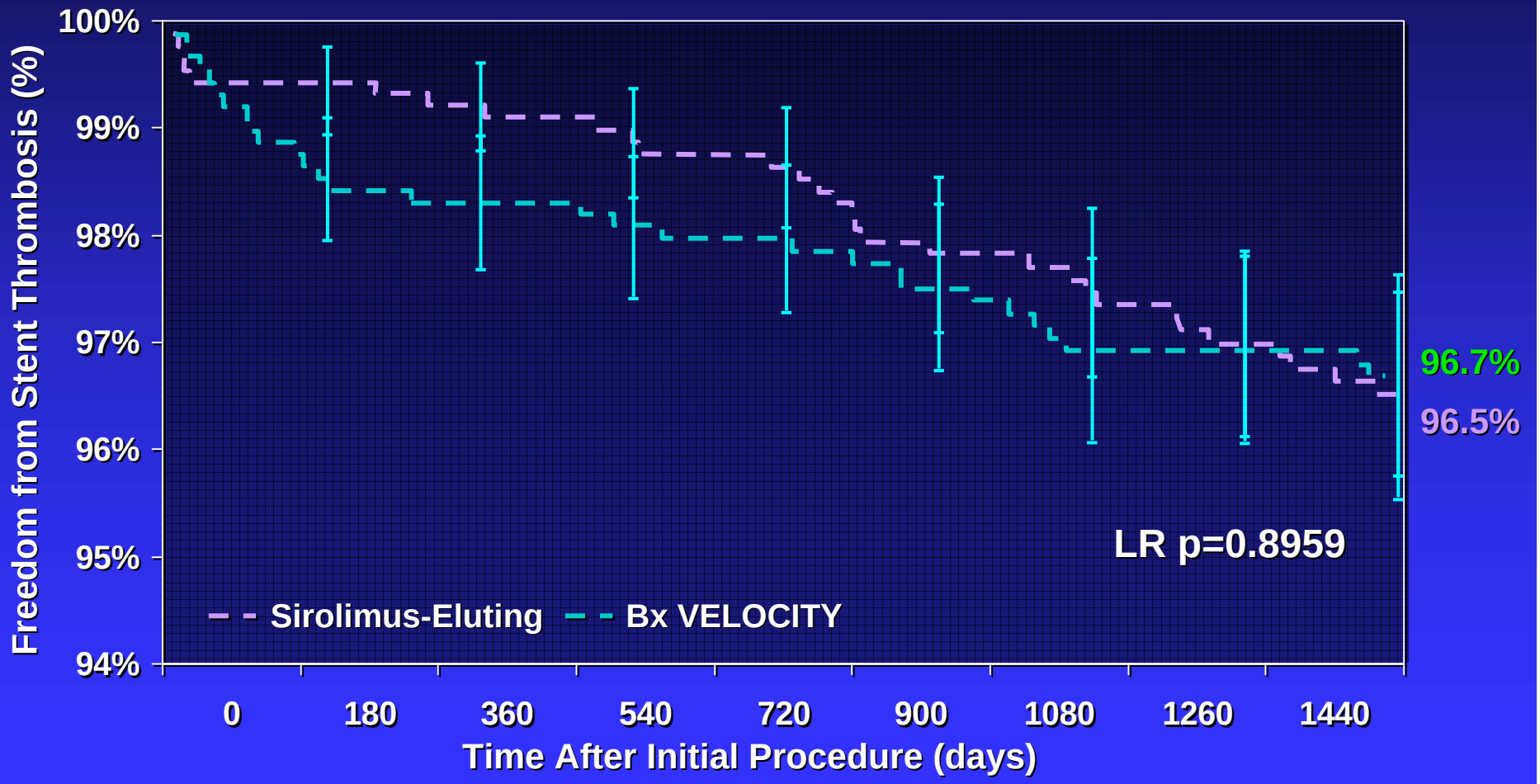
ARC: The New Standard

- FDA requirement for December 2006 Panel Meeting
- Endorsed by British Cardiovascular Intervention Society (BCIS)

"BCIS believes these agreed definitions should be used in all future reports of the data, and that events should be independently adjudicated in all trials and registries."

Freedom From Thrombosis: 0 – 1,440 Days
All Patients: ARC Total

Pooled data from the RAVEL, SIRIUS, E-SIRIUS, and C-SIRIUS Trials

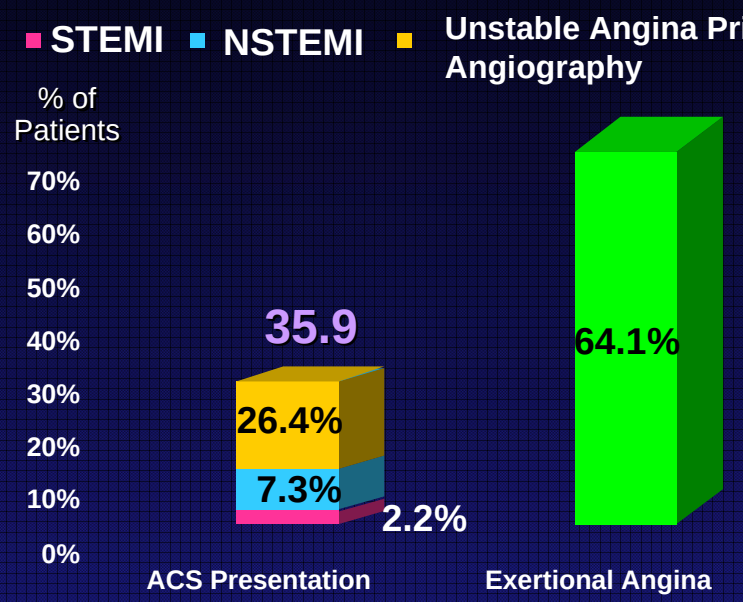


Thrombosis from Day 0 Incidence Analysis: *ARC Total*

	SES (N=878 Patients)	BMS (N=870 Patients)
ARC Definition Stent Thrombosis		
Stent thrombosis (0 – 30 days)	0.5% (4/877)	0.3% (3/870)
Stent thrombosis (0 - 1 year)	0.7% (6/871)	1.6% (14/864)
Stent thrombosis (0 - 4 years)	3.5% (29/832)	3.4% (28/825)

NOTE: Of the 57 subjects with stent thrombosis during 0-4 years, 10 underwent an intervening TLR prior to the thrombosis. However, only 1 of those 10 received any DES (SES) during TLR

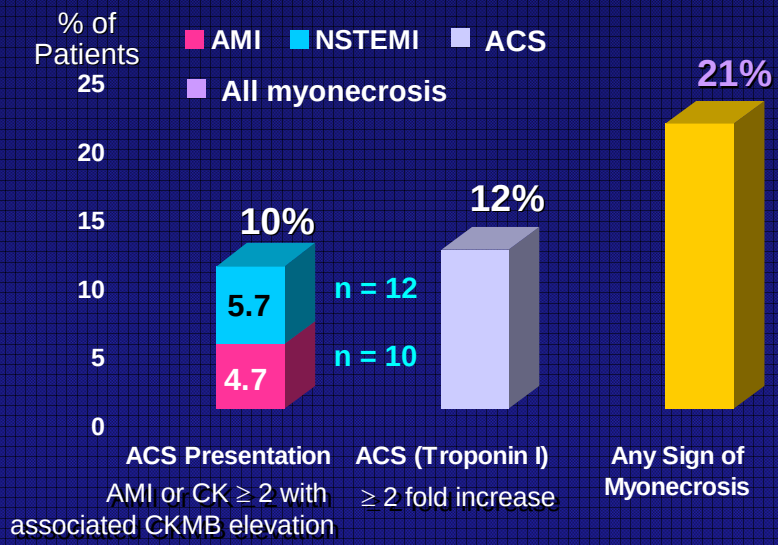
Percentage of Bare Metal Stents (BMS) ISR Cases Presentation



9.5% of BMS In-Stent Restenosis Cases Presented as an MI

Chen M., et al., *Am Heart J* 2006;151:1260-64.

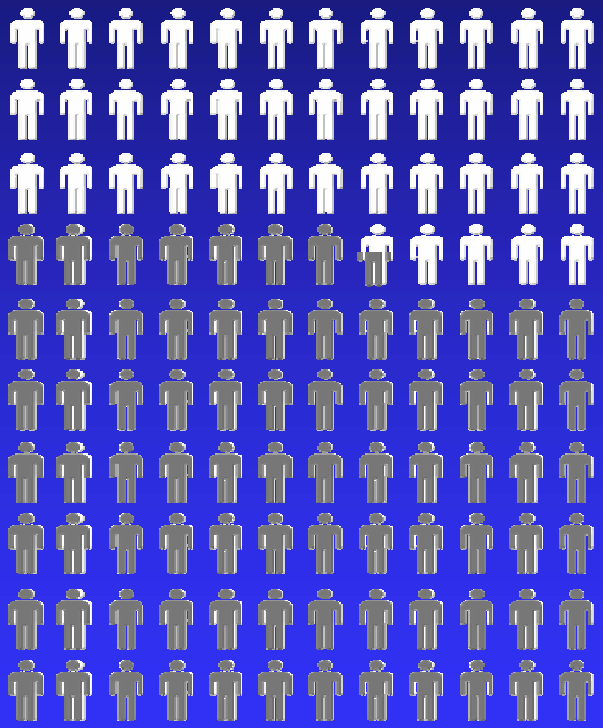
10% of BMS In-Stent Restenosis Cases Presented as an MI



Nayak AK., et al., Circ J 2006;70:1026-9.

Restenosis with BMS is NOT just a nuisance: It has potentially severe consequences

1186 consecutive cases of clinical episodes of bare metal ISR



= 10 patients

*Hospitalized before coronary angiography.
ISR = in-stent restenosis; UA = unstable angina.
Chen et al. *Am Heart J.* 2006;151:1260.

Hospitalized for UA* or MI = 36% (425/1186)

MI = 9.5% (112/1186)
Death = 0.7% (8/1186)

Hypothesis: By preventing 100 restenoses per 1,000 patients (clinical restenosis reduced from 20% → 10%)

DES could prevent ~10 restenosis-related MIs (9.5% of 100 prevented restenoses)

A 10 per 1,000 case reduction of restenosis-related MIs would be sufficient to offset a 5 per 1,000 case increase in VLST-related MI, to lead to the similar late death and MI rates for DES and the bare metal stent control

Impact of TLR on Stent Thrombosis Rate

Pooled Data from RAVEL, SIRIUS, E-SIRIUS, and C-SIRIUS Trials.

	CYPHER® Stent			BMS		
ARC Any	Primary ST	Post TLR ST	Total ST	Primary ST	Post TLR ST	Total ST
Early	4	0	4	3	0	3
Late	2	0	2	9	2	11
Very Late	23	0	23	6	8	14
Total	29	0	29	18	10	28

- Independent and meticulous adjudication using the new ARC definition of 4 double-blind randomized trials on drug-eluting stent (DES) involving 1,748 patients shows:
  no significant difference in the rate of thrombosis was demonstrated between the CYPHER® Stent and BMS out to 4 years, although mechanisms of primary stent thrombosis vs. stent thrombosis post TLR may be different.

What are my options?

Option A: There is a new problem

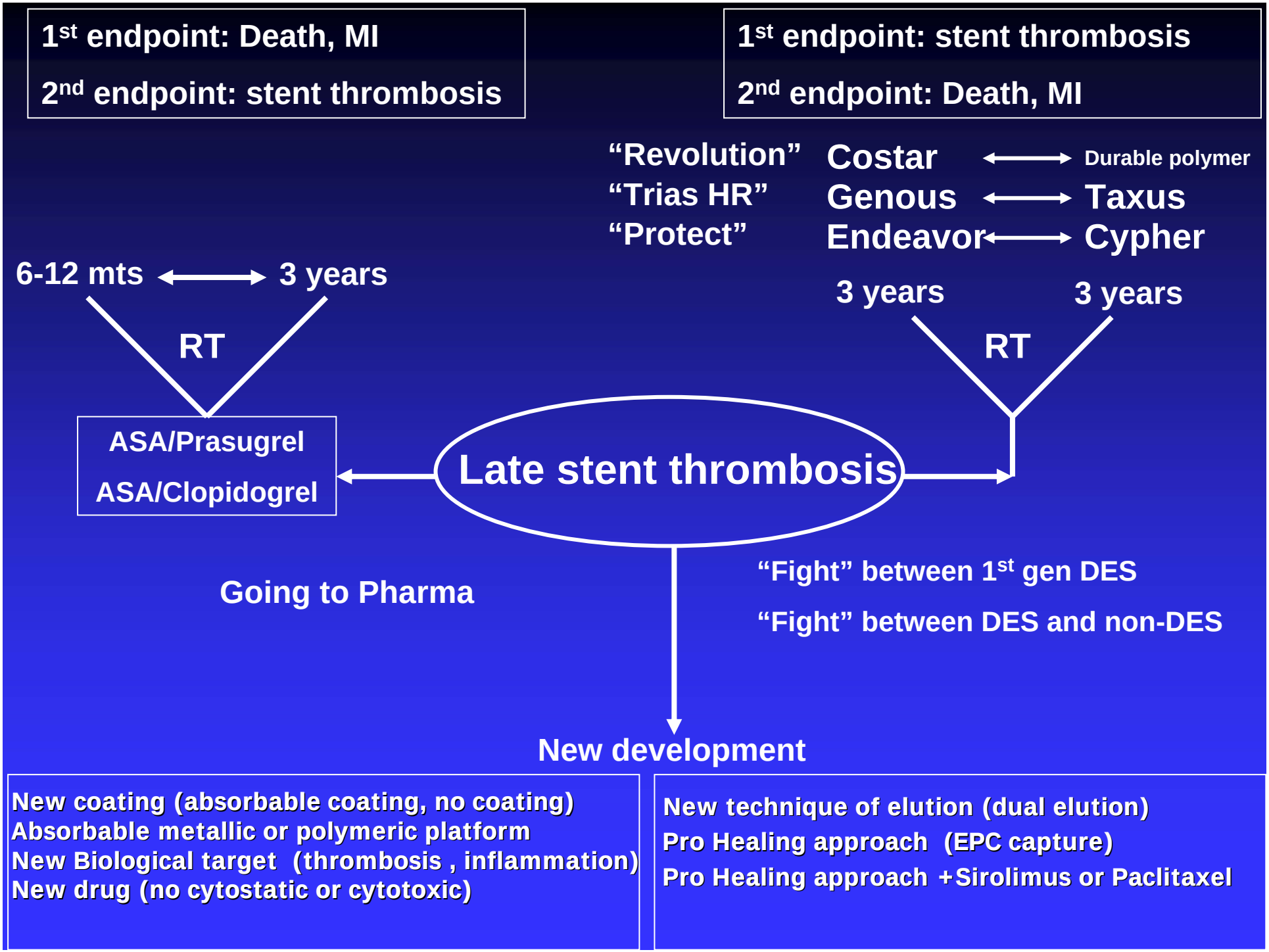
Use of DES results in more late thromboses than BMS

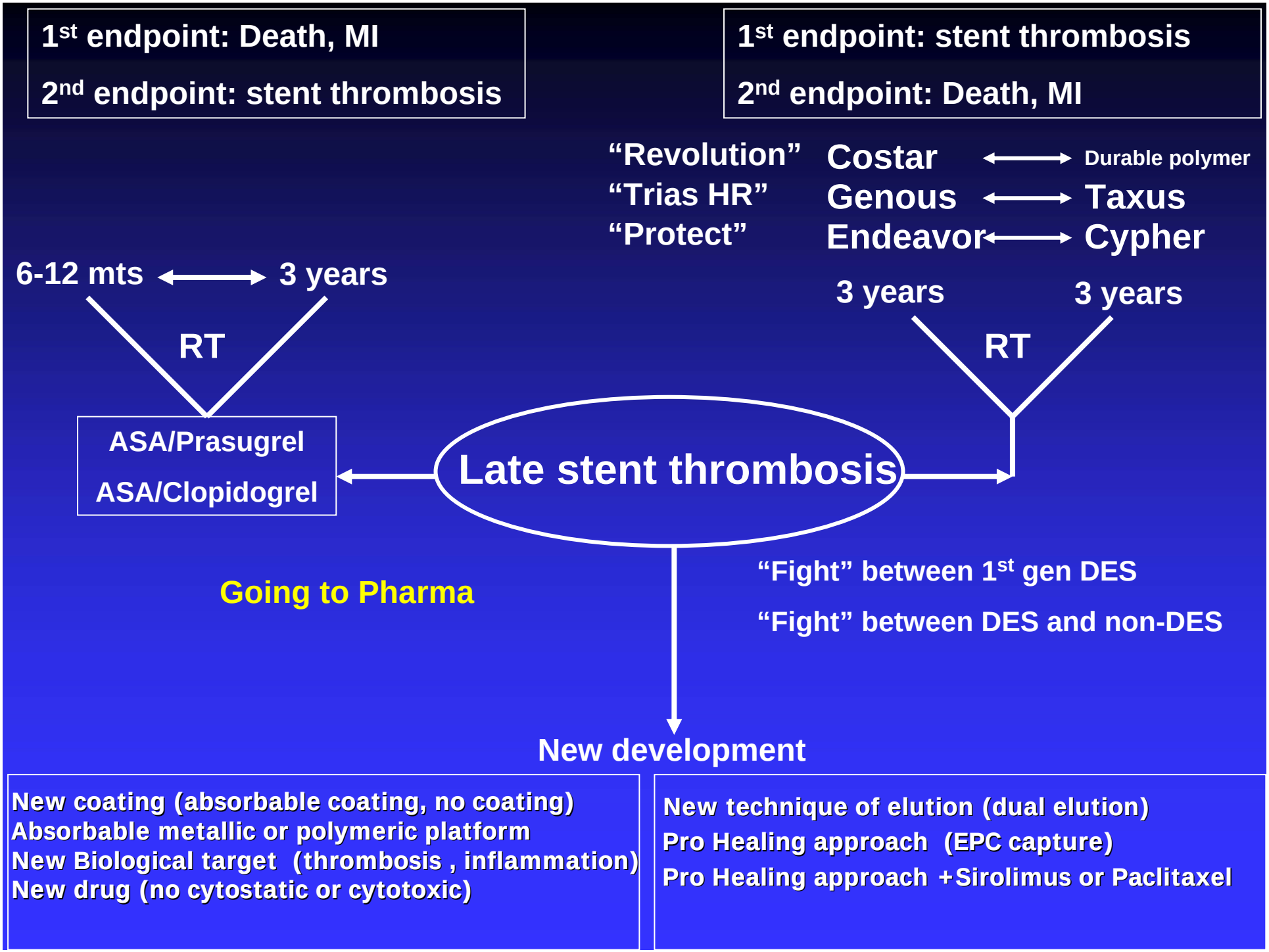
Option B: There is no new problem

The rate of early and late thrombosis (definite, probable, possible, ARC criteria) is similar to that of BMS

Option C: There is a problem. Early and late thrombosis should be abolished

What are my expectations?


1st endpoint: Death, MI
2nd endpoint: stent thrombosis
1st endpoint: stent thrombosis
2nd endpoint: Death, MI
"Revolution" Costar Durable polymer
"Trias HR" Genous Taxus
"Protect" Endeavor Cypher
6-12 mts 3 years
3 years 3 years
RT
RT
ASA/Prasugrel
ASA/Clopidogrel
Late stent thrombosis
Going to Pharma
"Fight" between 1st gen DES
"Fight" between DES and non-DES
New development
New coating (absorbable coating, no coating)
Absorbable metallic or polymeric platform
New Biological target (thrombosis , inflammation)
New drug (no cytostatic or cytotoxic)
New technique of elution (dual elution)
Pro Healing approach (EPC capture)
Pro Healing approach +Sirolimus or Paclitaxel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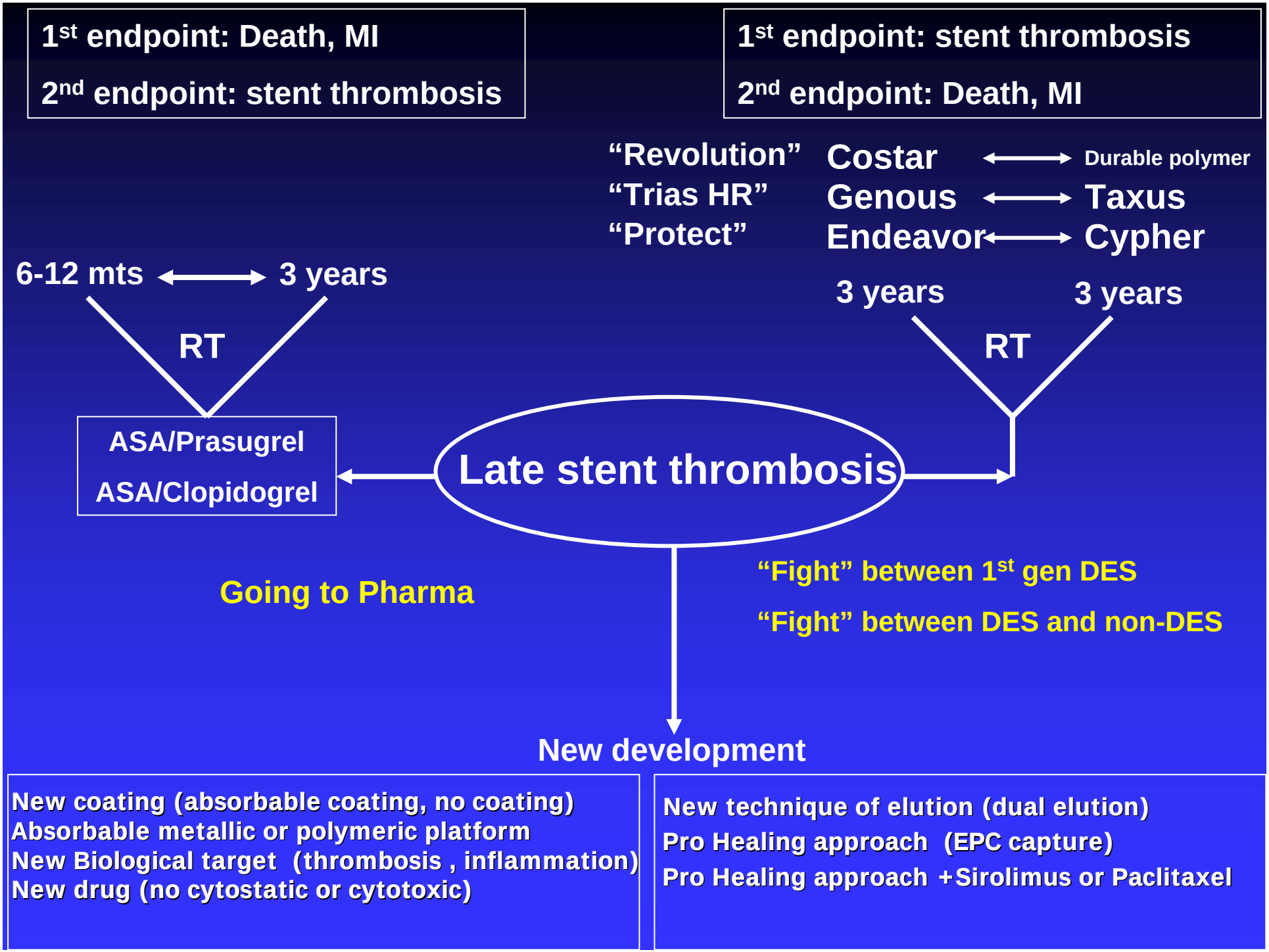
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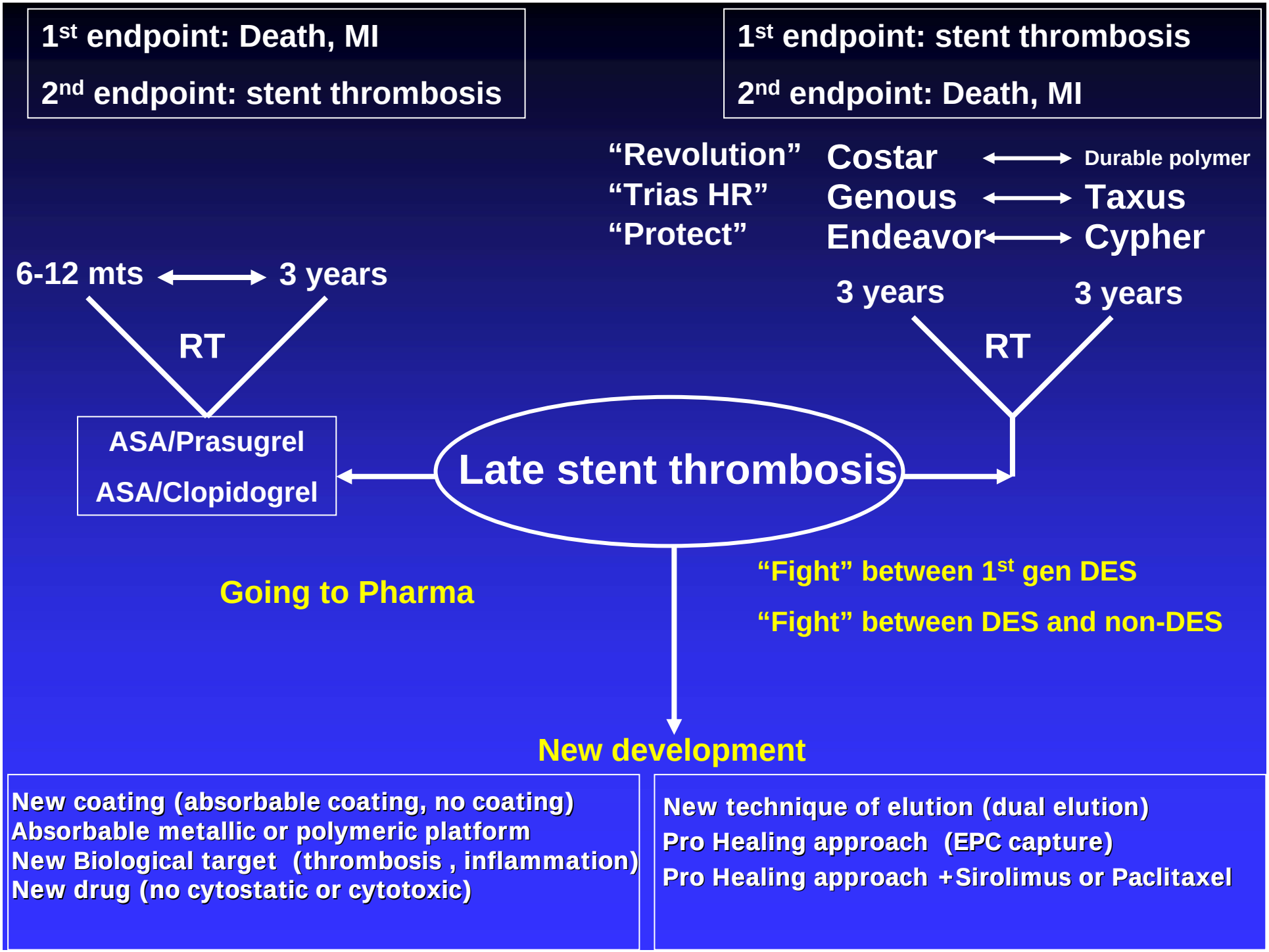
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Survey of the next generation of drug-eluting stents: meaningful advances or more of the same?

1. New coating (absorbable coating, no coating)
2. Absorbable metallic or polymeric platform
3. New Biological target (thrombosis , inflammation)
4. New drug (less cytostatic or cytotoxic)
5. New technique of elution (reservoir, dual elution)
6. Pro Healing approach (EPC capture)
7. Pro Healing approach +Sirolimus or Paclitaxel

Survey of the next generation of drug-eluting stents: meaningful advances or more of the same?

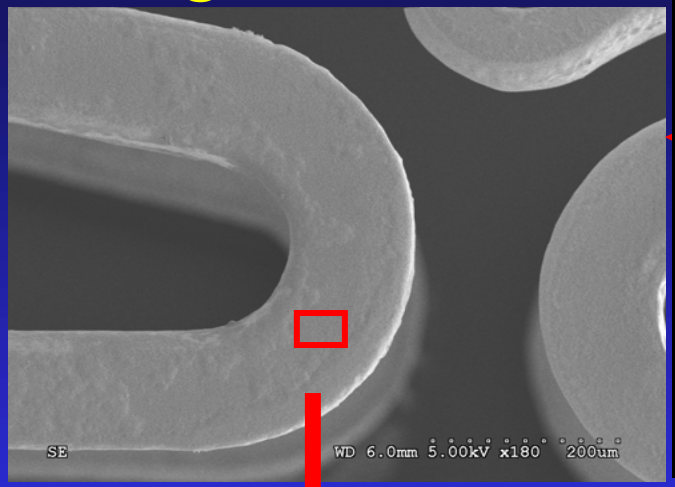
1 New coating (absorbable coating, no coating)

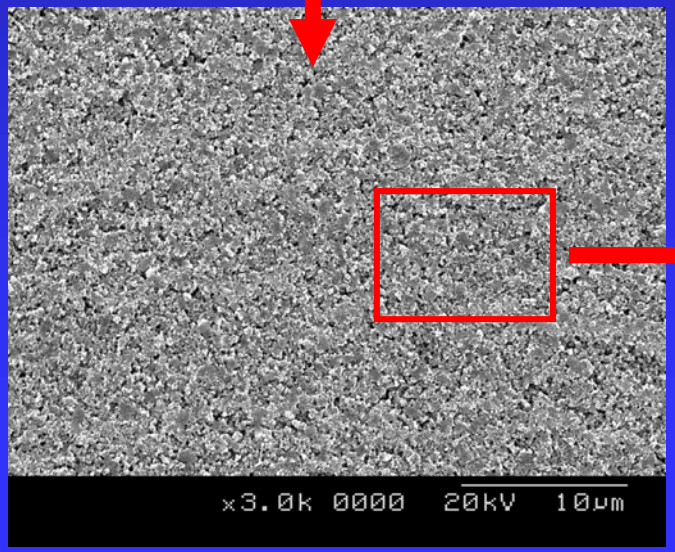
Problems with the polymer

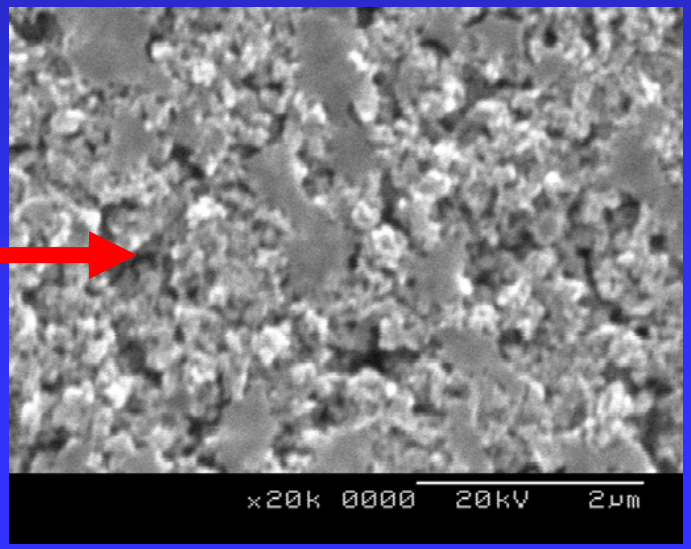
- Inflammatory response
- Increased thrombogenicity
- Non-homogenous drug distribution
- Flaking, peeling, webbing, bonding

NEW COATING, NO COATING, ABSORBABLE COATING

Hydroxyapatite Coating



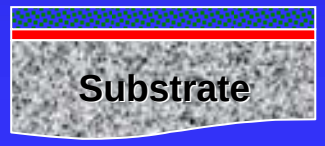




Closely resembling **biological apatite**

Hydroxyapatite (bone !) is natural to the human body

Biocompatible, bioactive and bioresorbable

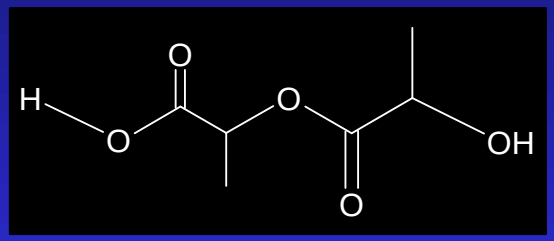


*Electro-Chemical Deposition

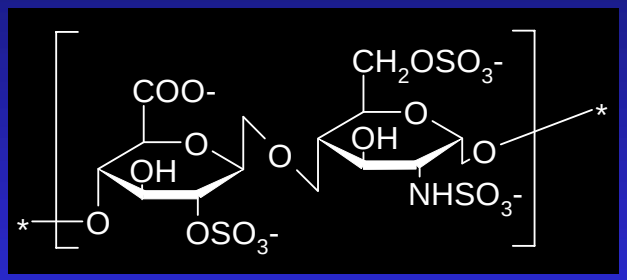
Rajtar A, et al. *EuroInterv* 2006; 2: 113-5

NEW COATING, NO COATING, ABSORBABLE COATING

Heparin is coupled with Poly L-Lactide to create a heparinized polymer which will serve as a reservoir for another drug



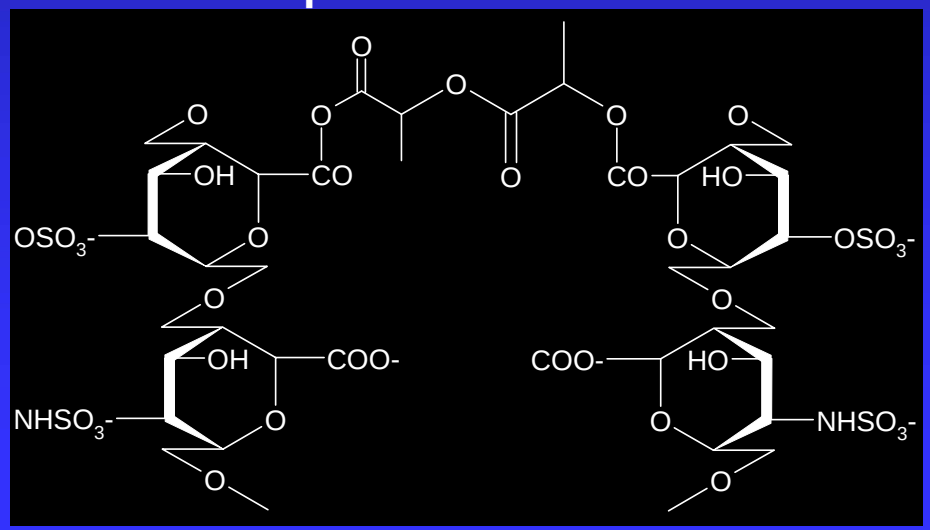
Monomer of PLA



Heparin molecule

DCC / DMAP

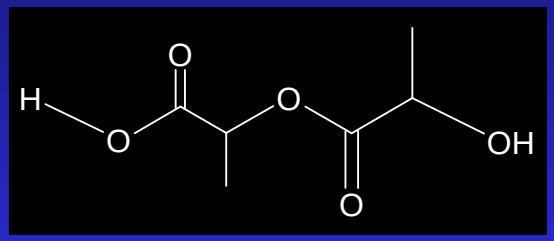
Formamide / DMF



PLA conjugate Heparin

ABSORBABLE COATING in Heparinized PLA polymer

Heparin is coupled with Poly L-Lactide to create a heparinized polymer which will serve as a reservoir for another drug



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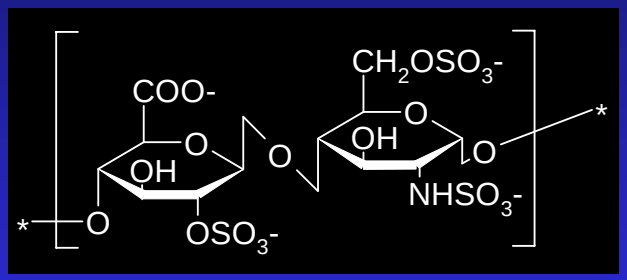

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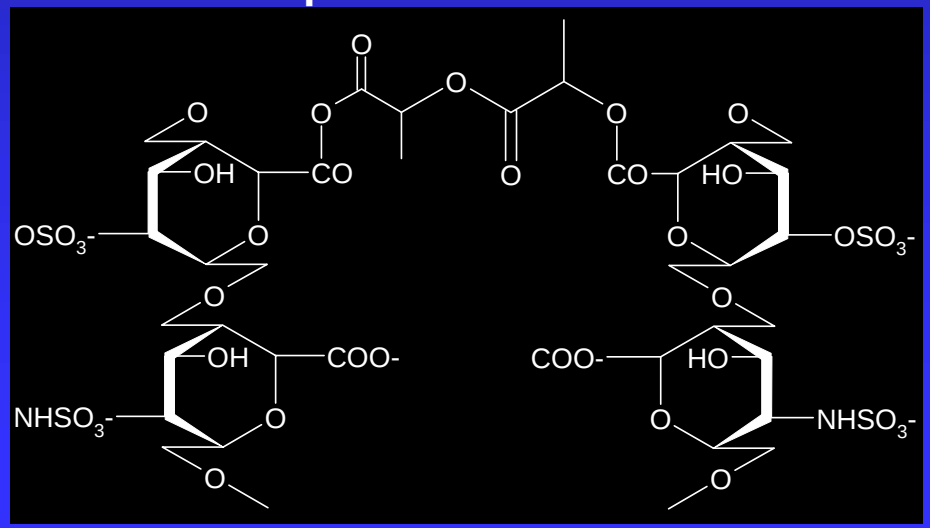
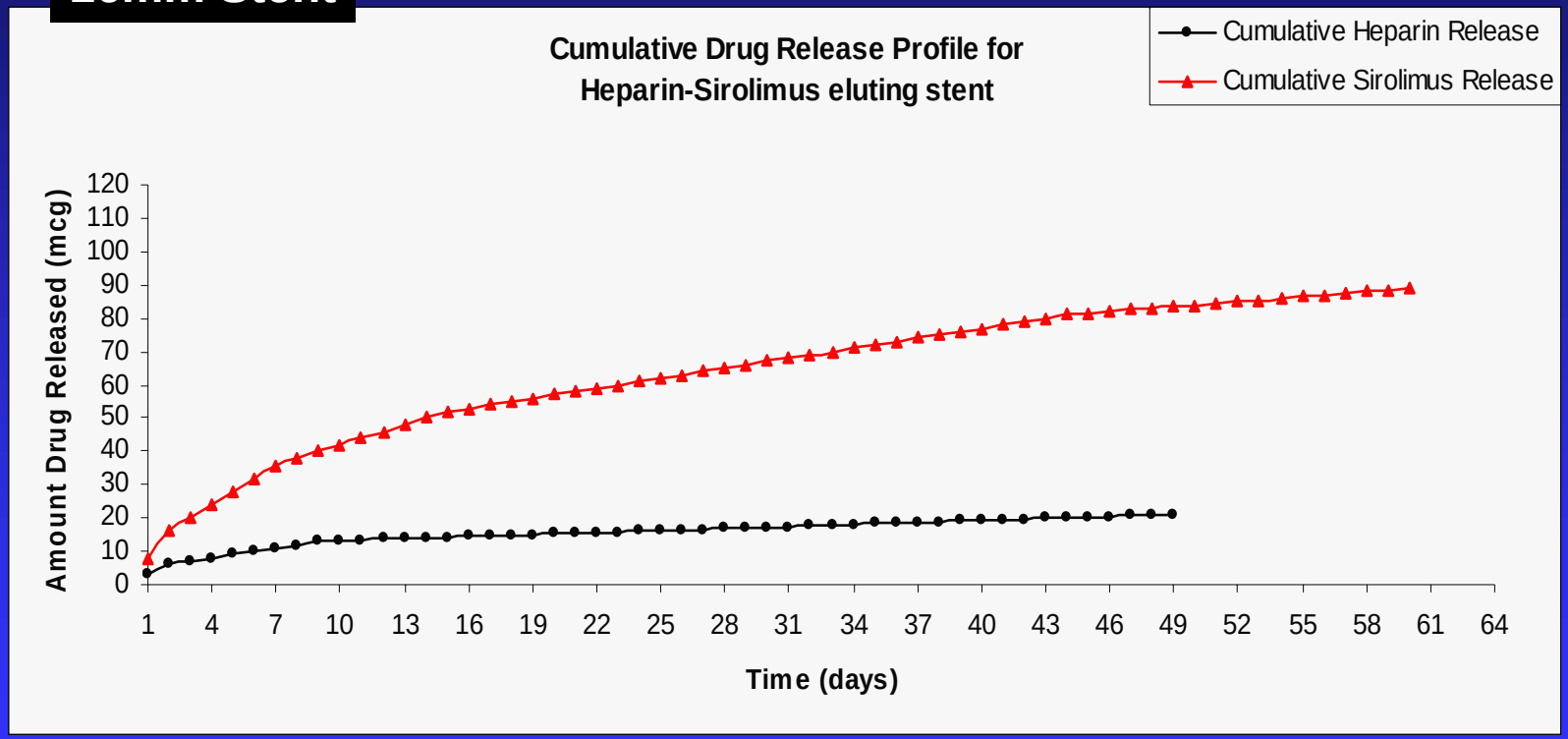


PLA conjugate Heparin

DUAL ELUTION HEPARIN AND SIROLIMUS

Elution Profile of Heparin – Sirolimus DES

16mm Stent

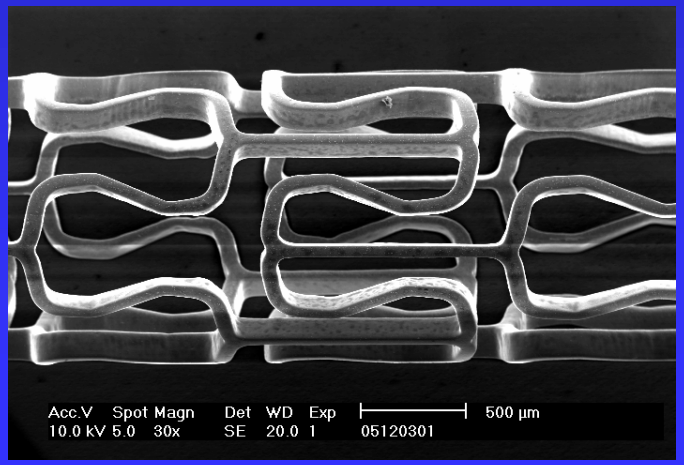


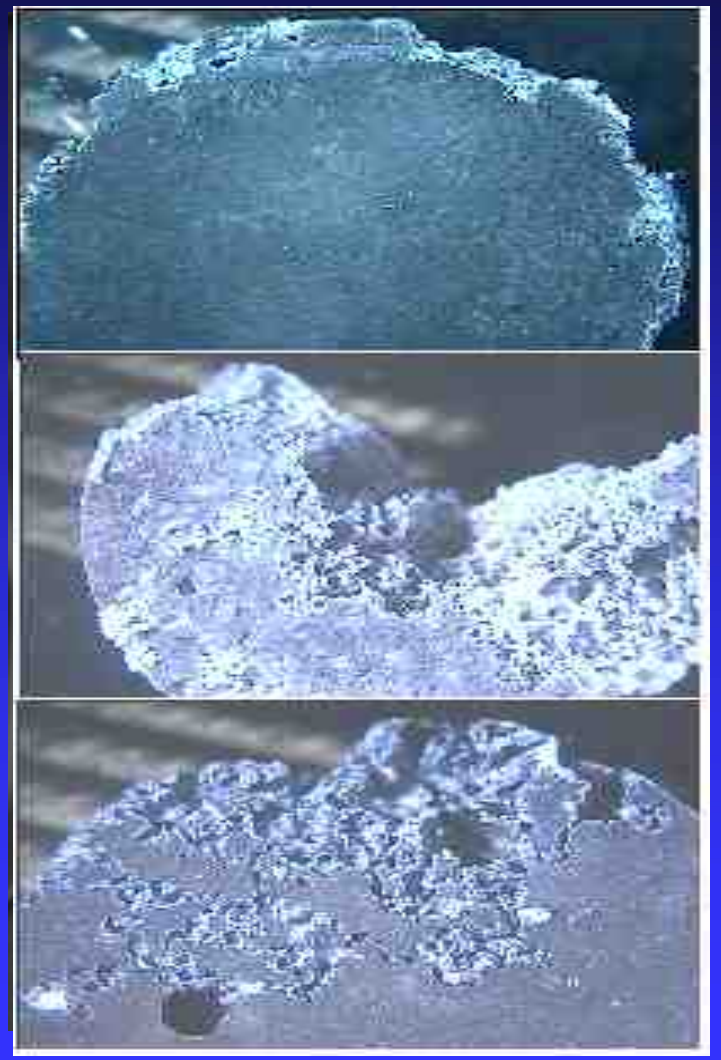
Both therapeutic agents elutes simultaneously. Heparin will give effect almost for 50 days and Sirolimus for 60 days.

BIOABSORBABLE METAL STENT in Magnesium

Light Microscopy

Scanning Electron Microscopy





Continuous immersion test of stents in 0.9 % NaCl; 37° C; pH 7.0

BIOABSORBABLE Poly-L Lactide Stent Eluting Everolimus

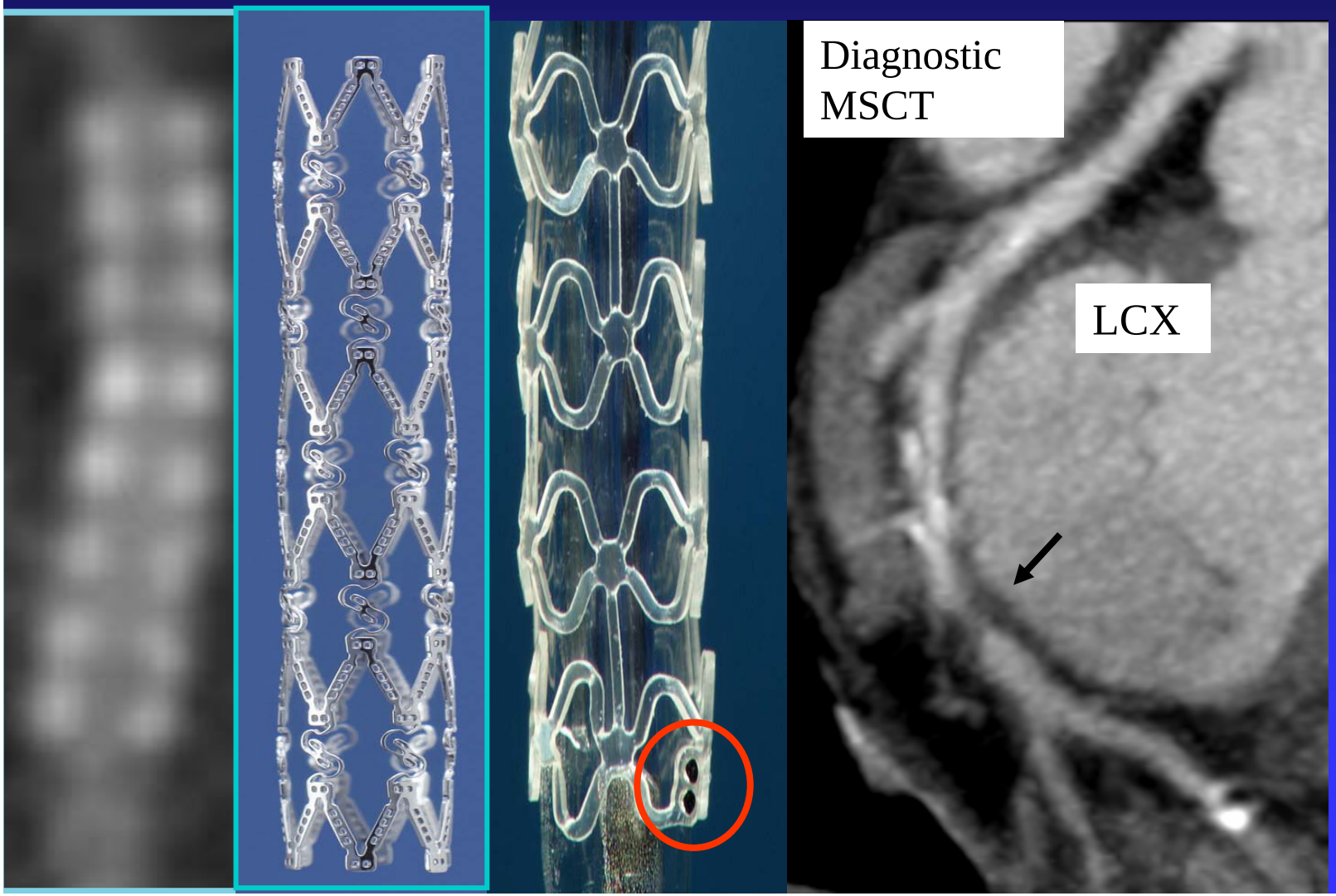
Bioabsorbable DES system

ML VISION® SDS

Polymeric Coating

Eluting Everolimus

Today, we can non-invasively diagnose stenosis with MSCT (64, ultrafast) and…Assess non-invasively the long-term result of non radio opaque absorbable stent



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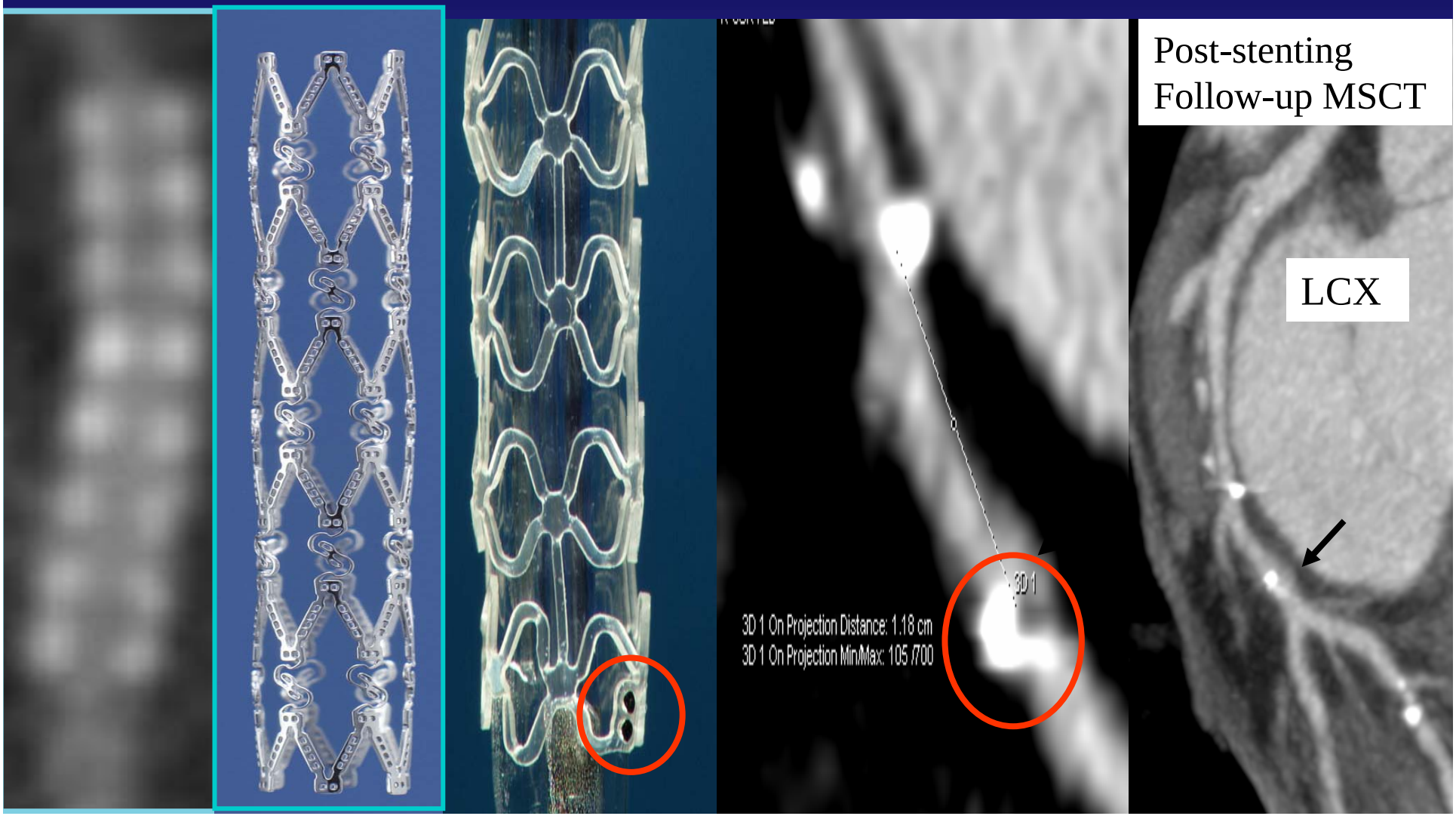
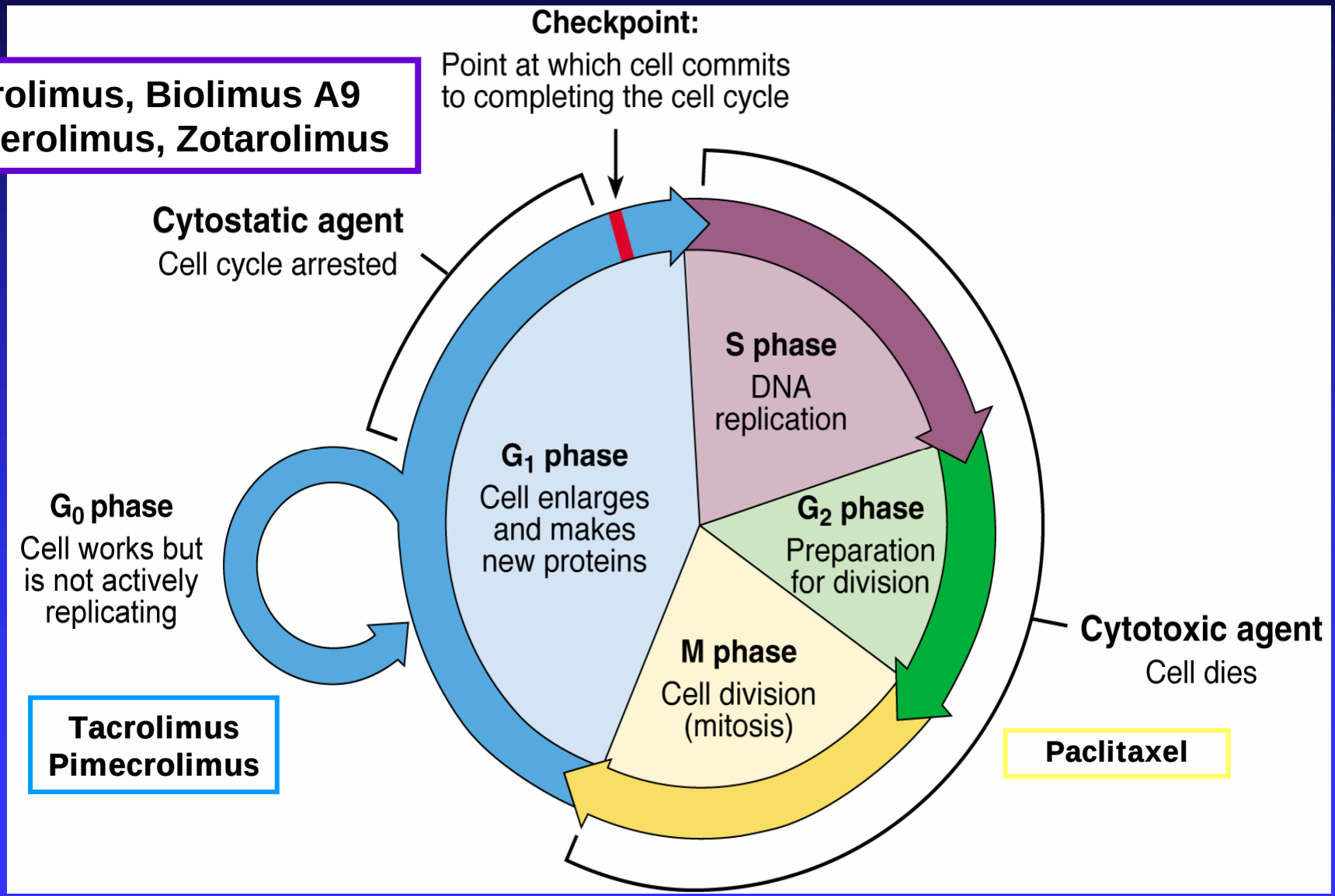
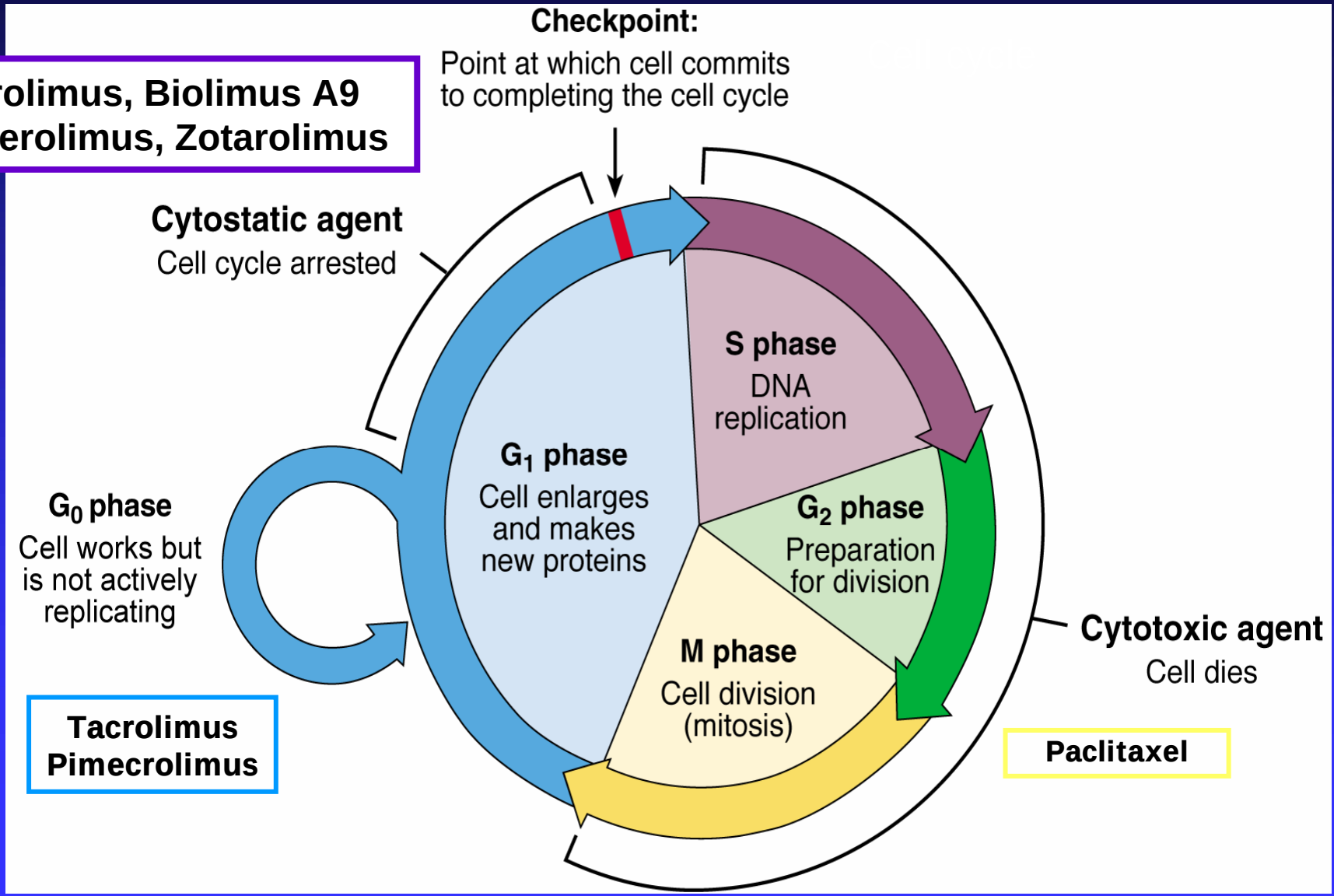


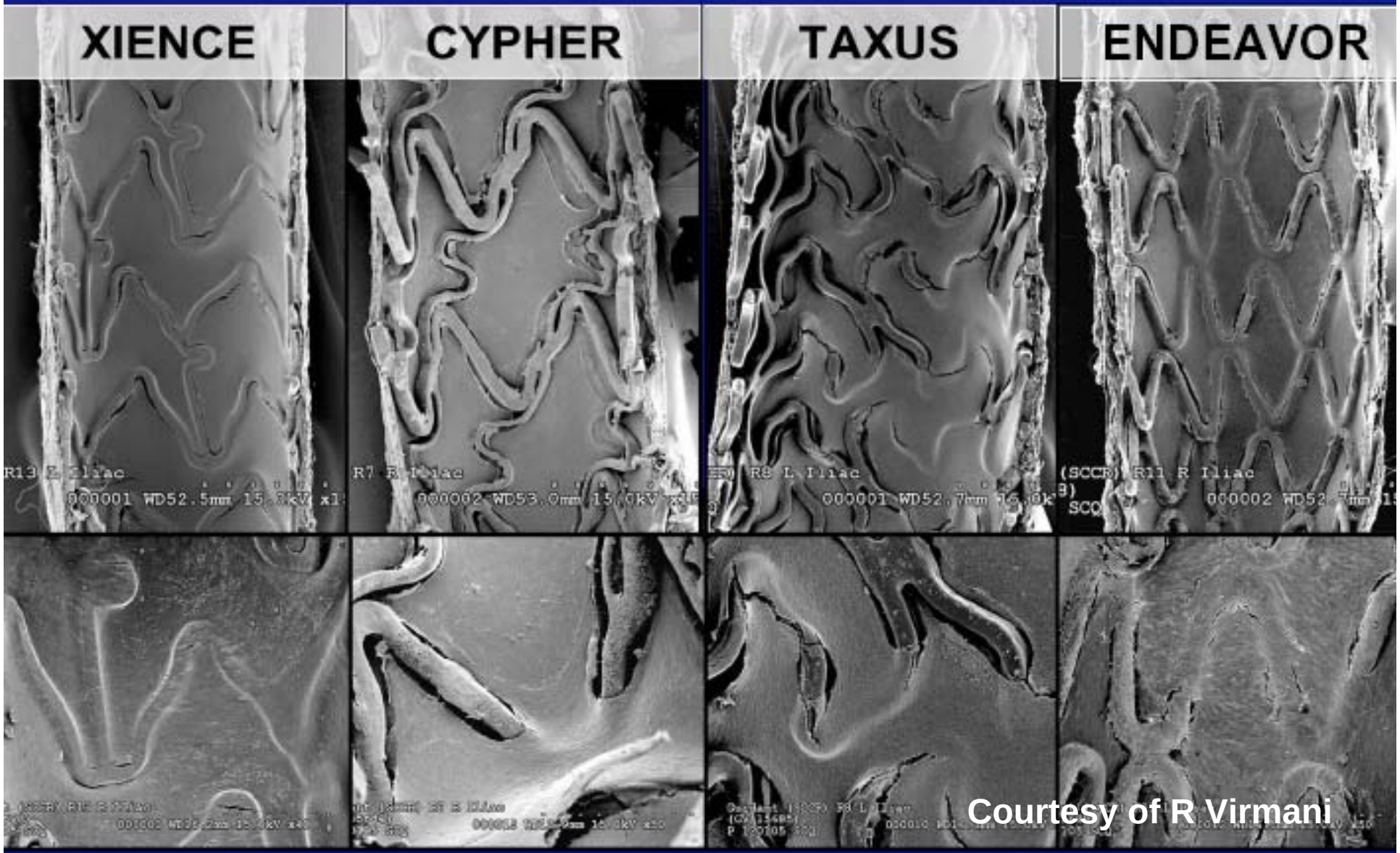
New Biological target, New drug, Dual elution



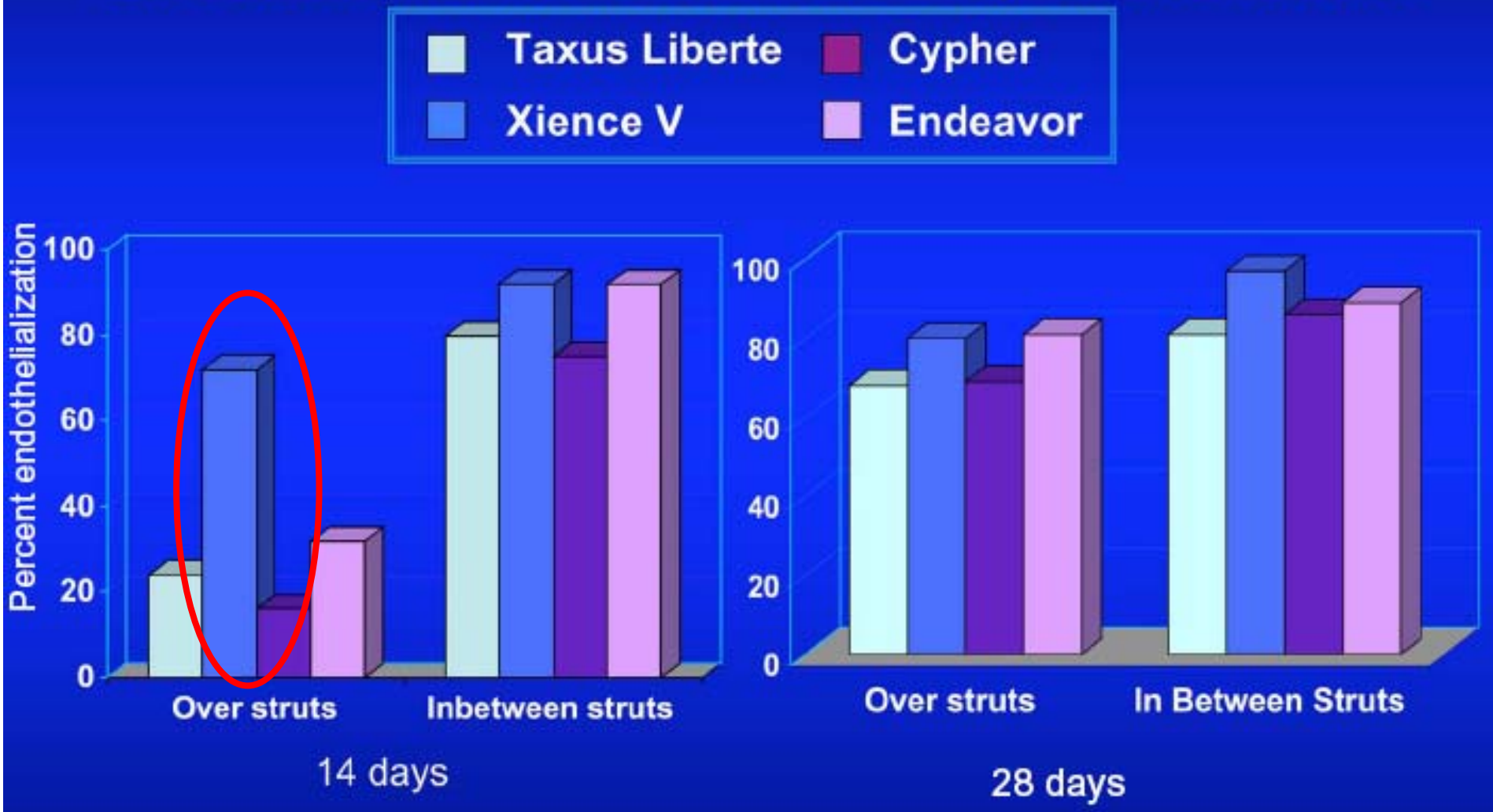
2 Drugs with 2 Different Targets: Pimecrolimus-Paclitaxel
Isoflavone-Sirolimus
Dexamethazone-Zotarolimus



Scanning Electron Microscopy: 14-day

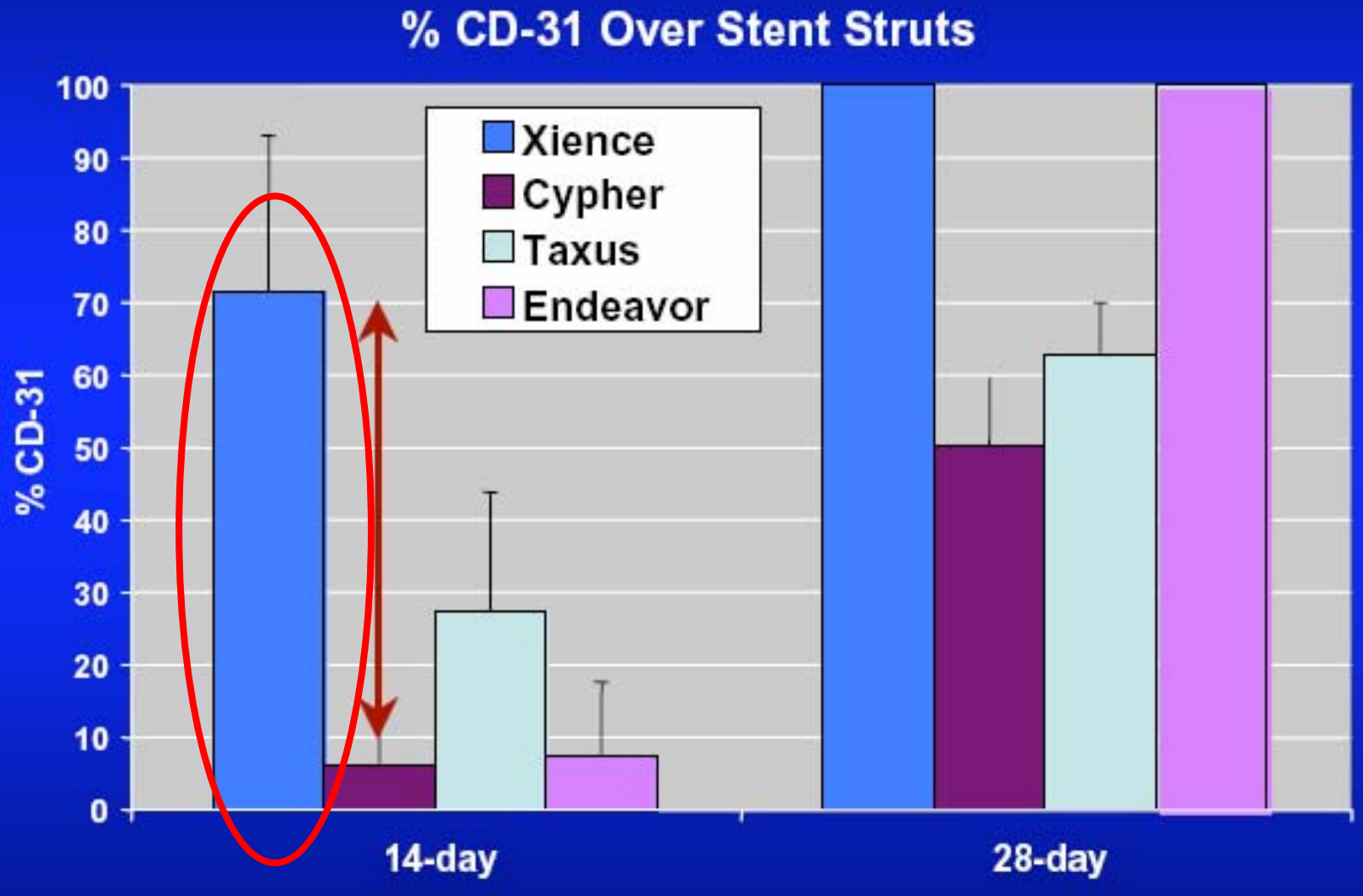


Morphometric Measurement of Extent of Endothelialization at 14 and 28 days in the Rabbit



Rapid re-endothelialization associated with Xience™ V

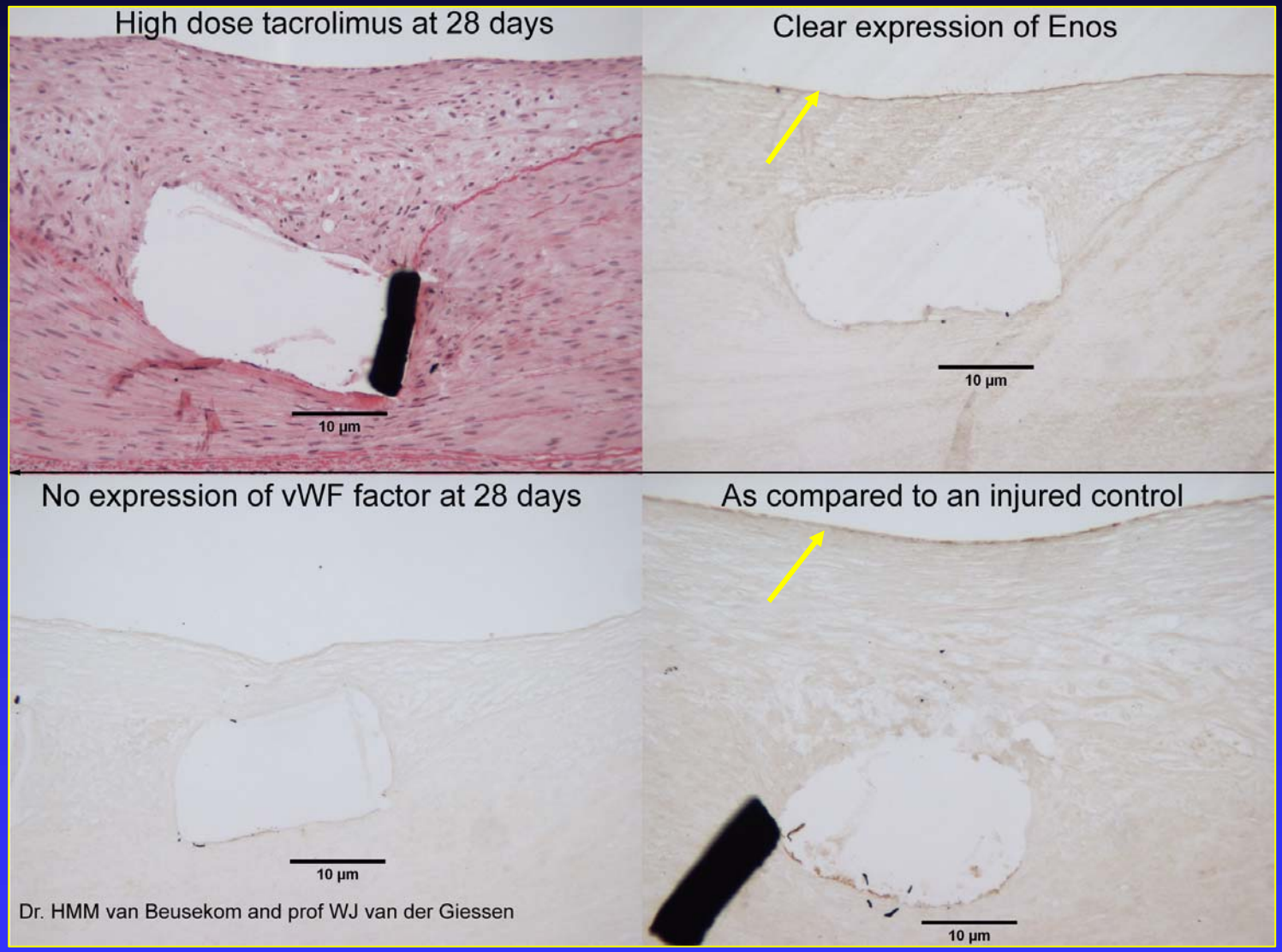
CD-31 Coverage



Results presented as mean ± standard deviation

Courtesy of R Virmani

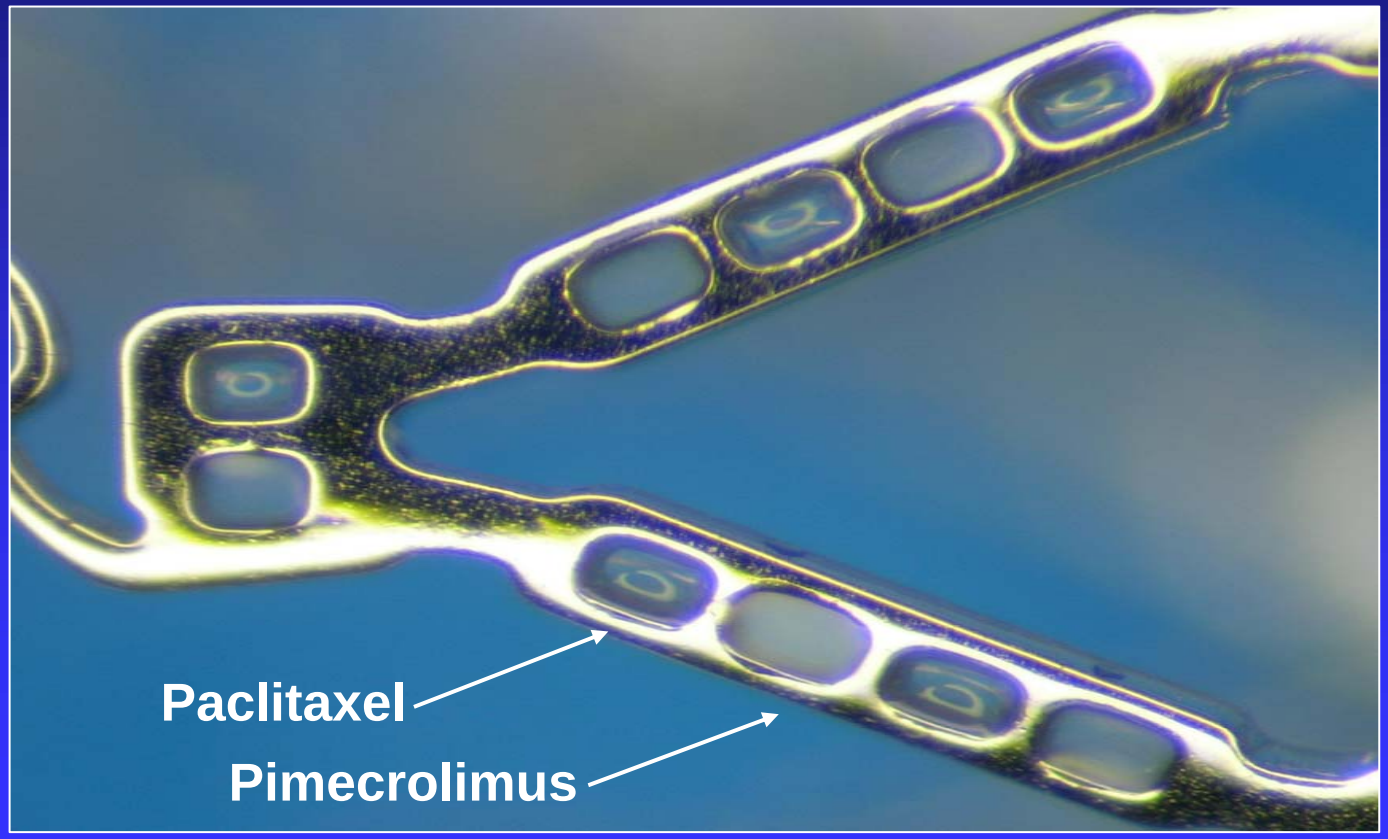
NEW BIOLOGICAL TARGET NEW DRUGS-TACROLIMUS



Immunocytochemistry of the endothelial layer shows a fully functional endothelium in the high dose group, as illustrated by the presence of E-NOS expression and the absence of vWF expression (the brown colored product on the endothelium (arrow))

#3 DUAL ELUTION PACLITAXEL AND PIMECROLIMUS

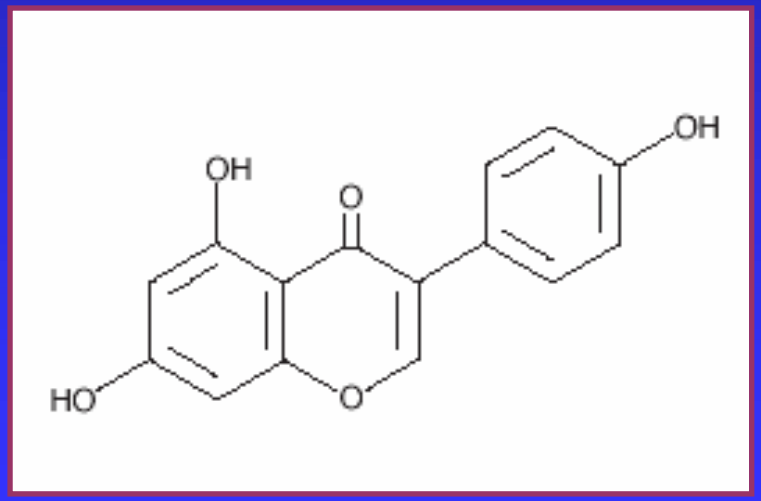
Conor Dual Drug Stent



#4 DUAL ELUTION GENISTEIN AND SIROLIMUS

Genistein

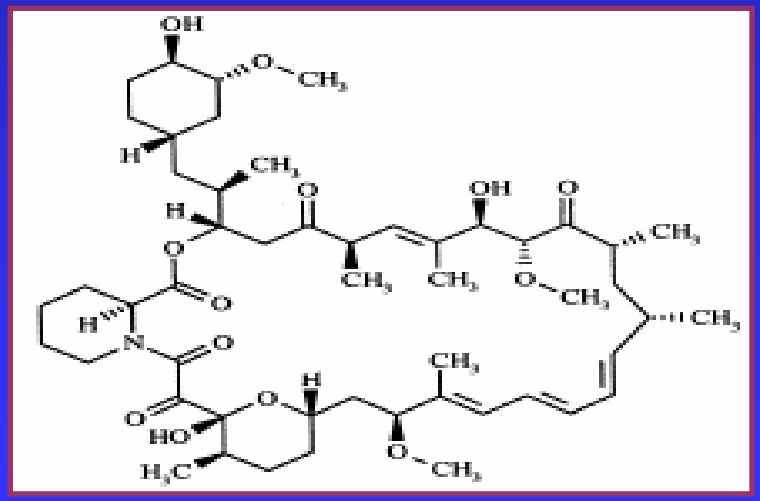
- Genistein is a potential isoflavone which possesses dose dependent anti-platelet and anti-proliferative properties.
- Genistein inhibits collagen-induced platelet aggregation which is responsible for primary thrombosis.



- Approved by FDA for prevention of blood clots (Nov. 2000).

Sirolimus

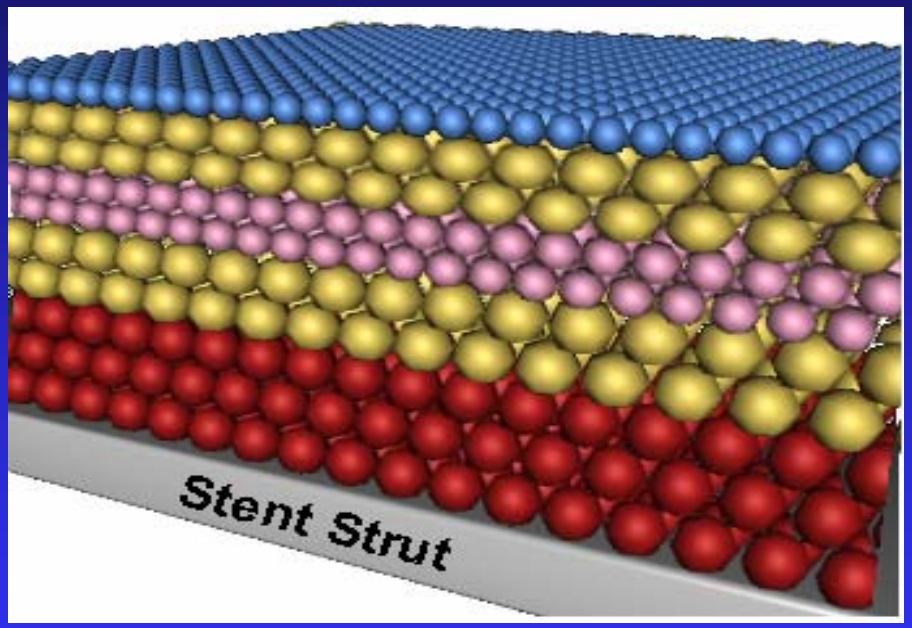
- Sirolimus is a naturally occurring Antibiotic drug.
- Wyeth-Ayerst Laboratories discovered its potent Immunosuppressive activity.
- Sirolimus prevent neointimal hyperplasia by inhibiting inflammatory response and cell proliferation.



- Approved by FDA for renal and kidney transplantation (1999).

#4 DUAL ELUTION GENISTEIN AND SIROLIMUS

Five Layers of Genistein -Sirolimus Eluting Stent



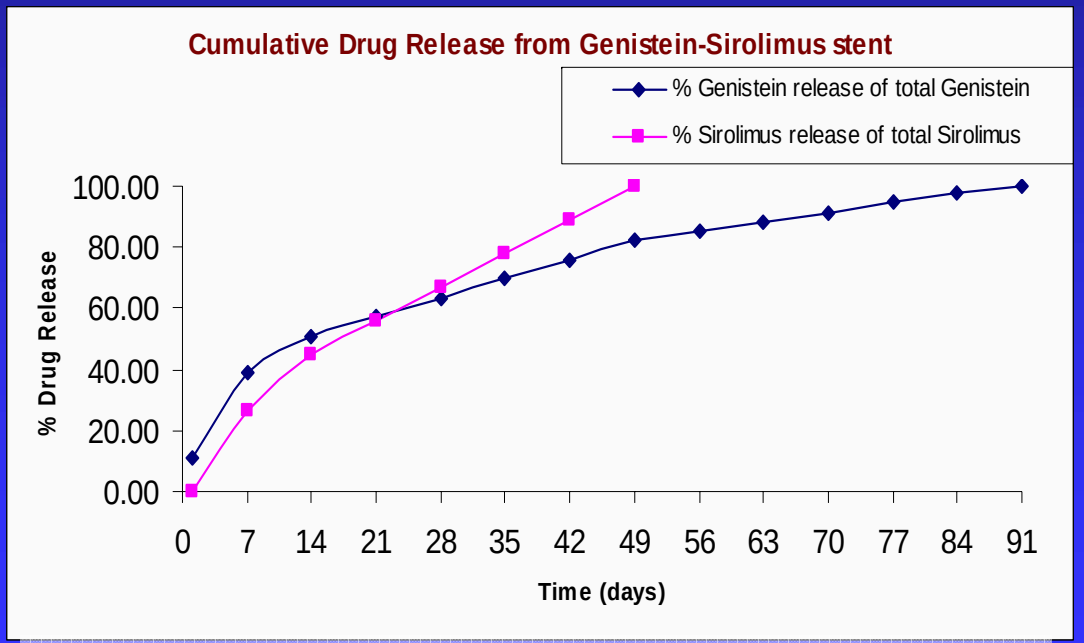
- No Drug- Top layer (Protective layer E)
- Genistein (Top layer D)
- Genistein + Sirolimus (Middle layer C)
- Genistein↓ + Sirolimus ↑ (Middle layer B)
- Genistein (Base layer A)

- Total Drug Dose: 2.51 μg/mm^2 (112 μg Genistein and 76 μg Sirolimus content on 16 mm stent)
- Unique Biodegradable Heparinized Polymers Blend includes-Poly L-Lactide, 50/50 Poly DL-Lactide-co-Glycolide and Polyvinyl Pyrrolidone

#4 DUAL ELUTION GENISTEIN AND SIROLIMUS

Elution Profile for Genistein-Sirolimus Eluting Stent

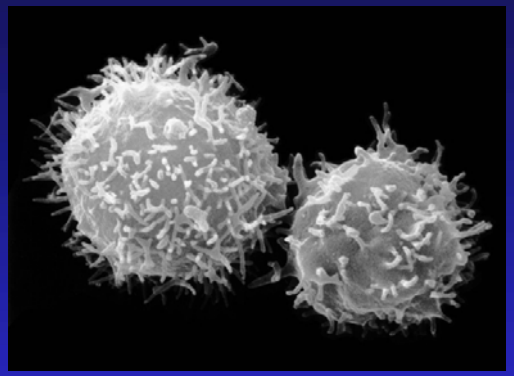
- **Initial high dose of Genistein for 2 days to prevent platelet aggregation. (Top layer D)**
- **Concurrent release of Genistein and Sirolimus from Layer C between 3 to 9 days will target primary thrombus formation and intimal cell proliferation**
- **Slow release of Genistein and Sirolimus (Layer B) between 10 to 49 days to prevent mainly cell proliferation**
- **Finally slow release of Genistein (Layer A) from 50 to 89 days will prevent late thrombosis up to 3 months**



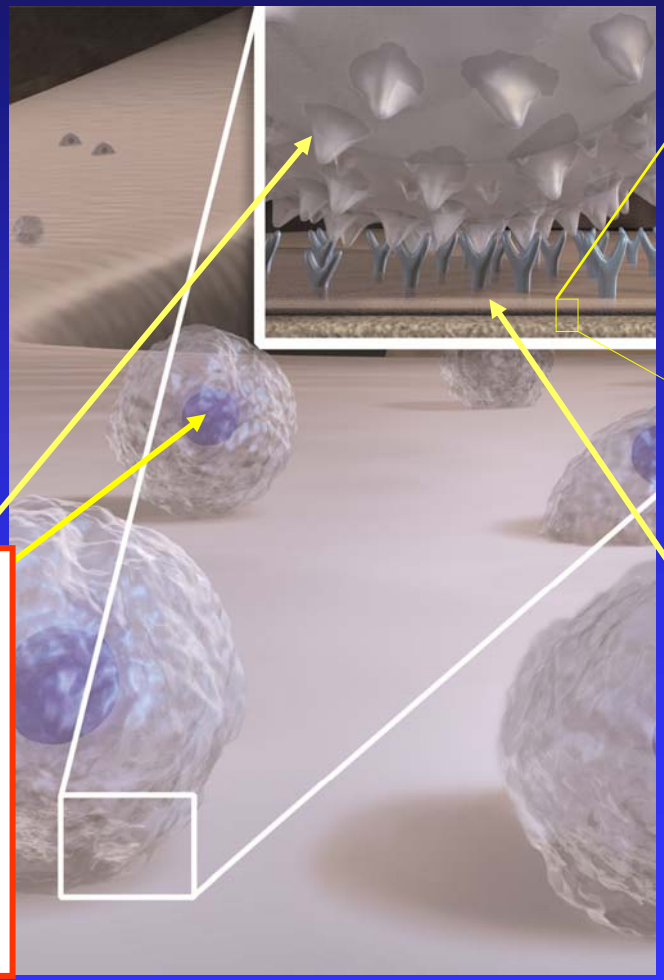
% drug release profile for 16-mm long Genistein-Sirolimus eluting stent

ENDOTHELIAL PROGENITOR CELL CAPTURE

EPC Capture Coating Technology



Human progenitor cell with CD34 Cell Surface Antigen

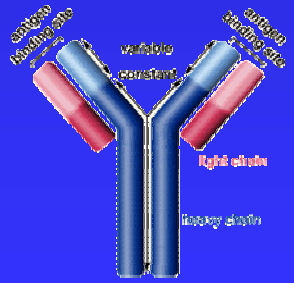


Intermediate Layer

Stent Adhering Bottom Layer

Stent Surface

CD34 Antibody Layer



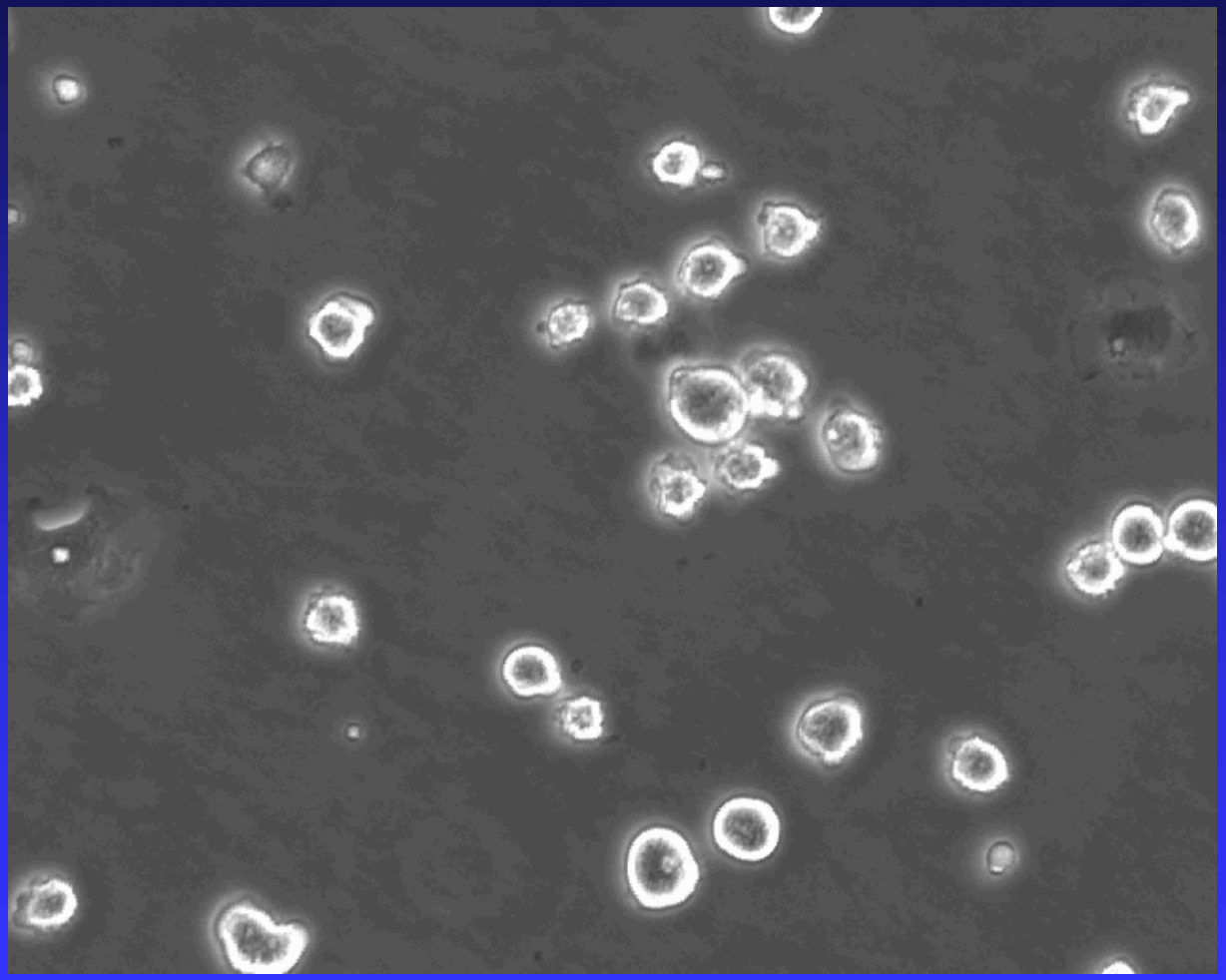
Endothelial Progenitor Cell Capture by Stents Coated With Antibody Against CD34

The HEALING-FIM (Healthy Endothelial Accelerated Lining Inhibits Neointimal Growth-First In Man) Registry

Jiro Aoki, MD,* Patrick W. Serruys, MD, PhD, FACC,* Heleen van Beusekom, MD, PhD,* Andrew T. L. Ong, MBBS, FRACP,* Eugene P. McFadden, MBChB, MD, FRCPI, FACC,* Georgios Sianos, MD, PhD,* Willem J. van der Giessen, MD, PhD,* Evelyn Regar, MD, PhD,* Pim J. de Feyter, MD, PhD, FACC,* H. Richard Davis, MSc,† Stephen Rowland, PhD,† Michael J. B. Kutryk, MD, PhD‡

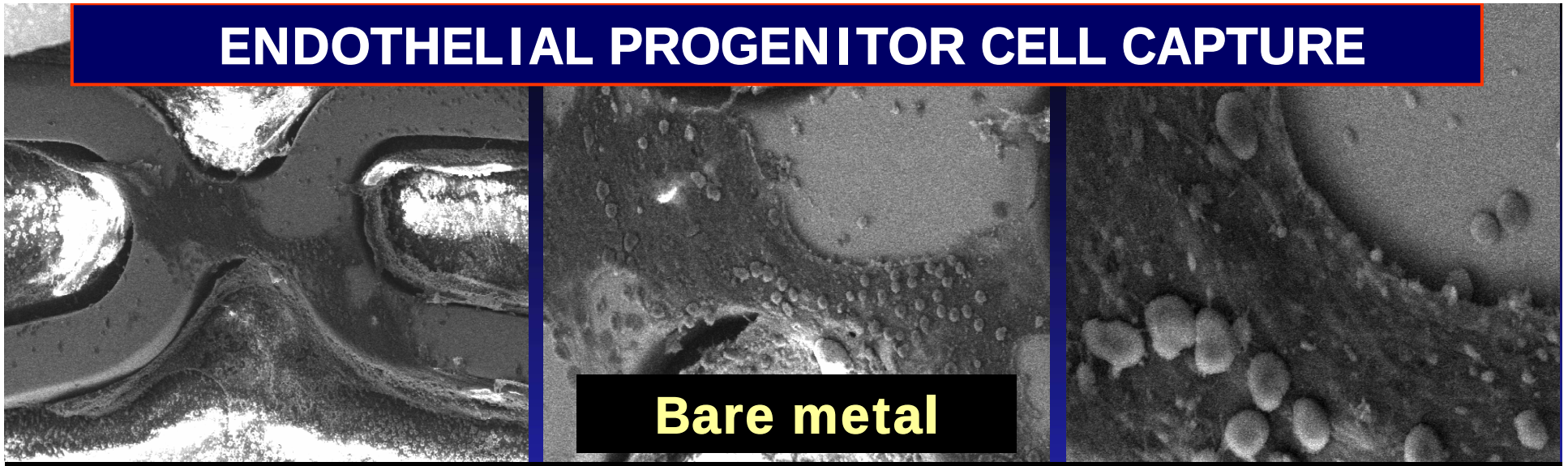
Rotterdam, the Netherlands; Fort Lauderdale, Florida; and Toronto, Canada

EPC Capture Coating

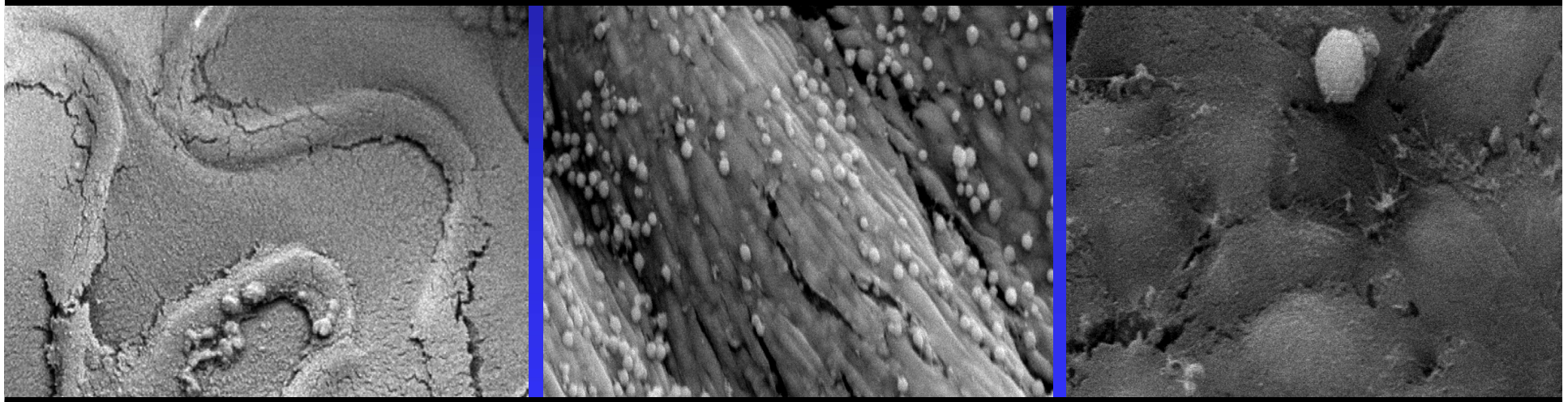


HUVEC Cells attaching to AB Coated glass plate

ENDOTHELIAL PROGENITOR CELL CAPTURE



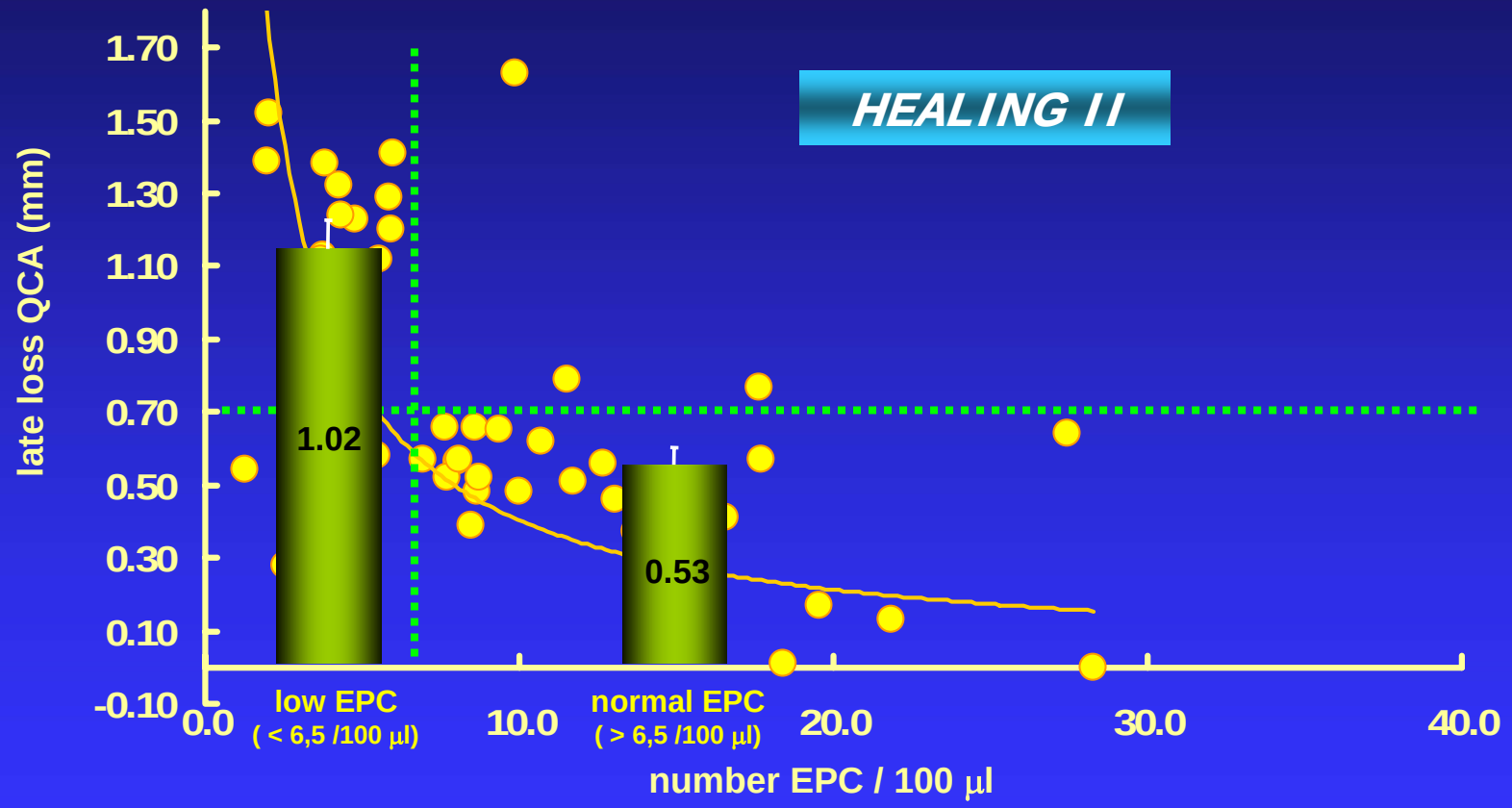
48 hr explant of bare metal stent in porcine arteries



coated stents with monoclonal antibody against CD34 capturing Endothelial Progenitor Cell to accelerate the Healing Process are in clinical trial !

ENDOTHELIAL PROGENITOR CELL CAPTURE

Correlation in-stent late luminal loss and circulating EPC titer at 6 months FU



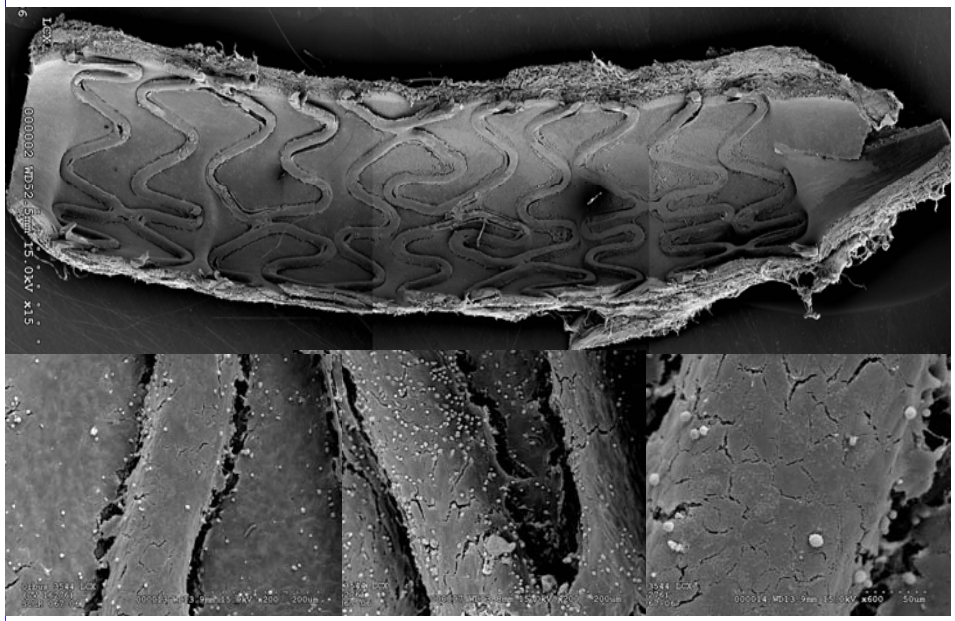
R = 0.727

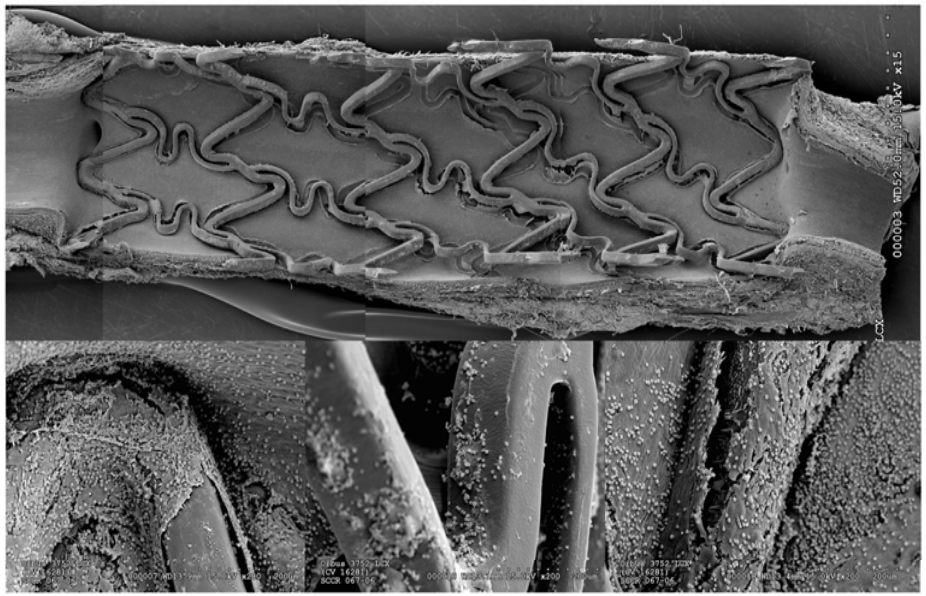
ENDOTHELIAL PROGENITOR CELL CAPTURE

DES COMBO with EPC Technology

EPC capture coating with Sirolimus Eluting Stent

Sirolimus Eluting Stent (Cypher Select)





3-Day Porcine Implants

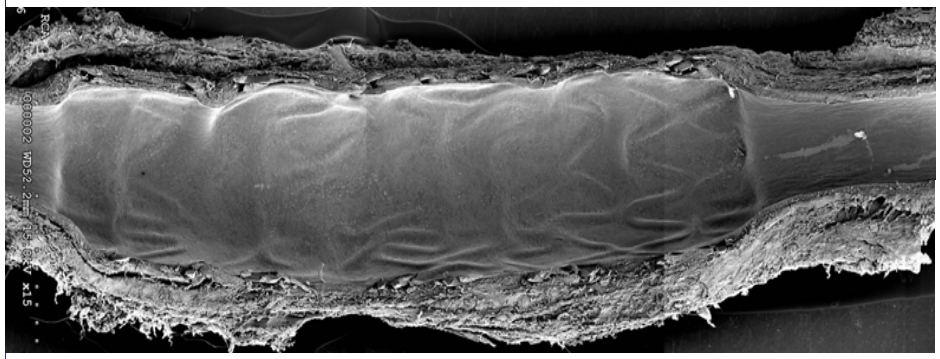
Virmani/Leon unpublished data 2006

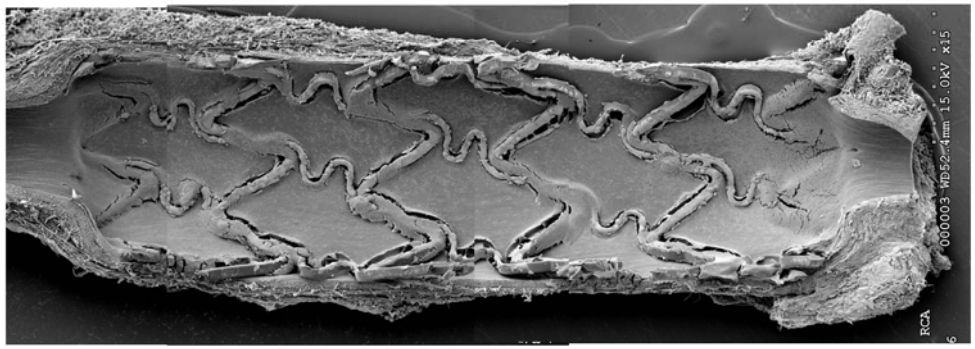
ENDOTHELIAL PROGENITOR CELL CAPTURE

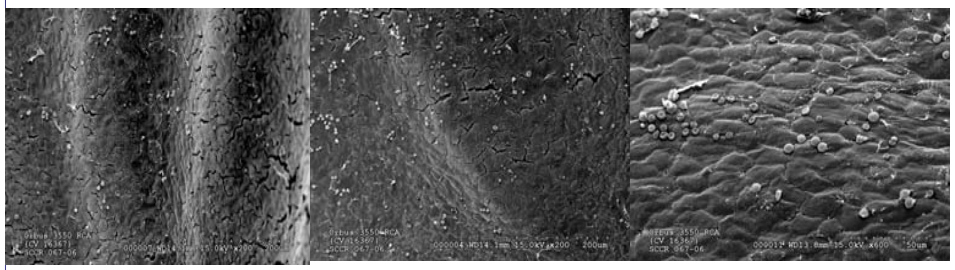
DES COMBO with EPC Technology

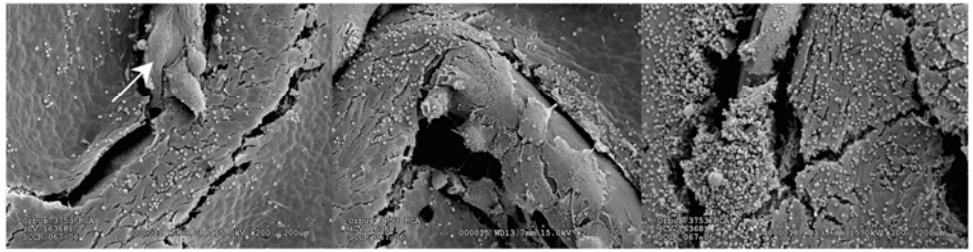
EPC capture coating with Sirolimus Eluting Stent

Sirolimus Eluting Stent (Cypher Select)









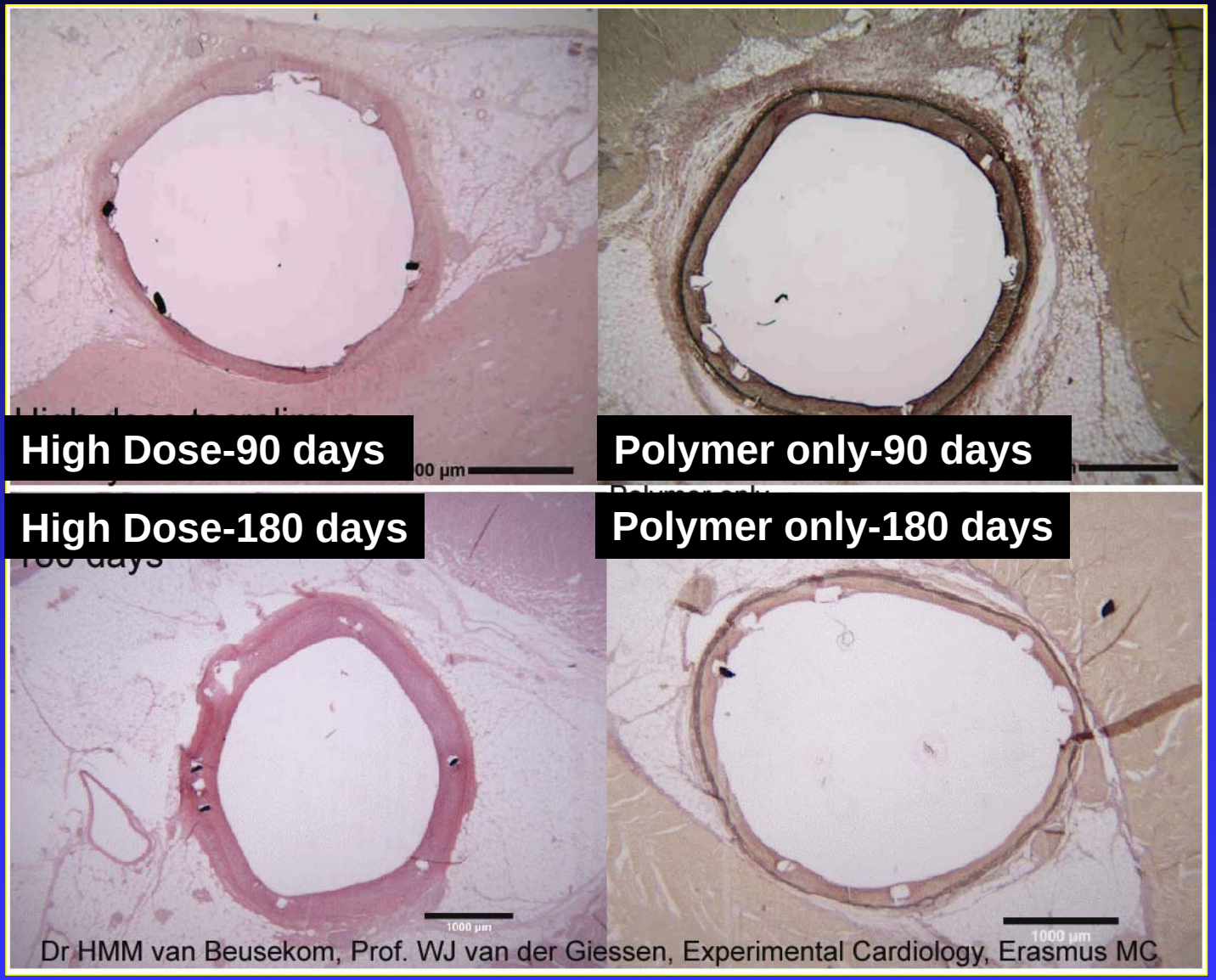
14-Day Porcine Implants

Virmani/Leon unpublished data 2006

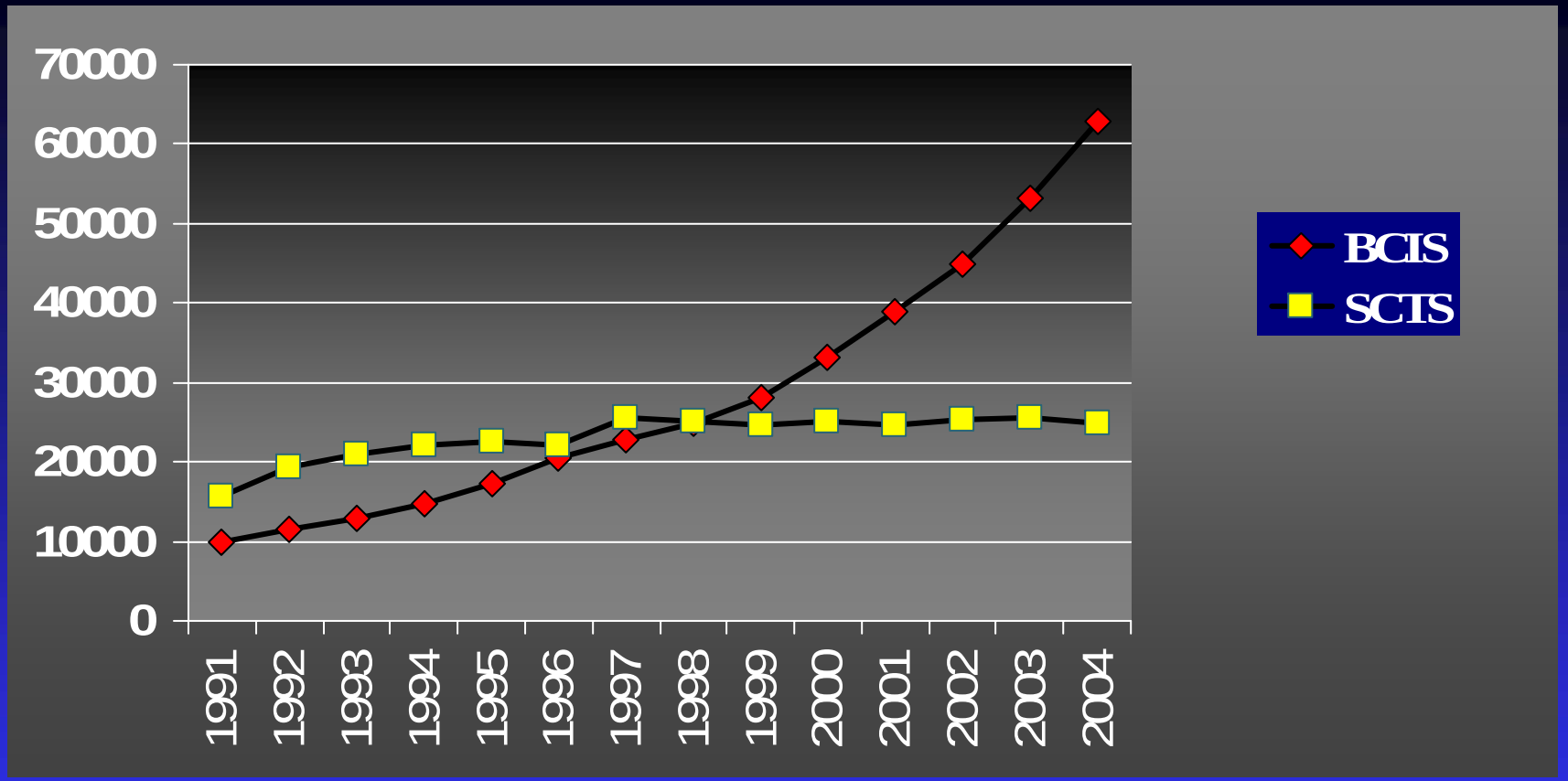
Conclusions

- Following the 2 pioneers of DES (Cypher and TAXUS), various types of new designed coated stents will emerge and become available in a few years time.
- Although these conventional DESs have produced promising outcomes, their remarkable effectiveness is not yet established for all anatomic subsets.
- Besides, there are several caveats and concerns about conventional DESs (late thrombosis, hypersensitivity, abnormal vasomotion, etc).
- Abolition of neointimal hyperplasia is no longer the ultimate goal. Development of more biocompatible and bioabsorbable stent facilitating adequate endothelialization, is expected in the near future.

NEW BIOLOGICAL TARGET NEW DRUGS-TACROLIMUS



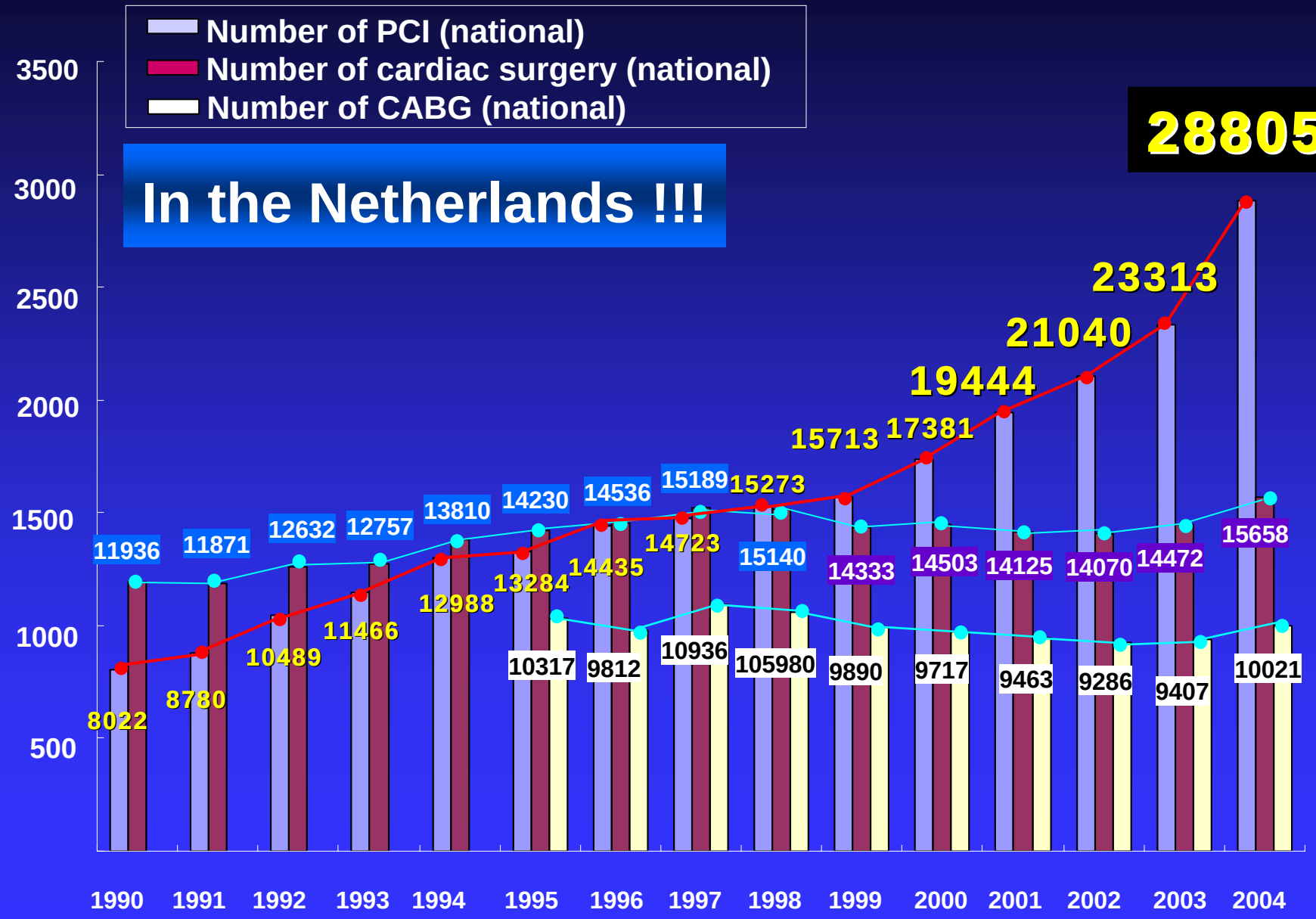
High dose tacrolimus at 90 and 180 days shows a complete healing response without inflammation or a late catch-up . The polymer control also shows good healing at both 90 and 180 days. There is some inflammation in the polymer group, but only deep in the adventitia without neointimal involvement.



PCI in the UK continues to increase at a rate of about 17% per annum
no real change in surgical revascularisation, which has not increased since about 1997
The ratio between PCI and CABG in 2004 was 2.5 and in 2005 is 3.1

The British Cardiovascular Intervention Society (BCIS)
Ludman PCI vs CABG Audit in the UK 2004

The beginning of the end and… the end of the beginning



Overview of this lecture

Part I

The rosy prophecy and the beginning of the end

Part II

The DES journey from the rosy prophecy to harsh reality

Part III

Perspective and future expectations