The Great Debate II: All Patients Should Receive a Drug-Eluting Stent

Martin B. Leon, MD

Principles and Perspectives in Interventional Cardiology

Mauna Kea, Hawaii; July 14-18, 2003

Cardiovascular Research Foundation

Lenox Hill Heart and Vascular Institute of New York

The Great Debate II: DES

vs.

Global
(Leon)

Selective
(Holmes)

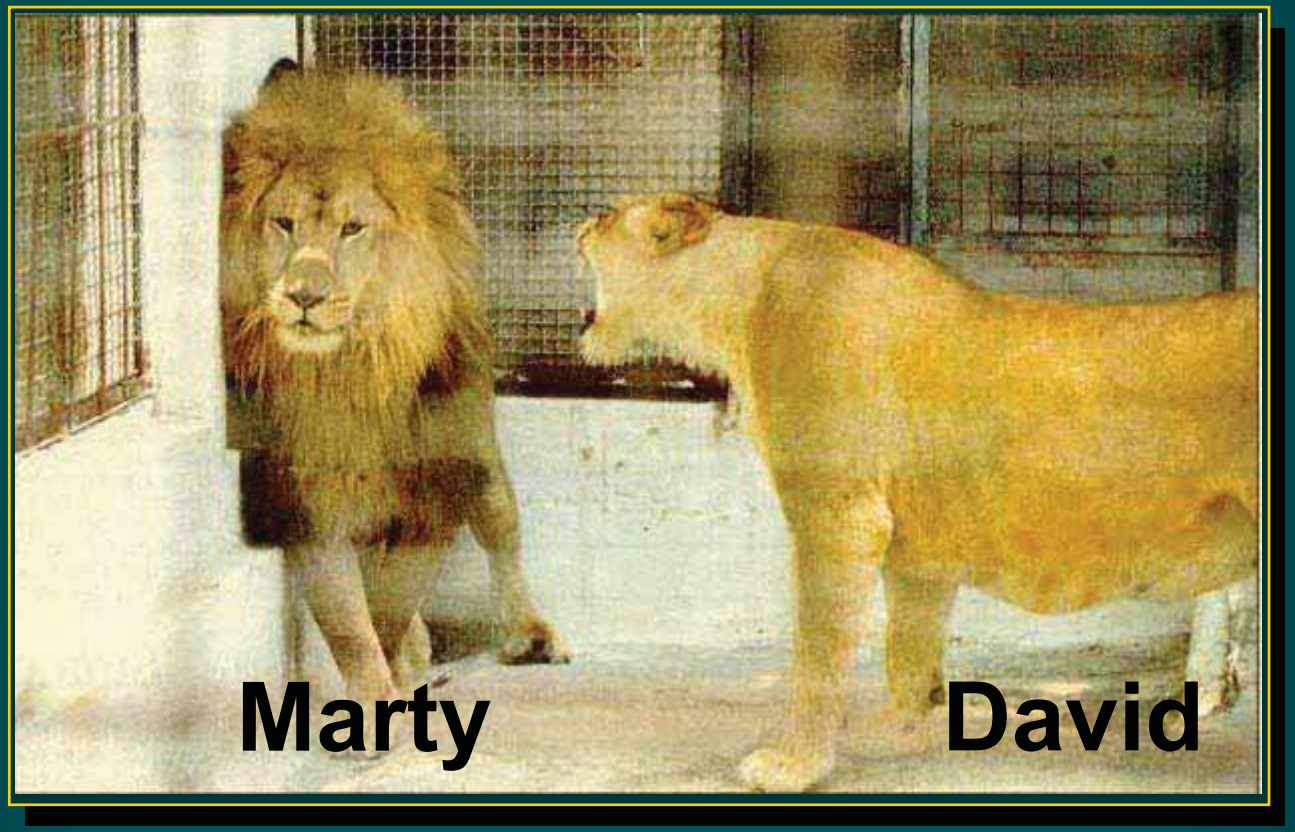
DEBATES: Derivation and Value

The DEBATE is an anglosaxon concept exported by the British to the "new world" in the early days of the United States of America. In general, debates are a waste of time and energy, as the participants become preoccupied with exaggerated presentations of a controversial topic. However, debates keep the audience entertained by artificially discussing issues which are going to be resolved spontaneously.

Debating Strategies

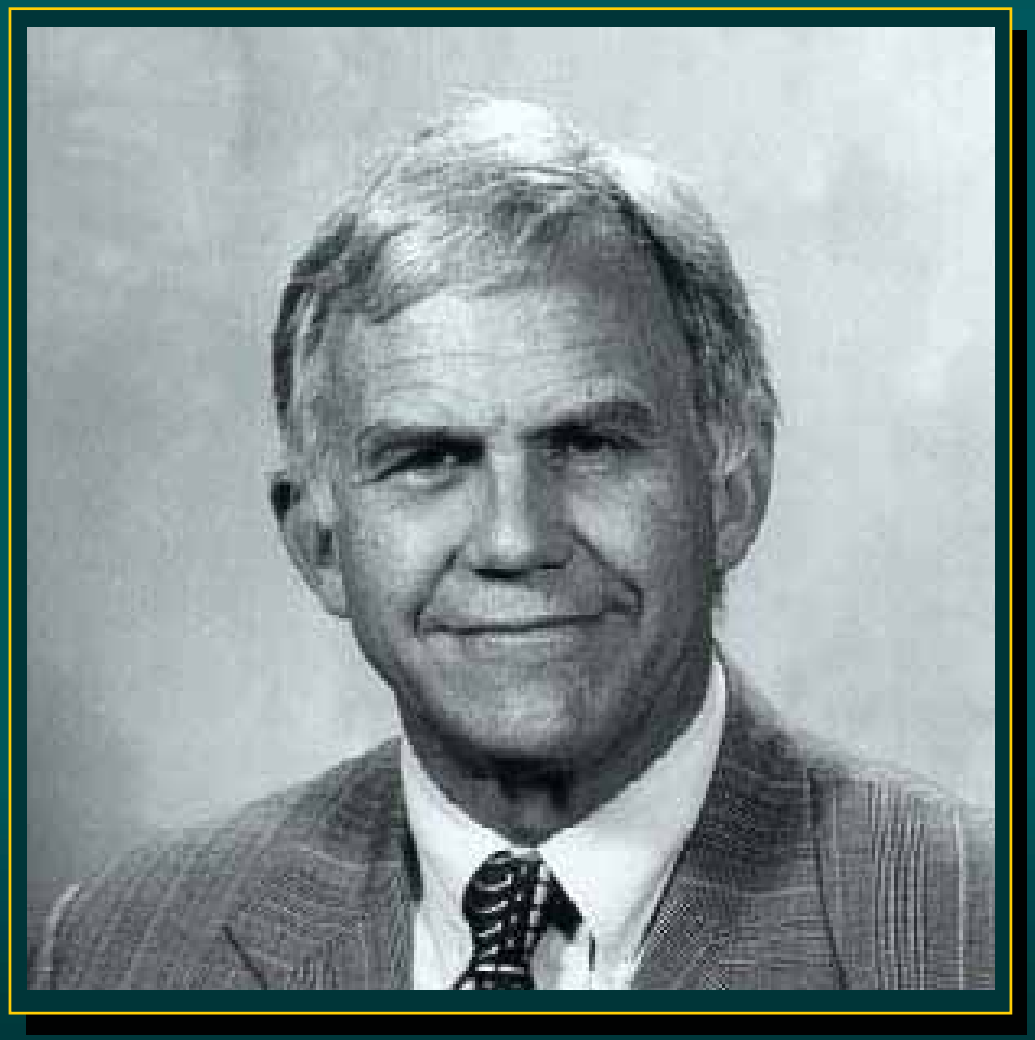
- Attack the opponent's academic worthiness
- Attack the opponent's technical competence
- Attack the opponent's viewpoint
- Present compelling arguments supporting your viewpoint
- Use the best "gag" slides
- If all else fails, attack the opponent's sexual preferences

Debates can get a bit out of hand....



Usually the loudest or most passionate or funniest debater wins!

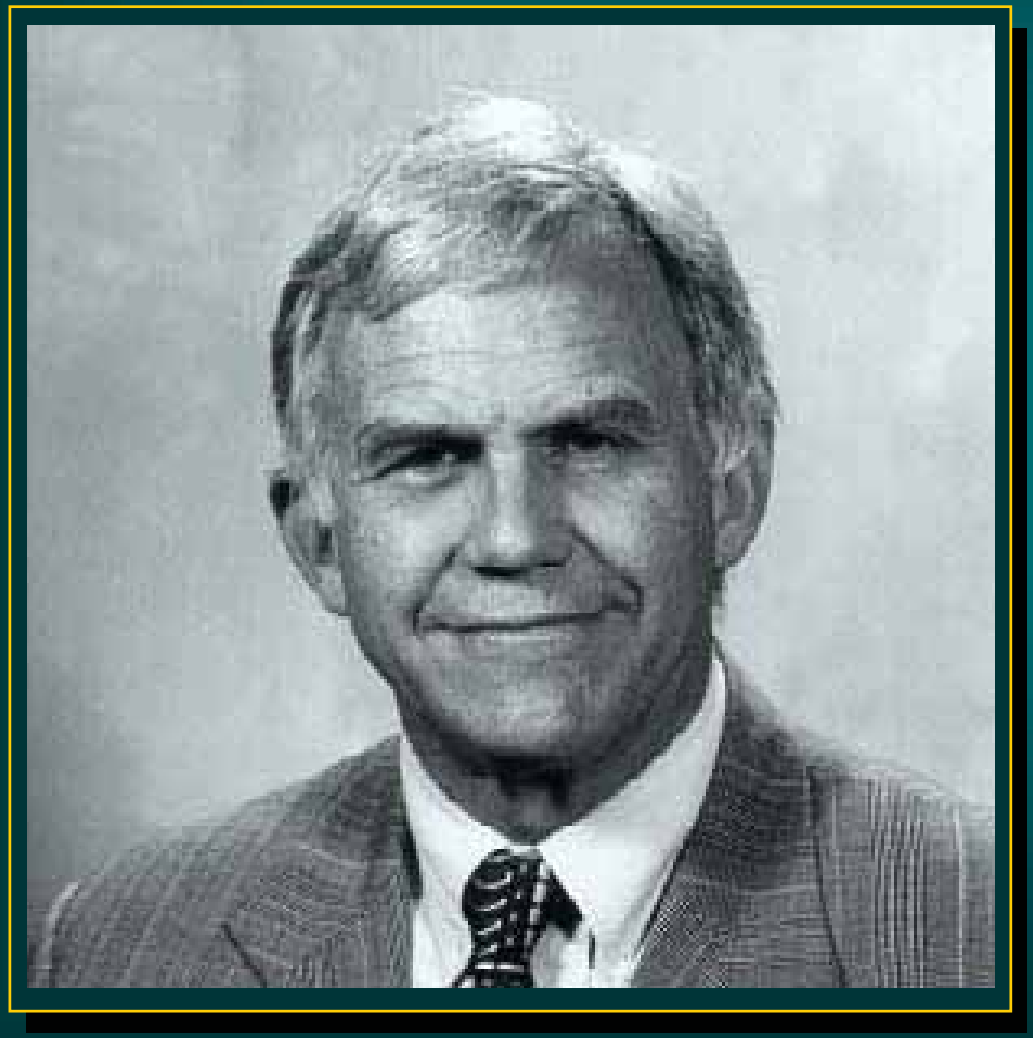
Special problems with debating against David Holmes…



Special problems with debating against David Holmes…

- He comes from the Mayo Clinic
- He is perceived as the "model" of a thoughtful academician
- He's a leader in cardiology societies
- He's so sincere (it's that mid-Western, down home, "trust me" look)
- He's so funny
- He has the best "gag" slides
- He may have poor (or no) data, but noone seems to care

Debating against David Holmes…



Is like debating against mother and apple pie!

The Great Debate II Outcome?

David…you're going down!!!

This debate is merely the "latest" in a series of debates between a new evolutionary (? revolutionary) therapy for CAD and the historic conventional standard…

- ***CABG vs. Medical therapy***
- ***PTCA vs. CABG***
- ***Stents vs. PTCA***
- ***Drug-eluting stents vs. Stents***

This debate is also the “latest” in a series of stent debates over the past decade…

- ✓ *Stents should only be used as a bailout technique*
- ✓ *Stents should only be used in Benestent/Stress lesions*
- ✓ *Provisional stenting is preferrable to elective stenting*
- ✓ *Direct stenting can only be applied in a minority of lesions*
- ✓ *Stents cannot compete with CABG for multivessel disease*

Against Global DES Use

Argument #1

- The SAFETY of DES are a concern….so let's be careful out there until more definitive data are available

Against Global DES Use

Argument #1 = Scare Tactics

- Stent thrombosis
- Incomplete apposition
- Aneurysms

Do Cypher™ Stents Cause Thrombosis?

THE NEW YORK TIMES, WEDNESDAY, JULY 9, 2003

Warning on Artery Stent Cites Some Cases of Clots

By MELODY PETERSEN

Johnson & Johnson sent a letter to doctors on Monday night advising them about rare cases of life-threatening blood clots linked to its new drug-coated stent, a fast-selling device used to keep blood flowing through the arteries.

The Food and Drug Administration said yesterday that it had received 47 reports of blood-clotting, or thrombosis, that occurred at the time the company's stent was implanted or within a few days. Regulators said five patients had died.

More than 50,000 patients have received the Cypher stent since it was approved in April. The stent is a tiny metal scaffold that props open an artery. Unlike other stents, Johnson & Johnson's device emits a drug to reduce the chance that the artery will clog again.

The F.D.A. said it was reviewing the reports and working with the company to determine what was causing the blood clots. "It is unclear what effect the Cypher stent has on thrombosis' risk," regulators said yesterday.

Martin E. Schildhouse, global director for corporate communications at the Cordis Corporation, a subsidiary of Johnson & Johnson, said some of the problems were caused by doctors improperly using the stent and not by the device itself.

"At this point, you can't draw the conclusion that it is because of the Cypher stent that you are seeing these events," Mr. Schildhouse said.

Two patients died after receiving the Cypher stent at St. Francis Hospital in Roslyn, N.Y., said Dr. Lawrence A. Reduto, the hospital's executive vice president for medical affairs. He said it was not clear that the stent had caused the deaths.

Dr. Reduto said that the overall incidence of thrombosis with the Cypher stent appeared to be no greater than that associated with stents that had not been coated with a drug.

Five deaths are reported in patients who got a Johnson & Johnson product.

"I think we saw an abnormality," Dr. Reduto said.

Mr. Schildhouse said the company had agreed with the F.D.A. that the letter should be sent to advise doctors about the problem and remind them of the proper technique to use in implanting the Cypher sent.

In the company's letter, Dr. Dennis Donohoe, vice president for therapeutics and clinical research at Cordis, said that some of the problems might have been caused when doctors used a stent that was too small for the patient's artery.

Because of high demand for the stent, the company has been unable to manufacture enough to fill doctors' orders and has focused on making the two smallest versions. Dr. Donohoe said that the company had recently begun to ship a larger version.

Dr. Donohoe also wrote that some patients might not have taken the proper amounts of medications that help keep blood from clotting.

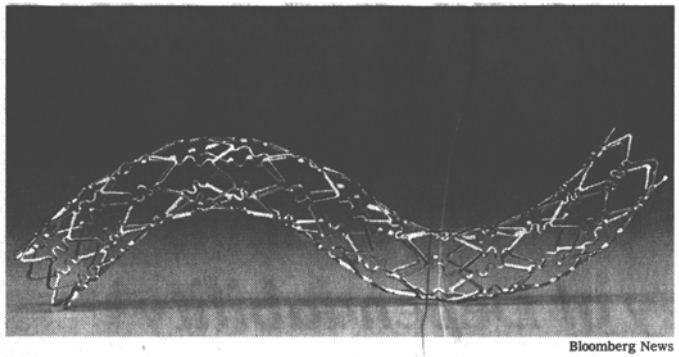
He also advised doctors not to use the drug-coated stent in patients with conditions that the device was not approved for, including restenosis, or a renarrowing of the artery where a stent procedure has already taken place.

Michael N. Weinstein, a medical device industry analyst at J. P. Morgan, said he did not think the reports of thrombosis would hurt sales of the Cypher stent. He said the problem had been aggravated by Johnson & Johnson's failure to supply all the appropriate sizes of device.

"Cardiologists are, as a result, 'using what they have,' and at times trying to deploy undersized stents into larger vessels, or in some cases using too many stents in a single vessel," Mr. Weinstein wrote in a recent research report after talking to numerous physicians.

Mr. Weinstein estimates that the company's sales of the Cypher stent will be $1.57 billion this year and $2.1 billion next year.

Shares of Johnson & Johnson fell 50 cents yesterday, to $52.48.



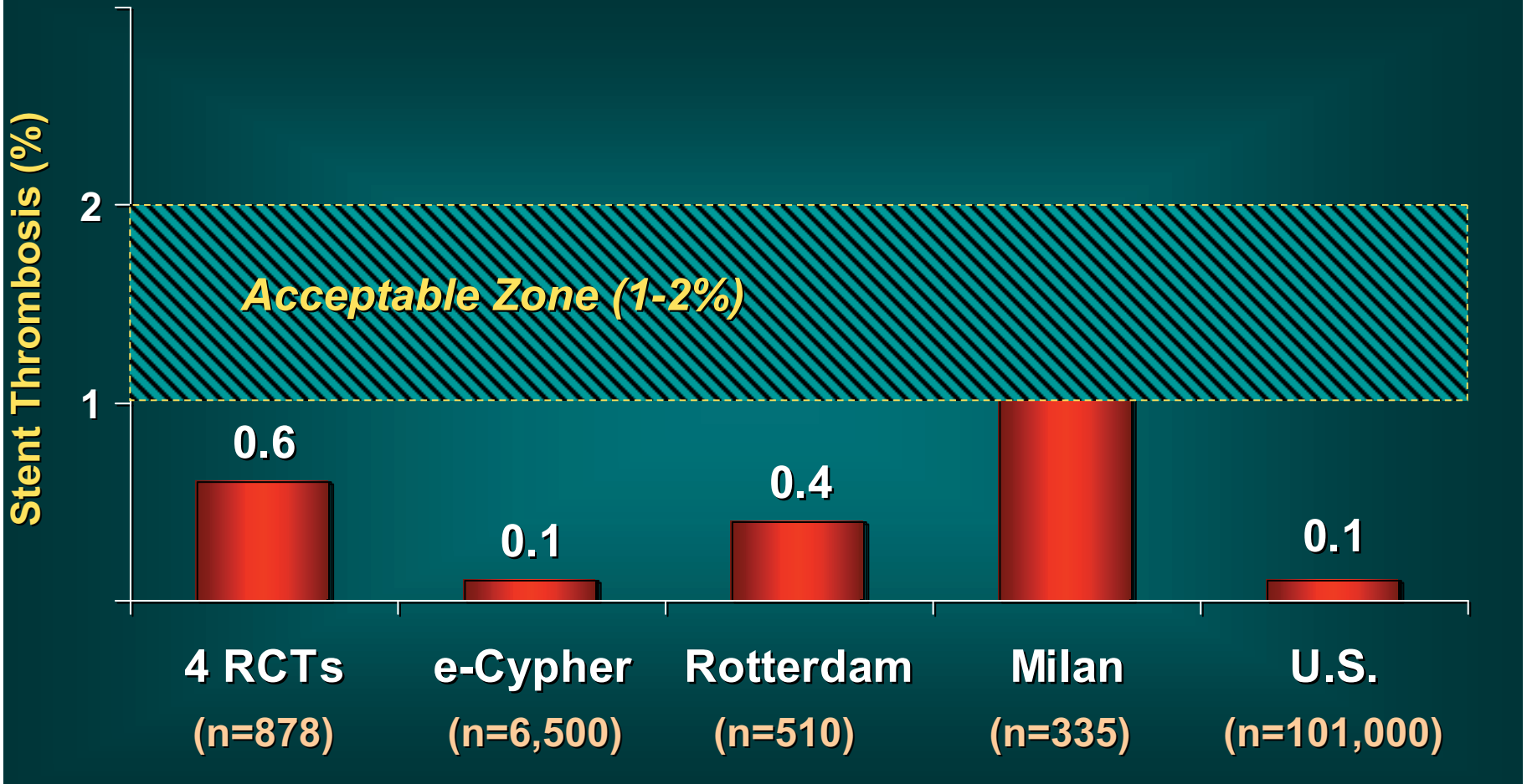
Bloomberg News

The Cypher stent, made by Johnson & Johnson, is coated with a drug meant to prevent arteries from clogging again.

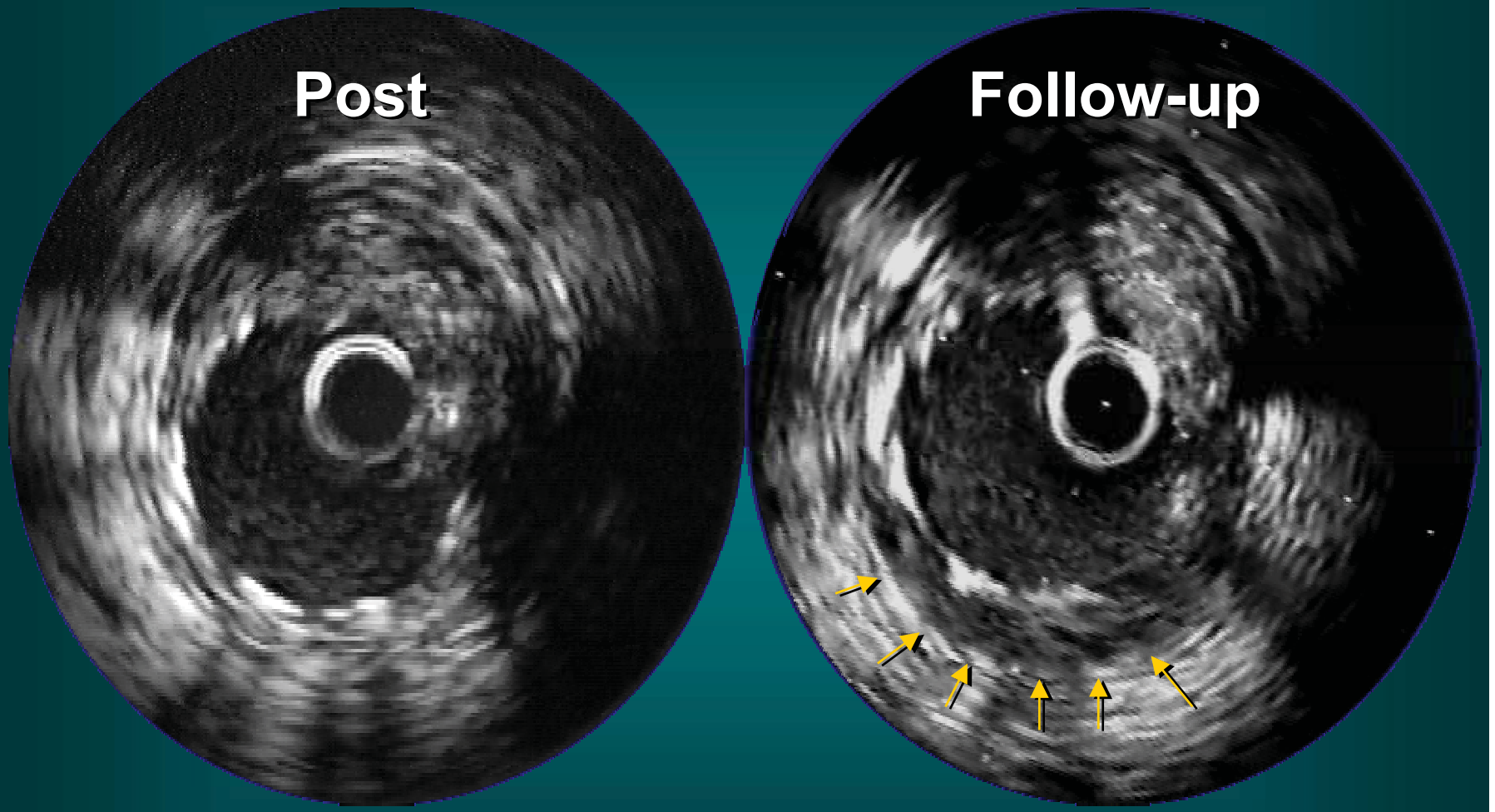
Cypher™ Stent Thrombosis

All Available Data

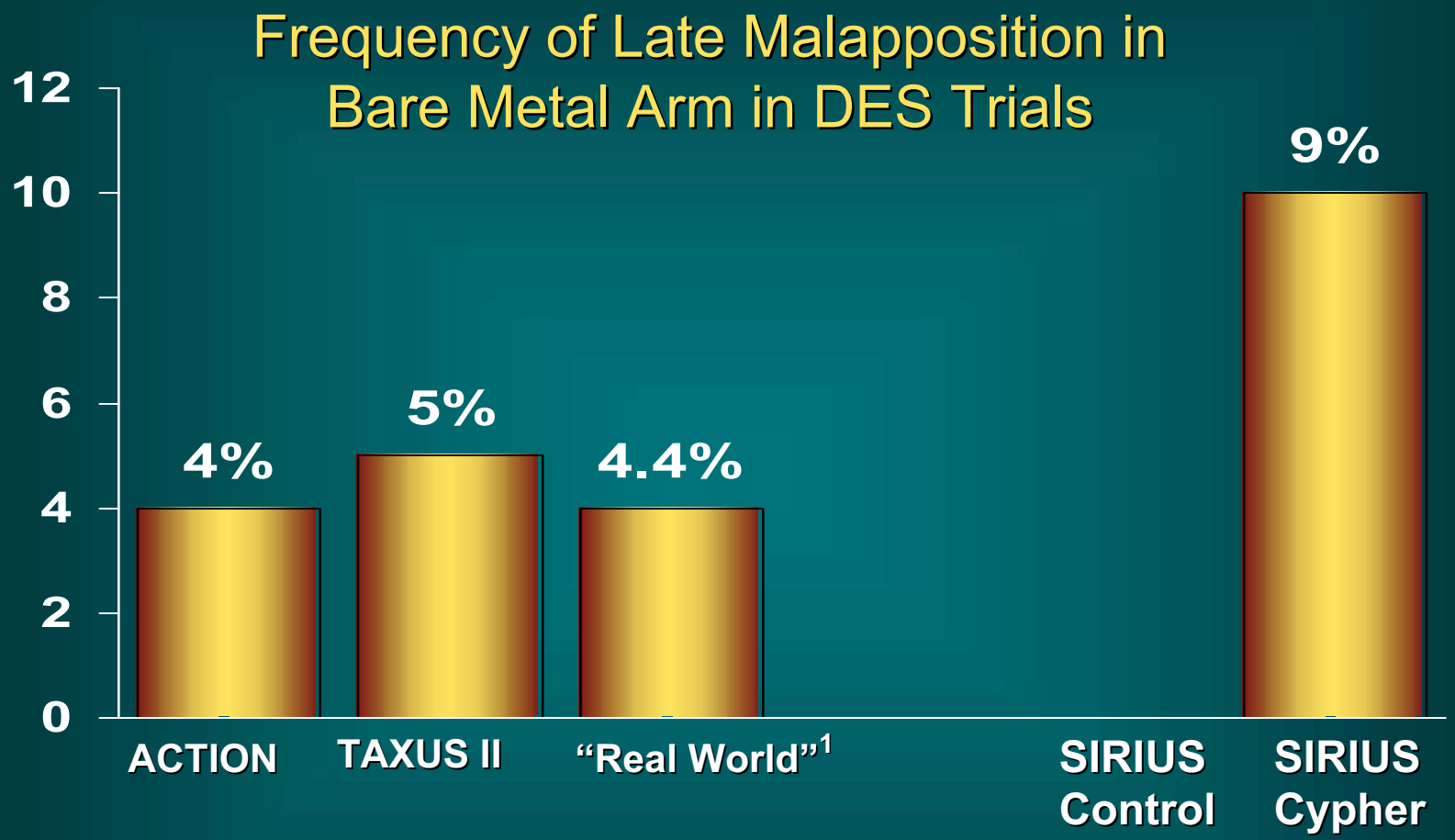
(total = 109,223 patients)



IVUS: Late Incomplete Apposition



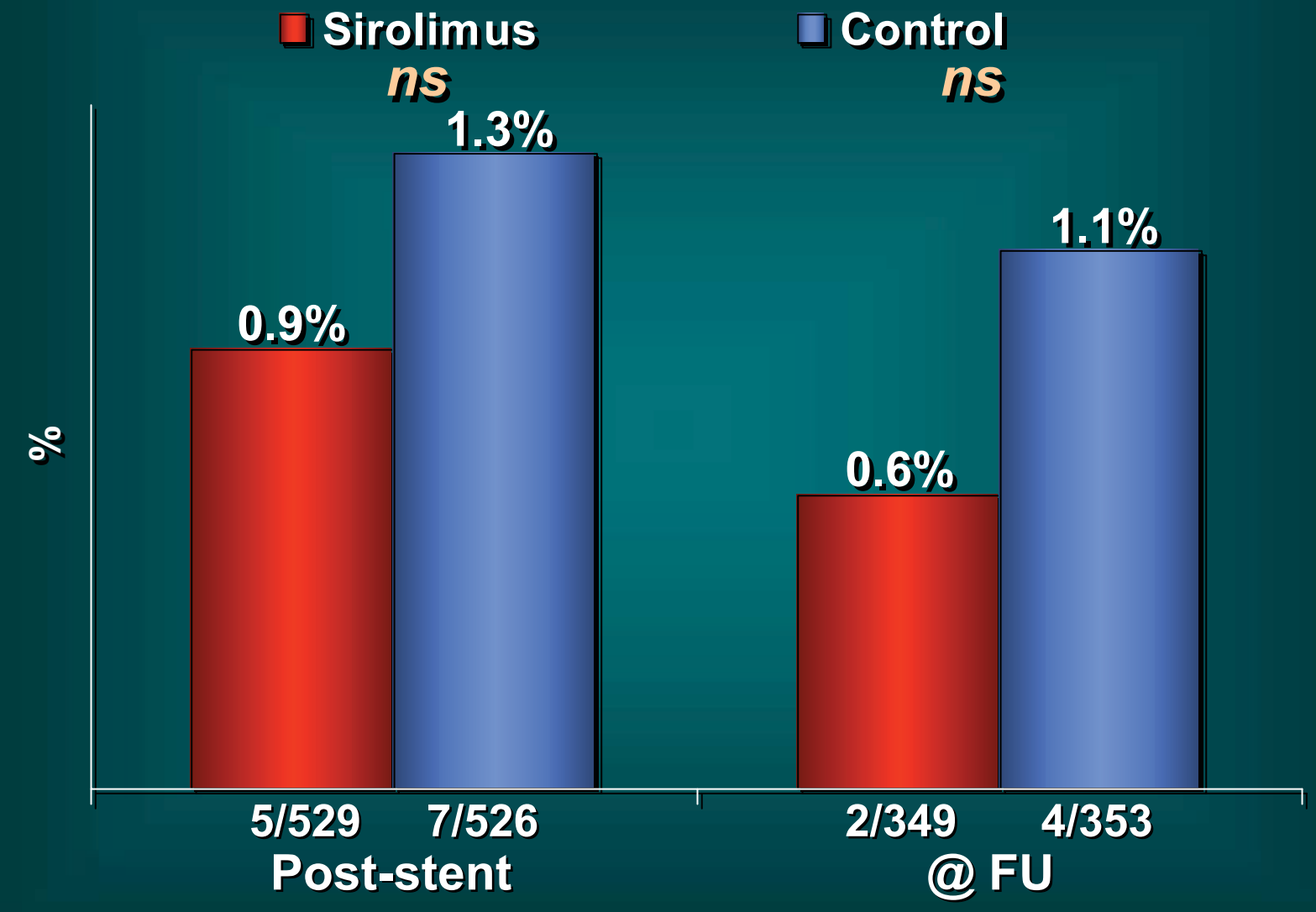
IVUS: Late Incomplete Apposition



No Clinical Events Attributed to Malapposition!

[1]*GS Mintz et al, Circulation 2002*

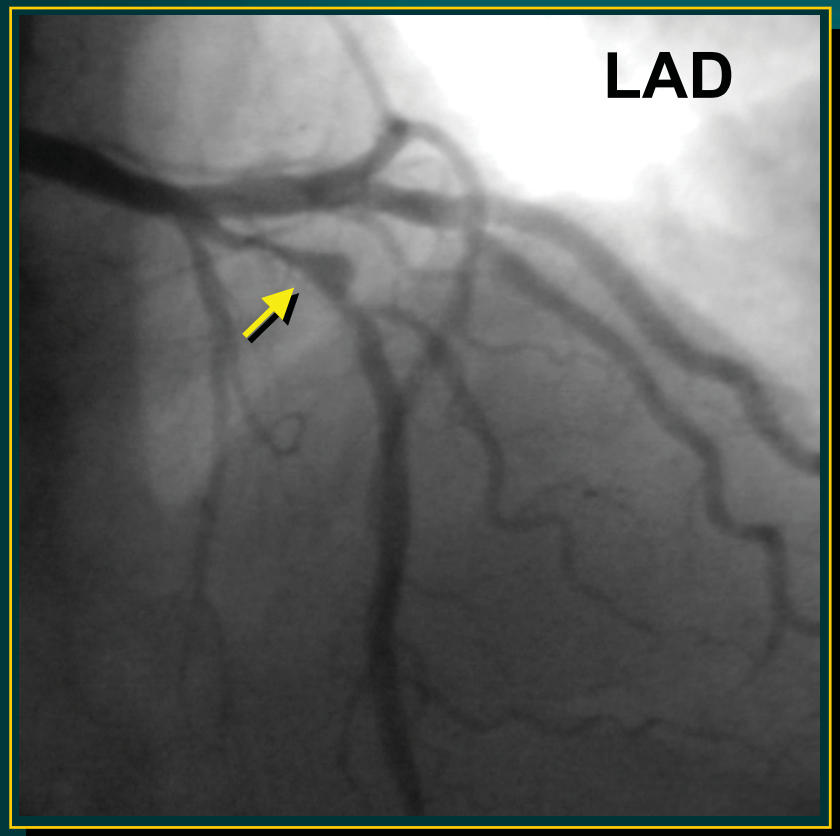
SIRIUS - Angio Aneurysms*

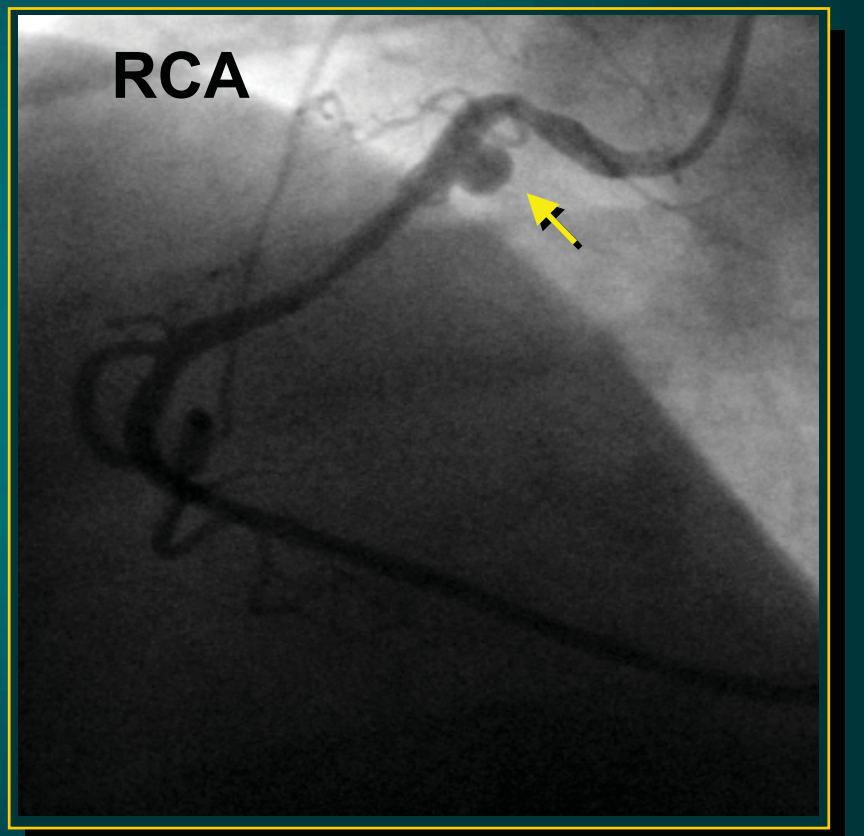


* angio aneurysm = $\frac{\text{treatment site diameter}}{\text{normal reference diameter}} \geq 1.2$

SIRIUS - Angio Aneurysms @ FU

The Two Worst SIRIUS Cases with Aneurysms at 8 mos Angio FU





Both in control bare metal stents!

Against Global DES Use

Argument #2

= more scare tactics

- **We're going to hear that some other DES systems have failed and have caused problems**

The rumors are rampant and the spin artists are having a field day!

www.usatoday.com

USA TODAY

Life

SECTION D

Tuesday, April 15, 2003

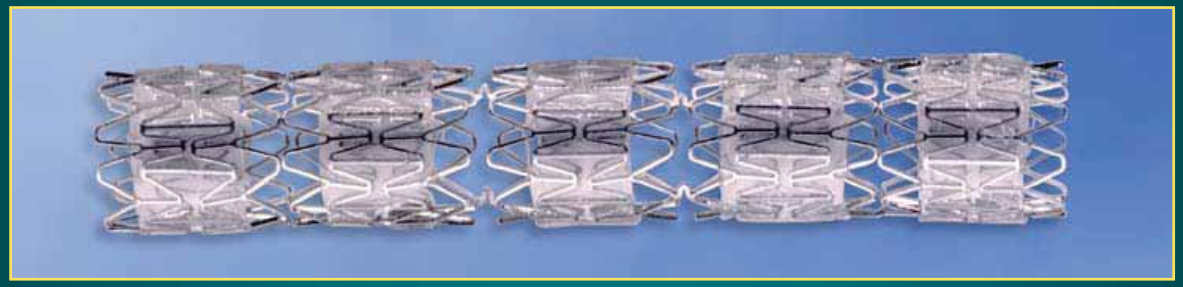
Hidden toll of DES, a generation later

Anti-restenosis drug now linked to cancer

National Cancer Institute

An Early Prototype DES

Quanam QUADS-QP-2 Stent



Issues:

- *polymer too thick, bulky, peels, and deforms in vivo*
- *side-branch closure*
- *drug dose too high – very toxic*
- *late erosion and infammatory reaction of "non-degradable" polymer*

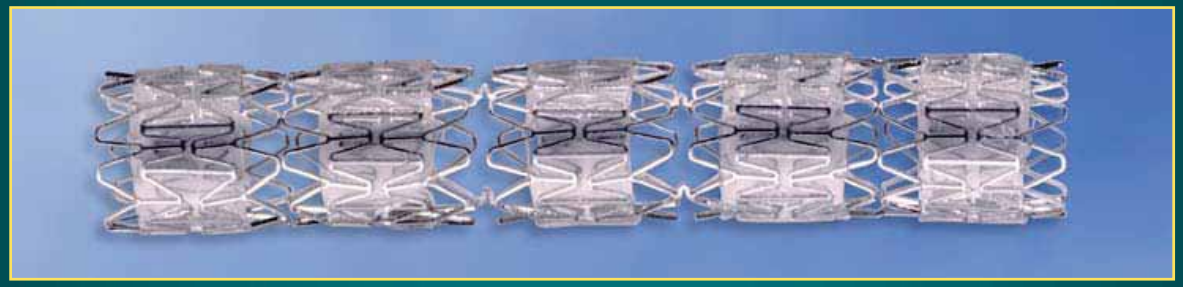
DES - The Clinical Data

Undoubtedly, you can design a DES system that doesn't work!

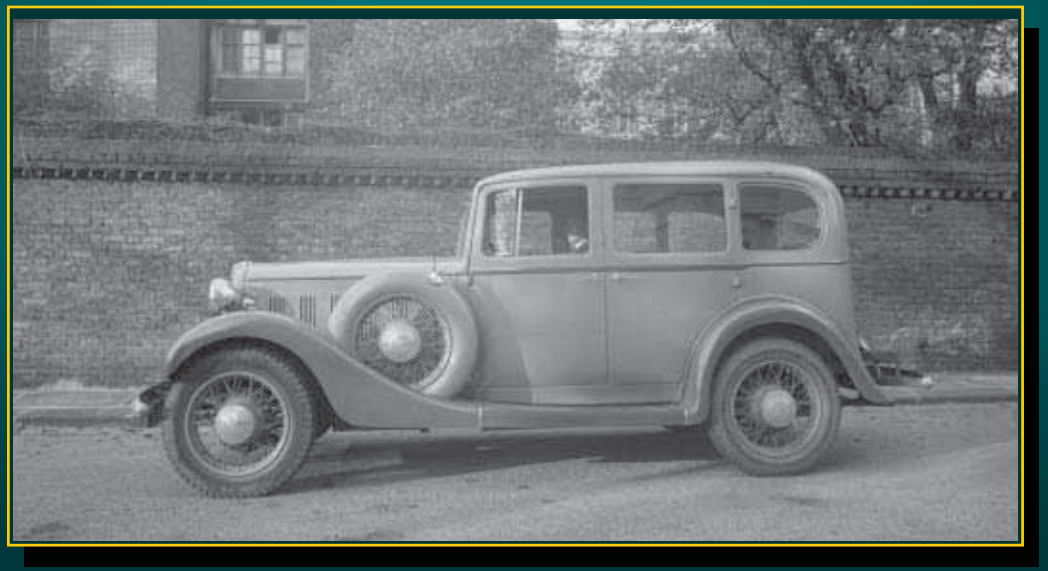
- Quanam - Taxane (polymer sleeve)
- Guidant - Actinomycin D (polymer matrix)
- Guidant/Cook – Paclitaxel (direct application)
- Abbott - Batimastat and Dexamethasone (PC coating)

The Model "T" DES

Quanam QUADS-QP-2 Stent

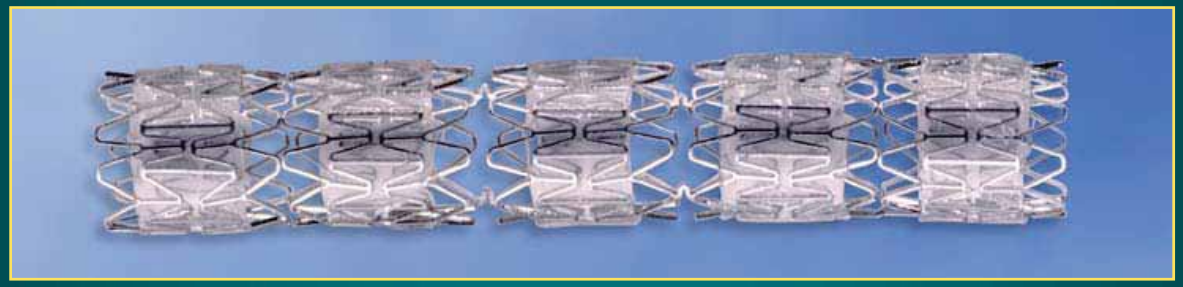


II



The Model "T" DES

Quanam QUADS-QP-2 Stent

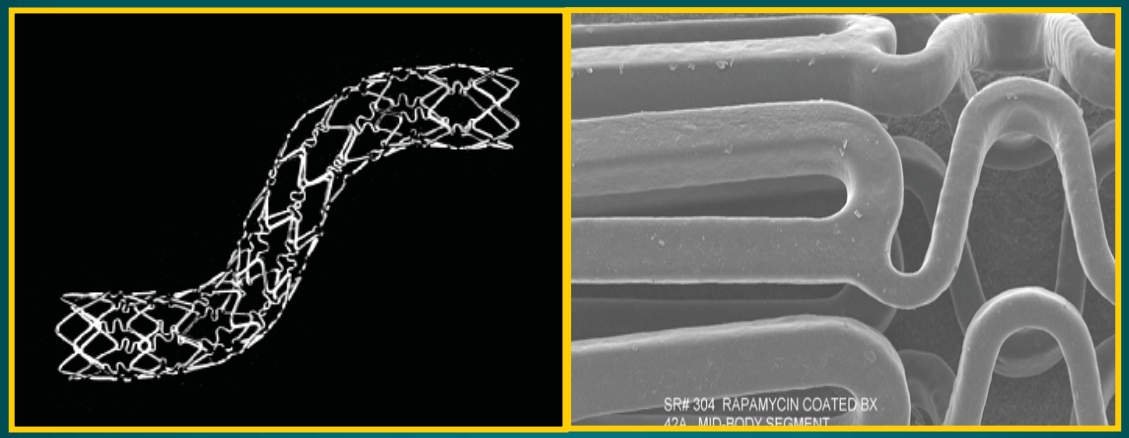


II

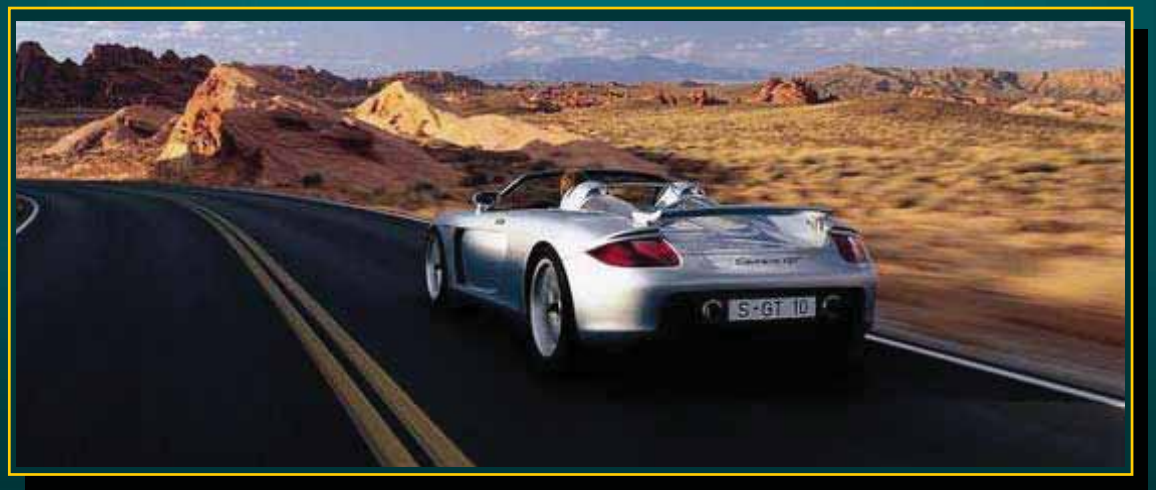
Vineberg

The Sleek "Porsche" DES

Cordis Cypher™ Stent

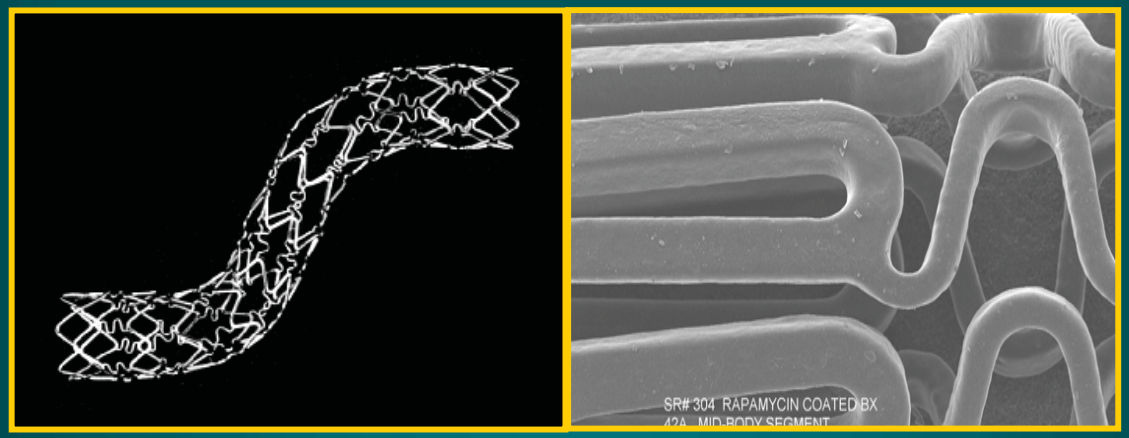


=



The Sleek "Porsche" DES

Cordis Cypher™ Stent



II

LIMA

Against Global DES Use

Please David….

Let’s not perseverate over the DES systems which have failed in animal studies or early clinical trials and will never achieve commercial reality!

The GR (guaranteed restenosis) II Coronary Stent

Only slightly worse than a balloon!

Against Global DES Use

Argument #3

- We're going to hear that even the best DES systems have limited data and it's too premature to generalize to the population-at-large (the « real world »)

Against Global DES Use

Argument #3

= the voice of reason

- Let's get more data
- What's the harm in waiting
- We've been burnt before
- We need to apply strict evidence-based medicine principles

SIRIUS - TLR @ 9 months

Sirolimus

Non–Diabetic

Ref Diam	Lesion Length <12mm	12-15mm	≥15mm
>3.0mm	1.6%	2.0%	2.6%
2.5-3.0mm	2.7%	3.2%	4.3%
<2.5mm	4.0%	4.8%	6.4%

Diabetic

Ref Diam	Lesion Length <12mm	12-15mm	≥15mm
>3.0mm	2.8%	3.3%	4.4%
2.5-3.0mm	4.5%	5.4%	7.2%
<2.5mm	6.7%	8.0%	10.5%

SIRIUS - TLR Treatment Effect Between Control and Sirolimus

Non–Diabetic

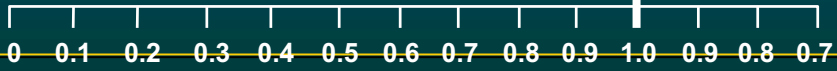
Ref Diam	Lesion Length <12mm	12-15mm	≥15mm
≥3.0mm	77.8%	77.6%	77.0%
2.5-3.0mm	77.0%	76.6%	75.7%
<2.5mm	75.9%	75.3%	74.1%

Diabetic

Ref Diam	Lesion Length <12mm	12-15mm	≥15mm
≥3.0mm	76.9%	76.5%	75.6%
2.5-3.0mm	75.5%	74.8%	73.4%
<2.5mm	73.8%	72.8%	70.8%

SIRIUS - TLR Events

	Sirolimus	Control	P-value	# events prevented per 1,000 patients
Overall	4.1	16.6	0.0001	124
Male	4.4	16.6	0.0001	122
Female	3.4	16.5	0.0007	130
Diabetes	6.9	22.3	0.0006	154
No Diabetes	3.2	14.3	0.0001	111
LAD	5.1	19.8	0.0001	147
Non-LAD	3.4	14.3	0.0001	109
Small Vessel (<2.75)	6.3	18.7	0.0001	125
Large Vessel	1.9	14.8	0.0001	128
Short Lesion	3.2	16.1	0.0001	129
Long Lesion (>13.5)	5.2	17.4	0.0001	122
Overlap	4.5	17.7	0.0003	131
No Overlap	3.9	16.1	0.0001	121



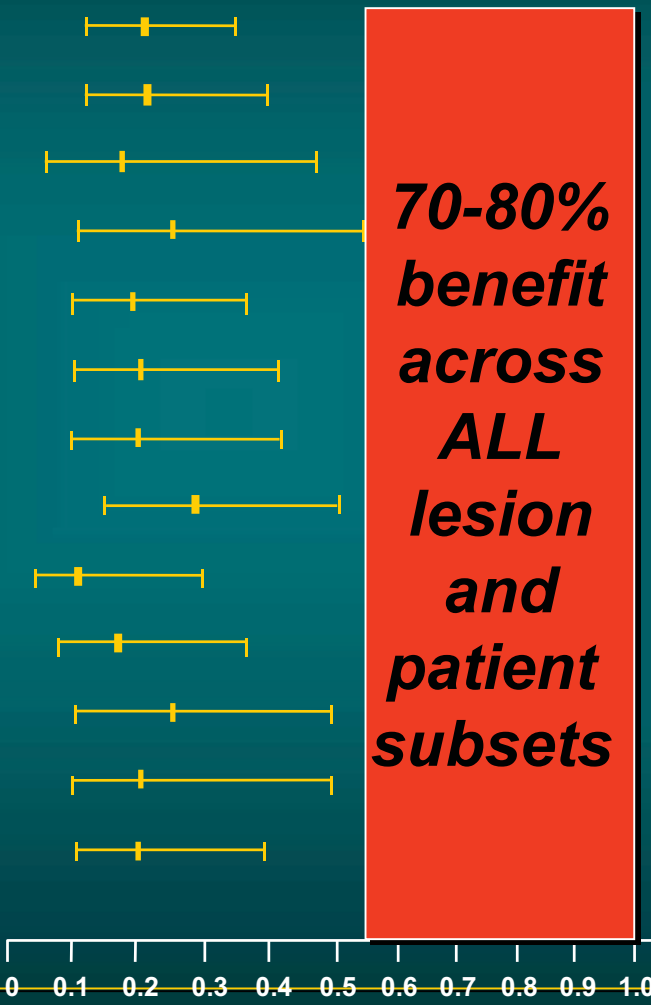
Sirolimus better

The Cardiovascular Research Foundation

Lenox Hill Heart and Vascular Institute of New York

SIRIUS - TLR Events

	Sirolimus	Control	P-value	# events prevented per 1,000 patients
Overall	4.1	16.6	0.0001	124
Male	4.4	16.6	0.0001	122
Female	3.4	16.5	0.0007	130
Diabetes	6.9	22.3	0.0006	154
No Diabetes	3.2	14.3	0.0001	111
LAD	5.1	19.8	0.0001	147
Non-LAD	3.4	14.3	0.0001	109
Small Vessel (<2.75)	6.3	18.7	0.0001	125
Large Vessel	1.9	14.8	0.0001	128
Short Lesion	3.2	16.1	0.0001	129
Long Lesion (>13.5)	5.2	17.4	0.0001	122
Overlap	4.5	17.7	0.0003	131
No Overlap	3.9	16.1	0.0001	121



Hazards Ratio 95% CI 0 0.1 0.2 0.3 0.4 0.5 0.6 0.7 0.8 0.9 1.0 0.9 0.8 0.7

Sirolimus better

The Cardiovascular Research Foundation

Lenox Hill Heart and Vascular Institute of New York

DES…the facts

They work!

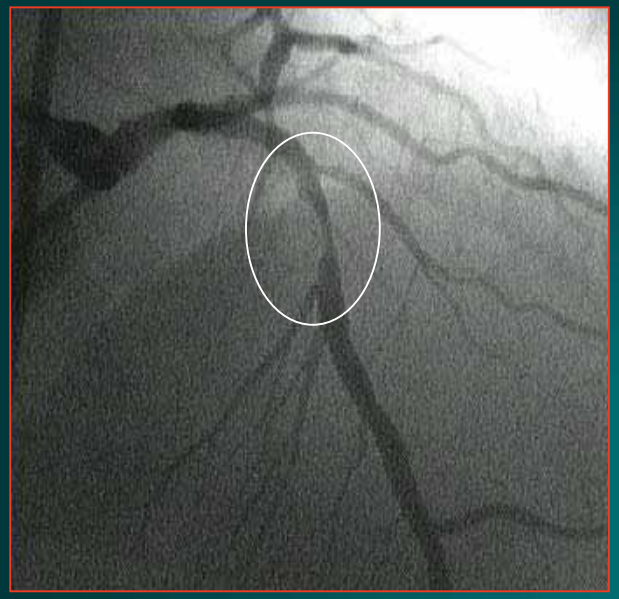
…for the most part, restenosis will be a thing of the past!

For the past 25 years our goal has been to make PCI…

- ***Safe*** **(complication-free)**
- ***Predictable*** **(consistent procedural results)**
- ***Widely applicable*** **(all patients)**
- ***Definitive*** **(no restenosis)**

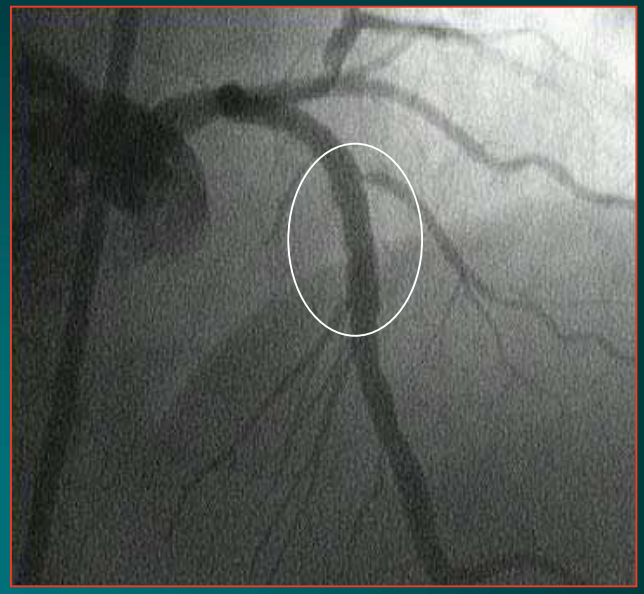
With drug-eluting stents we are finally on the verge of achieving that goal!

FIM: 2-year Follow-up



Pre

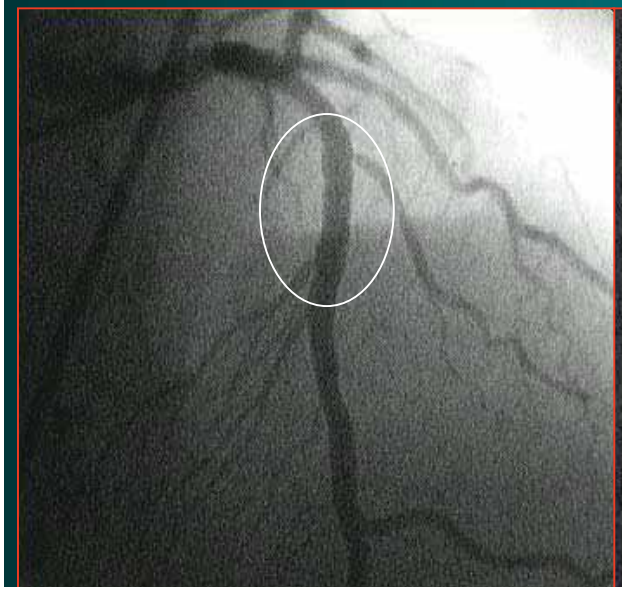
Post

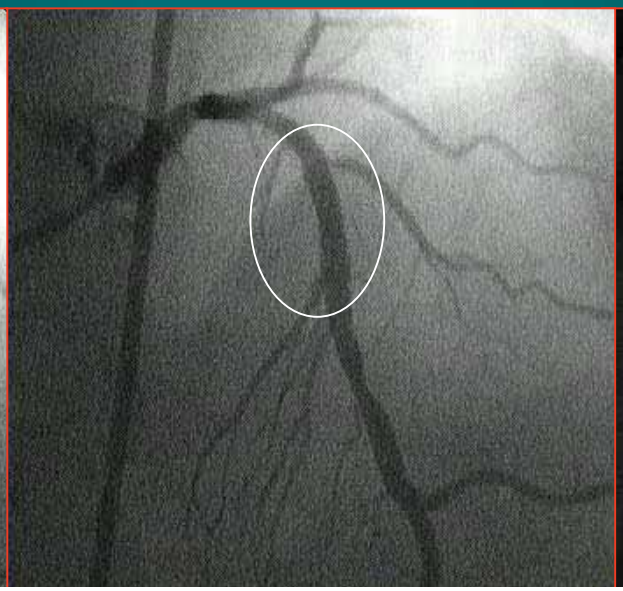


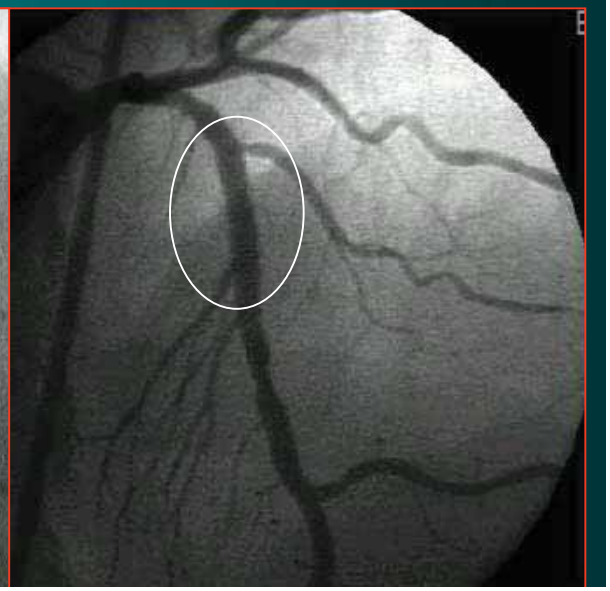
4 mos

12 mos

24 mos







DES…the facts

David Holmes

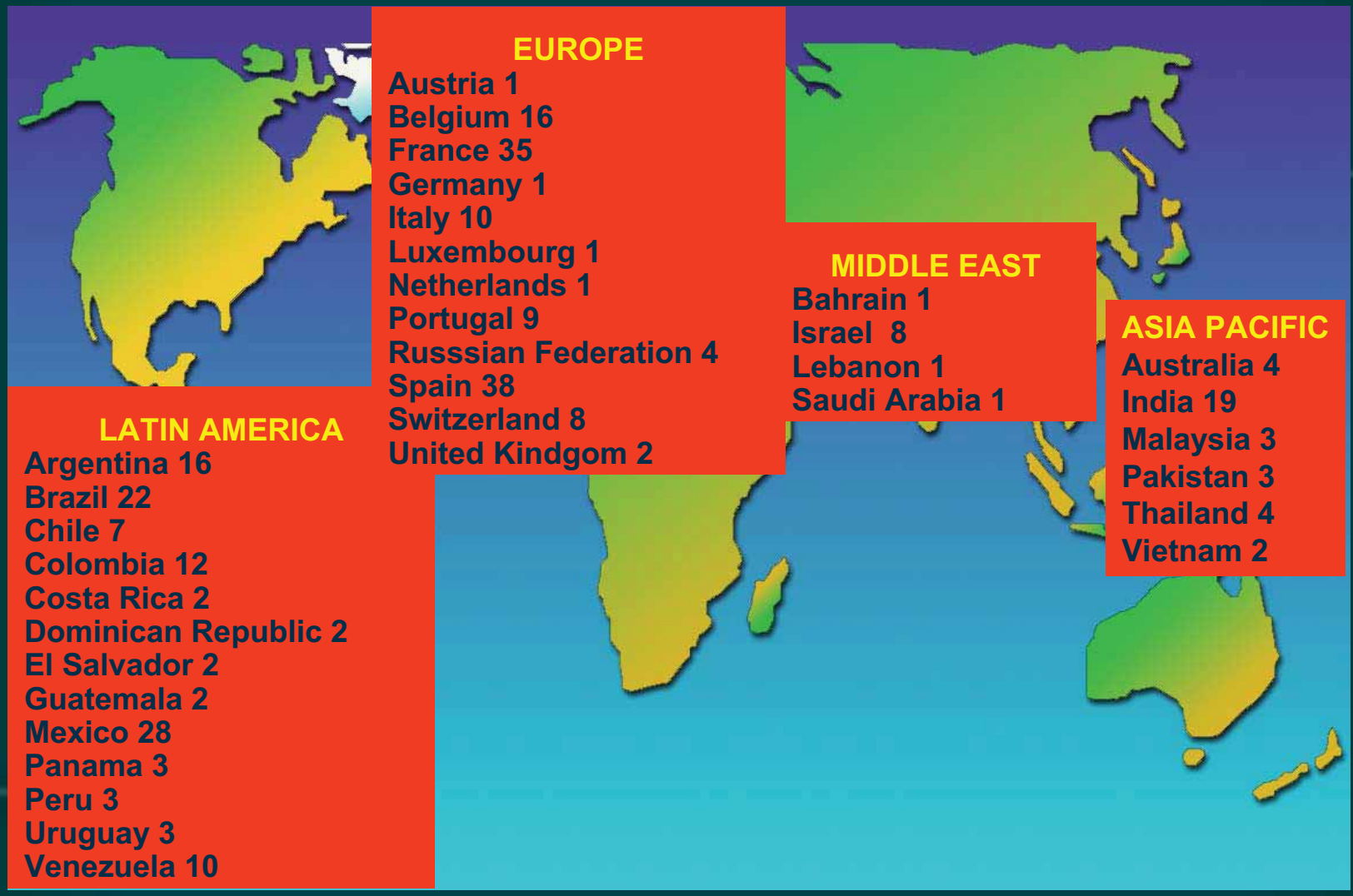
To doubt the overwhelming benefit of DES as an anti-restenosis therapy is…burying your head in the sand!

Sirolimus DES Worldwide ClinicalTrial P rogram

1	FIM	22	FREEDOM
2	RAVEL	23	SECURE
3	SIRIUS	24	DIRECT
4	Sirolimus PK Study	25	SVELTE
5	E-SIRIUS	26	2.25mm
6	C-SIRIUS	27	4.0mm
7	ISR-Feas	28	REDOX
8	US ISR Feas	29	3D
9	BIF-Feas	30	SIROCCO I
10	ARTS II	31	SIROCCO II
11	ATLAS (Left Main)	32	GREAT
12	SVG -Feas	33	SC US
13	SISR	34	SC EU
14	ARGentina	35	SVS -Feas
15	CHINA	36	BRIDGE
16	Taiwan	37	PORTO
17	ISR -Barragan	38	SCORPIUS
18	DECODE US	39	EVASTENT
19	DECODE	40	CYPHER-SMART
20	Tropical	41	TYPHOON
21	SICTO	42	DESSERT

* White Indicates Trial Completed

The e-Cypher Registry



EUROPE
Austria 1
Belgium 16
France 35
Germany 1
Italy 10
Luxembourg 1
Netherlands 1
Portugal 9
Russsian Federation 4
Spain 38
Switzerland 8
United Kindgom 2

MIDDLE EAST
Bahrain 1
Israel 8
Lebanon 1
Saudi Arabia 1

ASIA PACIFIC
Australia 4
India 19
Malaysia 3
Pakistan 3
Thailand 4
Vietnam 2

LATIN AMERICA
Argentina 16
Brazil 22
Chile 7
Colombia 12
Costa Rica 2
Dominican Republic 2
El Salvador 2
Guatemala 2
Mexico 28
Panama 3
Peru 3
Uruguay 3
Venezuela 10

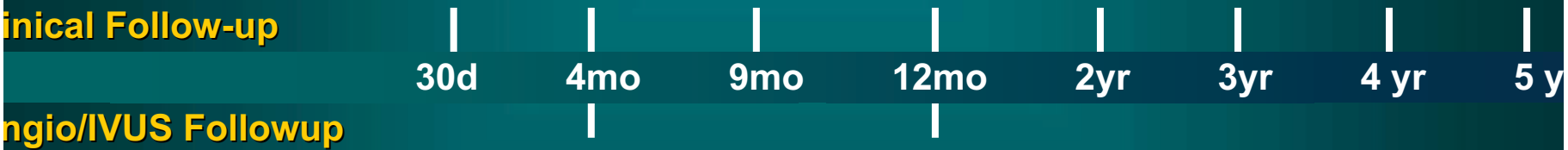
25,000 Patients from 317 Worldwide Sites

The TAXUS Trials

ENDEAVOR I
Feasibility Trial (AUS/NZL)

Single De Novo Native
Coronary Artery Lesions (Type A-B2)
Stent Diameter: 3.0-3.5 mm
Stent Length: 18 mm
Lesion Length: < 15 mm
Pre-dilation required

~ 100 patients



Primary Endpoints: MACE at 30 days and late loss (QCA) at 4 months
Secondary Endpoints: TVF and TLR at 9 months, late loss at 12 months

Antiplatelet therapy for 3 months

10 μg/mm

ENDEAVOR II
Randomized, Double-blind Trial

Single De Novo Native
Coronary Artery Lesions (Type A-C)
Stent Diameter: 2.25-3.5 mm
Stent Lengths: 18-30 mm (8/9 mm bailout)
Lesion Length: 14-27 mm
Pre-dilation required

~ 1,200 Patient

Control Driver Stent
n=600

Europe, Canada, Israel,
Asia Pacific and Australia/NZL

Endeavor Stent
n=600

Clinical/MACE

30d | **6mo** | **8mo** | **9mo** | **12mo** | **2yr** | **3yr** | **4 yr** | **5 y**

Angio/IVUS

Angio n=600
IVUS n=400

Primary Endpoint: TVF (cardiac death, MI, TVR) at 9 months
Antiplatelet therapy for 3 months
Potential PK sub-study

10 μg/mm

ENDEAVOR III
Randomized, Double-blind Trial

Single De Novo Native
Coronary Artery Lesions (Type A-C)
Stent Diameter: 2.25-3.5 mm
Stent Lengths: 18-30 mm (8/9 mm bailout)
Lesion Length: 14-27 mm
Pre-dilation required

~ 480 Patients

Control Cypher Stent
n=240

United States

Endeavor Stent
n=240

Clinical/MACE

30d | 6mo | 8mo | 9mo | 12mo | 2yr | 3yr | 4 yr | 5 y

Angio/IVUS

ABRR &
Volumetric Obstruction

Primary Endpoint: Late lumen loss by QCA at 8 months

Antiplatelet therapy for 3 months

Potential PK sub-study

10 μg/mm

Do we need to apply more rigorous standards for DES systems?

- ✓ *To gain FDA-approval of stents, we randomized ~1,000 pts in Stress and Benestent…we've already randomized over 7,000 pts with Cypher and Taxus stents*
- ✓ *How many pts/studies did it take for David and others to switch to clopidogrel?*
- ✓ *How many pts/studies did it take for David and others to use the cutting balloon*
- ✓ *Can anyone seriously make the claim that DES are a less toxic therapy than vascular brachytherapy?*

FREEDOM Trial

(Multivessel Sirolimus Stenting vs. CABG in Diabetics)

Eligibility: DM patients with MV-CAD eligible for stent or surgery
Exclude: Patients with acute MI and/or cardiogenic shock

2300 pts Randomized 1:1

MV-sirolimus stenting With abciximab

CABG With or without CPB

All concomitant Meds shown to be beneficial are encouraged, including: Plavix, ACE inhibitors, β-blockers, Statins, etc.

1° Endpoint: 5-year mortality 5-year MACE
2° Endpoint : MACE/stroke at 12 months

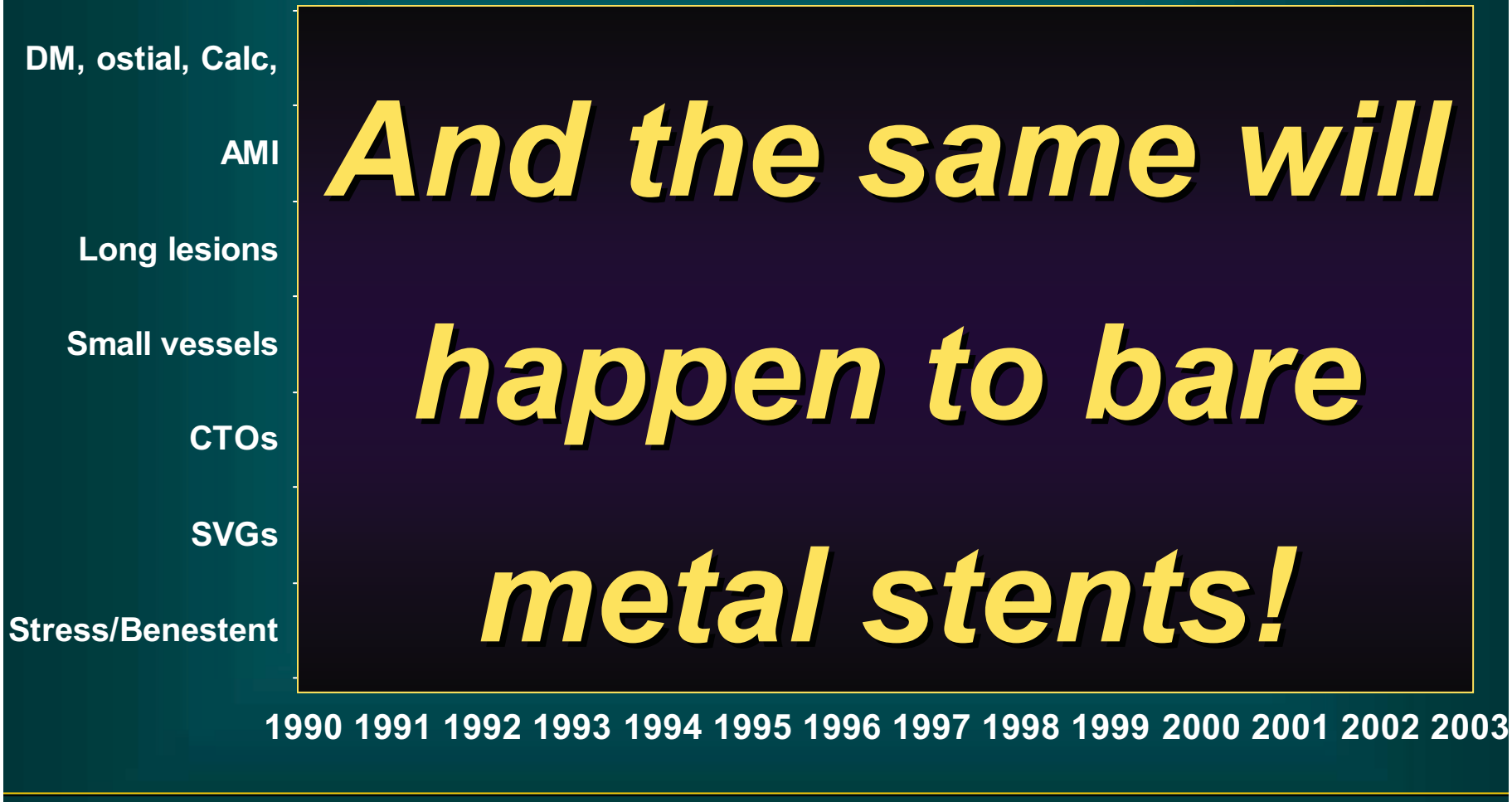
Waiting for evidence-based medicine to "catch-up" with good judgement in clinical decision-making … have we learned nothing from the past?

- *CABG … 10 years*
- *Stents … 5 years*
- *DES … ???*

Is there any reason to assume that DES won't work equally as well in other lesion subsets?

2003: Drug-eluting stents for unstudied lesions?

1994: Stents for unstudied PTCA lesions?



Drug-eluting stents for unstudied lesions

Do you really want to bet against them?

Ticket for his first OSU - Michigan game : $30.00

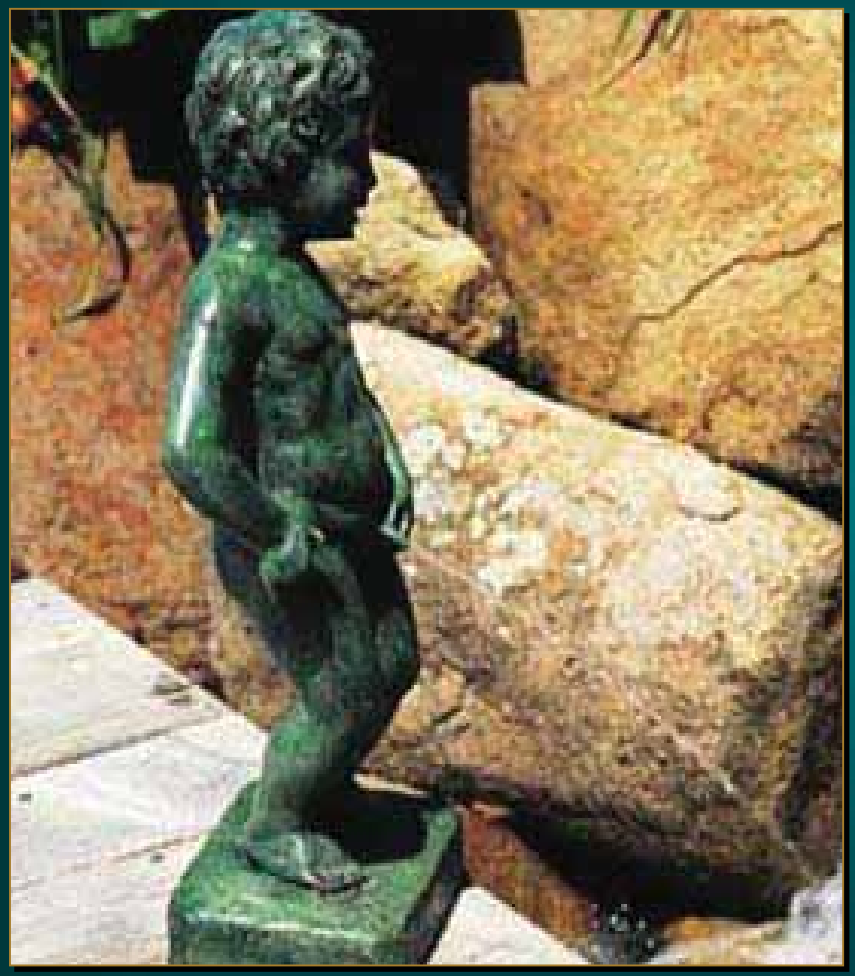
OSU jersey: $40.00

Stadium hot dog and soft drink: $8.00

Temporary tatoo: $3.00

Teaching him to salute the Michigan team as they enter the Shoe: Priceless...

What Does a P(ee) Value of 0.05 Mean?



- 'Fisherian' P value of 0.05 originally based on n=30!
- Always demand a P value of <0.001 for a sample size > 200 as strong evidence against the null hypothesis of zero difference

Al Feinstein

Courtesy: Sanjay Kaul

Against Global DES Use

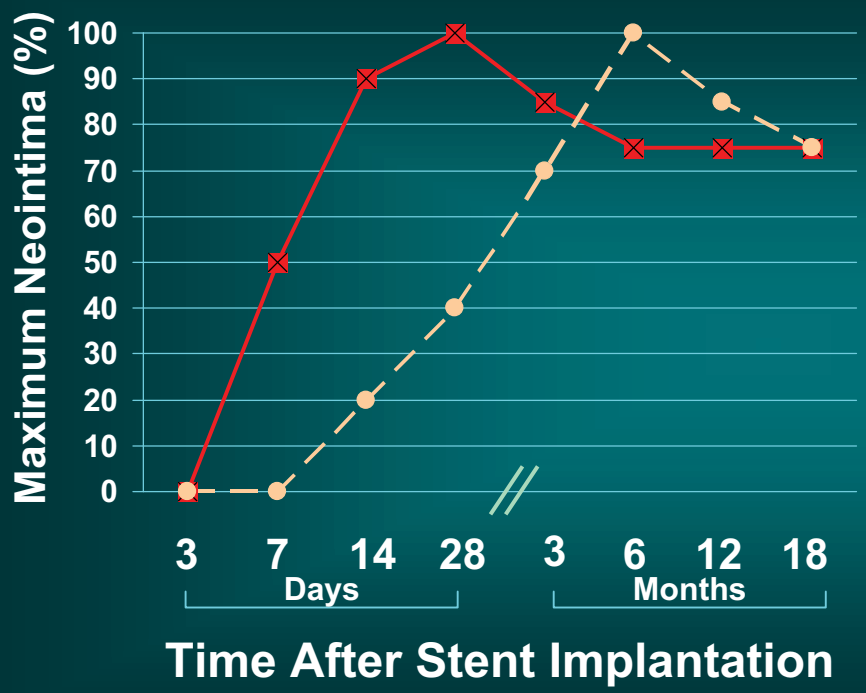
Argument #4

= we're back to more scare tactics

- **We're going to hear that DES systems only have short-term data…the durability issue…must stand the test of time!**

DES - Animal Studies

Comparing porcine coronary and human arterial healing responses…



Stainless Steel Balloon Expandable Stent

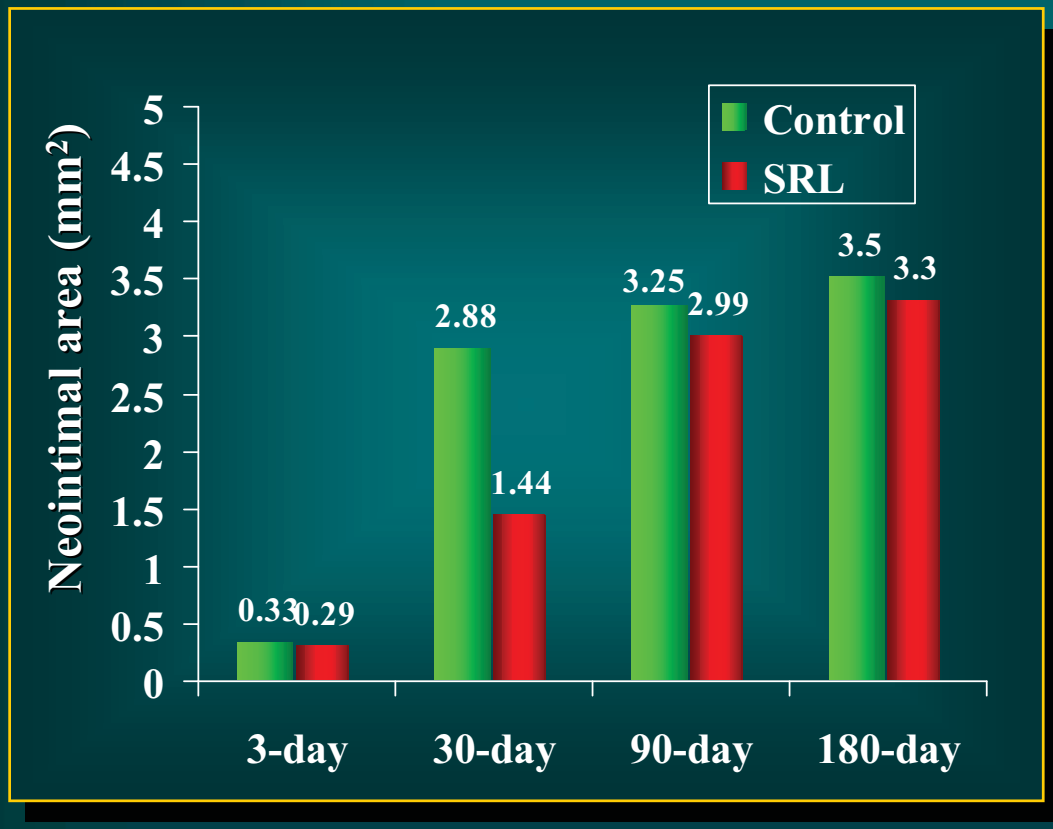
Animals

Humans

There is a six-month "offset" between the porcine coronary and human responses

DES - Animal Studies

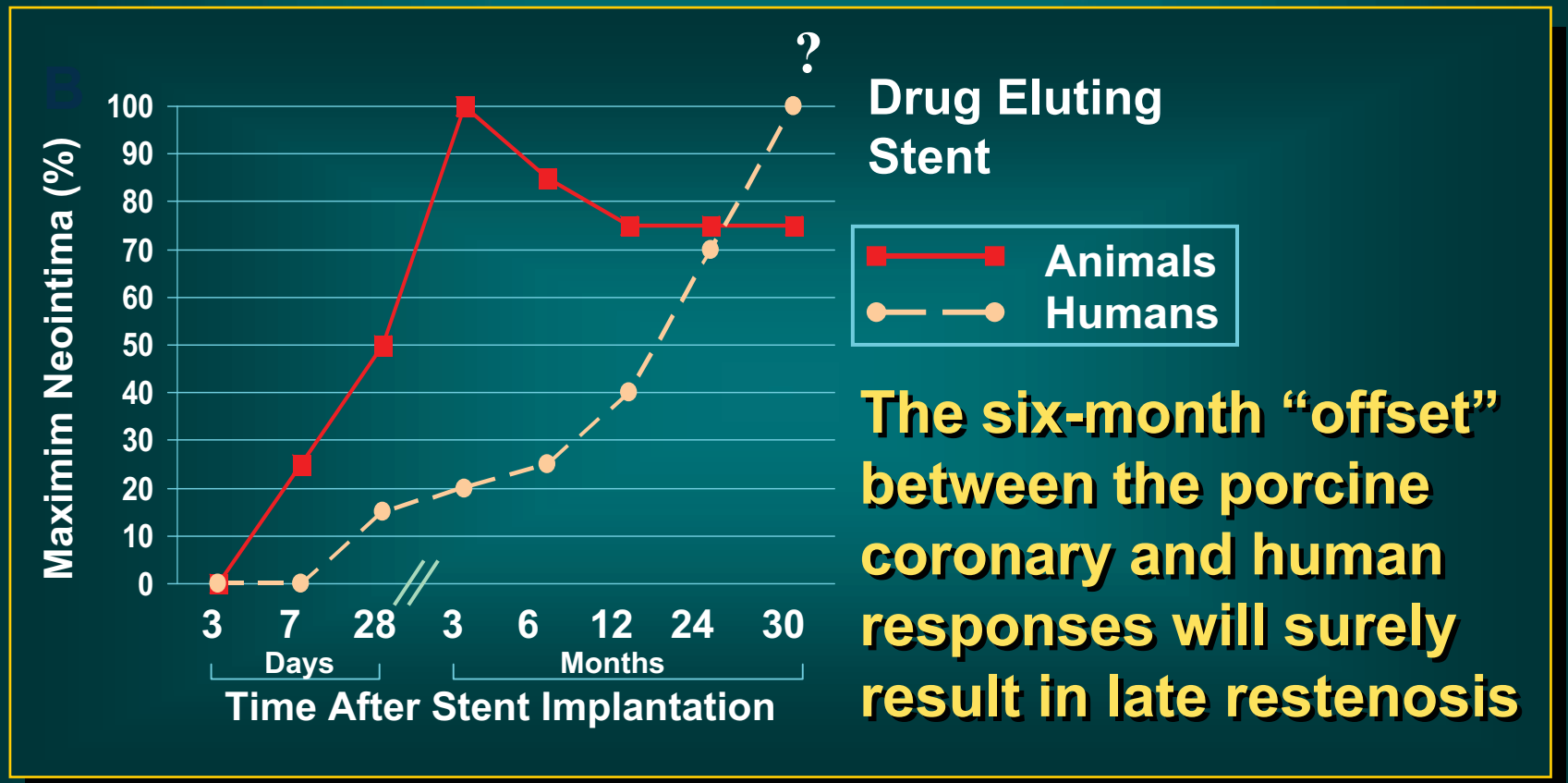
Porcine coronary results with sirolimus-eluting stent…



Complete loss of efficacy in reducing neointimal area by three and six months

DES - Animal Studies

Comparing porcine coronary and human arterial healing responses…



The six-month "offset" between the porcine coronary and human responses will surely result in late restenosis

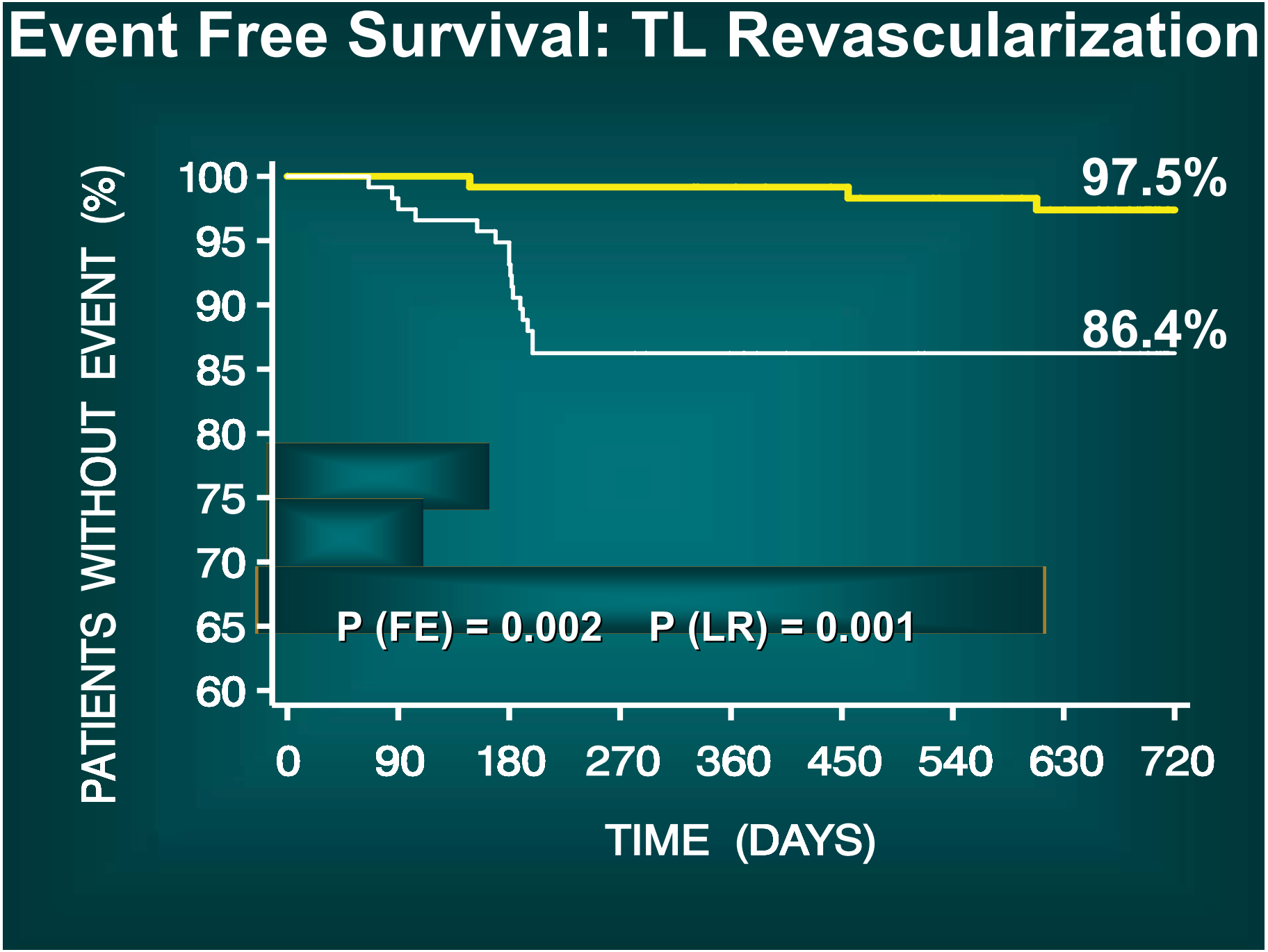
Dante azzanese

First In Man
Cumulative Clinical Outcomes

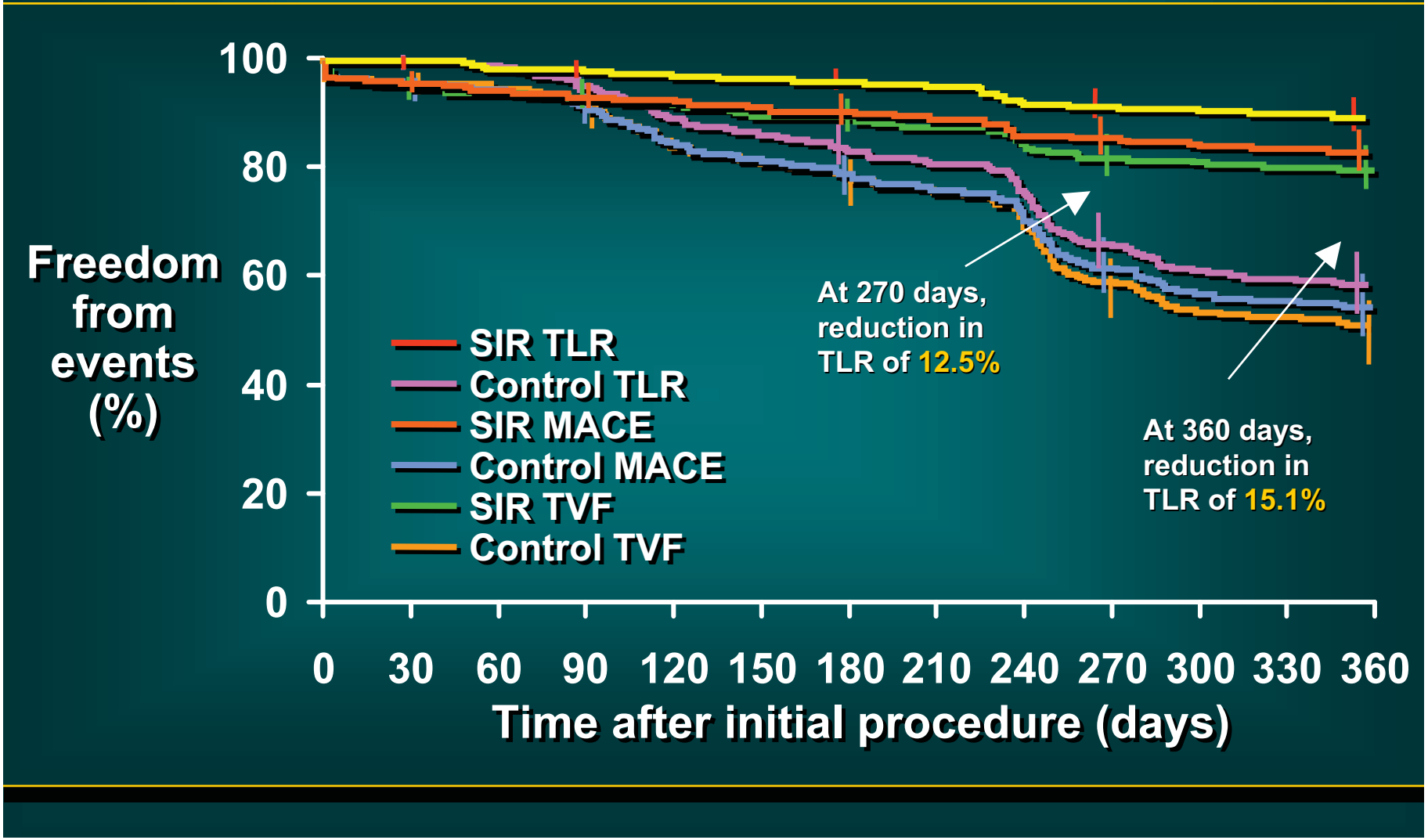
	1 year (n = 30)	2 years (n = 30)	3 years (n = 30)
Clinical fu (%)	100	100	100
Follow-up (mo)	12	24	up to 39
Death (N)	0	0	1
Q-wave MI (N)	0	1	1
TVR (N)	0	1	1

Q-wave MI occurred at 14 months due to progression of prox. LAD obstruction not related to the target lesion; TVR = CABG for ostial LCX progression; no in-stent restenosis; TVR = Lesion progression

Event Free Survival: TL Revascularization



Event-Free Survival at 360 Days for TLR, MACE and TVF



Against Global DES Use

Argument #5

= sound bites and data dredging

- We're going to hear that DES systems don't work well in diabetics, bifurcations, small vessels, ISR, etc.
- In fact, we're probably going to hear nothing but rumors and « bad news » about DES for the next year

DES - 2003

Problem clinical subsets

- Diabetics (esp. Type I)
- Small vessels (< 2.5 mm)
- ISR lesions (esp. « ultra-diffuse » and s/p VBT)
- Bifurcations (esp. ostial sidebranch)
- ? SVGs
- ? LM disease (esp. distal bifurcation)

DES…in Diabetics

"Spin artists" from around the world…

"The data from SIRIUS indicate that sirolimus-eluting stents don't work very well in diabetics and don't work at all in insulin-receiving diabetics"

SIRIUS - Diabetic Subgroup (Insulin)

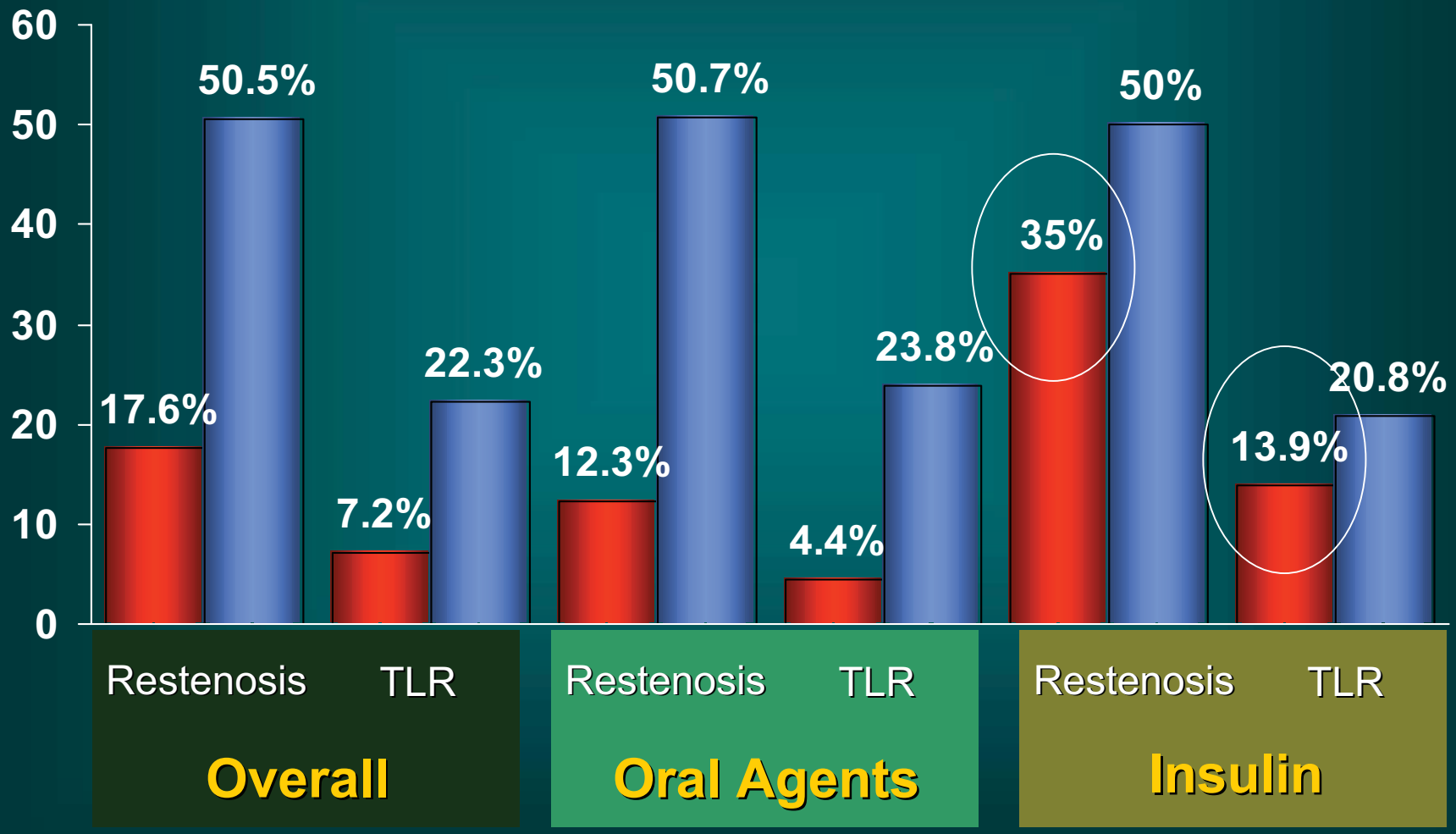
Summary FU Results (82 pts)

	Sirolimus (n=38)	Control (n=44)	P-value
Late loss (mm)			
in-stent	0.35	1.18	<0.001
in-segment	0.59	1.00	0.043
Restenosis (%)			
in-stent	10.5	46.4	0.012
in-segment	35.0	50.0	0.382
TLR (%)	13.9	20.8	0.420
MACE (%)	15.8	22.7	0.578

Lesion length = 14.2mm and Reference vessel size = 2.67mm

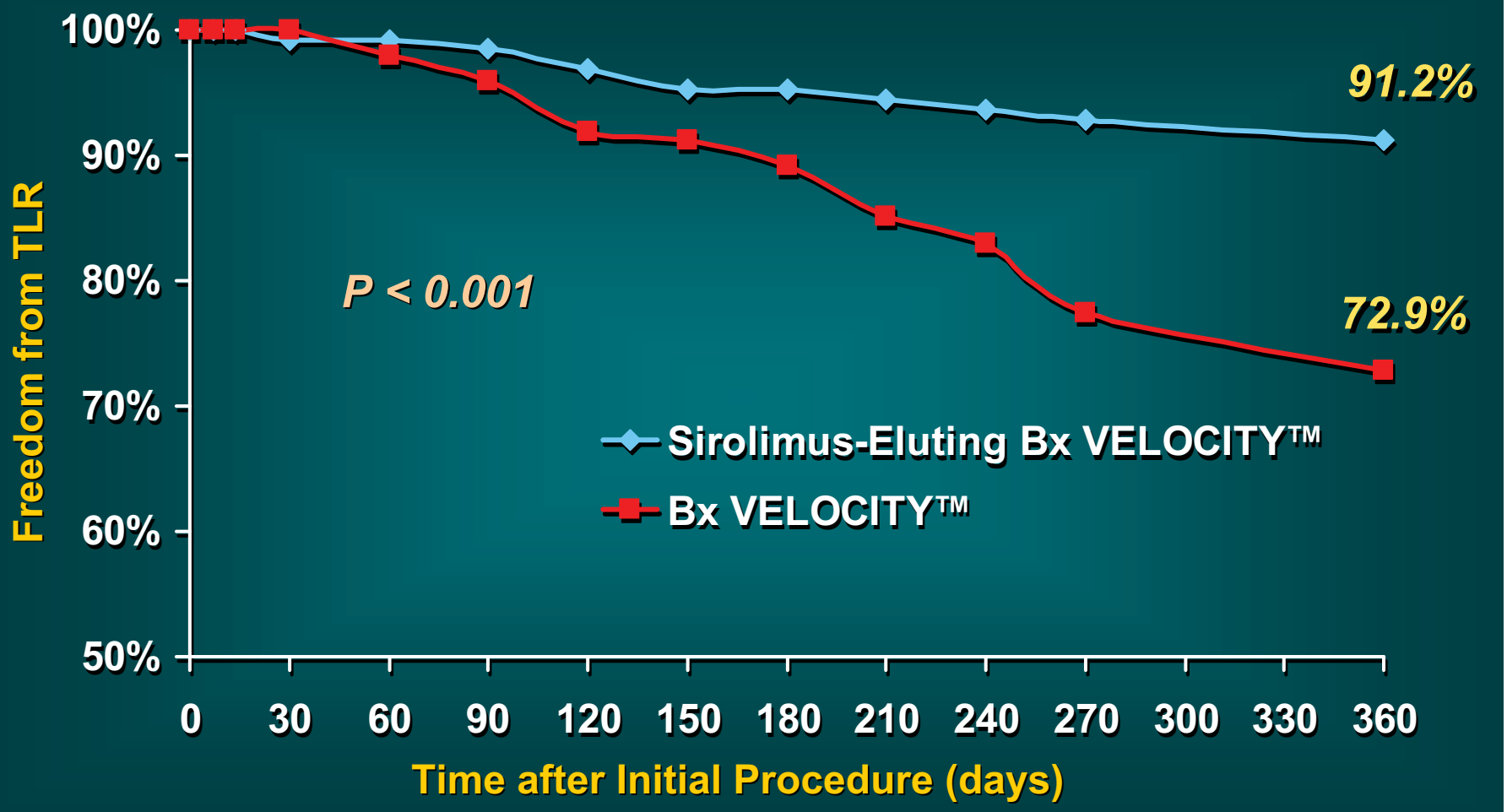
SIRIUS DM - Subanalysis

In-Segment Restenosis and TLR (@ 12 mos)



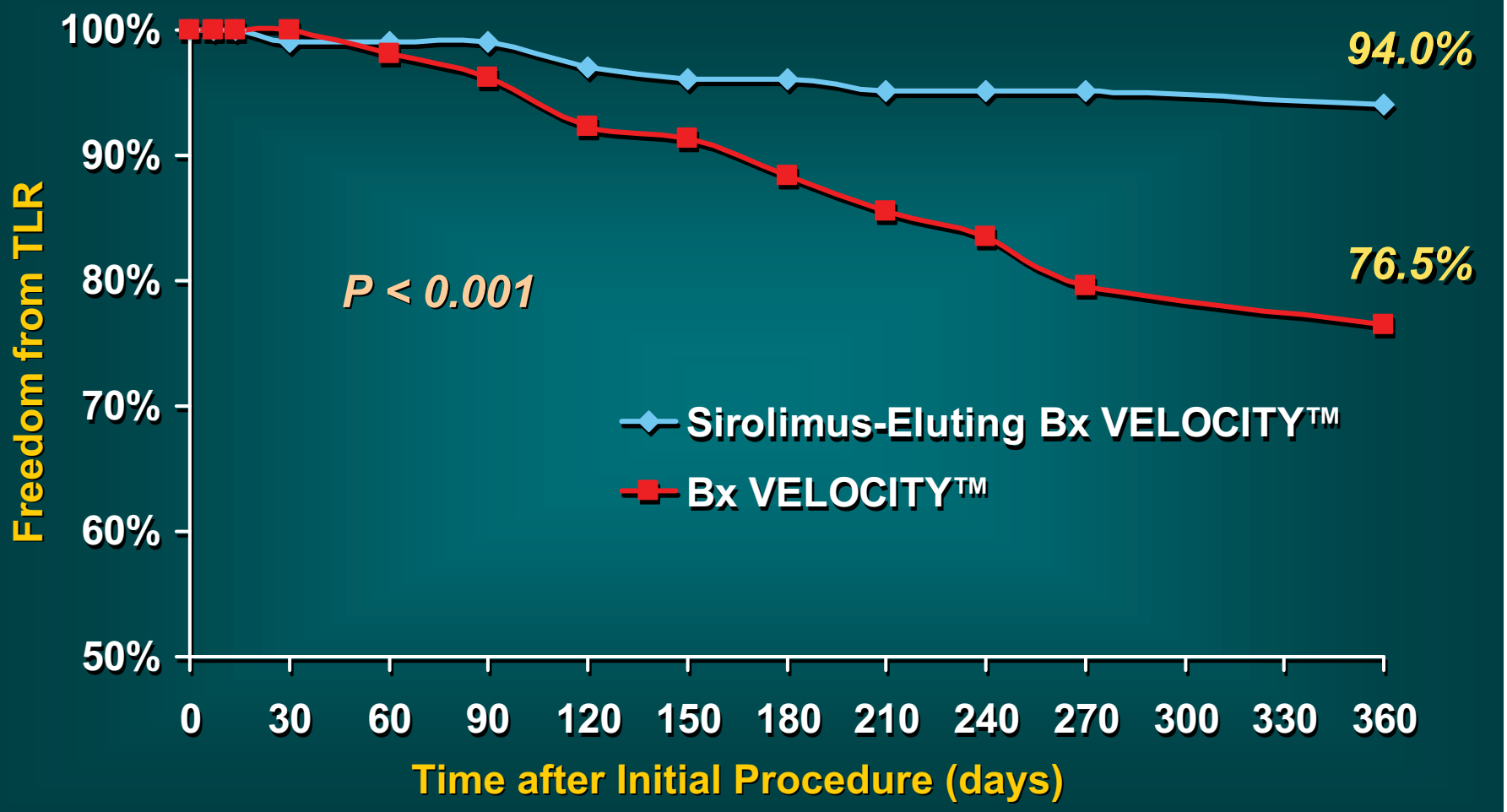
SIRIUS DM - EFS Curves

Survival Free From TLR



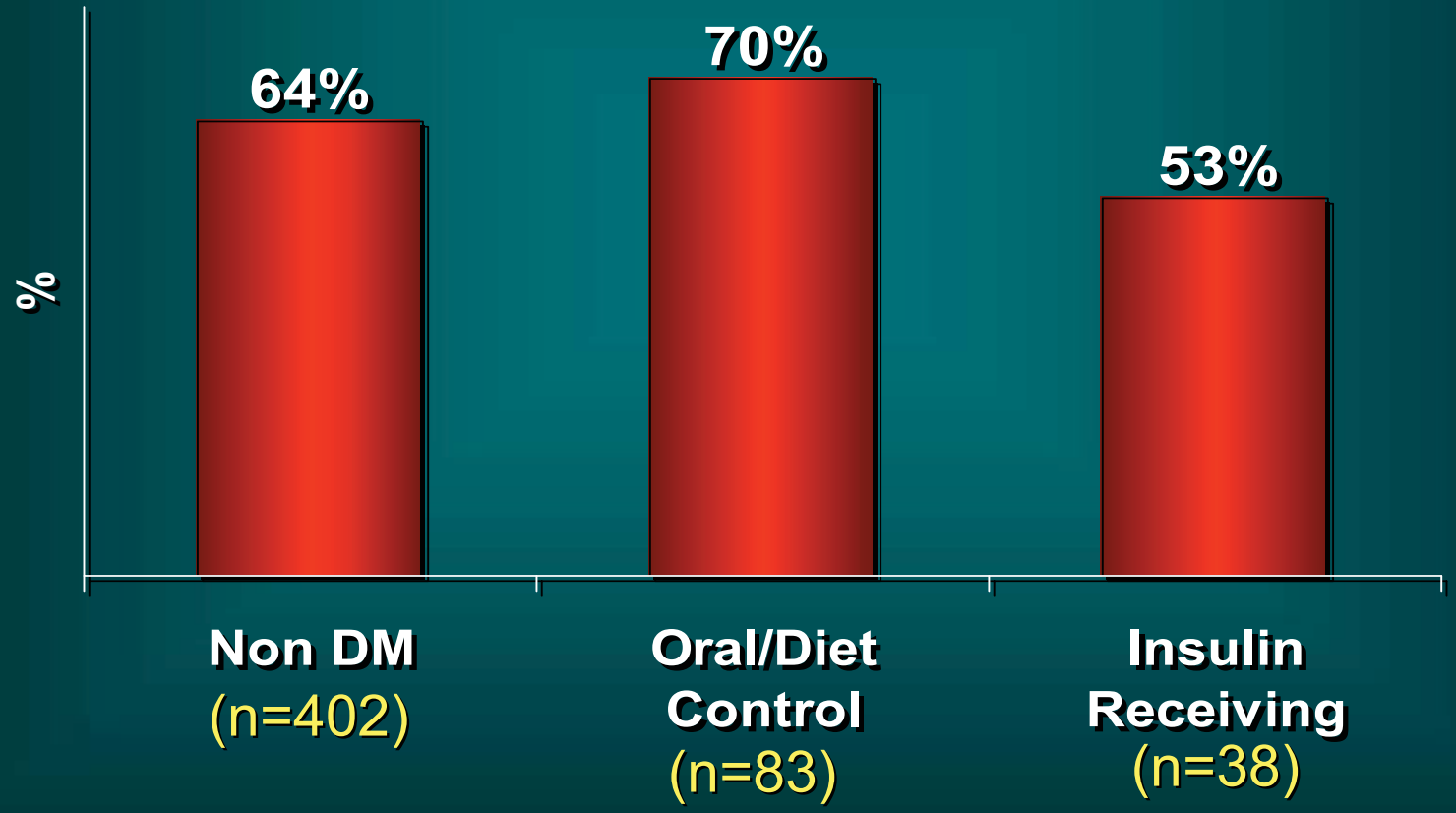
SIRIUS DM - Oral/Diet Subgroup

Survival Free From TLR

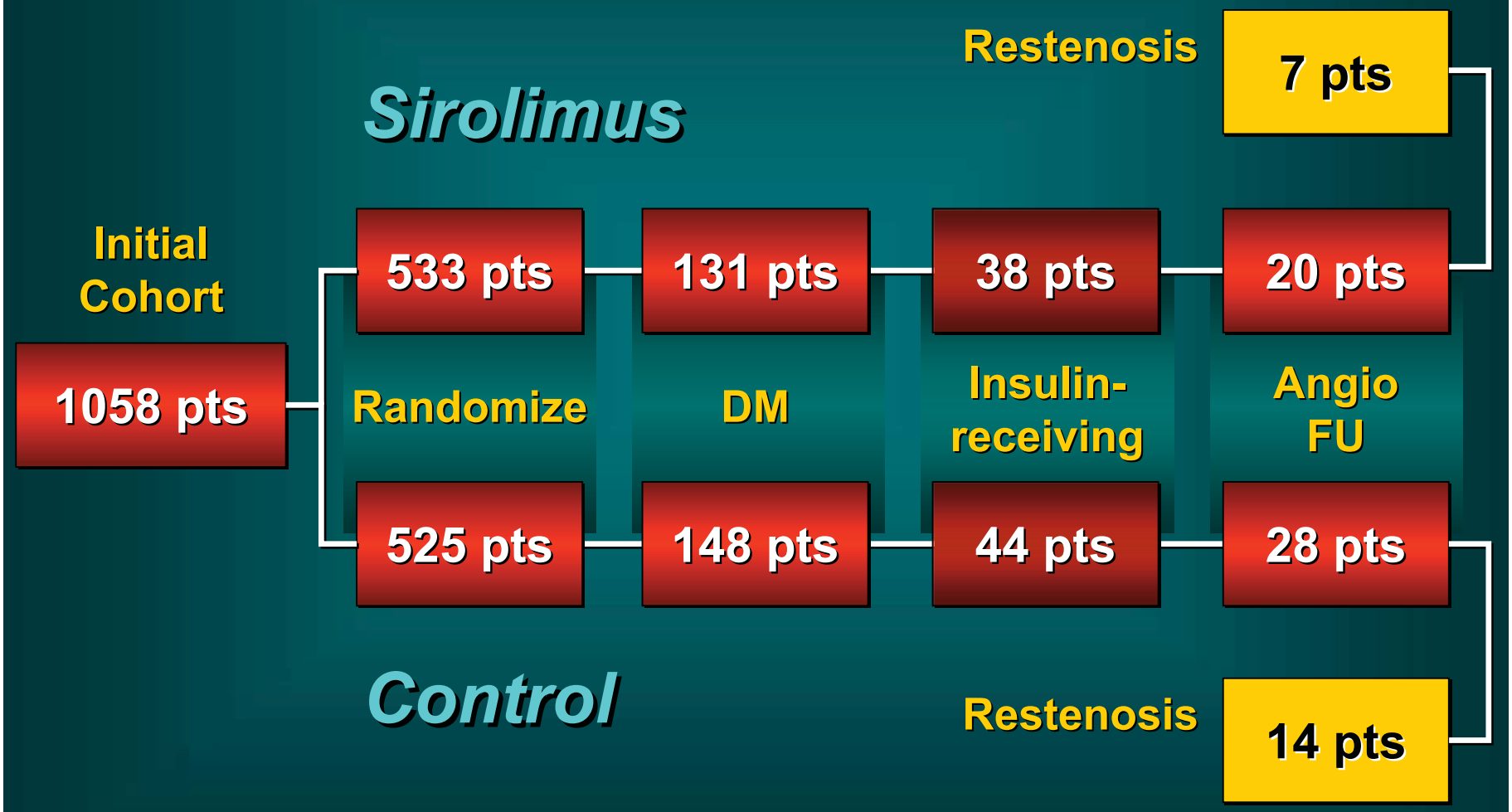


SIRIUS DM - Angio FU

Angiographic FU Rates in Sirolimus-Eluting Stent Patients

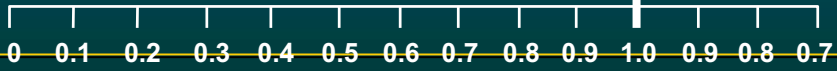


SIRIUS DM - *SubSubSub*Group Analysis



SIRIUS - TLR Events

	Sirolimus	Control	P-value	# events prevented per 1,000 patients
Overall	4.1	16.6	0.0001	124
Male	4.4	16.6	0.0001	122
Female	3.4	16.5	0.0007	130
Diabetes	***6.9***	***22.3***	***0.0006***	***154***
No Diabetes	3.2	14.3	0.0001	111
LAD	5.1	19.8	0.0001	147
Non-LAD	3.4	14.3	0.0001	109
Small Vessel	***6.3***	***18.7***	***0.0001***	***125***
Large Vessel	1.9	14.8	0.0001	128
Short Lesion	3.2	16.1	0.0001	129
Long Lesion (>13.5)	5.2	17.4	0.0001	122
Overlap	4.5	17.7	0.0003	131
No Overlap	3.9	16.1	0.0001	121



The Cardiovascular Research Foundation

Sirolimus better

Lenox Hill Heart and Vascular Institute of New York

DES ISR Studies – Outside U.S.

Clinical Studies Factors

	# pts	study design	DES system
Sao Paulo	25	registry	Cordis/Sirolimus
Rotterdam	16	registry	Cordis/Sirolimus
Leuven	21	registry	Cook/Paclitaxel
Milan	15	registry	Quanam/Paclitaxel
TAXUS III	28	registry	BSC/Paclitaxel

Total = 105 Patients

DES ISR Studies – Outside U.S.

Angiographic Results (QCA)

	Late loss (mm)	Restenosis
Sao Paulo	-0.05 ➡ 0.16	4%
Rotterdam	0.26 ➡ 0.51	12.5%
Leuven	na	14.3%
Milan	0.47 ➡ 1.36	13% ➡ 61.5%
TAXUS III	0.54	16%

DES ISR Studies – Outside U.S.

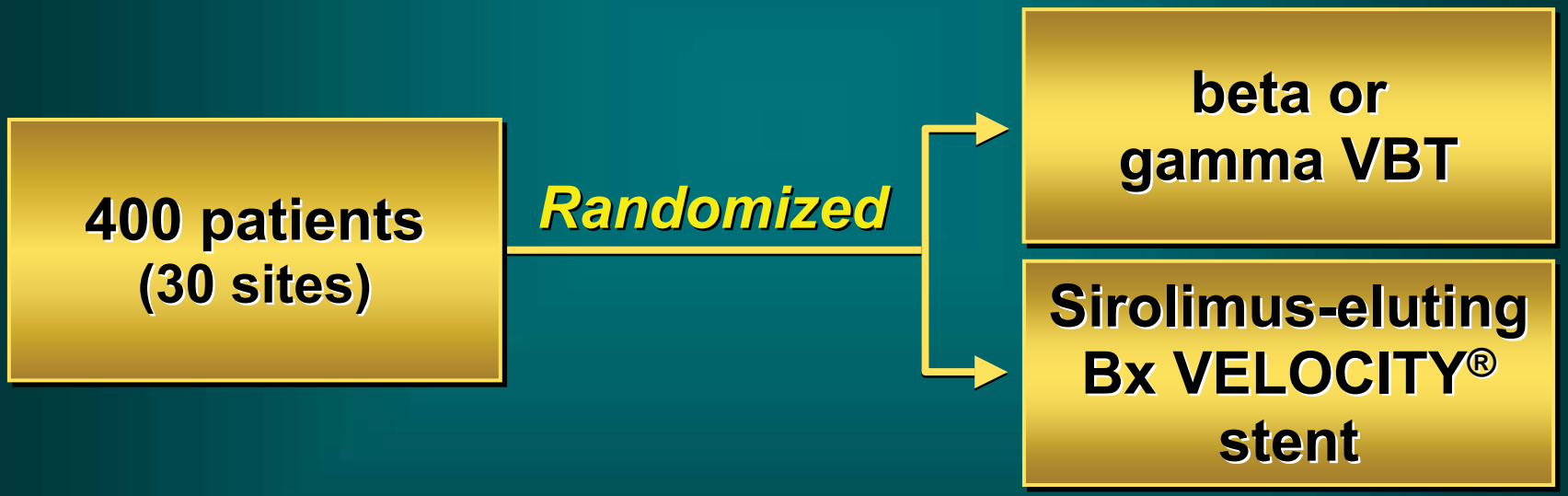
Clinical Outcomes

	Death	MI	TLR	Stent thrombosis
Sao Paulo	0	0	0	0
Rotterdam	12.5%	6.3%	12.5%	12.5%
Leuven	na	na	na	9.5%
Milan	0	20%	20% ➡ 40%	6.7%
TAXUS III	0	7.2%	21.4%	0

SISR

A Multicenter, Randomized Study of the Sirolimus-Eluting Bx Velocity® Balloon Expandable Stent vs. Intravascular Brachytherapy in the Treatment of Patients with In-Stent Restnotic Coronary Artery Lesions

Inclusion: ***Lesion length*** ≤ 45 mm
RVD ≥ 2.75 mm and ≤ 3.5 mm

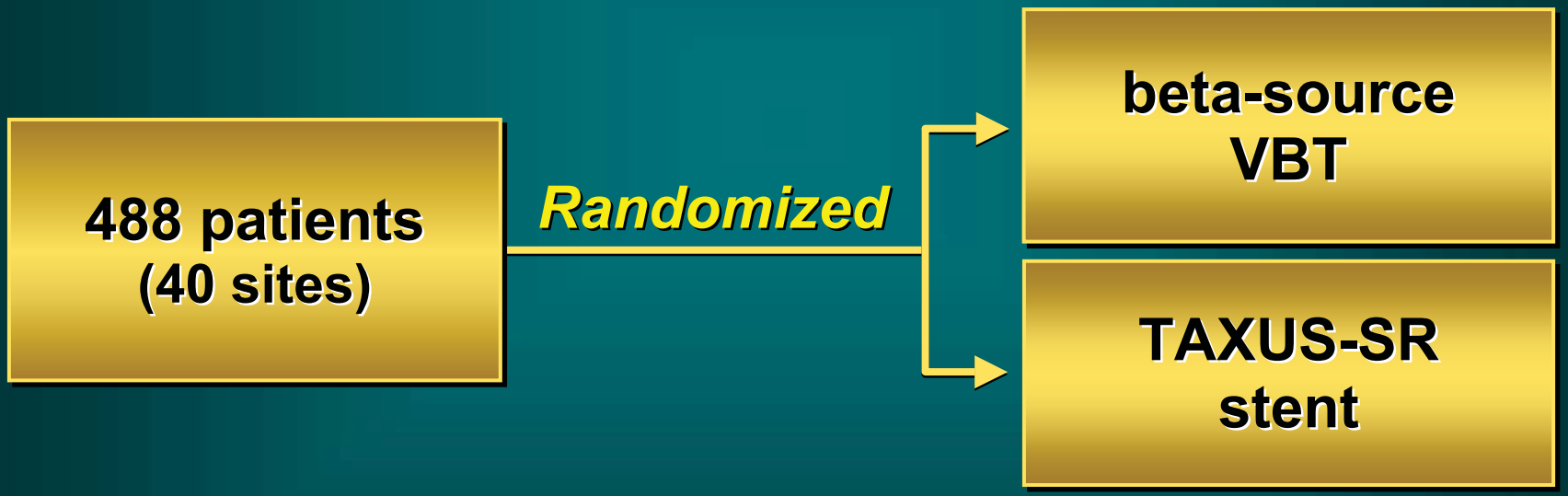


Endpoints ***1ry:*** TVF @ 9 months
Angiographic: all patients @ 6 mos.
IVUS: 5-7 center substudy @ 6 mos.

TAXUS V – ISR

A Prospective, Randomized Trial Evaluating the Slow-Release Formulation TAXUS™ Paclitaxel-Eluting Coronary Stent in the Treatment of In-Stent Restenosis

Inclusion: ***Lesion length*** ≤ 46 mm
RVD ≥ 2.5 mm and ≤ 3.75 mm



Endpoints ***1ry:*** TVR @ 9 months
Angiographic: all patients @ 9 mos.
IVUS: 250 patients @ 9 mos.

Against Global DES Use

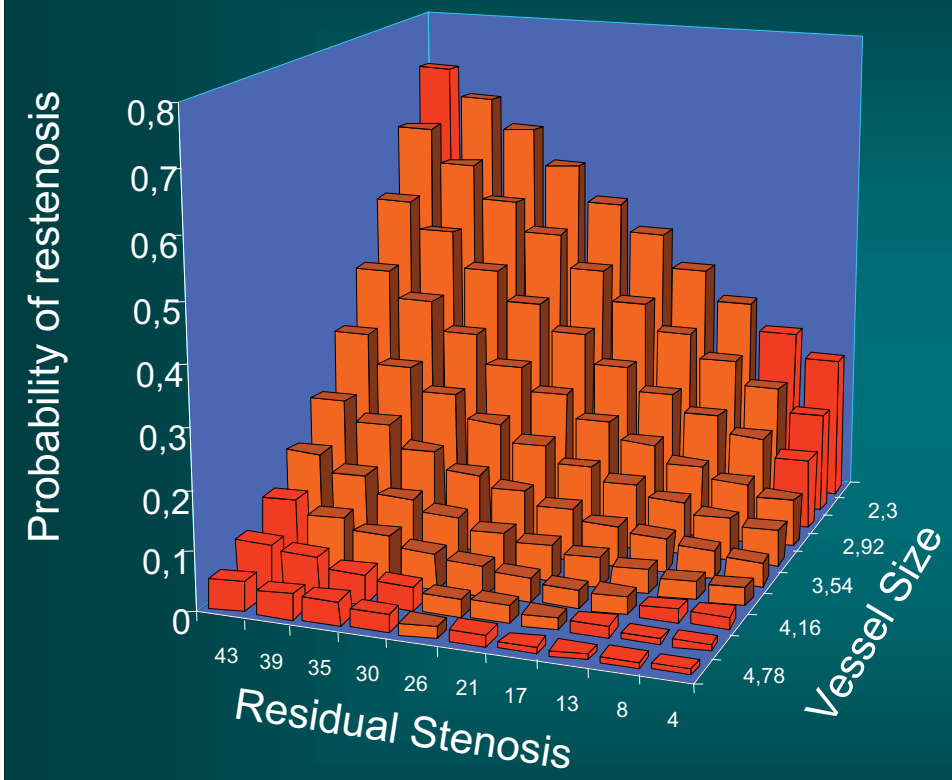
Argument #6

= the compromise solution

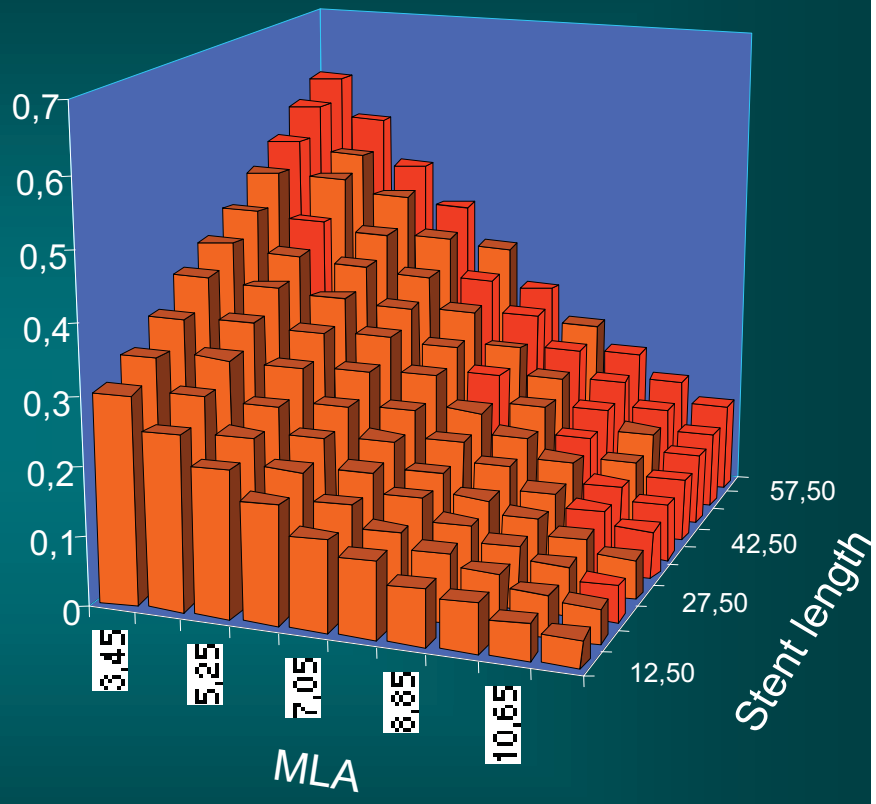
- We're going to hear that DES rationing for only the « high restenosis risk » subgroups is the best approach… presupposing that we can accurately select such patients

In-Stent Restenosis - is it predictable ?

Angiography (n=775)



IVUS (n=858)



- indicate the range without actual observations in the data set

de Feyter and Serruys Circulation. 1999; 100
Serruys and de Feyter JACC 1999; 34

Reference chart for restenosis risk IVUS MLA vs stent length

Stent Length, mm	Minimum In-Stent Area, mm²									
	3.0–3.9	3.9–4.8	4.8–5.7	5.7–6.6	6.6–7.5	7.5–8.4	8.4–9.3	9.3–10.2	10.2–11.1	11.1–12.0
10–15	0.30 (0.22–0.40)	0.25 (0.19–0.32)	0.21 (0.16–0.26)	0.17 (0.13–0.21)	0.13 (0.11–0.17)	0.11 (0.08–0.14)	0.08 (0.06–0.12)	0.07 (0.04–0.10)	0.05 (0.03–0.09)	0.04 (0.02–0.08)
15–20	0.33 (0.25–0.42)	0.28 (0.22–0.34)	0.23 (0.19–0.28)	0.19 (0.16–0.22)	0.15 (0.12–0.18)	0.12 (0.09–0.16)	0.10 (0.07–0.13)	0.08 (0.05–0.12)	0.06 (0.04–0.10)	0.05 (0.02–0.09)
20–25	0.36 (0.28–0.46)	0.31 (0.25–0.37)	0.25 (0.21–0.30)	0.21 (0.18–0.24)	0.17 (0.14–0.20)	0.14 (0.11–0.17)	0.11	0.09	0.07	0.05* (0.03–0.10)
25–30	0.40 (0.31–0.49)	0.34 (0.27–0.41)	0.28 (0.24–0.33)	0.23 (0.20–0.27)	0.19 (0.16–0.23)	0.15 (0.12–0.20)				0.06 (0.03–0.11)
30–35	0.43 (0.34–0.53)	0.37 (0.30–0.44)	0.31 (0.26–0.38)	0.26 (0.22–0.31)	0.21 (0.17–0.26)	0.17 (0.13–0.22)				0.07* (0.04–0.13)
35–40	0.46 (0.36–0.			0.29 (0.23–0.35)	0.24 (0.19–0.29)	0.19 (0.14–0.25)	(0.11–0.22)	(0.08–0.19)	(0.06–0.17)	0.08* (0.04–0.15)
40–45	0.50 (0.39–0.			0.31 (0.25–0.39)	0.26 (0.20–0.34)	0.22* (0.15–0.29)	0.18 (0.12–0.25)	0.14* (0.09–0.22)	0.11 (0.06–0.19)	0.09* (0.05–0.17)
45–50	0.53* (0.41–0.			0.34 (0.26–0.44)	0.29 (0.21–0.38)	0.24 (0.17–0.33)	0.20 (0.13–0.29)	0.16* (0.09–0.25)	0.13 (0.07–0.22)	0.10* (0.05–0.19)
50–55	0.57* (0.43–0.69)	(0.38–0.62)	(0.33–0.55)	0.38 (0.28–0.49)	0.32* (0.22–0.43)	0.27* (0.18–0.38)	0.22* (0.14–0.33)	0.18* (0.10–0.29)	0.14* (0.08–0.26)	0.11* (0.05–0.22)
55–60	0.60* (0.45–0.73)	0.54* (0.40–0.67)	0.47* (0.34–0.60)	0.41* (0.29–0.54)	0.35 (0.24–0.48)	0.29* (0.19–0.42)	0.24 (0.15–0.38)	0.20* (0.11–0.33)	0.16* (0.08–0.29)	0.13* (0.06–0.26)

0.34 (0.27–0.41)

0.04 (0.02–0.08)

de Feyter and Serruys Circulation. 1999; 100

Predicting Restenosis

PRESTO

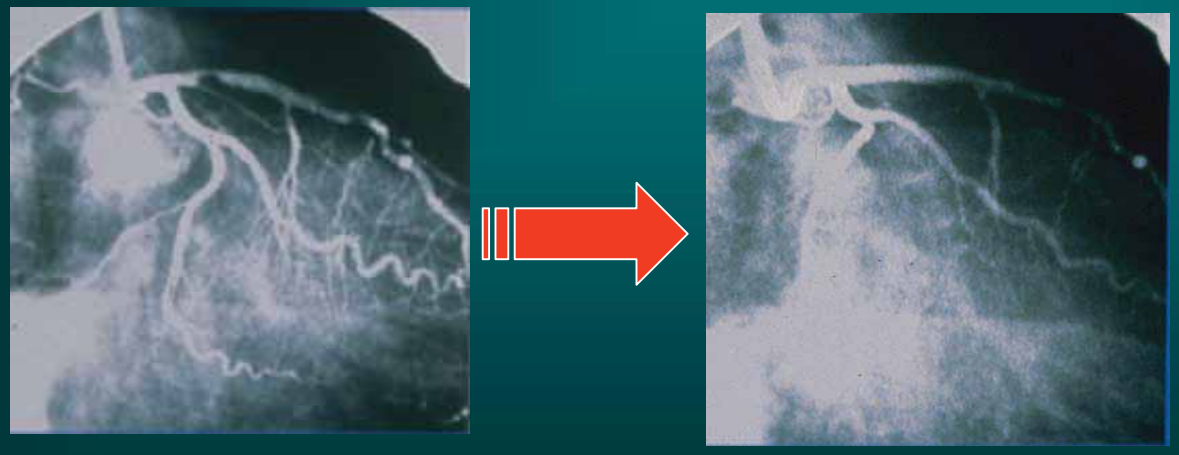
Source: David Holmes

- From 1312 patients, attempts to predict restenosis from baseline variables and boot strapping statistical methodologies
- ROC = 0.63 (slightly better than flipping a coin)…*you cannot reliably predict restenosis!*

Which Would You Rather Have?

The "Bare Metal Stent" Option

	Pre-RX	Post-Rx
LAD	70	0
RCA	20	20
Circ	10	10



Rx:

✓1 bare metal sten

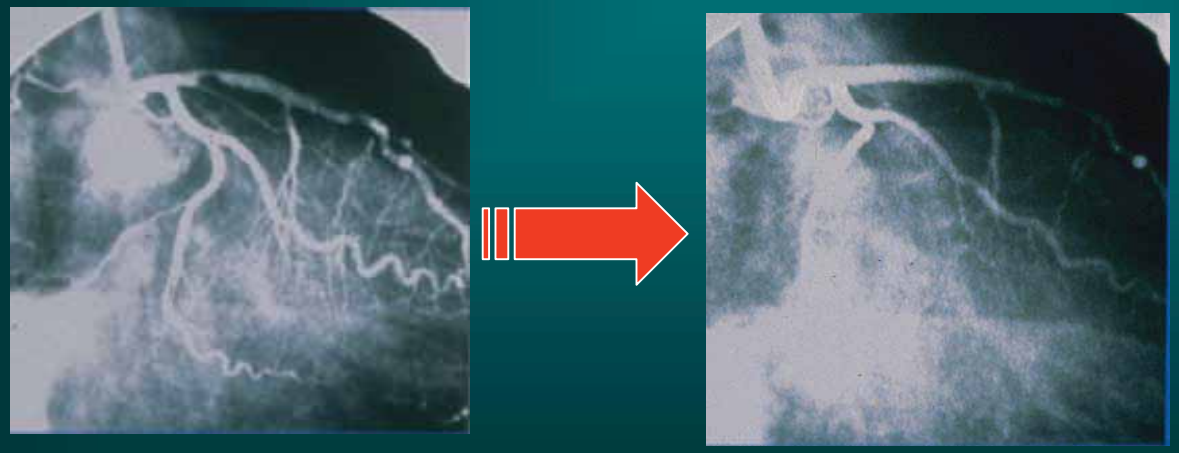
✓30-40% chance o

restenosis in the next 3-9 months

Which Would You Rather Have?

The "DES Rx" Option

	Pre-RX	Post-Rx
LAD	70	0
RCA	20	20
Circ	10	10



Rx:

✓DES (1 stent)

✓ASA, Plavix and statins

✓NORMAL LIFESTYLE

John (Jane) Q. Public

What does he (she) want?

- Wants to avoid a stroke or a heart attack
- Wants to live forever
- Doesn’t want you to change his (her) lifestyle
- Wants to avoid surgery
- Wants to avoid angioplasty
- Isn’t all that wild about having to return for repeat procedures

New Consent For Angioplasty

1) I _____ authorize Dr. David Holmes and such other physicians as necessary to perform the following procedure – bare metal stenting. I acknowledge the nature, purpose and risks of complications, which include a four-fold higher chance that I will have to return to the hospital in the next 3-9 months for another procedure, the success of which is unpredictable.

Against Global DES Use

Argument #7

= the doom and gloom scenario

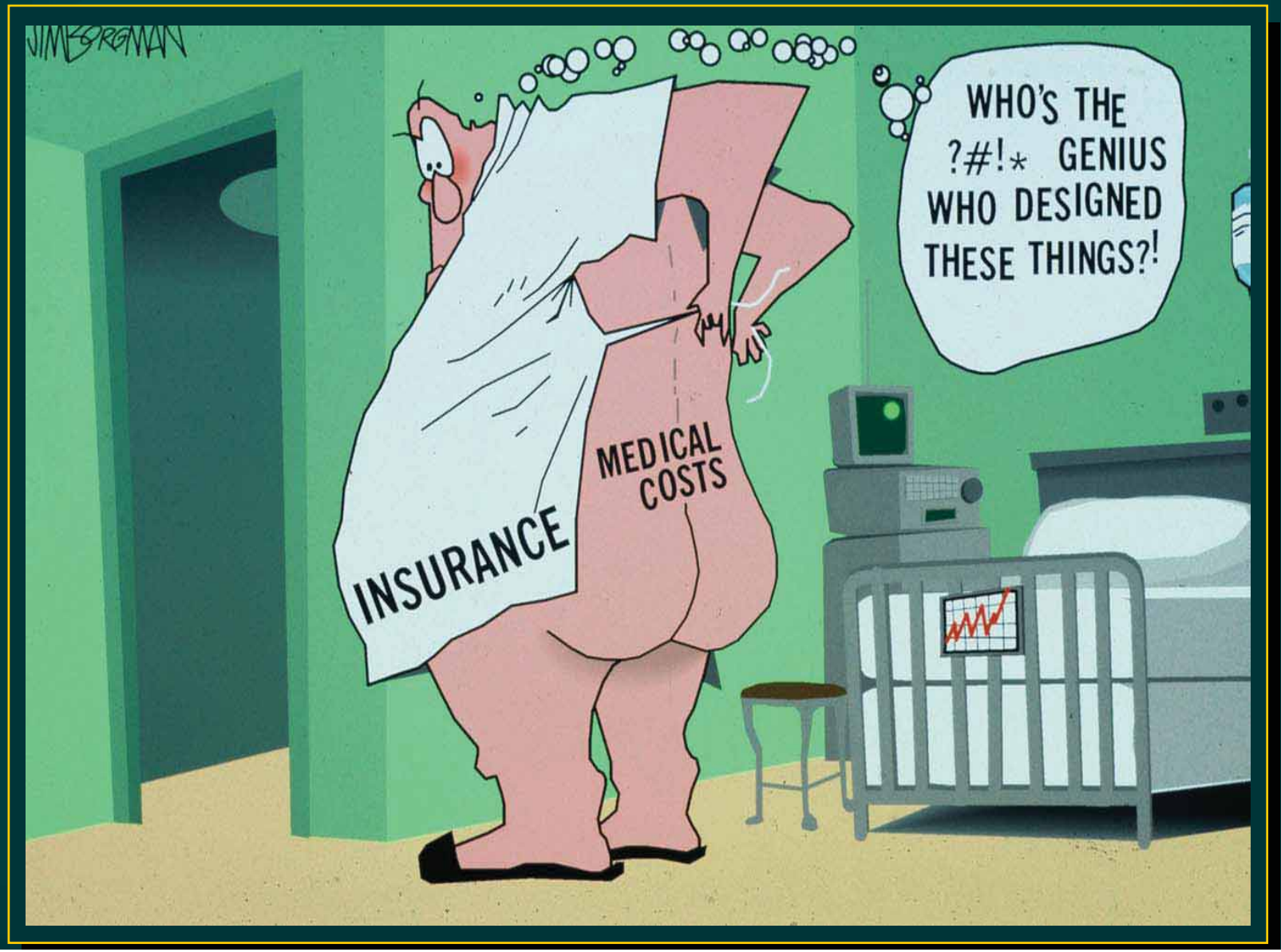
- We're going to hear that DES systems are an economic disaster, threatening to bankrupt hospitals (and put us all out of business)
- Let's all be responsible physicians and protect our hospital administrators

Drug-Eluting Stents

A Practical Dilemma…

Can anyone afford a $3,195 drug-eluting stent???

Will DES Bankrupt Hospitals?



Impact on High Volume Centers

Economic Analysis (100% DES use)

Reimbursement		Expenses	
CABG to DES	$(741,984)	CABG to DES	$(136,814)
PTCA to DES	$299,573	PTCA to DES	$335,277
BMS to DES	$6,107,598	BMS to DES	$10,480,140
Reduction in Readmission	$(1,607,638)	Reduction in Readmission	$(1,393,470)
Total	$4,057,548	Total	$9,285,133

Projected Gain/(Loss) $(5,227,584)

(Assumes similar CMS DRG 527 % increase to all Payors)

Impact on High Volume Centers

Economic Analysis (50% DES use)

Reimbursement		Expenses	
CABG to DES	$(741,984)	CABG to DES	$(136,814)
PTCA to DES	$299,573	PTCA to DES	$335,277
BMS to DES	$3,053,799	BMS to DES	$5,240,070
Reduction in Readmission	$(1,607,638)	Reduction in Readmission	$(1,393,470)
Total	$1,003,750	Total	$4,045,063

Projected Gain/(Loss) $(3,041,313)

(Assumes similar CMS DRG 527 % increase to all Payors)

DES…the facts

Cost remains an important consideration!

…affects operator strategy and clinical penetration rates

DES - 2003

Easing the Economic Burden

- Preferential use of long stents
- At present, no DES for vessels >3.5 mm diameter
- Judicious procedure staging for complex MVD patients
- Price reductions linked to volume DES use
- Procedure-based pricing (price cap per procedure) for MVD treatment
- Competition with other DES systems

Within 2-3 years, we won't use price as the DES scapegoat!

Drug-Eluting Stents

An Ethical Dilemma…

Can anyone "afford" not to use drug-eluting stents for the majority of their patients???

The Hippocratic Oath

As long as the hospital makes a profit!

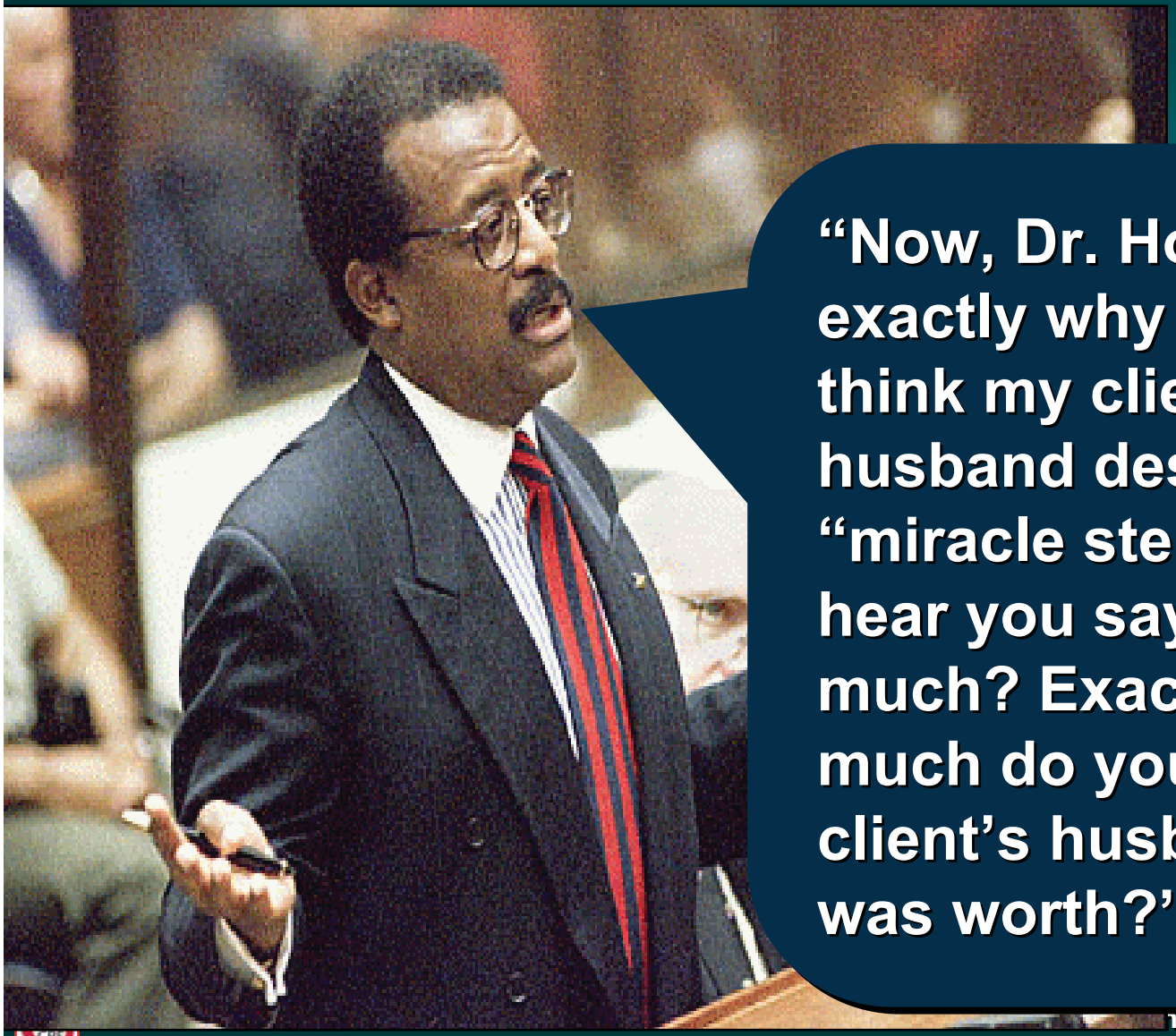
For 15-30 mm long lesions only??

I will apply, [illegible] measures which are required, avoiding those twin traps of overtreatment and therapeutic nihilism.

I will remember that there is art to medicine as well as science, and that warmth, sympathy, and understanding outweigh the surgeon's knife .....

Written in 1964 by Louis Lasagna, Academic Dean of the School of Medicine at Tufts U.

How would you like to face him in court?



"Now, Dr. Holmes, exactly why didn't you think my client's husband deserved the "miracle stent". Did I hear you say it costs too much? Exactly how much do you think my client's husband's life was worth?"

Against Global DES Use

Argument #8

= the old "gotcha" gambit

- We're going to see editorials from Circulation and other « out of context » references indicating that I'm inconsistent and falsely representing my true position!

Vol 107, No 24, June 24, 2003
ISSN 0009-7322
http://circ.ahajournals.org

American Heart Association
Fighting Heart Disease and Stroke

Circulation

JOURNAL OF THE AMERICAN HEART ASSOCIATION

MINI-REVIEW:
EXPERT OPINIONS

Drug-Eluting Stents

Costs Versus Clinical Benefit

William W. O'Neill, MD; Martin B. Leon, MD

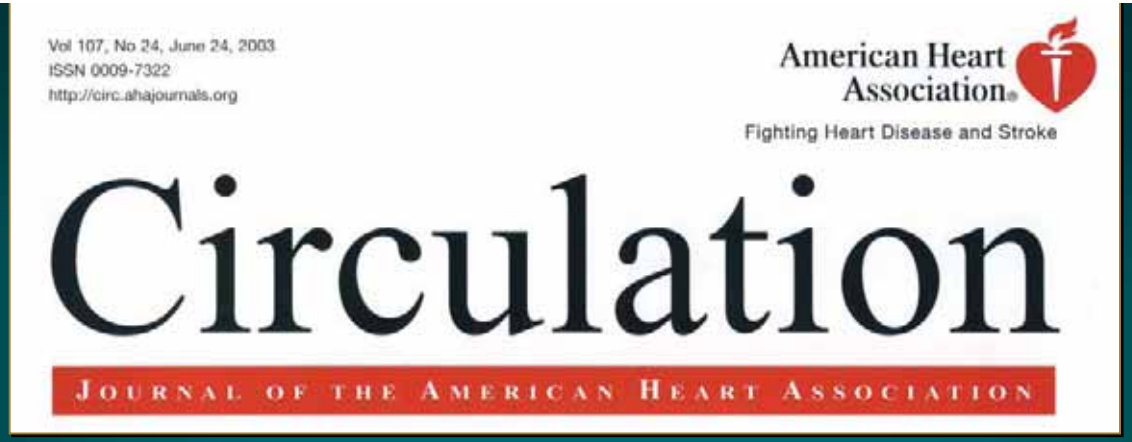
DES – 2003

Class	Condition
I	1. Lesions 15 to 30 mm in length and 2.5 to 3.5 mm in diameter, with 50% to 99% obstruction preprocedure*
	2. Diabetes**
	3. Lesions <15 mm in length and 2.5 to 3.5 mm in diameter**
IIa	1. Ostial RCA, LAD, LCX, or protected left main lesions***
	2. Parent vessel bifurcation lesion with PTCA of side branch
IIb	1. Recanalized CTO
	2. Lesions >30 mm in length and 2.5 to 3.5 mm in diameter
	3. In-stent restenosis—focal pattern
III	1. SVBG disease
	2. In-stent restenosis—diffuse pattern
	3. Unprotected left main lesions

* Level of evidence A, entry criteria for SIRIUS, RAVEL and TAXUS II trials.

** Level of evidence B.

*** In 2003, registry data from the Guidant Corp. Radomized Paclitaxel-Coated Stent trial (DELIVER II) and the SIRIUS studies will be available.



"In summary, DES promise to revolutionize the field of interventional cardiology. It is incumbent on industry to sponsor clinical trials that address the gaps in safety and efficacy. It is incumbent on investigators to conduct rigorous, properly designed, and adequately powered studies to address gaps in knowledge. And, most important, it is incumbent on clinicians to carefully weigh the evidence to judiciously apply this new technology in the best interests of our patients."

THE WALL STREET JOURNAL.

FRIDAY, APRIL 25, 2003 - VOL. CCXLI NO. 81 - ★★★★ $1.00

Wait for Drug-Coated Stent Is Over

Right After FDA Approval, Johnson & Johnson Devices Put in First Heart Patient

By Ron Winslow

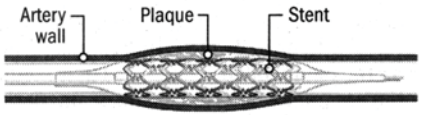
For Kenneth Ballenger and thousands of other heart patients around the U.S., the wait is over.

Late yesterday, just hours after the Food and Drug Administration approved Johnson & Johnson's new device called a drug-eluting stent, the 65-year-old retired truck driver from Brooklyn in New York got not just one but four of them during an artery-clearing angioplasty procedure at New York's Lenox Hill Hospital.

"This is going to make a big difference in how we treat patients with coronary disease," says Martin Leon, the cardiologist who oversaw the procedure—the first in the U.S. after the FDA decision—and a co-leader of the major clinical trial that led to the stent's approval.

The drug-coated stent is considered a major advance over old models because it substantially reduces the need for repeat procedures. Conventional stents have a tendency to reclog within a few months, a process called in-stent restenosis that requires a second procedure in 15% to 30% of cases. The new device has been shown in clinical trials to reduce restenosis by more than two-thirds and to reduce the need for repeat procedures to less than 5%.

But along with the hype comes caution, especially concerning price. Johnson & Johnson will charge $3,195 per stent, with discounts based on volume and other factors. The price is at least $2,000 more than current, widely used models of the device. Though insurers are already signaling that they will cover at least a portion of the cost, "You have to be responsible and come up with some plans and protocols to use these stents," says Samin Sharma, director of interventional cardiology at Mount Sinai Medical Center in New York. "If you start using them indiscriminately, the hospital will lose money."



The FDA *granted approval to Johnson & Johnson's new drug-coated stent.*

Photo: Johnson & Johnson

The device is a tiny metal sheath that is delivered to obstructed coronary arteries via a catheter to prop them open after they have been cleared by an angioplasty balloon. The key ingredient is a drug called Sirolimus, which is marketed by **Wyeth** to prevent organ rejection in kidney transplants, and which is embedded in a polymer that coats the metal stent. Over the first 30 to 45 days after the stent is implanted in the coronary arteries, the drug seeps into the artery wall surrounding the device and prevents the accumulation of scar tissue that can form and reblock the artery. (Wyeth has licensed the drug to J&J and its Cordis unit, for the stent application.)

In recent weeks, heart programs around the U.S. have been keeping lists of patients who were waiting for the new stent to be approved rather than go with a conventional device. Robert Croce, company group chairman at J&J with responsibility for the Cordis unit, estimated that nationwide, more than 35,000 patients are lined up to get the device.

Mr. Croce says the pent-up demand was enough to accelerate the company's distribution plan.

Mr. Ballenger of Brooklyn, who had a heart attack a decade ago, has been waiting for the new stent since he developed worsening chest pain two weeks ago.

Greg Geneviva, a 53-year-old retired policeman from upstate New York whose condition had been more stable, has waited more than six months. While he could have been treated with a conventional stent, he has a long history of heart disease that indicated he would be at high risk of having restenosis and needing another procedure. His wife, Mary Rita, says she called the FDA and J&J every week for the past two months.

"We're very positive and happy the FDA came through," Mr. Geneviva says.

Meanwhile, **Aetna** Inc. is among the insurers to say they will cover the technology in the belief it will reduce long-term complications for patients, a spokeswoman says.

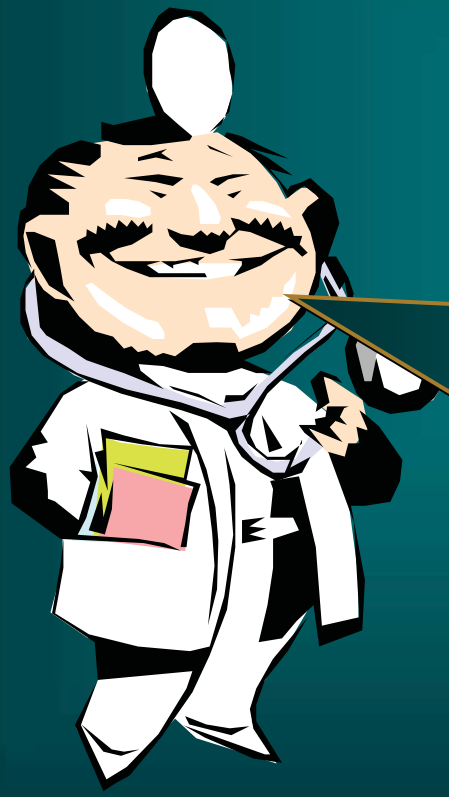
—Scott Hensley contributed to this article.

Restenosis has been the Achille's heel of angioplasty for the last 25 years

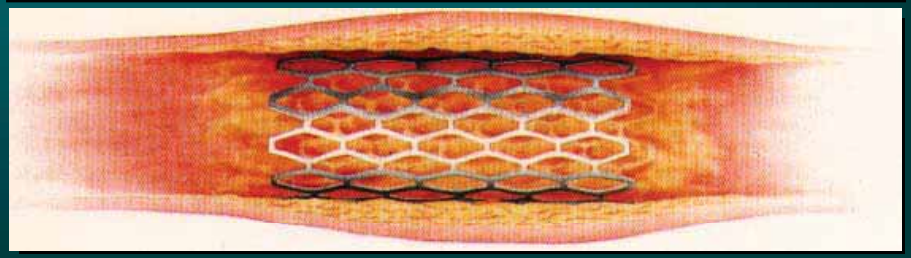
No more Achille's heel…
Restenosis is finally being put to rest

Intervention 2003

DES Euphoria…



DES are the greatest advance in interventional cardiology since the advent of the balloon!



DES – What to Expect

- DES will become the « core technology » for interventional vascular therapy
- All previous « high risk » restenosis scenarios will be aggressively challenged (e.g. diabetics with MVD)
- The emphasis will shift to advanced operator-driven intervention (interventional technique will « reign supreme »)
- There will be frequent rumors of increased complications and poor outcomes with DES systems

DES – What to Expect

- There is a great need to generate more definitive clinical data in complex subsets to justify widespread DES applications
- There will be « speedbumps » along the road and patient/lesion cohorts which require special attention and improved iterative technology
- DES proliferation will significantly impact both medical and surgical treatment of CAD over the next decade

DES – What to Expect

- The impact will be slow and progressive, as physicans become better educated, as operators become better trained, and as more data becomes available
- The integration of DES in PCI therapy will follow a staged or tiered pathway
- Economic factors will continue to play a major role in strategic case-based decision-making
- Future advances in biotechnology will refine and supplant current DES systems in a telescoped timeframe

PCI ➡ DES Euphoria

Tier 1…"low hanging fruit"

- Erasing the restenosis stygma associated with angioplasty…public awareness campaign
- Erasing the LIMA-LAD "will always be better" myth
- Following labeled indications (with some latitude)… single or double vessel disease, 2.5-4.0 mm vessel diameter, 0-30 mm lesion length

PCI ➡ DES Euphoria

Tier 2…high restenosis risk pts

- Improved operator training to “generalize” advanced technique requirements
- Extend routine treatment to “simple” diabetics, ostial disease, bifurcations, CTOs, acute MIs, diffuse disease (>30mm lesion length), and more complex double and triple vessel disease
- Need more clinical trial data in complex lesion subsets (it’s on the way!)

PCI ➡ DES Euphoria

Tier 3…the ultra-complex

- Advanced interventional training to treat the most challenging anatomic scenarios
- Attacking the “unthinkable”… left main disease (unprotected) and diabetics with complex multivessel disease
- Hybrid procedures (combined CABG + PCI) when appropriate
- Still some problem subsets…chronic total occlusions (uncrossable), “too diffuse” disease, technically unapproachable

Drug-eluting stents are here to stay!!!

Drug-Eluting Stents: Prediction

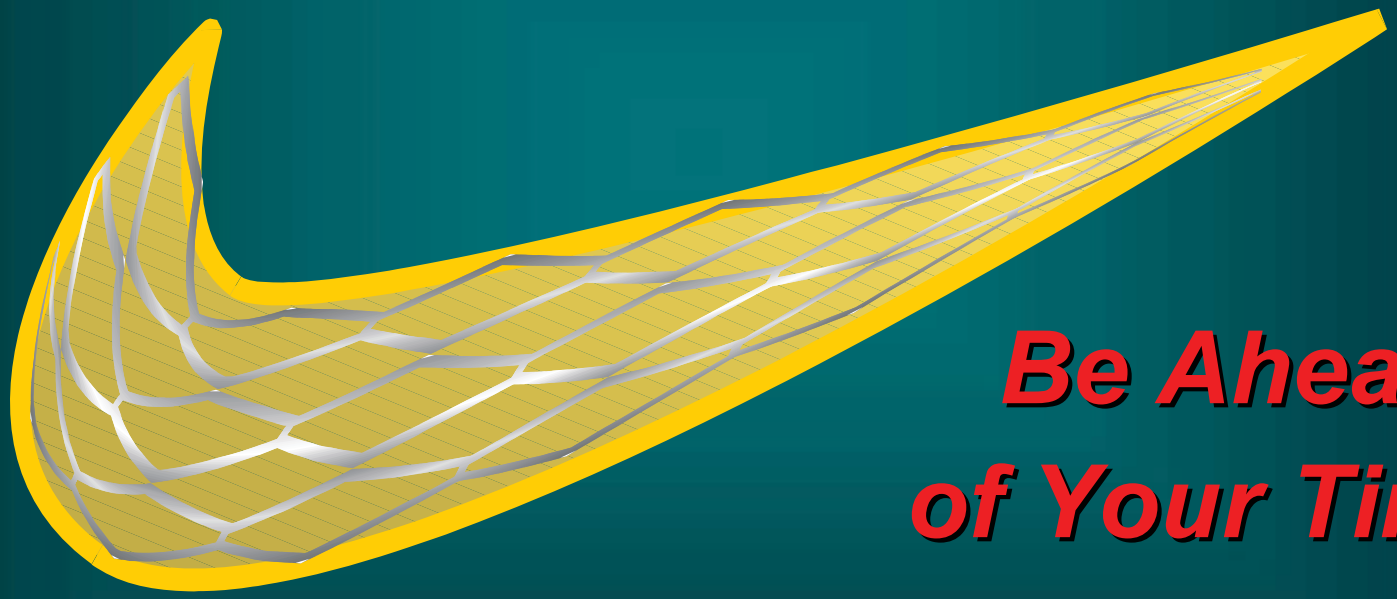
A Multi-Lesion Single Device Approach…

- Ostial lesions
- Bifurcations
- In-stent restenosis
- SVGs
- Small vessels
- Diffuse disease
- Left main disease
- Total occlusions

A Drug-Eluting Stent

Intervention 2003

The Rising Tide of Drug-eluting Stent Therapy is Fully Justified!

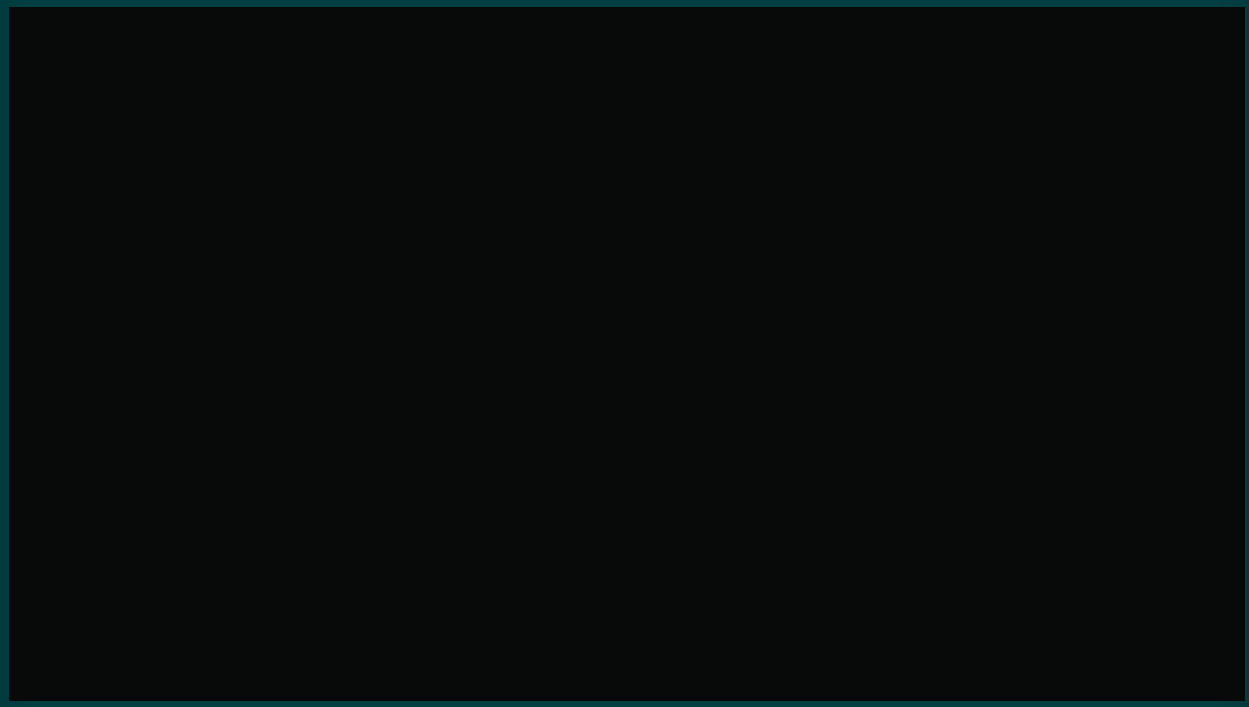


Be Ahead of Your Time!

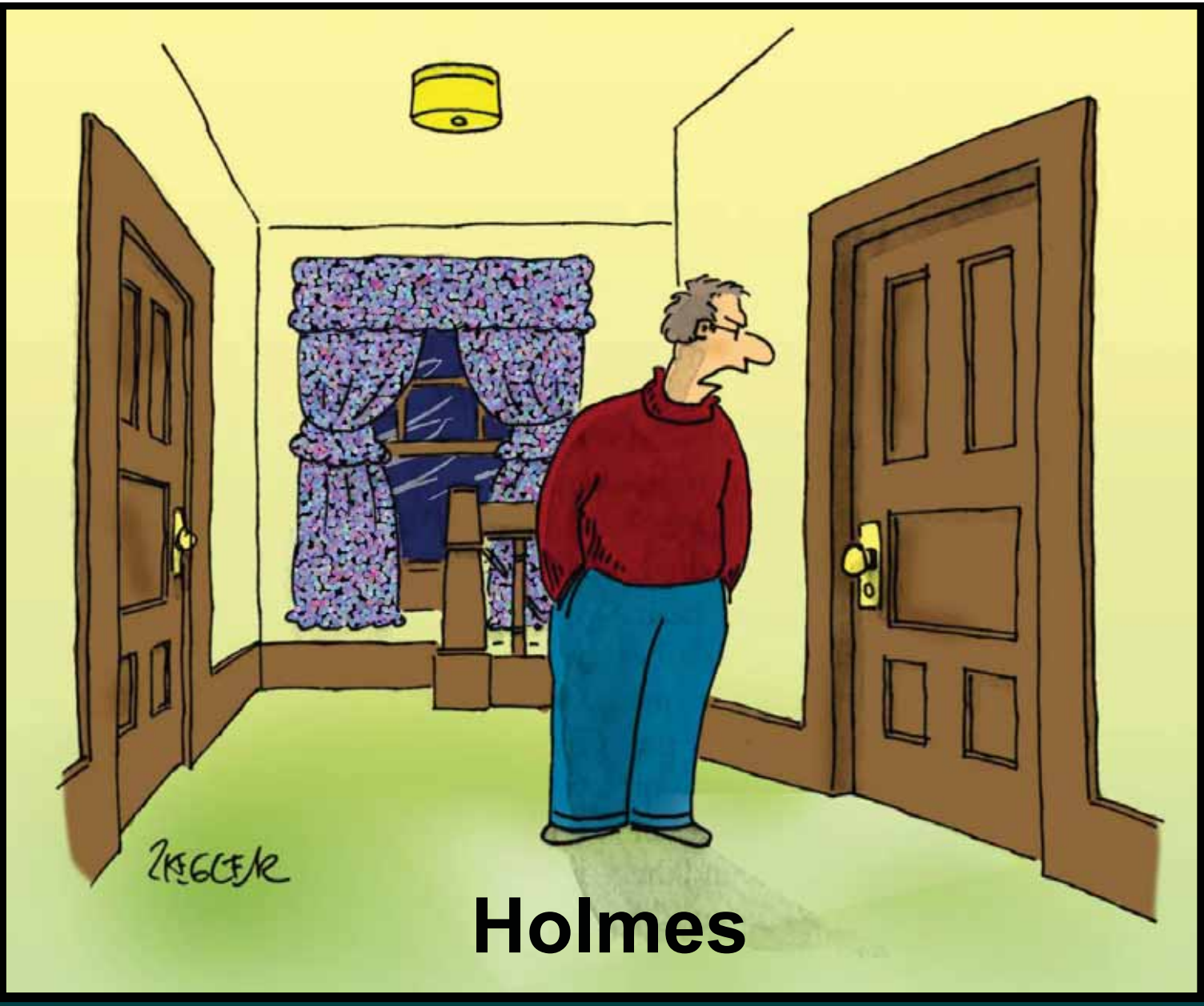
Just DES It!

David – Have I Changed Your Mind?

The bottom line is…



DES just happen to work!!!



"My concession speech will be brief. You win."