



Interventional Cardiology

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Interventional Cardiology



PTCA - 1977

Percutaneous
Transluminal
Coronary
Angioplasty

PTCA

Indications for PTCA:



- Single vessel disease
- Proximal Lesions

Contra- indications:


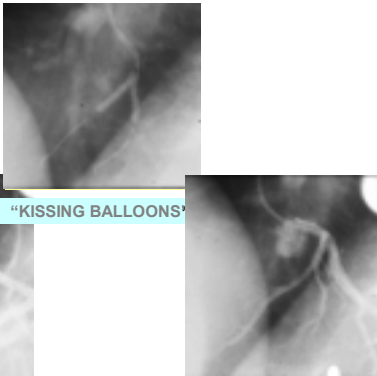
- Left main, Multivessel, Acute MI, Total occlusion, Bifurcation's, Tortuosity ...

TOTAL OCCLUSION

Stiff Tip Guide Wires

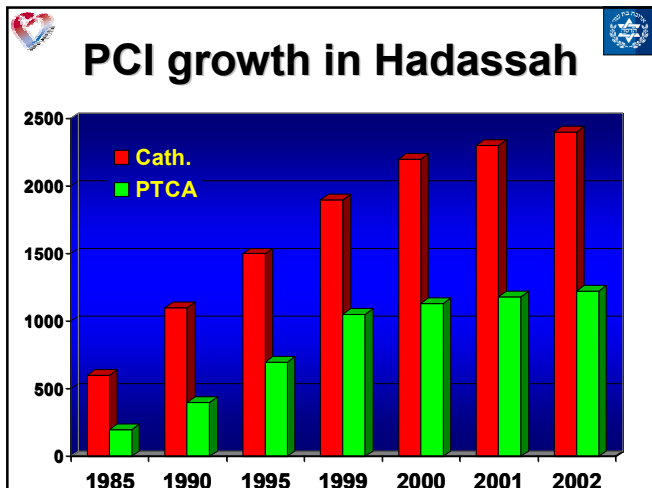
TRANS RADIAL ANGIOPLASTY

"KISSING BALLOONS"

TRANS RADIAL ANGIOPLASTY

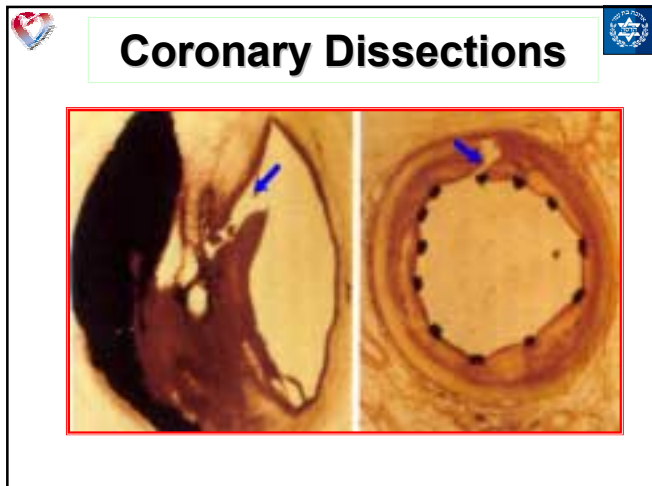




PCI

Early Problems:

1. Dissections/ acute occlusion (~5%)
2. Restenosis (30-40%)
 - Recoil
 - Intimal Hyperplasia



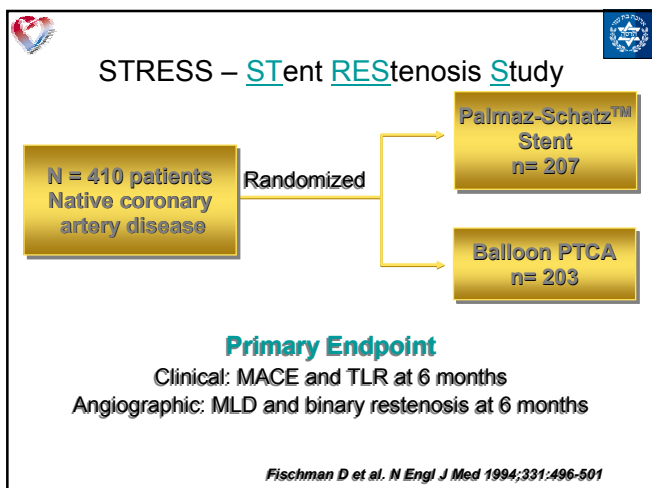
The Beginning of the Stent Era

The First-In-Man Palmaz-Schatz™ Stent

- Sousa JE. Personal communication

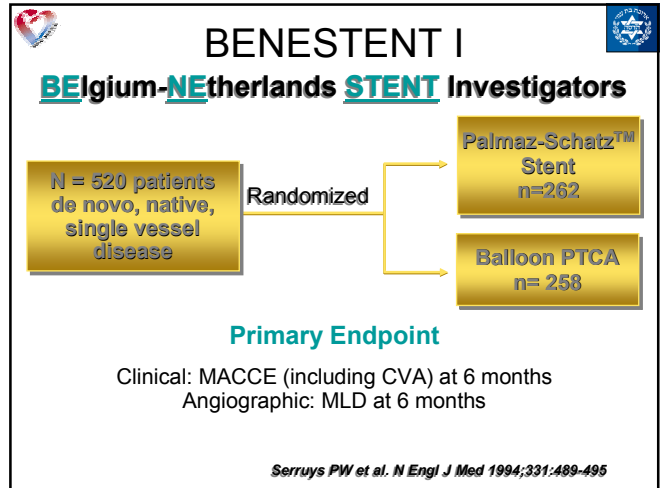
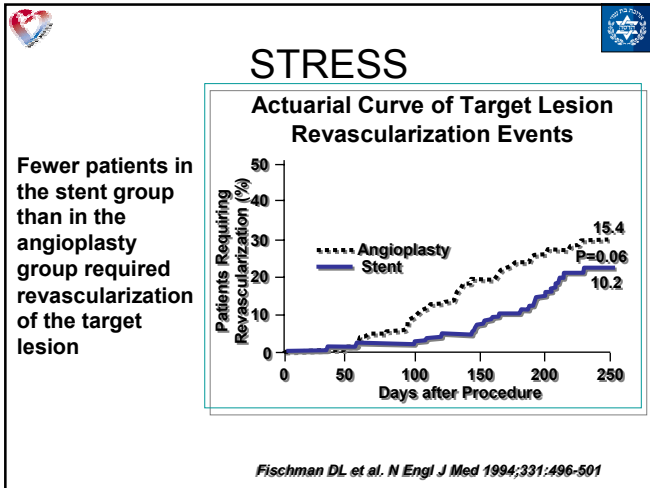
The First Randomized Trials

- STRESS - Stent versus balloon PTCA for de novo lesions
 - Fischman DL, et al. N Engl J Med 1994;331:496-501
- BENESTENT I - Stent versus balloon PTCA for de novo lesions
 - Serruys PW, et al. N Engl J Med 1994;331:489-495



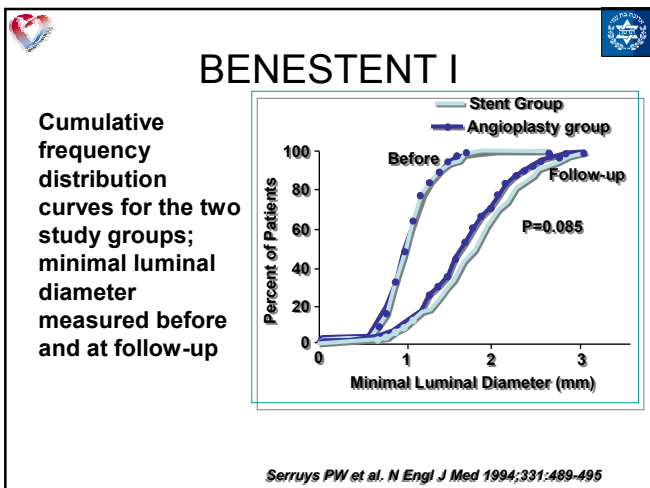
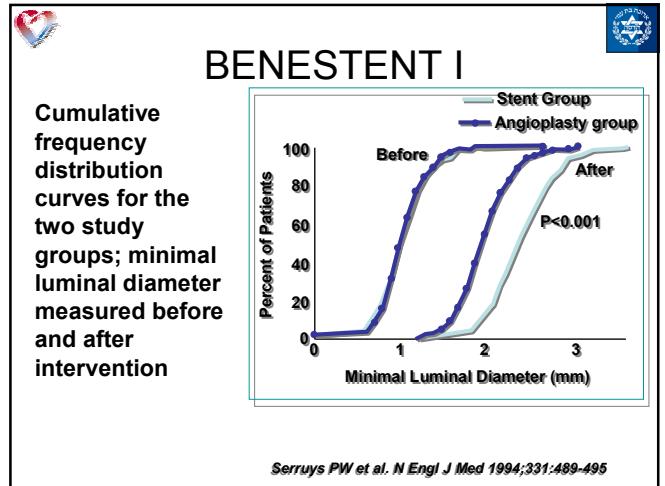
STRESS

	PS Stent	Balloon	p-value
<i>In-hospital results</i>			
Procedural success (%)	99.5	92.6	<0.001
Abrupt/subacute closure (%)	3.4	1.5	NS
Bleeding/vasc. complic. (%)	7.3	4.0	NS
<i>6 months results</i>			
Death (%)	1.5	1.5	NS
MI (%)	6.3	6.9	NS
CABG (%)	4.9	8.4	NS
Any MACE (%)	19.5	23.8	NS
Restenosis (%)	31.6	42.1	0.046



BENESTENT I

	PTCA	Stent	p-Value
<i>7 Month Follow-up</i>			
Subacute thrombosis (%)	2.7	3.5	NS
Death (%)	0.4	0.8	NS
Bleeding/vasc. complic. (%)	3.1	13.5	<0.001
Any event (%)	29.6	20.1	0.02
<i>Angiographic Outcomes</i>			
Final MLD (mm)	1.73 ± 0.55	1.82 ± 0.64	0.09
Restenosis (%)	32	22	0.02



- ## Improved Anti-thrombotic Regimens
- The New Era of High-Pressure Stenting
 - Colombo A, et al. *Circulation* 1995;91:1676
 - BENESTENT II – Heparin-coated Palmaz-Schatz™ stent
 - Serruys PW, et al. *Lancet* 1998;352:673-681
 - STARS - Aspirin plus ticlopidine antithrombotic regimen
 - Leon MB, et al. *N Engl J Med* 1998;339:1665-71

The New Era of High-Pressure Stenting

Acute and 6-month Results

Inflation pressure (atm)	14.9 ± 3.0
Balloon/artery ratio	1.17 ± 0.19
Procedural success (%)	96
Subacute thrombosis (%)	0.3
Bleeding/vascular complications (%)	0.6
6-month	
Death (%)	1.9
Q-wave MI (%)	5.7
Non Q-wave MI (%)	3.2
TLR (%)	<u>13.1</u>

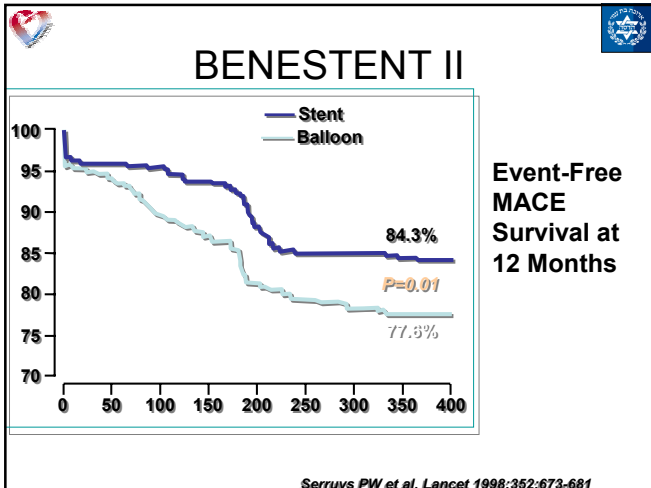
BENESTENT II

30 Day Results	Balloon	Stent
Death (%)	1	1.0
Q-wave MI (%)	1.5	1.9
Non Q-wave MI (%)	2.9	1.5
Vascular Complications (%)	1.0	1.2
Subacute Thrombosis (%)	1.7	0.2

1-year Results	Balloon	Stent
Repeat CABG (%)	1.5	1.9
Repeat PCI (%)	15.6	9.4*
Any MACE (%)	22.4	15.7*

* p < 0.05

Serruys PW et al. Lancet 1998;352:673-681



STARS

Stent Anti-thrombotic Regimen Study

N = 1653

Optimal Stent Implantation in native coronary arteries (< 3 stents, < 10% residual stenosis, no dissections)

ASA Alone n = 557	ASA + Coumadin n = 550	ASA + Ticlopidine n = 546
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Primary Endpoint

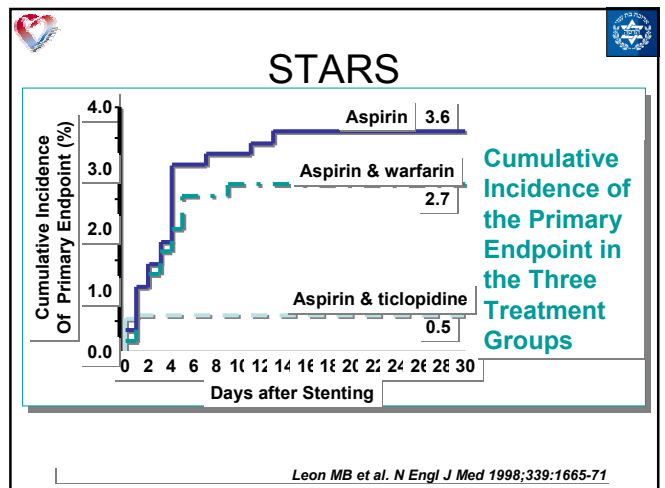
Death, revascularization of the target lesion, angiographically evident thrombosis, or myocardial infarction at 30 days

Leon MB et al. N Engl J Med 1998;339:1665-71

STARS

Results at 30 days	ASA Alone	ASA + Coumadin	ASA + Ticlopidine	p-Value
Death (%)	0.2	0	0	NS
Angiographic thrombosis (%)	2.9	2.7	0.5	0.005
Recurrent MI (%)	2.7	2.0	0.5	0.01
Hemorrhagic complications (%)	1.8	6.2	5.5	< 0.001
Vascular complications (%)	0.4	2.0	2.0	0.02
Thrombocytopenia (%)	0.2	0.3	0.5	NS

Leon MB et al. N Engl J Med 1998;339:1665-71



Expanded Clinical Indications

- **REST** - Restenotic lesions
 - Erbel R, et al. *N Engl J Med* 1998;339:1672-78
- **STENT PAMI** - Acute myocardial infarction
 - Grines CL, et al. *N Engl J Med* 1999;341:1949-56
- **TOSCA** - Total occlusions
 - Buller CE, et al. *Circulation* 1999;100:236-242
- **SAVED** - Saphenous vein grafts
 - Savage MP, et al. *N Engl J Med* 1997;337:740-47
- **ARTS** - Multivessel disease
 - Serruys PW, et al. *N Engl J Med* 2001;344:1117-24

REST – Restenosis Stent Study

Primary Endpoint
Restenosis at 6 months ($\geq 50\%$ DS)

Erbel R et al. N Engl J Med 1998;339:1672-78

REST

Results at 6 Months	PS Stent	PTCA	p-Value
Subacute thrombosis (%)	3.9	0.6	0.01
Any bleeding (%)	6.2	1.6	0.01
Final MLD (mm)	2.04 ± 0.66	1.85 ± 0.56	0.01
TVR (%)	10	27	0.001
Restenosis (%)	18	32	0.03
Event-free survival (%)	84	72	0.04

Erbel R et al. N Engl J Med 1998;339:1672-78

STENT PAMI

Stent Primary Angioplasty in Myocardial Infarction

Primary Endpoint
Death, re-infarction, ischemic-driven TVR or disabling stroke at 6 months

Grines CL et al. N Engl J Med 1999;341:1949-56

STENT PAMI

Results at 6 Months	Heparin-coated Stent	PTCA	p-Value
Death (%)	4.2	2.7	NS
Re-infarction (%)	2.4	2.2	NS
Disabling stroke (%)	0.2	0.2	NS
Ischemic TVR (%)	7.5	17.0	< 0.001
Composite endpt (%)	12.4	20.1	< 0.01
Final TIMI III (%)	89.4	92.7	0.01
Restenosis (%)	20.3	33.5	< 0.001

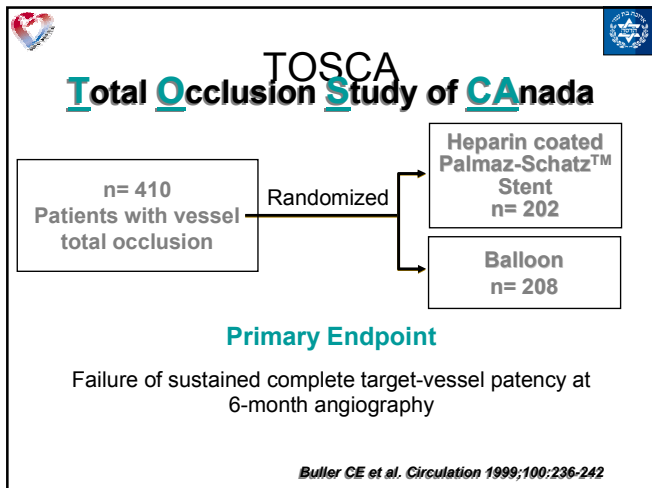
Grines CL et al. N Engl J Med 1999;341:1949-56

STENT PAMI

Event-free Survival according to Treatment Group

This difference was due to the lower proportion of patients in the stent group who underwent TLR for ischemia

Grines CL et al. N Engl J Med 1999;341:1949-56



TOSCA

6 Month Event Rates	Balloon PTCA n = 208	Stent n=202
Procedure Success (%)	87.9	94.5
Death (%)	0.5	0.5
Q-wave MI (%)	1.0	2.5
Non Q-wave MI (%)	2.8	9.4
Patency Failure (%)	19.5	10.9*
Target Revascularization (%)	15.4	8.4%*
Repeat CABG (%)	1.4	1.5
Repeat PCI (%)	19.7	6.9*
Binary Restenosis (%)	70	55*
Any MACE (%)	23.1	15.8

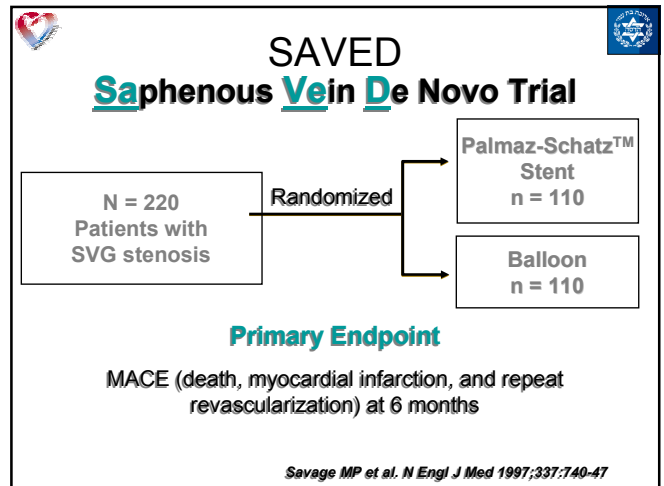
*** p < 0.001**

STOP study

STOP

Clinical Events during follow up (%)

	PTCA	STENT	P
Recurrent AP	17	11	ns
Death	0	0	ns
Q wave MI	2	0	ns
CABG	2	4	ns
Repeat PTCA	39	24	ns
Total MACE	60.4	39.6	<0.05

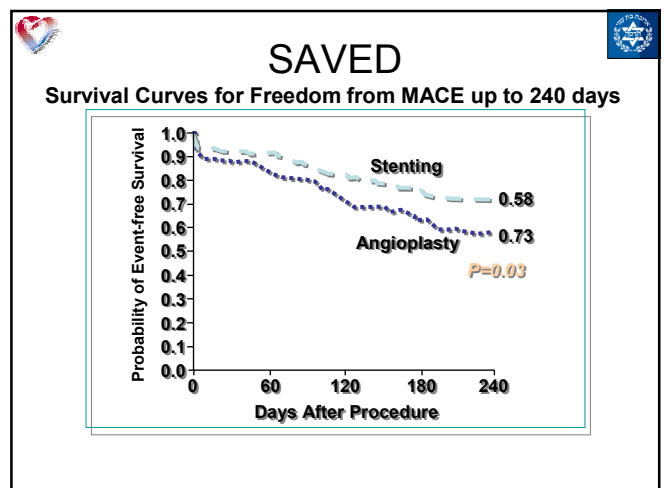


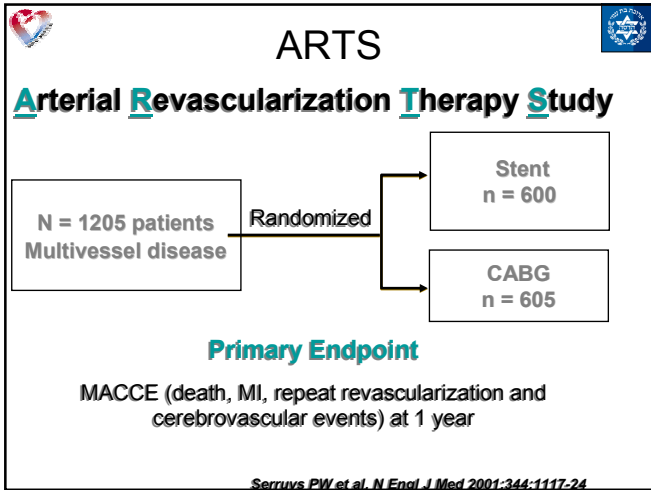
SAVED

Acute and 6 Month Results	Balloon PTCA n = 208	Stent n = 202
Procedural Success (%)	69	92*
Death (%)	1.0	2.5
Q-wave MI (%)	1.0	2.0
Target Revascularization (%)	15.4	8.4*
Binary Restenosis (%)	46	37
Any MACE (%)	39	26*

*** p < 0.01**

Savage MP et al. N Engl J Med 1997;337:740-47

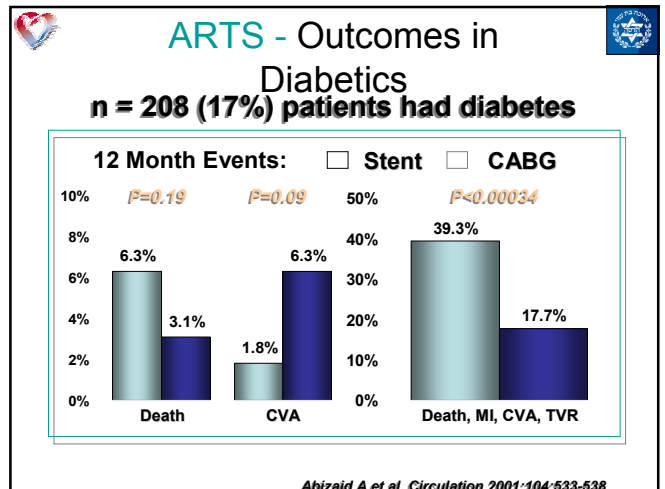
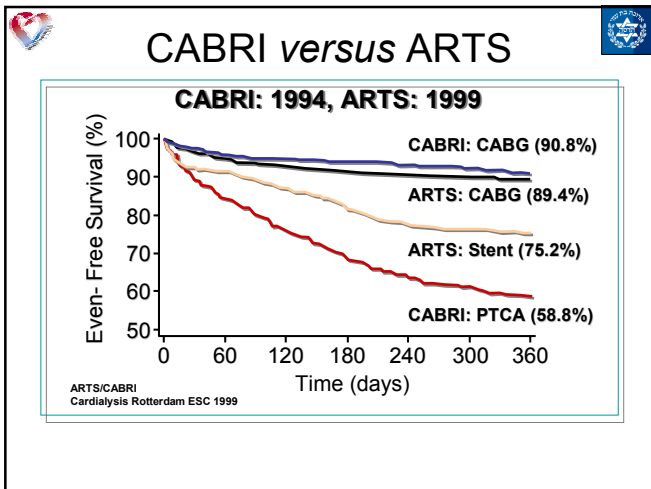
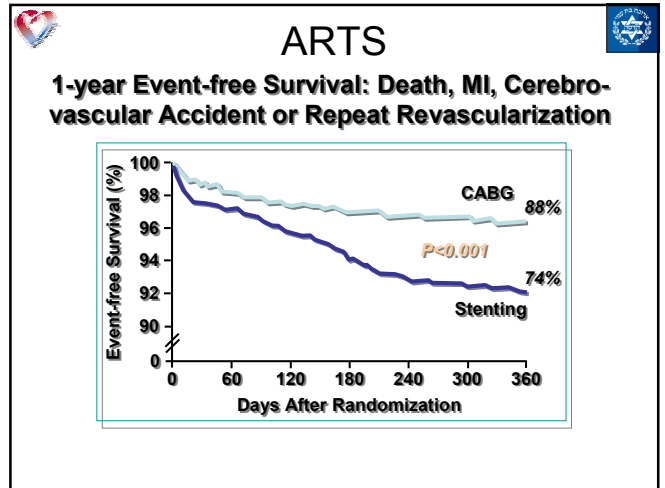
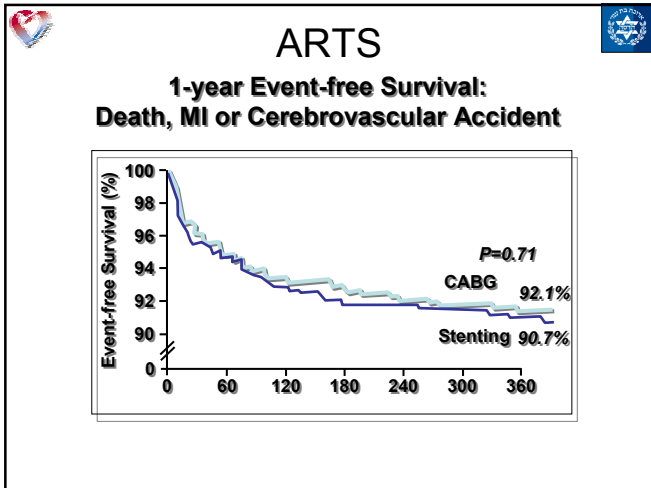




ARTS

1 Year Follow-up	Stent	CABG
Death (%)	2.5	2.8
Myocardial Infarction (%)	5.3	4.0
Cerebrovascular accident (%)	1.5	2.0
Repeat revascularization (%)	16.8	3.5
Event-free MACCE survival (%)	73.8	87.8
Initial cost (Euros)	6,441	10,653
1 year cost (Euros)	10,665	13,638

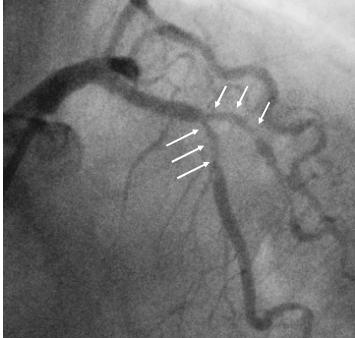
Serruys PW et al. N Engl J Med 2001;344:1117-24



Bifurcation Lesions

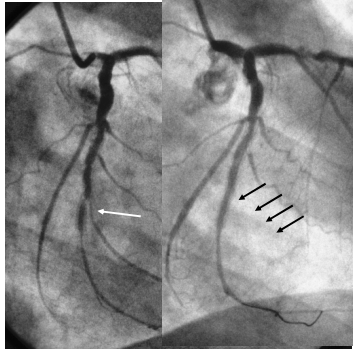
- 50% lesion in main and side branch.

True bifurcation lesion - 4-16%

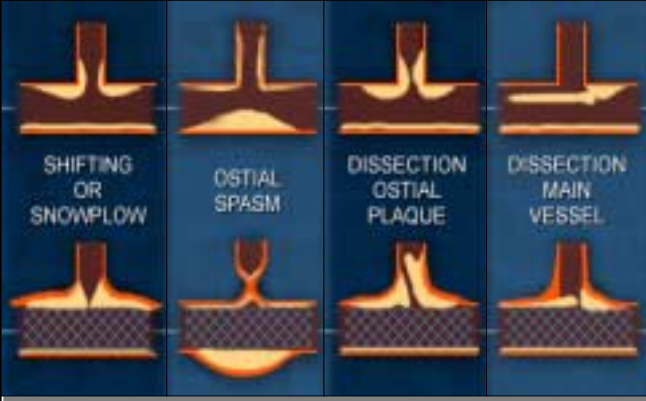


Intervention in Bifurcation Lesions

- Short-term complications
 - Side branch occlusion
- Long-term complications
 - Restenosis



Complications of Conventional Stents



SHIFTING OR SNOWPLOW

OSTIAL SPASM

DISSECTION OSTIAL PLAQUE

DISSECTION MAIN VESSEL

Complications of PCI

Acute or Subacute	Chronic
Dissection	Restenosis
Embolization	Inflammation
Thrombosis	
Inflammation	

PCI

Legend: Device (Purple), Pharmacologic (Red)

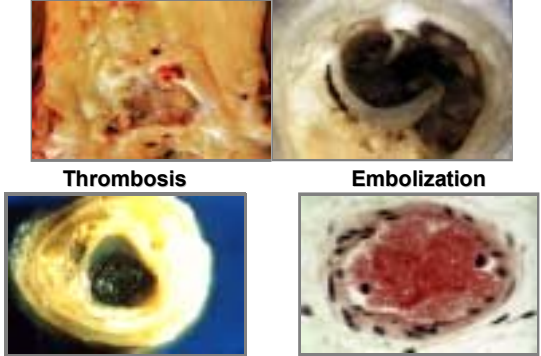
Thrombus Containing Lesions



Large thrombus

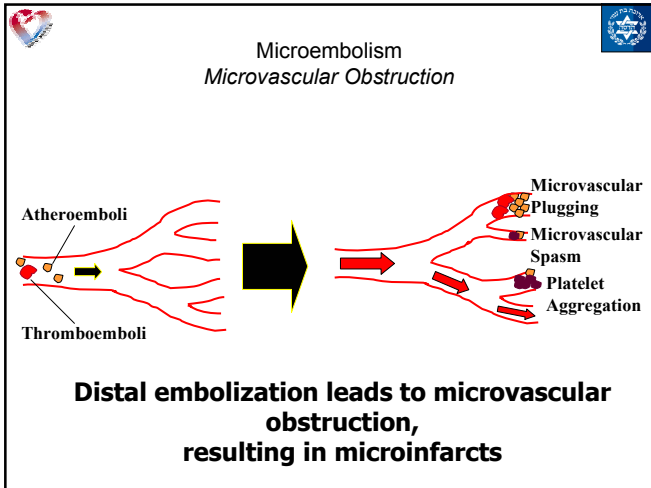
ACS and PCI

Plaque Rupture



Thrombosis

Embolization



Prevention of Distal Embolization

- **I**IIb/IIIa** Inhibitors**
- **Direct Stenting**
- **Thrombus Removal**
- **Distal Protection**



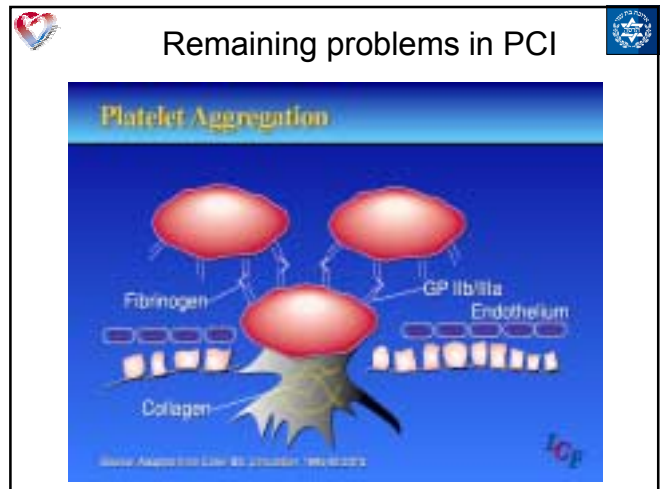
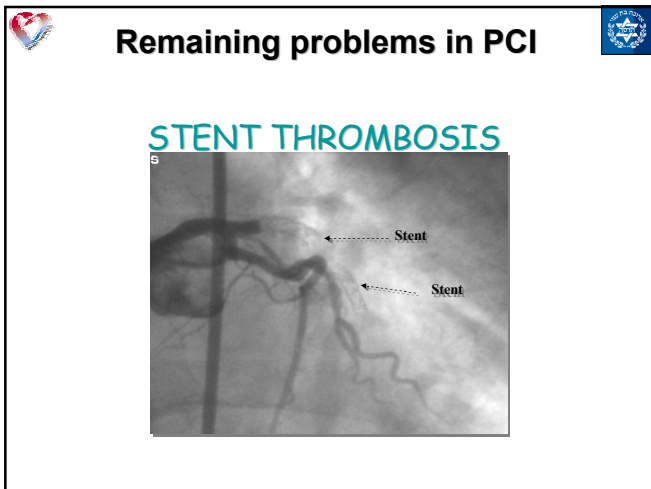
SVG Clinical Data

SAFER – U.S. Multi-Center Randomized Study
Saphenous Vein Graft Angioplasty Free of Emboli
Randomized

801 patients, 73 sites
randomized against standard care

MACE = 9.6% vs. 16.5% (**42% ↓**)

Circulation, 2002



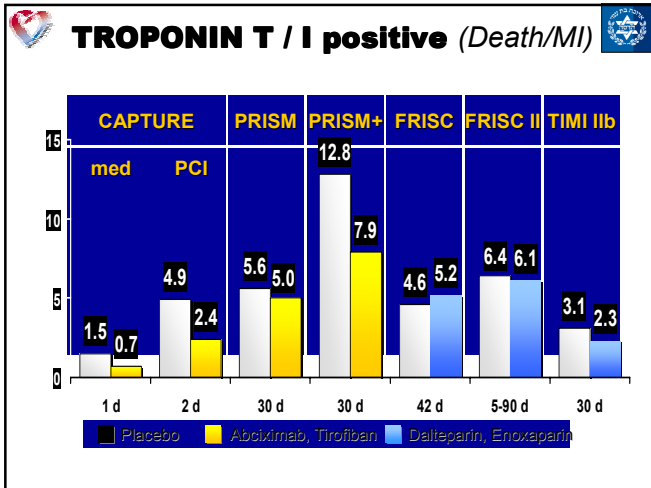
STENT THROMBOSIS

Stent
Stent

Following multiple inflations throughout stented areas and with the benefit of bolus & infusion of abciximab (ReoPro) excellent flow restored in large LAD

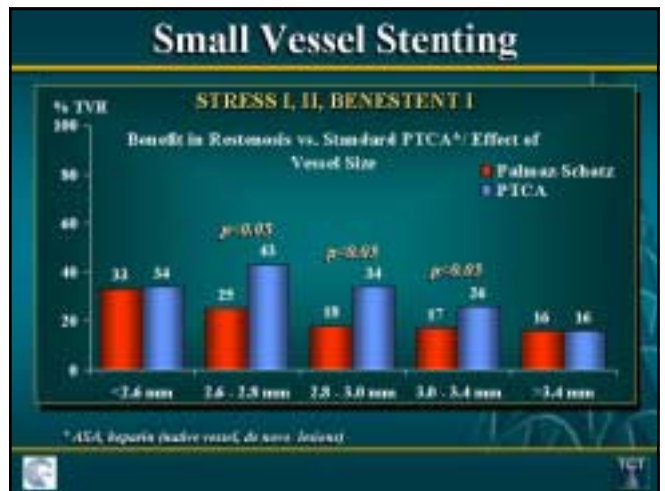
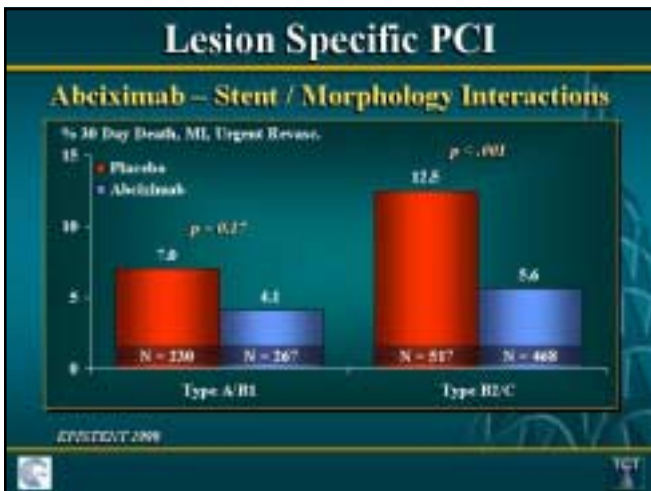
PCI patients Death, MI at 30 days

abciximab
eptifibatid
tirofiban
xemilofiban



Lesion Specific PCI Old ACC/AHA Lesion Type Criteria

~~Old ACC/AHA Lesion Type Criteria~~





- ### Operator Technique Improvements
- MUSIC - IVUS-guided stenting
 - de Jaegere P, et al. Eur Heart J 1998;19:1122-4
 - CRUISE – IVUS-guided stenting (STARS sub-analysis)
 - Fitzgerald PJ, et al. Circulation 2000;102:523-530

Flow Measurements

- Doppler Flow Wire
- Maximal Flow Reserve

MUSIC

Multicenter Ultrasound Stenting In Coronary Arteries

IVUS-guided stenting and Aspirin Alone
n = 161

Primary Endpoint
Adverse clinical events including Subacute Thrombosis at 30 days

de Jaegere P et al. Eur Heart J 1998;19:1122-4

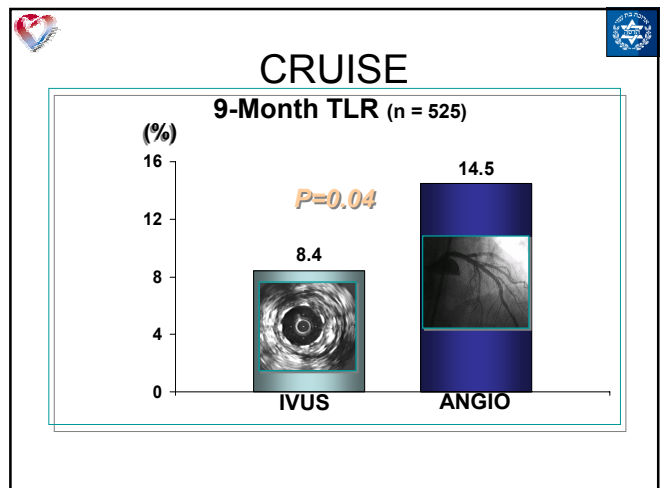
MUSIC

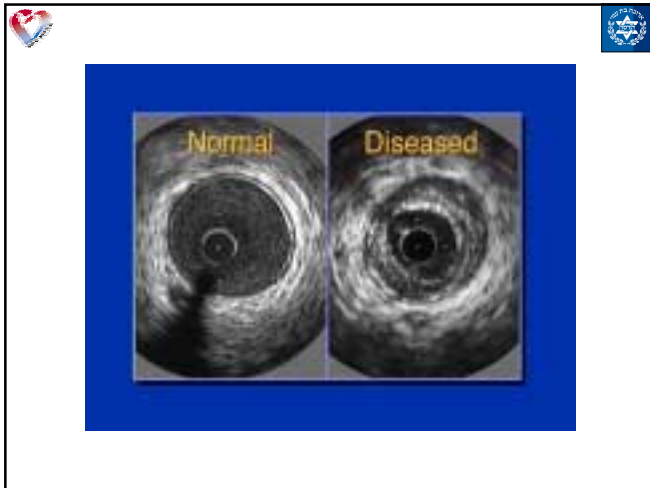
IVUS criteria of optimal stent expansion

Stent expansion $\geq 90\%$ and/or minimal lesion lumen CSA $\geq 9\text{mm}^2$

Lumen CSA at Proximal reference Lumen CSA at Lesion Site Lumen CSA at Distal reference

Stent Expansion = $\frac{\text{Proximal lumen CSA} + \text{Distal lumen CSA}}{\text{Lesion minimal lumen CSA}}$



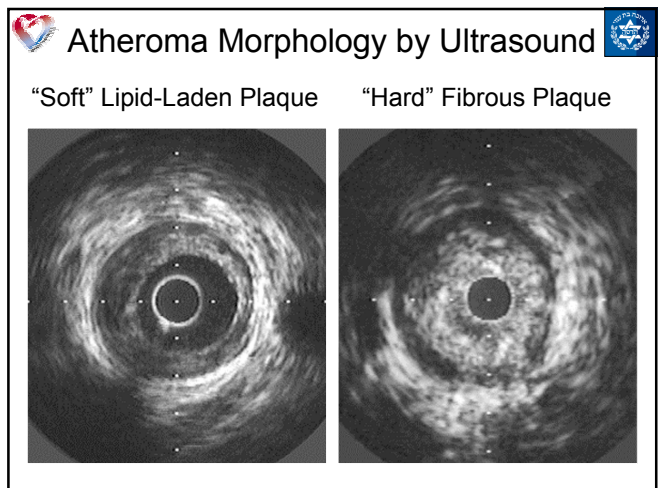
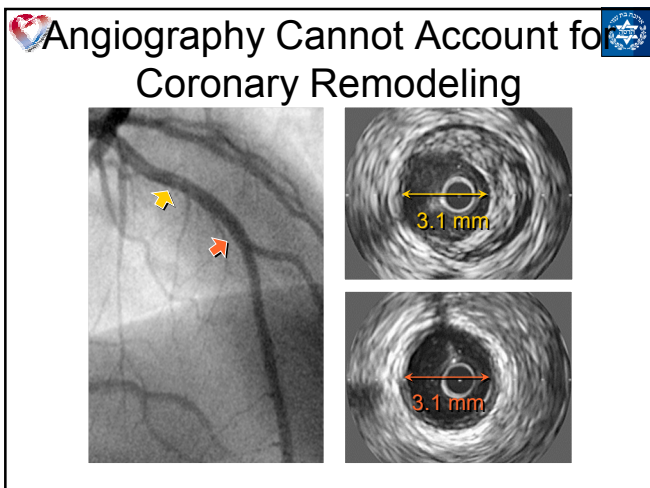
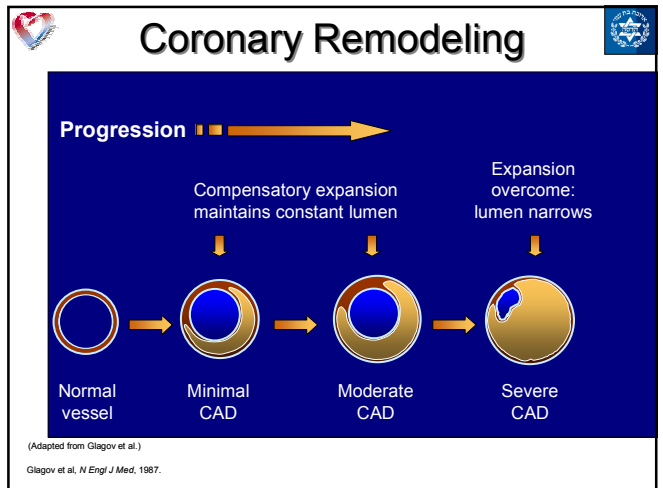


Angiography: Significant Limitations in Atheroma Assessment

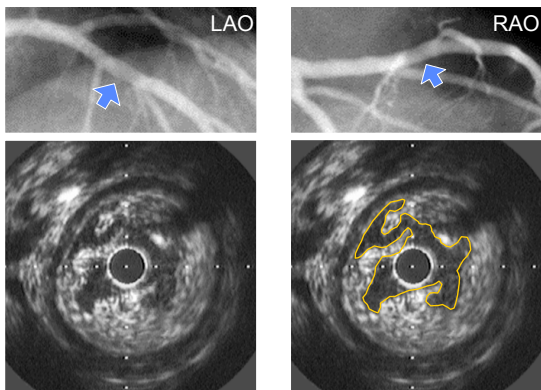
- Angiography reflects a planar, 2-dimensional silhouette of the lumen
- Remodeling
 - Because angiography does not visualize the vessel wall, it cannot account for positive or negative remodeling

Angiography: Significant Limitations in Atheroma Assessment

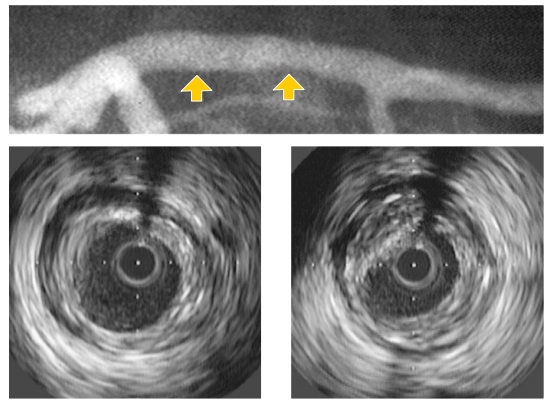
- Composition
 - Because angiography does not assess plaque composition, it cannot differentiate lipid-rich, more vulnerable plaques
- Postprocedure
 - Due to plaque fissuring, angiography may overestimate the degree of postintervention lumen expansion



Angiography Masks Complicated Lesions

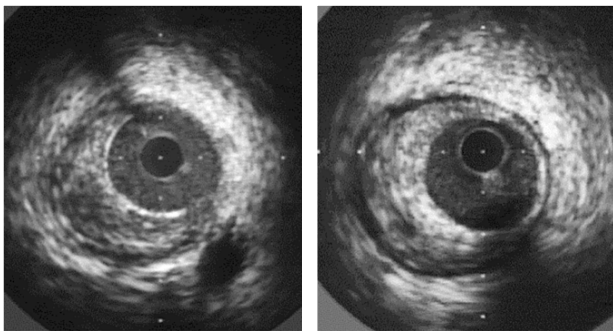


Angiography Underestimates Diffuse Disease



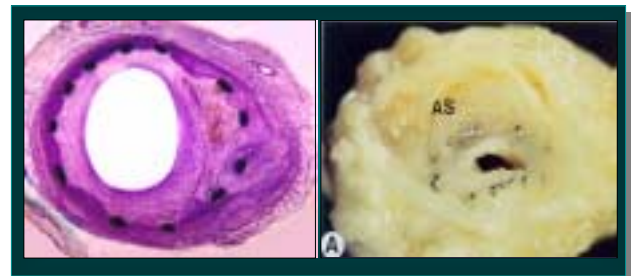
Same Lumen Size: Different Atheromas

Thin Cap With Lipid Core Thick Stable Fibrotic Cap



In-Stent Restenosis

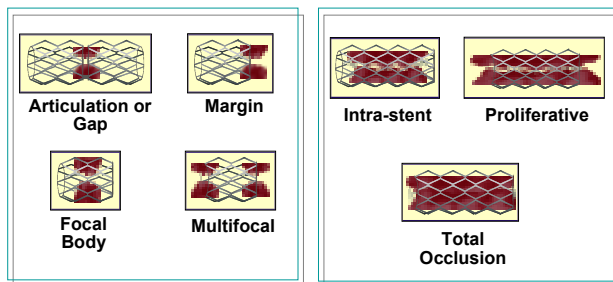
...is all intimal hyperplasia?



Patterns of In-Stent Restenosis

FOCAL

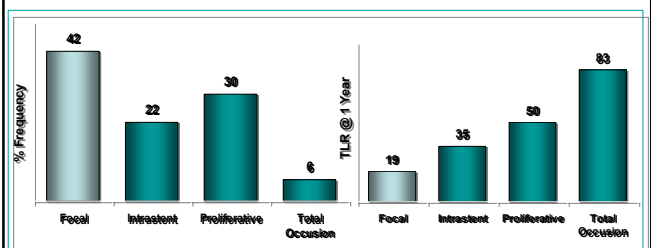
DIFFUSE



Mehran R et al. Circulation 1999;100:1872-78

Patterns of In-Stent Restenosis

282 lesions; restenosis patterns classified by angiography and confirmed by IVUS



The predictors of TLR were diabetes, previous ISR and ISR patterns

Mehran R et al. Circulation 1999;100:1872-78



In-Stent Restenosis (cont) Vascular Brachytherapy Solutions

- **SCRIPPS I** – Gamma radiation versus placebo
 - Teirstein PS, et al. *N Engl J Med* 1997;336:1697 (6-months results)
 - Teirstein PS, et al. *Circulation* 2000;101:360-5 (3-year results)
- **GAMMA I** - Gamma radiation versus placebo
 - Leon MB, et al. *N Engl J Med* 2001;344:250
- **WRIST** - Gamma radiation versus placebo
 - Waksman R, et al. *Circulation* 2000;101:2165-71

In-Stent Restenosis (cont) Vascular Brachytherapy Solutions

- **SVG-WRIST** – Gamma radiation to treat SVG
 - Waksman R. *ACC* 2001
- **Long-WRIST** – Gamma radiation to treat long lesions
 - Waksman R. *AHA* 2000
- **Scripps III** – Prolonged antiplatelet therapy
 - Teirstein P. *ACC* 2001

SCRIPPS I

Scripps **C**oronary **R**adiation to **I**nhibit **P**roliferation **P**ost **S**tenting

Primary Endpoint
Clinical: MACE (including CVA) at 6 months
Angiographic: MLD at 6 months

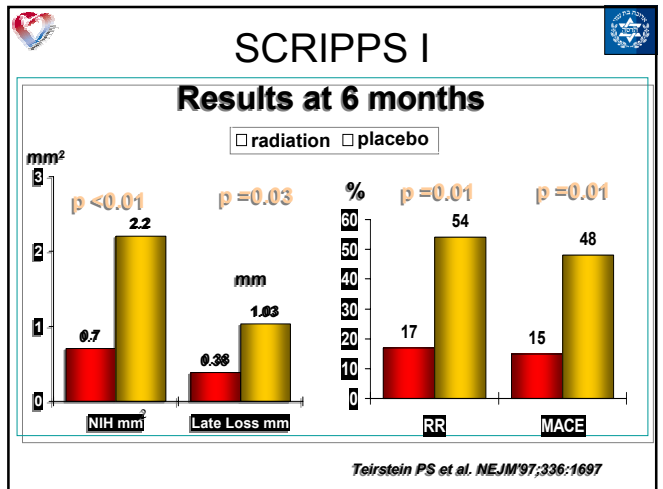
Teirstein PS et al. *NEJM*'97;336:1697

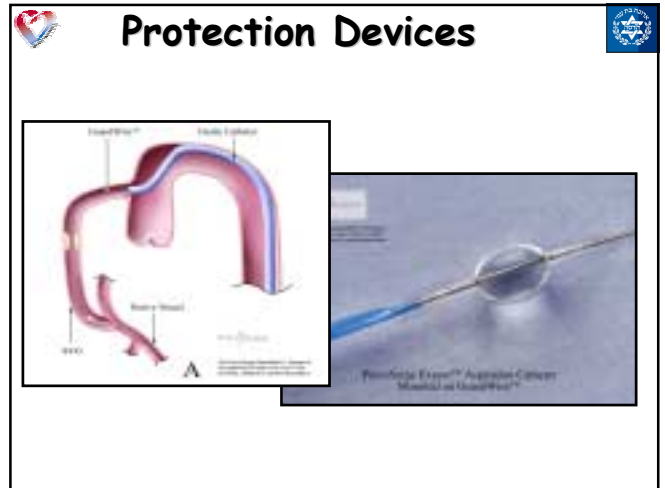
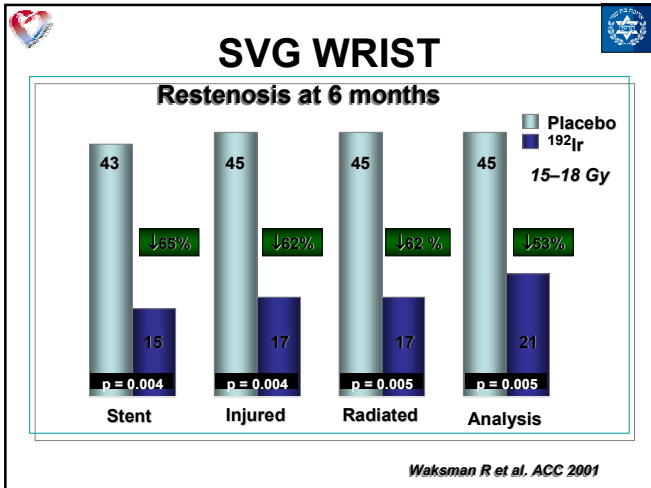
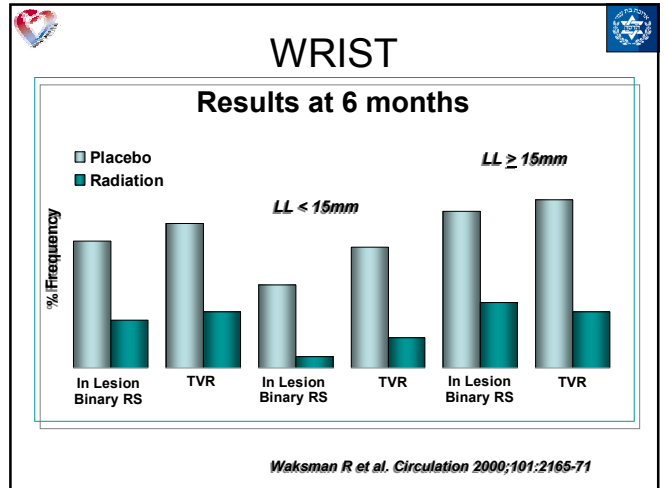
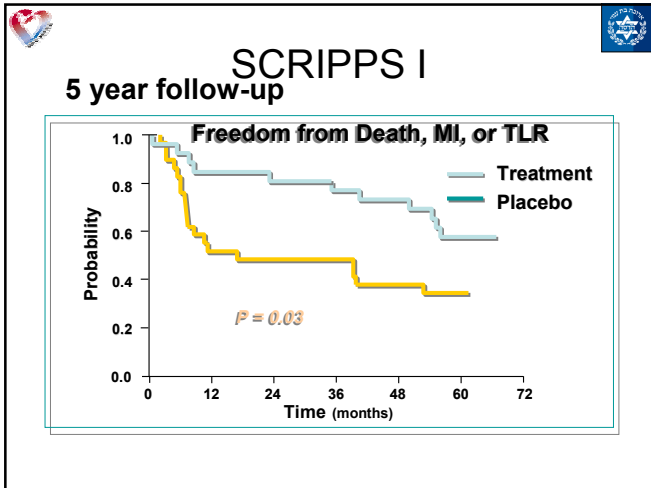
SCRIPPS I

Angiographic/IVUS & Clinical FU @ 6 months

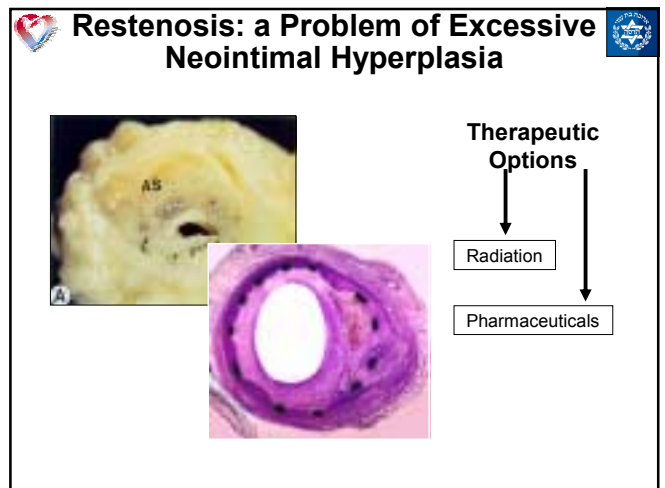
	192 IR (n = 24)	Placebo (n = 28)	p-Value
FU MLD (mm)	2.4	1.85	0.02
Late loss (mm)	0.038	1.38	0.03
Binary restenosis (%)	17	54	0.01
Δ mean lumen vol (mm ³)	16.4	44.3	0.01
TLR (%)	12	45	0.01

Teirstein PS et al. *NEJM*'97;336:1697





Drug coated stents



Generalised Process of Wound Healing

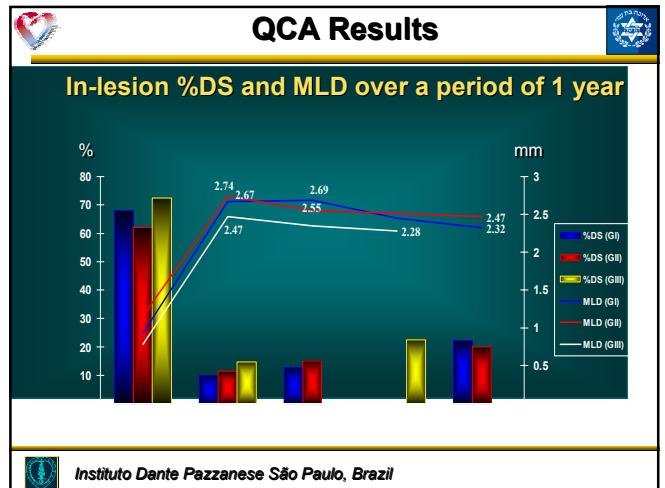
- Injury**
 - Induces cell stress
 - Elaborates growth factors and proteases
 - Early fibrin matrix
- Inflammation (0 - 3 days)**
 - Early - neutrophils and monocytes (cytokines)
 - Late - macrophage (digest debris)
- Granulation (3 - 14 days)**
 - Fibroblast proliferation
 - Matrix secretion
- Remodeling (weeks)**

The Mammalian Cell Cycle

The diagram illustrates the mammalian cell cycle as a circular process. It starts with a **G₀: Cell rests** phase. The cycle then enters the **G₁: Cell enlarges and makes new proteins** phase, followed by the **S: Cell replicates its DNA** phase, then **G₂: Cell prepares to divide**, and finally **M: Cell divides (mitosis)**. A **Check point-cell decides whether to complete cycle** is shown between the G₁ and S phases.

Rapamycin and Neointima Formation

The diagram shows the pathway from **Arterial injury** to **Neointimal formation**. Arterial injury leads to **Thrombus (Platelets)** and **Inflammation (Macrophage)**, which release **Growth factors & cytokines**. These factors act on **SMC receptor** on a **Smooth muscle cell (SMC)**. **Rapamycin** is also shown acting on the SMC. This leads to **Signal transduction** and **Cell proliferation** through the **Cell cycle** (G₀, G₁, S, G₂, M), resulting in **Neointimal formation**.



A Promising Future

The “Cypher™” Sirolimus Coated-Stent

Ongoing Randomized Trials:

RAVEL – Rapamycin-coated stent versus Bx Velocity™ stent (Europe and South America)

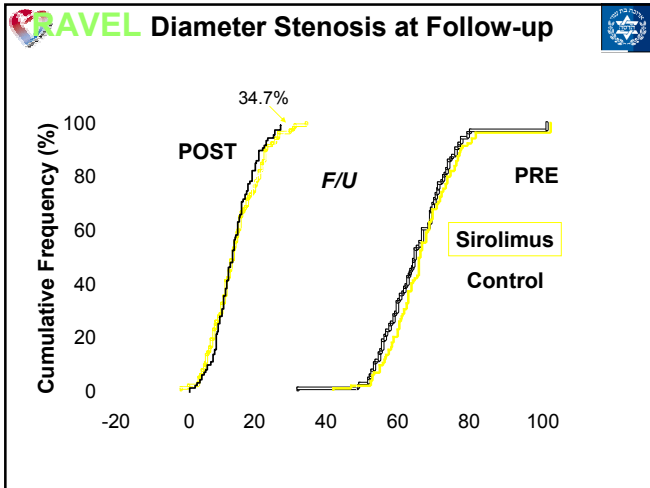
SIRIUS – Rapamycin-coated stent versus Bx Velocity™ stent (USA)

RAVEL –

Sirolimus-coated stent for coronary stenosis

N = 220 patients de novo, native coronary artery are **Randomized** into two groups: **Sirolimus-coated Bx Velocity™ Stent (n = 110)** and **Uncoated Bx Velocity™ Stent (n = 110)**.

Primary Endpoint: Minimum lumen diameter measured by quantitative angiographic analysis at 6 months



SIRIUS - Stent Thrombosis

	Sirolimus (%) (n=533)	Control (%) (n=525)
Acute (≤ 24 hours)	0	0
Subacute (1-30 days)	0.2% (1)	0.2% (1)
Late (31-270 days)	0.2% (1)*	0.6% (3)**
Total	0.4% (2)	0.8% (4)

*234 days post-procedure
**40, 150, and 181 days post-procedure

SIRIUS - QCA Peri-Stent Analysis

Restenosis (%)

	Sirolimus (%) (n=533)	Control (%) (n=525)	P-value
In-stent	3.2	35.4	<0.001
Proximal margin	5.8	8.1	0.285
Distal margin	2.0	7.2	0.002
In-segment	8.9	36.3	<0.001



SIRIUS - Diabetic Subgroup Summary FU Results (279 pts)

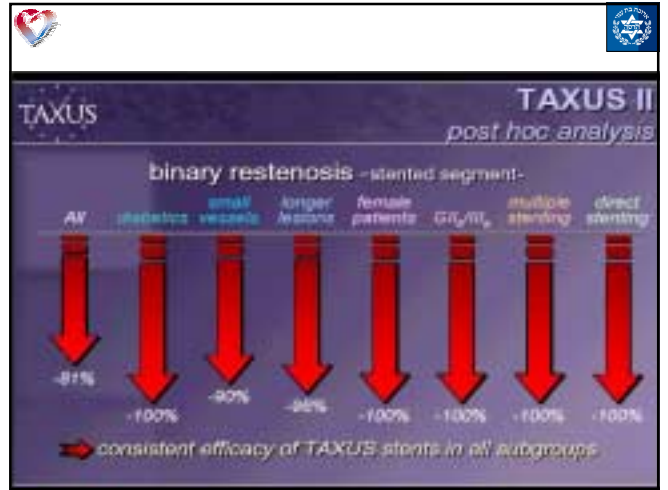
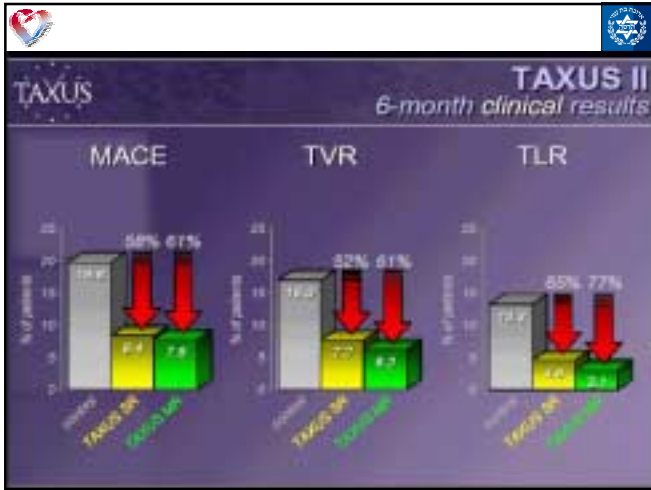
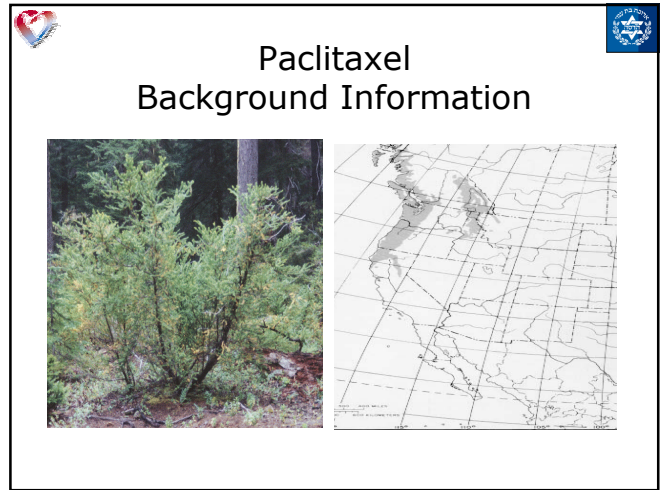
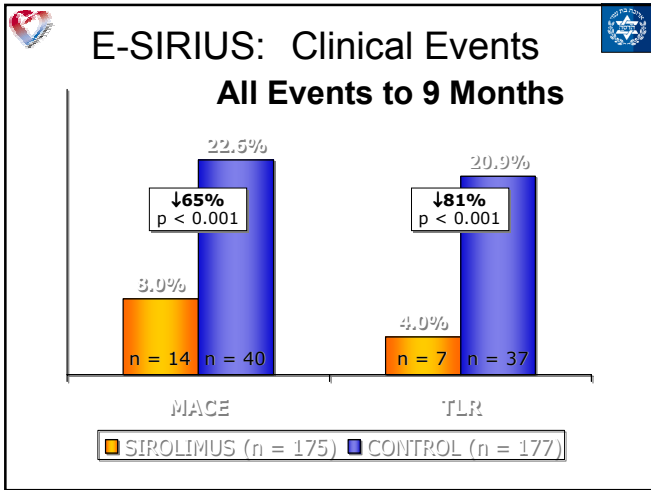
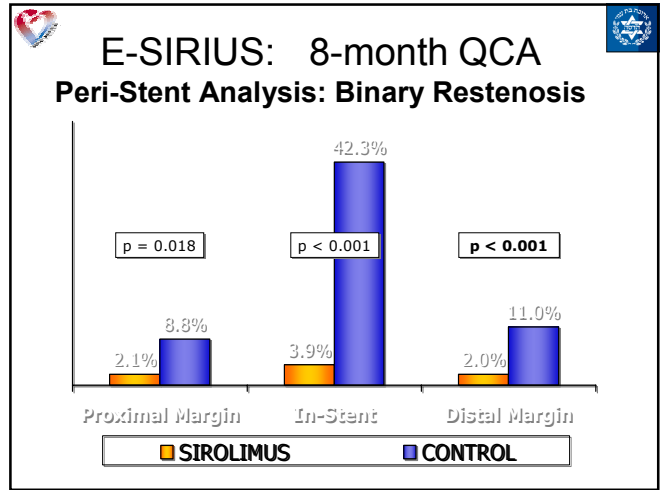
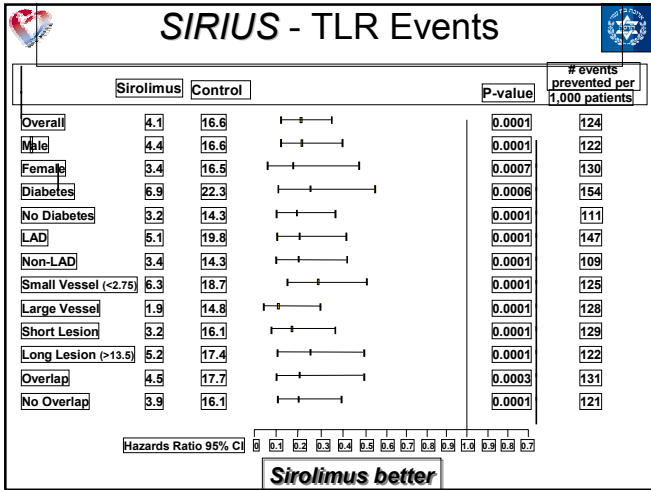
	Sirolimus (n=131)	Control (n=148)	P-value
Late loss (mm)			
in-stent	0.29	1.20	<0.001
in-segment	0.40	1.00	<0.001
Restenosis (%)			
in-stent	8.3	48.5	<0.001
in-segment	17.6	50.5	<0.001
TLR (%)	6.9	22.3	<0.001
MACE (%)	9.2	25.0	<0.001

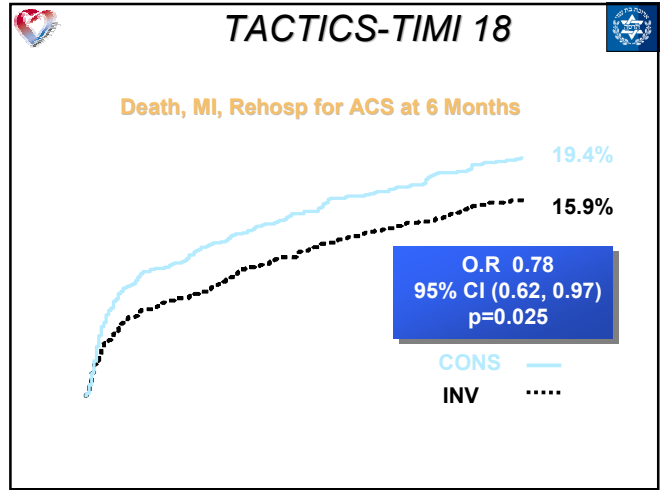
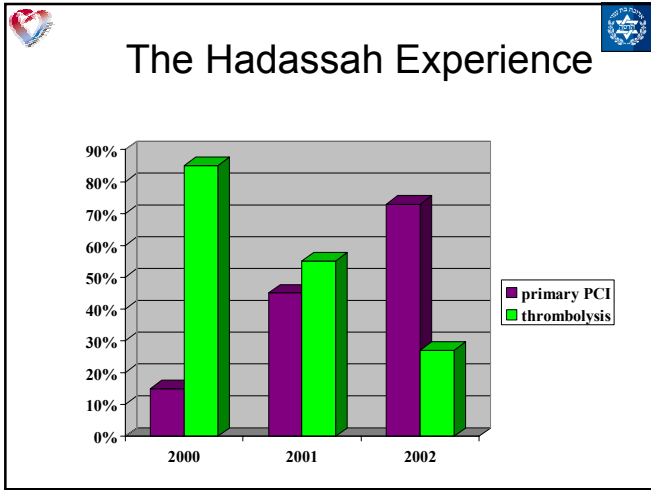
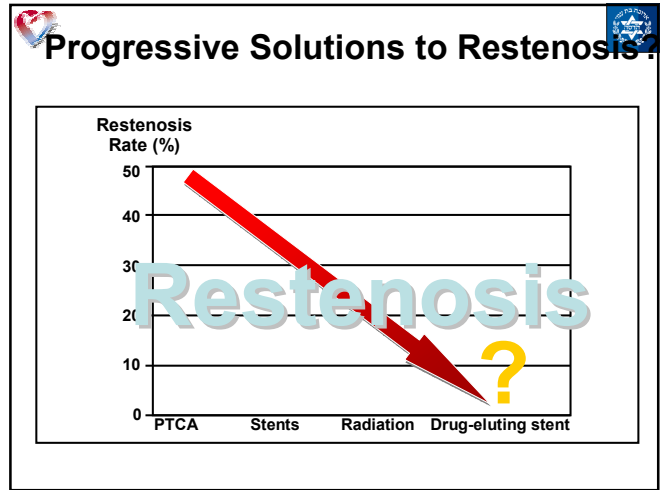
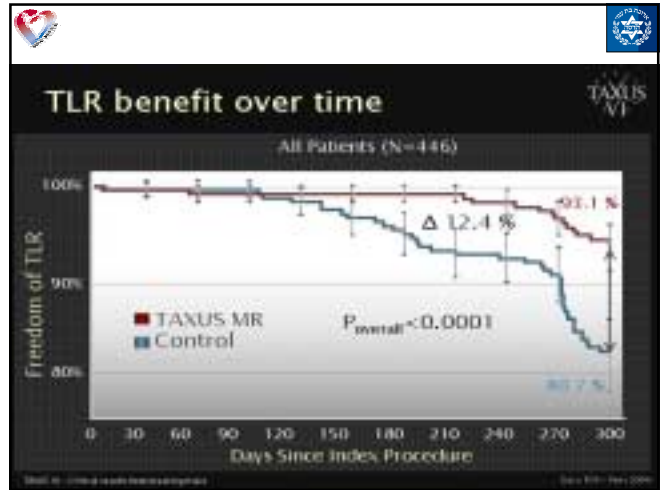
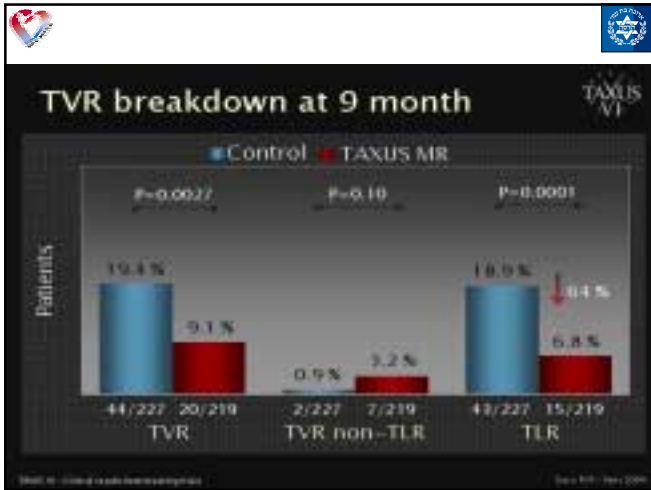
Lesion length = 14.5mm and Reference vessel size = 2.75mm

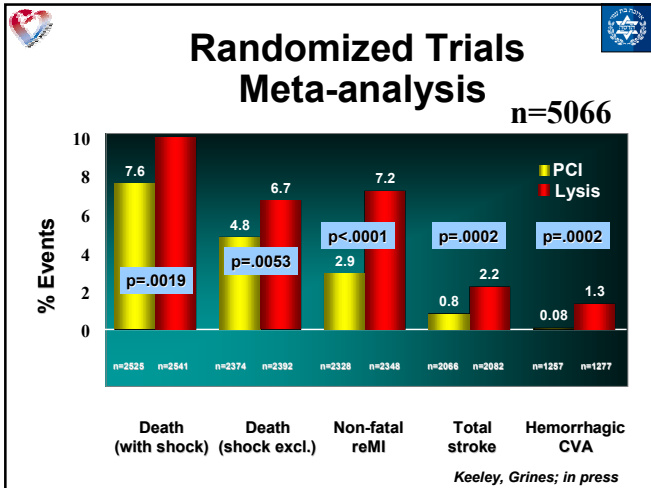
SIRIUS - LAD Subgroup Summary FU Results (462 pts)

	Sirolimus (n=234)	Control (n=228)	P-value
Late loss (mm)			
in-stent	0.20	1.04	<0.001
in-segment	0.26	0.81	<0.001
Restenosis (%)			
in-stent	2.0	41.6	<0.001
in-segment	10.1	41.6	<0.001
TLR (%)	5.1	19.7	<0.001
MACE (%)	8.5	22.4	<0.001

Lesion length = 14.0mm and Reference vessel size = 2.73mm







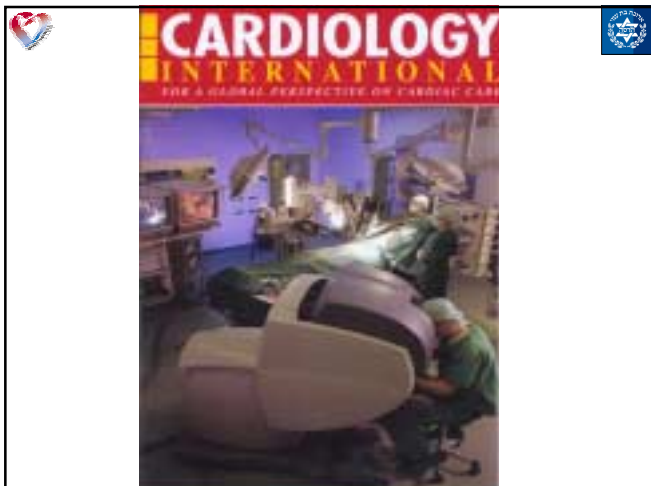
- ### PTCA → PCI changing indications
- Acute MI (rescue, primary)
 - Total occlusion
 - Multivessel involvement
 - Ostial Lesions (LAD)
 - Saphenous vein-grafts
 - Calcification, Tortuosity

Future Technologies

- Clot Extraction Devices
- Plaque Removal Devices
- Vein Graft Relining Devices
- PMR
- Improved Thrombolytics
- New Stents

Cardiovascular News

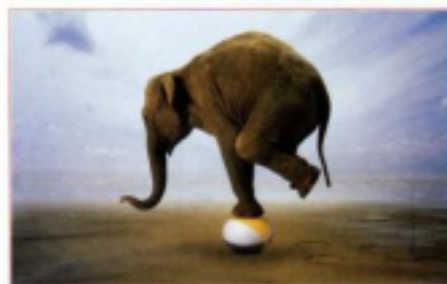
Percutaneous heart valve therapy – is there a future?



The future "hybrid" Endovascular Lab ?



מערך הלב ב"הדסה"



The key in life is balance

GOOD
LUCK!