A Data-driven Therapeutic Algorithm For Choosing Among Currently Available Tools For SFA Intervention

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Dissapointing results for non-nitinol stents

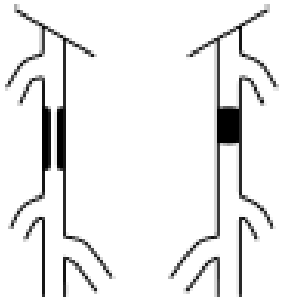
- Results of the first generation self-expanding stents (WallStent & Strecker stent) in the SFA

	FU	Lesion length	Primary Patency
Van Der Zaag et al EJVES 2004	12M	5-15 cm	43%
Conroy et al J Vasc Int Radiol 2000	24M	mean 13.5 cm	36%
Gordon et al Arch Surg 2001	12M	mean 14.5 cm	55%
Cheng et al Ann Vasc Surg 2003	24M	mean 16 cm	35%

TASC classifications of SFA lesions

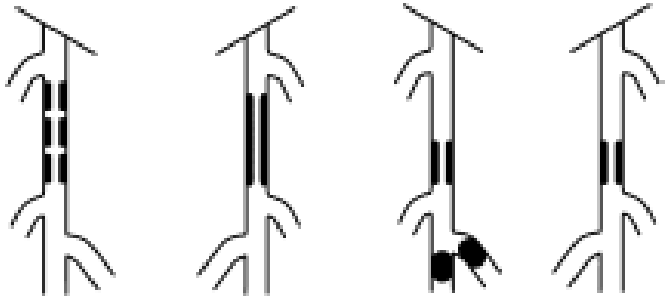
Type A lesions

- Single stenosis ≤10 cm in length
- Single occlusion ≤5 cm in length



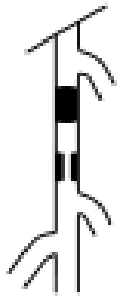
Type B lesions:

- Multiple lesions (stenoses or occlusions), each ≤5 cm
- Single stenosis or occlusion ≤15 cm not involving the infrageniculate popliteal artery
- Single or multiple lesions in the absence of continuous tibial vessels to improve inflow for a distal bypass
- Heavily calcified occlusion ≤5 cm in length
- Single popliteal stenosis



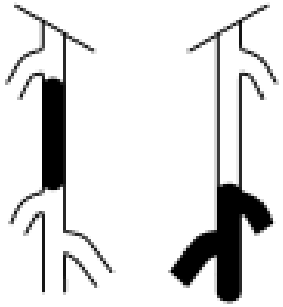
Type C lesions

- Multiple stenoses or occlusions totaling >15 cm with or without heavy calcification
- Recurrent stenoses or occlusions that need treatment after two endovascular interventions



Type D lesions

- Chronic total occlusions of CFA or SFA (>20 cm, involving the popliteal artery)
- Chronic total occlusion of popliteal artery and proximal trifurcation vessels



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Levels of evidence
Source: US Preventive Services Task Force

Level I	well-designed, prospective, randomized, controlled trials
Level IIa	well-designed, prospective, non-randomized, controlled trials
Level IIb	well-designed, prospective, non-randomized, non-controlled cohort or case-control analytic studies
Level IIc	retrospective, non-randomized, non-controlled multiple time series
Level III	expert opinions, based on clinical experience, descriptive studies or reports of expert committees

Summary of non-randomized trial results Levels IIa, IIb, IIc

Reference	stent name	lesion length (cm)	prim patency @12-months
Jahnke 2002	IntraCoil	3.6	86.2%
Wiesinger 2005	Covered SMART	5	89.8%
Henry 1996	VascuCoil	< 4	89 %
Sabeti 2004	any	5	75 %
Lugmayr 2002	Symphony	< 6	87 %
Lenti 2007	aSpire	unk	64 %
Schillinger 2001	any	10.1	63 %
Fischer 2006	Hemobahn/Viabahn	10.7	80 %
Jahnke 2003	Hemobahn	10.9	78.4%
Schlager 2005	any	12.5	80 %
Lammer 2000	Hemobahn	13.1	78.7%
Cheng 2001	any	13.8	62.6%
Daenens 2005	Hemobahn	15	66 %
Cheng 2003	any	16	56 %
Bray 2005	Hemobahn	17.8	60.8%
Biamino 2002	SMART	20.8	55 %

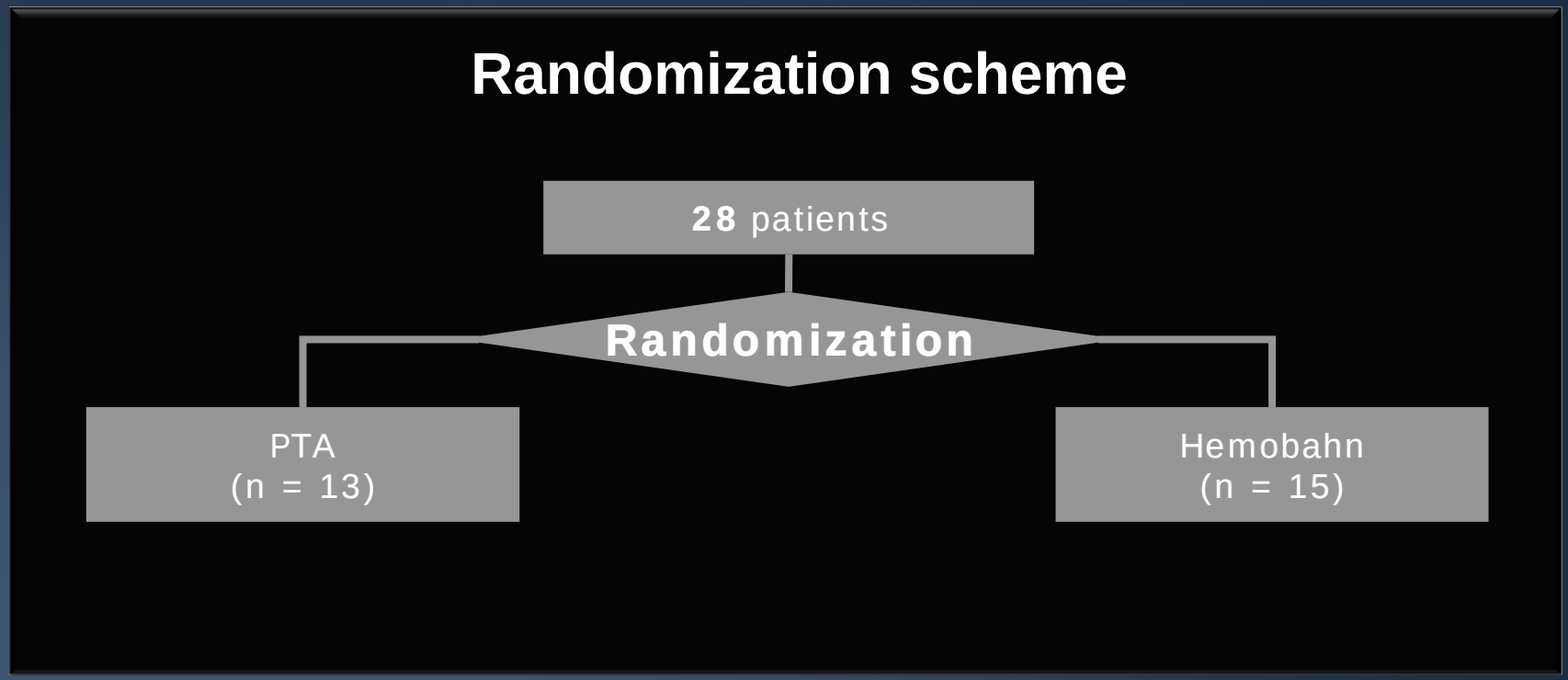
WL Gore Hemobahn vs. PTA

Study description:

- Single-center experience as part of a US prospective, randomized, controlled, multi-center study
- Balloon angioplasty vs. Hemobahn (Gore) ePTFE-covered endoprosthesis placement
- Inclusion period: Jun 1998 – Dec 1999

Saxon et al. J Vasc Interv Radiol 2003;14:303-311

WL Gore Hemobahn vs. PTA



Saxon et al. J Vasc Interv Radiol 2003;14:303-311

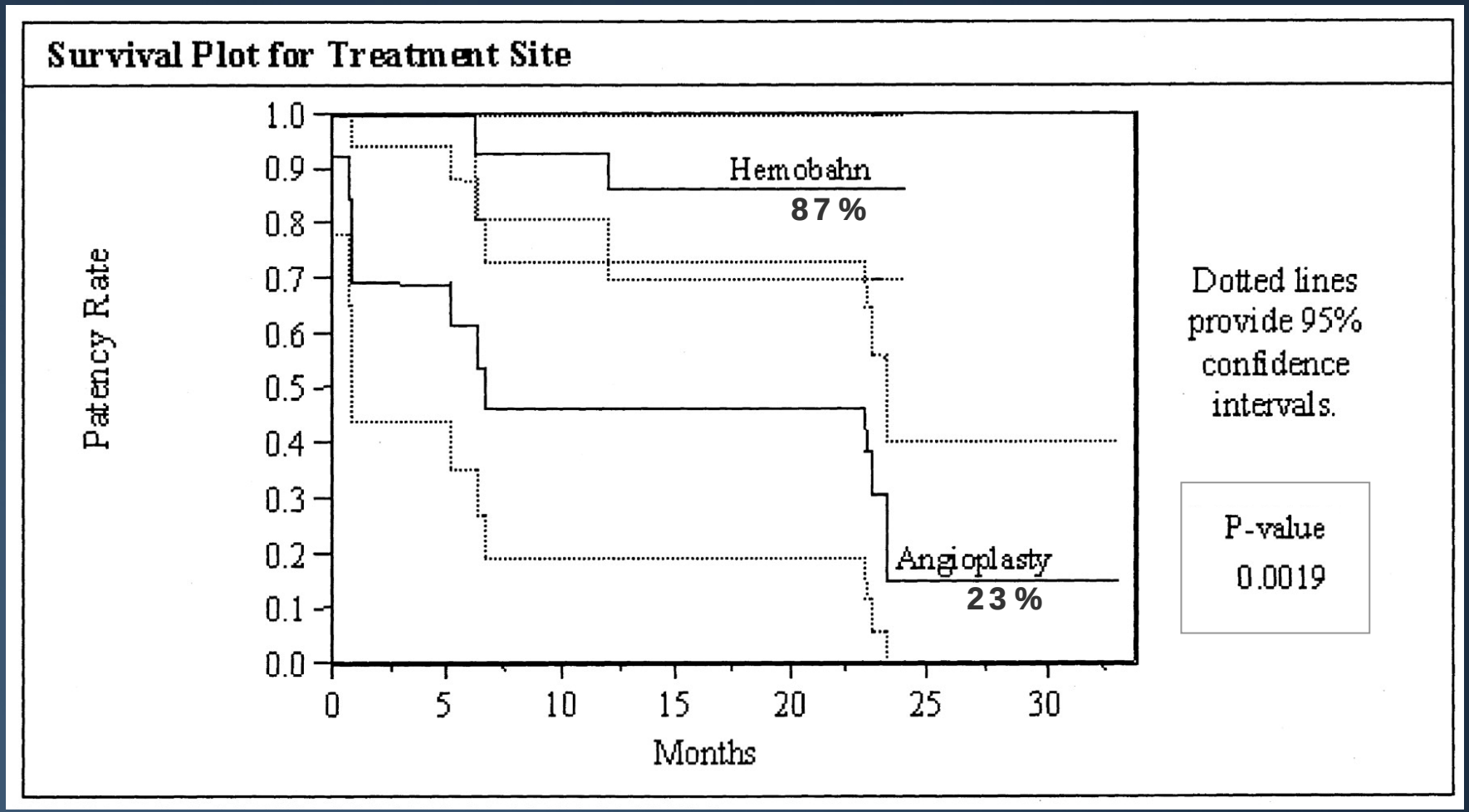
WL Gore Hemobahn vs. PTA

Lesion information

	PTA	Hemobahn
Average lesion length	6.32cm (4.44-8.20)	7.41cm (5.63-9.19)
TASC A	1	0
TASC B	8	5
TASC C	3	6
TASC D	1	4

Saxon et al. J Vasc Interv Radiol 2003;14:303-311

WL Gore Hemobahn vs. PTA



Saxon et al. J Vasc Interv Radiol 2003;14:303-311

WL Gore Hemobahn vs. PTA

Conclusions for medium length lesions

- Patency rates after Hemobahn implantation were significantly better than those after balloon angioplasty
- Clinical success rate was significantly higher in the Hemobahn group

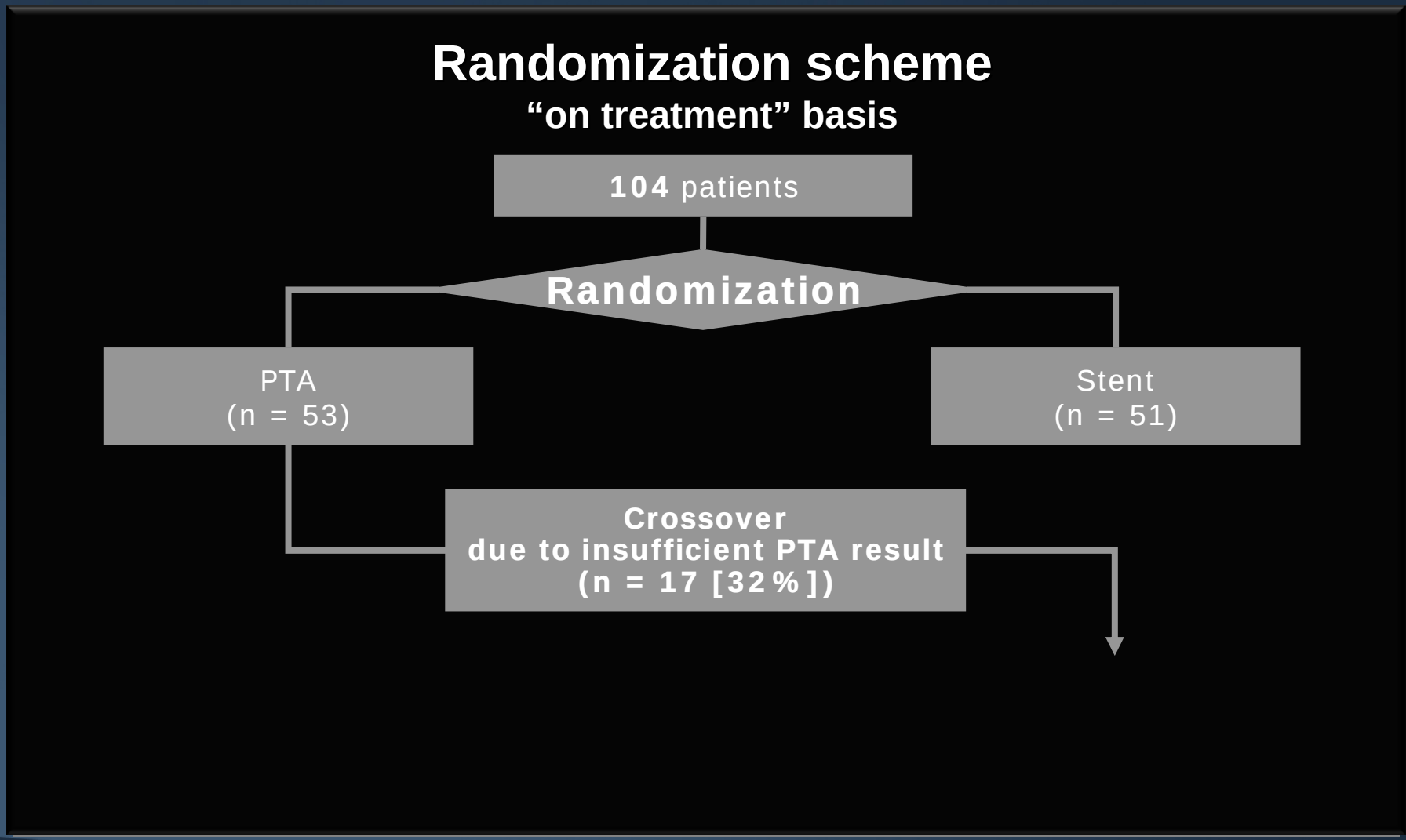
Saxon et al. J Vasc Interv Radiol 2003;14:303-311

Absolute stent vs. PTA

- Prospective, randomized, controlled, single-center
- Balloon angioplasty vs. nitinol stent implantation
- Inclusion period: Jun 2003 – Aug 2004

Schillinger et al. NEJM 2006;354:1879-1888

Absolute stent vs. PTA



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Schillinger et al. NEJM 2006;354:1879-1888

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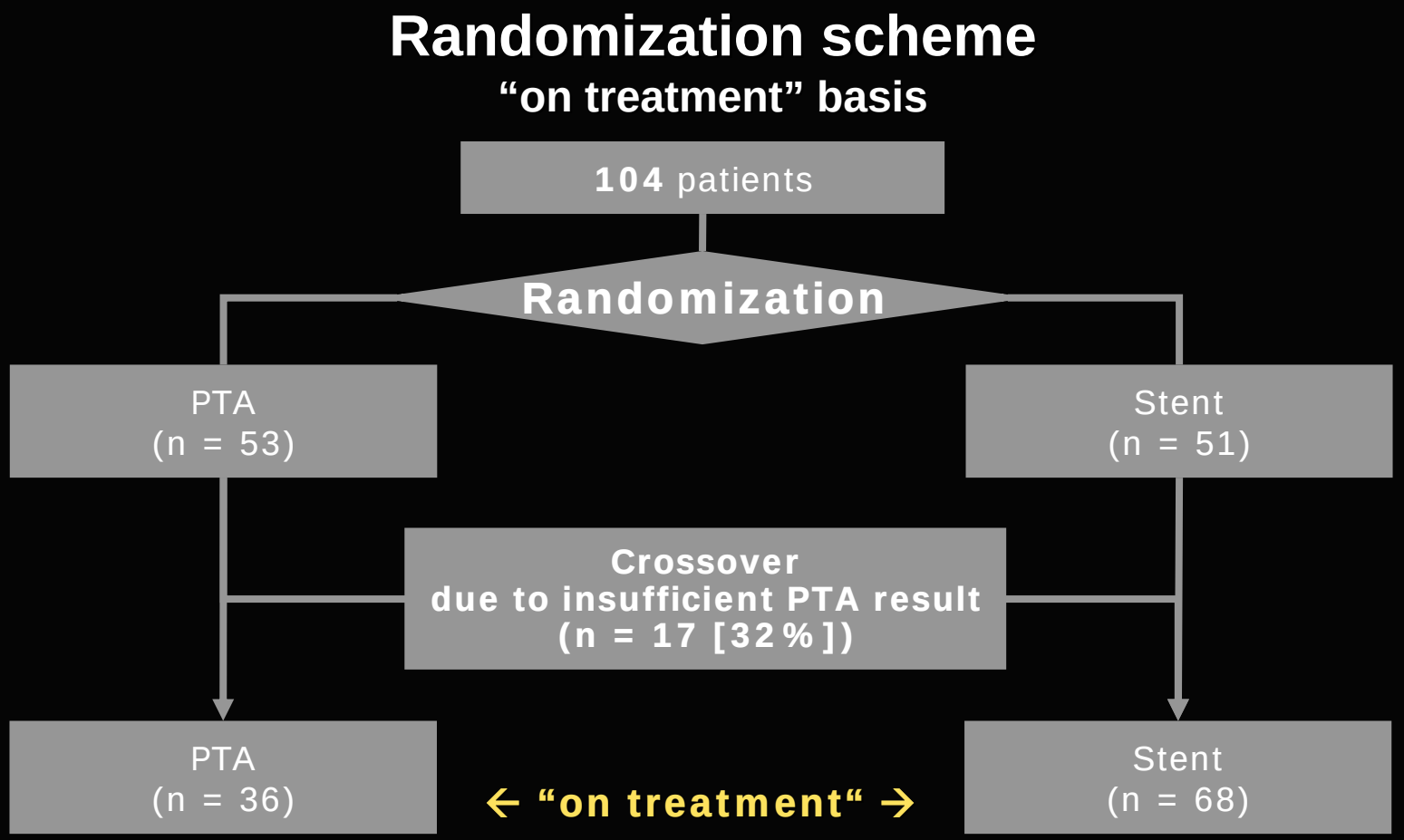

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Schillinger et al. NEJM 2006;354:1879-1888

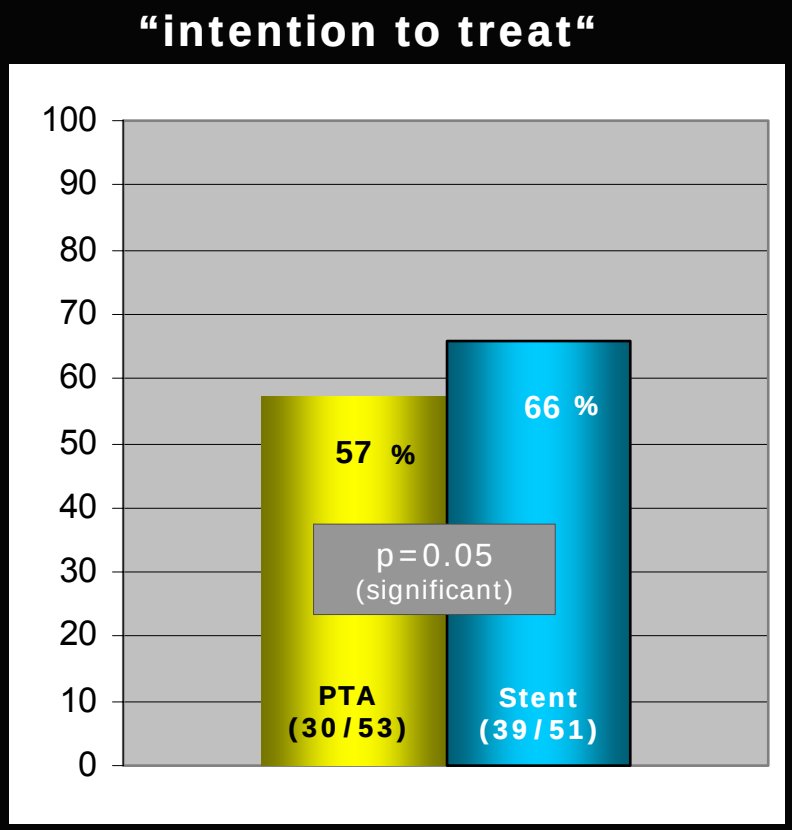
Absolute stent vs. PTA

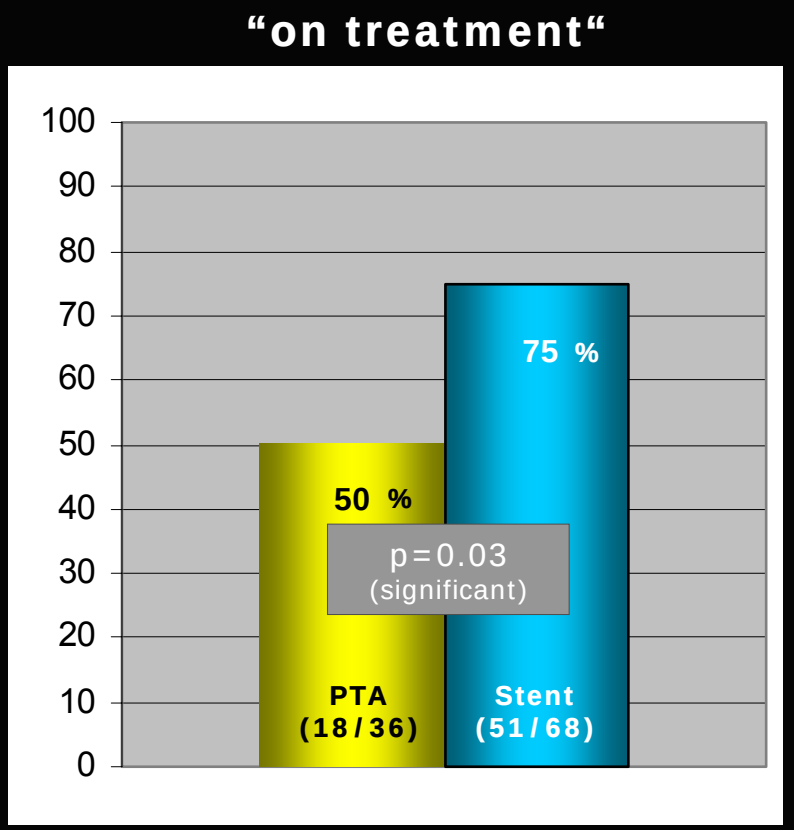
Lesion information

	PTA	Nitinol stent
Average lesion length	9.2cm (±6.4)	10.1cm (±7.5)
Occlusions	19% (±10)	17% (±10)

Schillinger et al. NEJM 2006;354:1879-1888

Absolute stent vs. PTA





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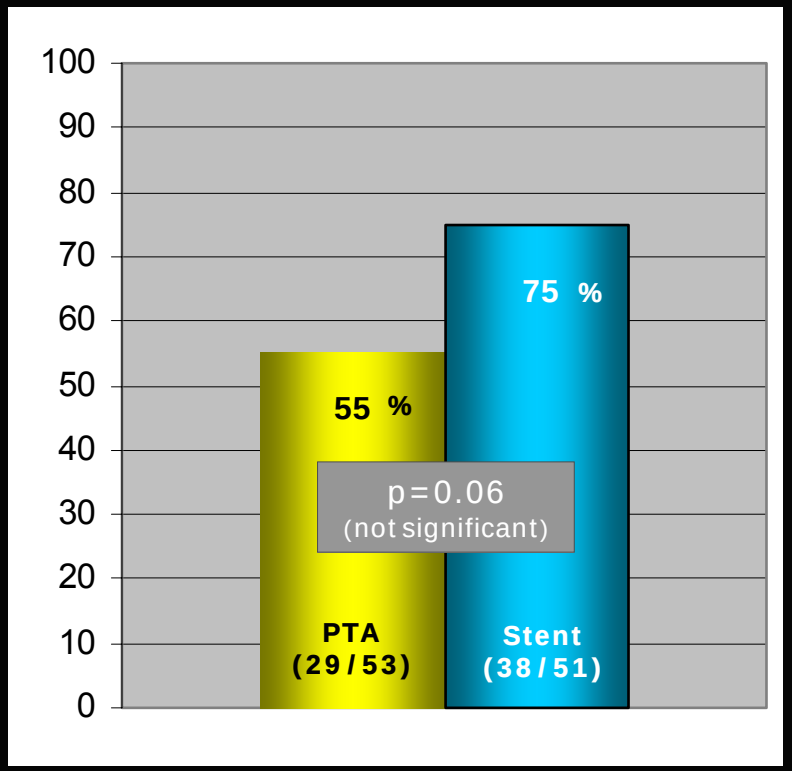
Schillinger et al. NEJM 2006;354:1879-1888

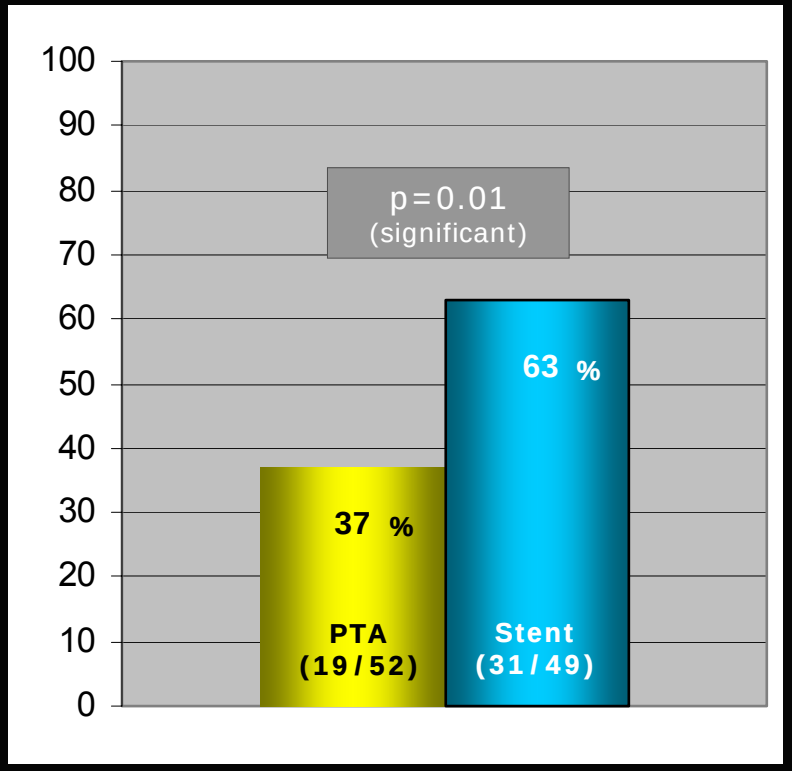
Absolute stent vs. PTA

Based on “intention to treat“ principle

After 6 months



After 12 months



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Schillinger et al. NEJM 2006;354:1879-1888

Absolute stent vs. PTA

Conclusion for medium length lesions

- Angiography showed significantly better restenosis rates for the stent group at 6 months
- Duplex sonography confirmed significantly better restenosis rates at 12 months
- Clinical worsening was rare in either group
- Reintervention rates were similar in both groups

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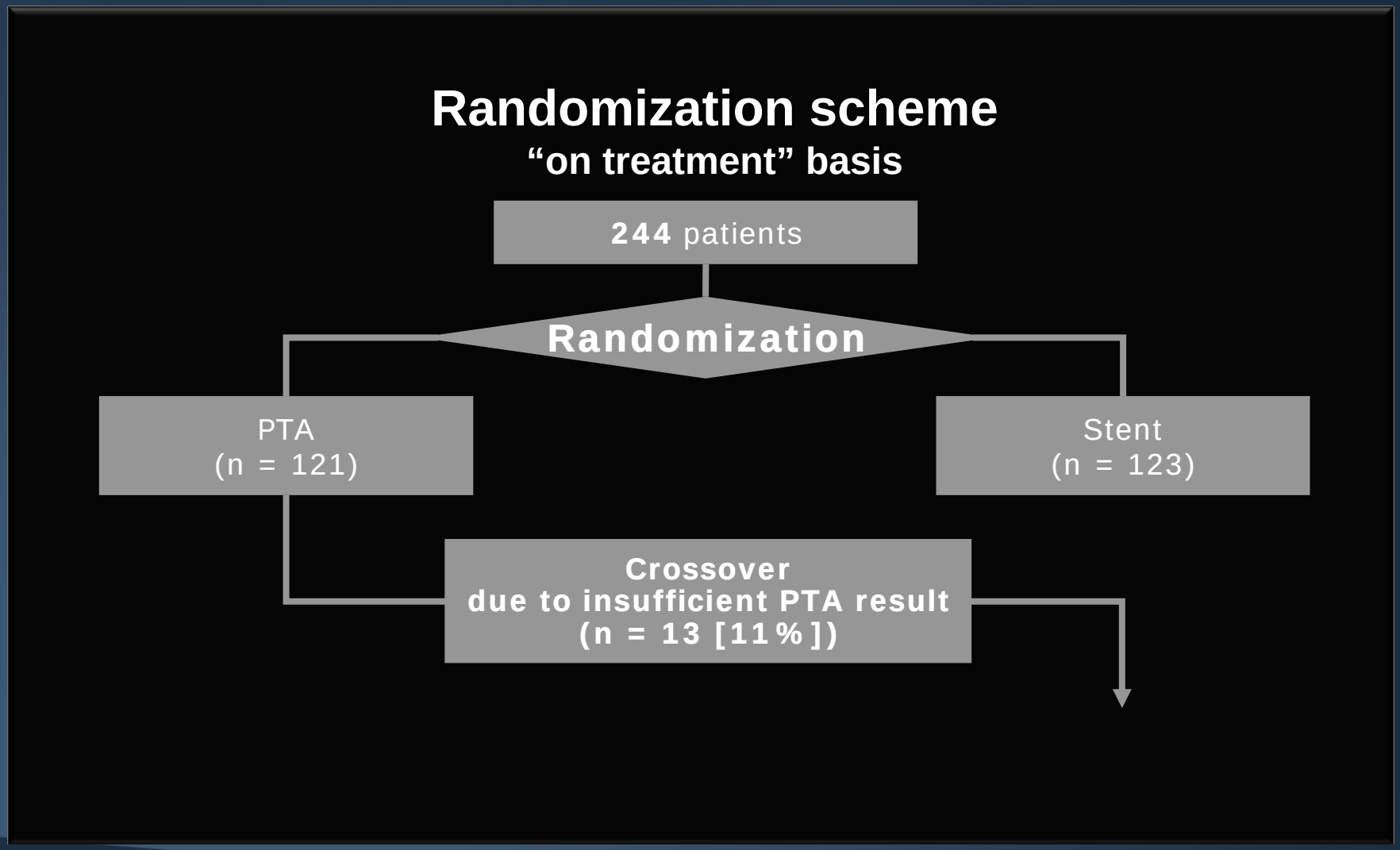
Schillinger et al. NEJM 2006;354:1879-1888

PTA vs. Lumunexx Stent

- Prospective, randomized, controlled
- Balloon angioplasty vs. Luminexx nitinol stent
- **F**emoral **A**rtery **S**tenting **T**rial
- SFA lesions between 1 and 10cm in length
- Only 1 stent per treated lesion

Krankenberg H et al. Circulation 2007;116;285-292;

PTA vs. Lumunexx Stent



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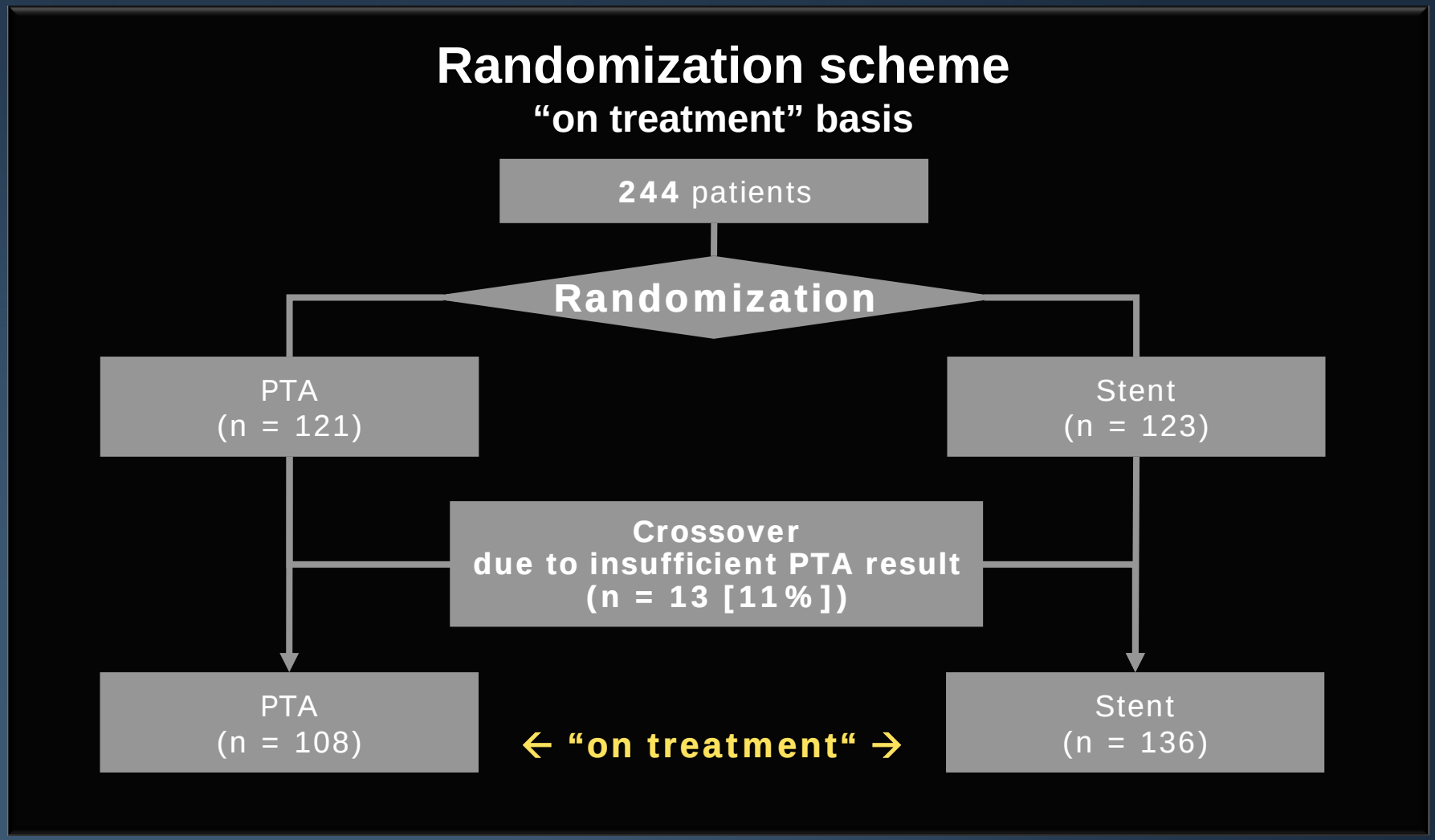

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Krankenberg H et al. Circulation 2007;116;285-292;

PTA vs. Lumunexx Stent

Lesion information: short to medium length lesions

	PTA	Luminexx stent	
Average lesion length	44.5mm	45.2mm	not signifcant
Occlusions	25%	37%	not signifcant

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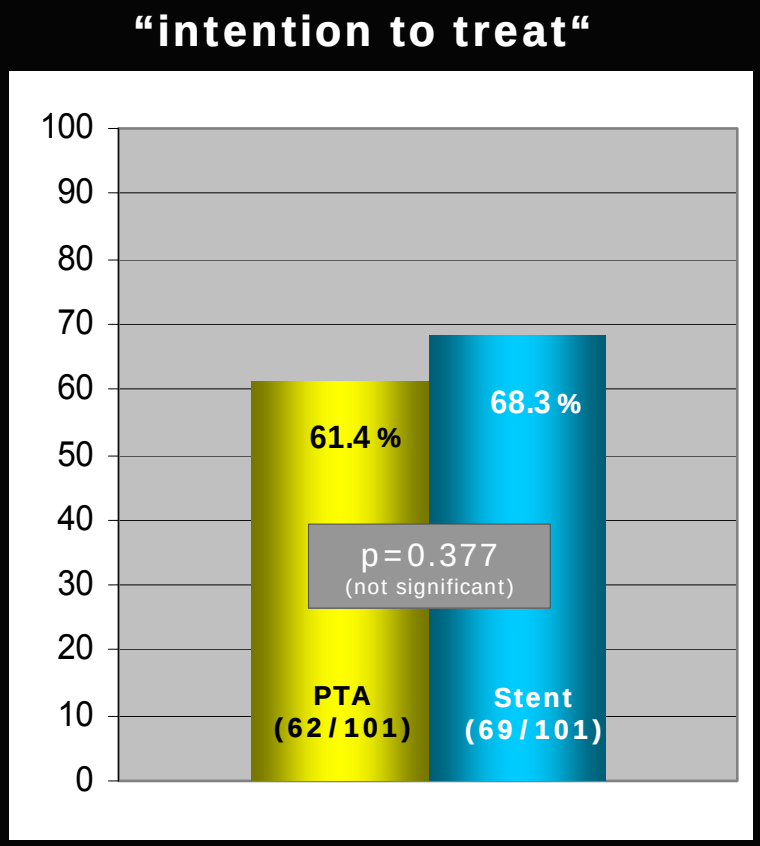
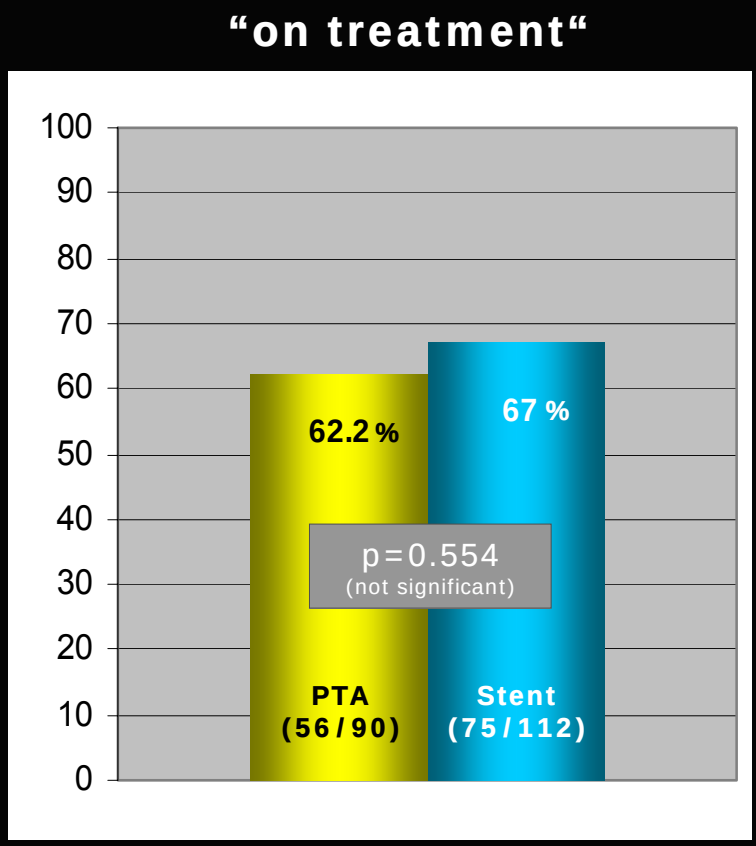
Krankenberg H et al. Circulation 2007;116;285-292;

PTA vs. Lumunexx Stent





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Krankenberg H et al. Circulation 2007;116;285-292;

PTA vs. Lumunexx Stent

Conclusion

- The Femoral Artery Stenting Trial failed to demonstrate the superiority of the Luminexx nitinol stent over stand-alone PTA in the treatment of patients with superficial femoral artery (SFA) lesions 1-10cm in length

SIROCCO I & II: SES vs. BMS

- Double-blind, randomized, prospective (sirolimus vs. bare stent)
- **SIRO**limus **C**oated **C**ordis SMART Nitinol Self-expanding stent for the treatment of **O**bstuctive SFA disease

- Phase 1: 36 patients
  - max 3 stents → >70% stenosis >7cm to <20cm
    → occlusion >4cm to <20cm
- Phase 2: 57 patients
  - max 2 stents → lesion length >7cm to <14.5cm
    → occlusion >4cm to <14.5cm

SIROCCO I & II

Baseline Lesion Characteristics

	Sirolimus (n=29)	Control (n=28)	P-value
Thrombus (%)	3.6	0	
Moderate/Severe Calcification (%)	**44.8**	**32.3**	0.42
Total Occlusion (%)	**75.9**	**57.1**	0.17
Lesion Length (mm)	86.5 ±36.6	76.3 ±45.7	0.39
Reference Vessel Diameter (mm)	4.92 ±0.77	4.61 ±0.72	0.12
Pre – Percent Diameter Stenosis (%)	95.8 ±7.82	89.1 ±14.8	0.09

SIROCCO I & II

Duplex Ultrasound @ 24-month

		Slower Eluting (n=5)	Fast Eluting (n=11)	Control (n=17)
Binary Restenosis Rate	%(n)	40.0 (2)	44.4 (4)	47.1 (8)
Total Occlusion	%(n)	0	0	5.8 (1)
Total Restenosis/Occlusions	%(n)	**40.0 (2)**	**44.4 (4)**	**52.9 (9)**
Target Lesion Revascularization	%(n)	**0**	**11.1 (1)**	**5.8 (1)**

SIROCCO I & II

Angiography @ 24-month

	Pooled SR SIROCCO I-II (n=16)	**Control** SIROCCO I-II (n=14)	*p value*
Minimum Lumen Diameter	2.15mm	2.15mm	*0.941*
Stent Mean Diameter	3.42mm	3.35mm	*0.995*
In-stent restenosis			
- unreadable	3 (18.8%)	2 (14.3%)	*0.370*
- patent	9 (56.3%)	8 (57.1%)	
- ≥50% and <70%	4 (25.0%)	2 (14.3%)	
- ≥70% and <100%	-	1 (7.1%)	
- occlusion	-	1 (7.1%)	

SIROCCO I & II: conclusions

- Fractures associated with
  - Multiple stents
  - Longer stented lengths
  - Frequently adjacent to the overlaps (not in the overlap areas themselves)
- No relationship between fracture and restenosis
- Sirolimus-eluting stents are safe for SFA treatment
- ***Excellent results with bare SMART stent***
  - ***In-stent binary restenosis rate : 28.5% @ 24 months (angiographically)***

Duda et al. Cx 2005

Zilver PTX: PES vs. BMS

- Randomized Study (480 pts)
  - Phase 1: 60 patients
    - lesions ≤ 7 cm, up to 1 stent per limb
    - enrollment complete
  - Phase 2: 420 patients
    - Lesions ≤ 14 cm, up to 2 stents per limb
    - Currently enrolling
- Registry Study (760 pts)
  - Up to 4 Zilver® PTX™ stents per patient
  - Currently enrolling:
    - more than 700 patients enrolled/approximately 2500 stents implanted

PTX: Baseline angiographic data

	Randomized Study (Phase 1)		Registry Study
	PTA (N = 33 lesions)	ZPTX (N = 29 lesions)	ZPTX (N = 91 lesions)
Lesion Length (cm)	3.6 ± 2.0 (range 1 to 7)	4.1± 3.1 (range 1 to 10)	10 ± 8.1 (range 1 to 33)
Proximal RVD (mm)	5.2 ± 1.0	5.0 ± 1.1	5.3 ± 0.8
Distal RVD (mm)	5.3 ± 1.0	4.9 ± 1.1	5.1 ± 0.8
MLD in lesion (mm)	1.3 ± 0.8	1.1 ± 0.7	0.6 ± 0.7
% Diameter Stenosis	76 ± 15	78 ± 14	89 ± 12

Zilver PTX: 6-month effectiveness

Study	Freedom from TLR
Phase 1 of the randomized study	
PTA	52% [17/33]
No PTA failure	100% [17/17]
PTA acute failure→BMS Zilver	75% [6/8]
PTA acute failure→PTX Zilver	100% [8/8]
Zilver PTX	90% [26/29]
Registry Zilver PTX	90% [82/91]

48%[16/33]

RESILIENT: LifeStent vs. PTA

n=20
PTA + LifeStent

Phase I: Feasibility
@ 6 sites

n=20 roll-in
PTA + LifeStent

Phase II: Pivotal
@ 24 sites

n=206
randomly allocated
1 : 2

PTA Only
Control Arm
n=69

PTA + LifeStent
Test Arm
n=137

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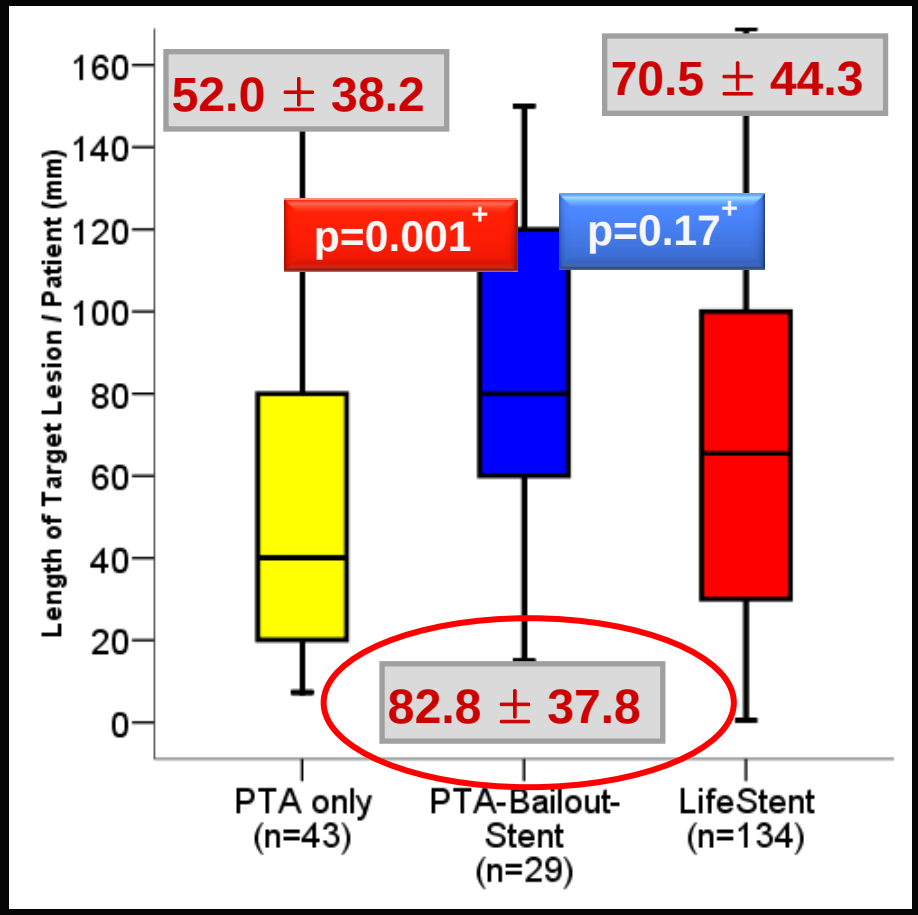
Biamino G, Katzen BT, Laird J. The RESILIENT Trial: 12-mos. results. Leipzig Interventional Course. Leipzig, Germany, 2008.

RESILIENT: Bail-out lesion characteristics

Lesion Length/patient (mm)



* = Visual Estimate
\+ = t-test for Equality of Means

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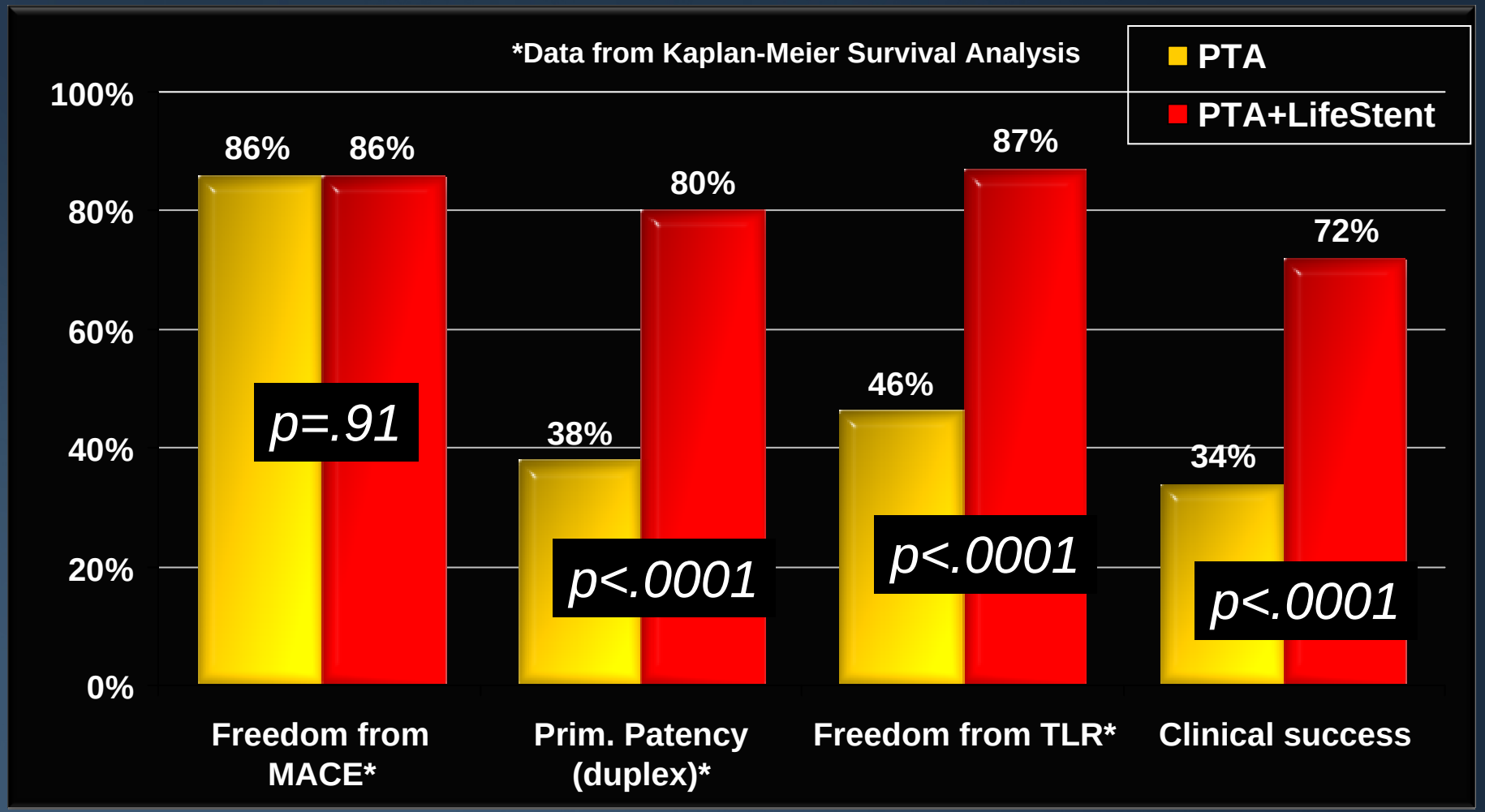
Biamino G, Katzen BT, Laird J. The RESILIENT Trial: 12-mos. results. Leipzig Interventional Course. Leipzig, Germany, 2008.

RESILIENT Results:12-Month



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Biamino G, Katzen BT, Laird J. The RESILIENT Trial: 12-mos. results. Leipzig Interventional Course. Leipzig, Germany, 2008.

RESILIENT: behind the numbers

- Bail-out stenting (crossover) in the PTA group occurred 40.2% (29/72) for:
  - Major flow-limiting dissection (38%)
  - Residual stenosis >30% (62%)
- Confirmed as acceptable by Core Lab and CEC
- Procedural crossover to stenting in the PTA group was defined as a TLR and counted as a primary endpoint and patency failure

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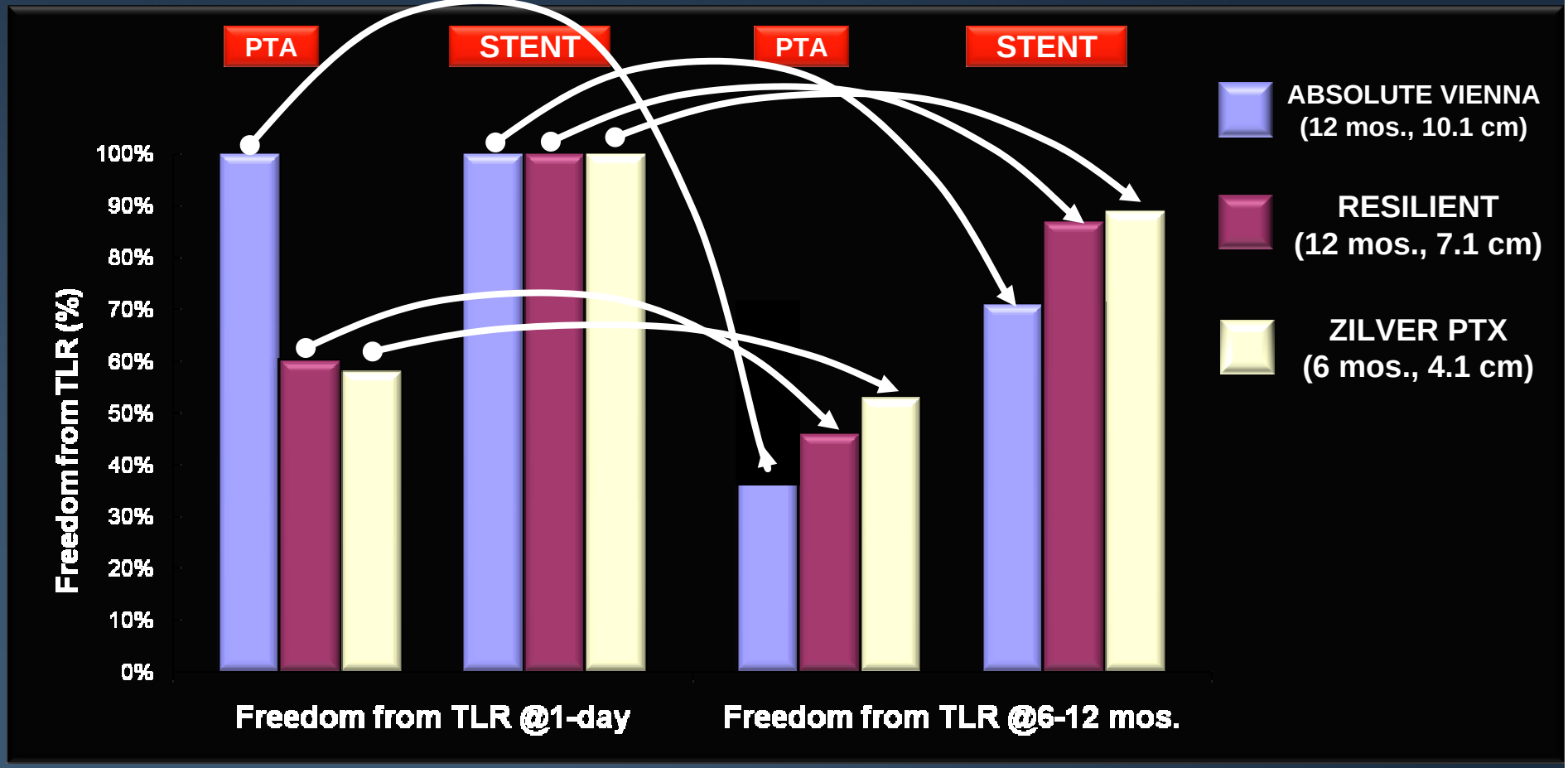
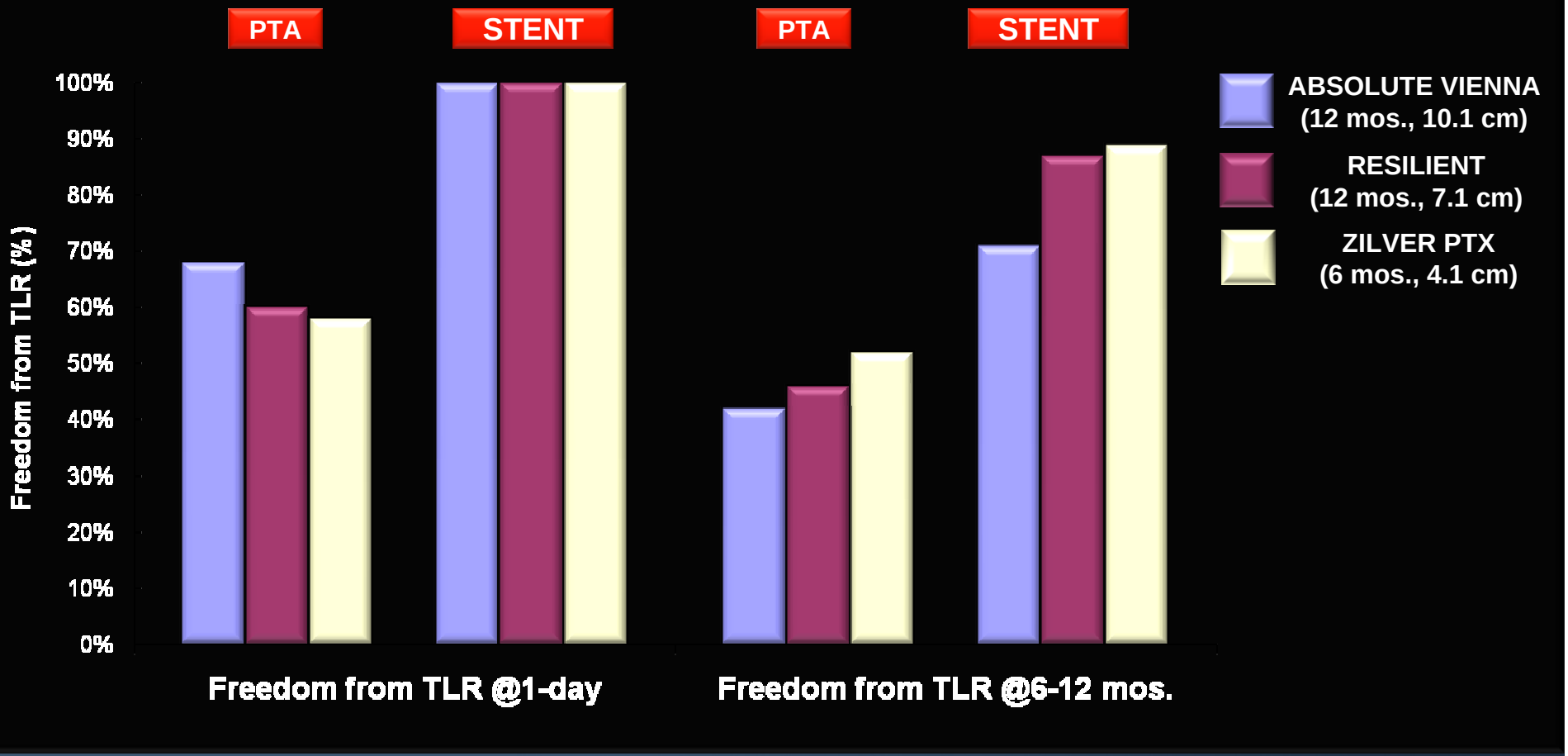
Biamino G, Katzen BT, Laird J. The RESILIENT Trial: 12-mos. results. Leipzig Interventional Course. Leipzig, Germany, 2008.

Clinical trial comparison using the reported rates of TLR



Clinical trial comparison using the RESILIENT/ZILVER PTX definitions of TLR



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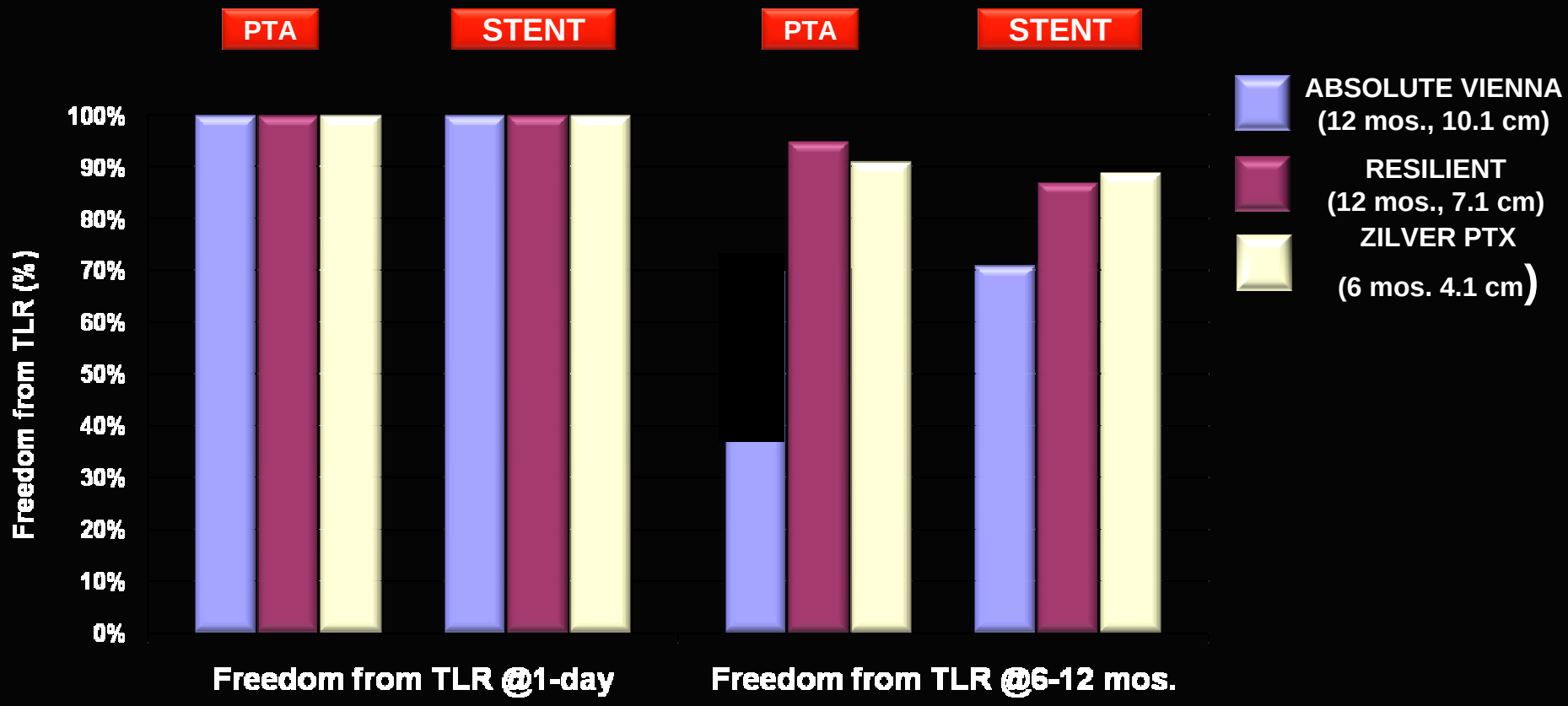
Clinical trial comparison using the ABSOLUTE/VIENNA definitions of TLR



SFA Challenges: Data collection

- Data collection
  - Endpoint definitions of success
    - Anatomic
      - Binary restenosis (>50%)
      - Discrete vs. diffuse vs. volume definitions
    - Clinical
      - Walking distance
      - ABI
  - Quantifying (and understanding) restenosis
    - Angiographic
    - Duplex
    - Intravascular ultrasound
  - Time course defining durability of intervention
  - Consistent and standardized reporting structure

Patient factors with unclear influence on interventional outcomes

- Inflow/Run-off status
- Length of disease
- Vessel diameter
- Occlusion vs. stenosis
- Diabetic status
- Tobacco status
- Atheroma volume
- Calcification
- Gender

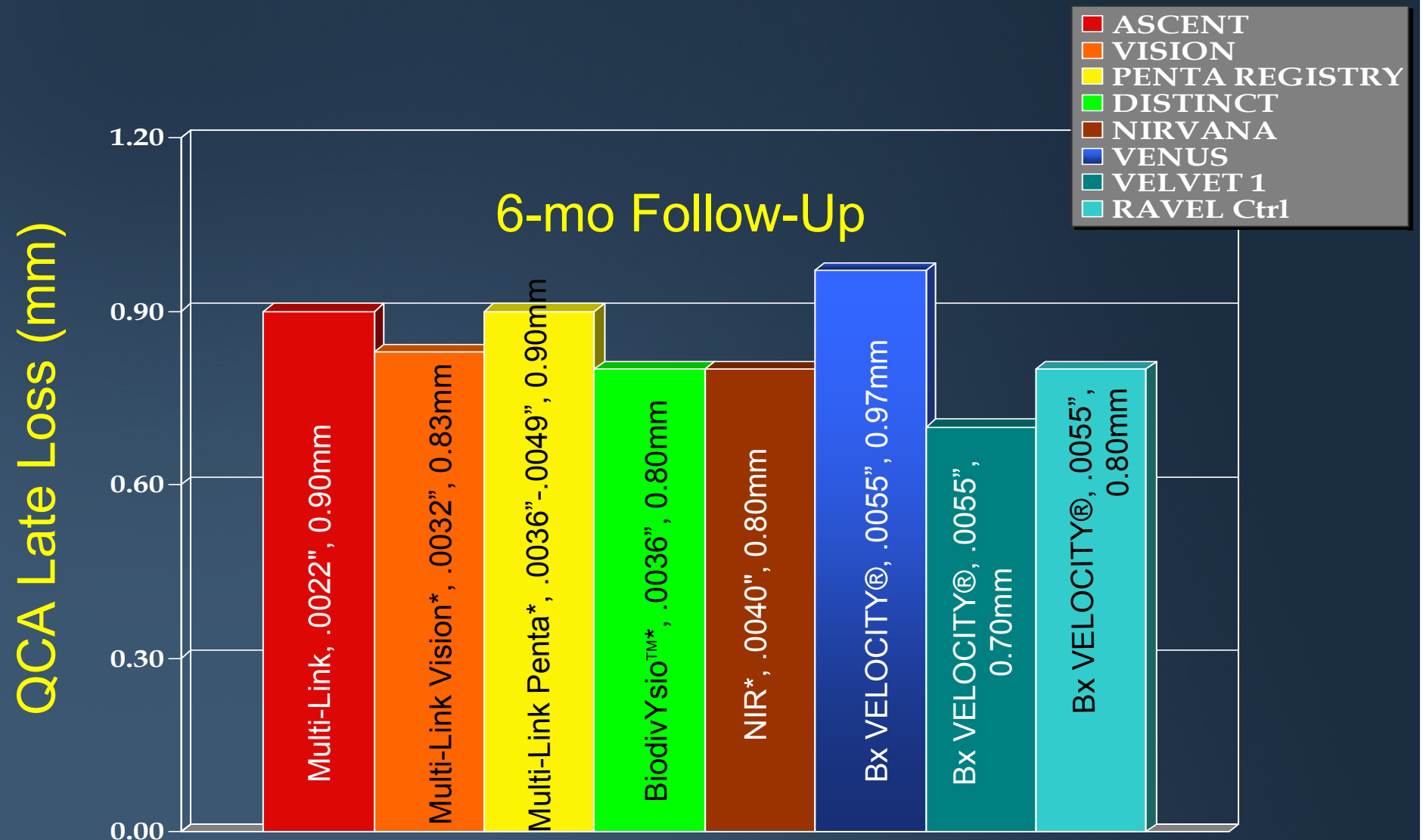
Procedural factors with unclear influence on interventional outcomes

- Stents
  - Number
  - Degree of overlap
  - Compression or stretch during implant
  - Significant oversizing or undersizing
- Adjunctive debulking

SFA: Design challenges

- This arterial territory response to intervention is poorly understood
  - There are no large-scale data sets from which to establish design goals
  - Such data was critical to the understanding of coronary stent behavior and the opportunity to improve the technology in a focused direction

Late Loss in Bare Metal Stents



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TAXUS IV – Impact of Vessel Size & Lesion Length

TLR (12-month)

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Result of lack of outcome data

- Current efforts at designing successful devices which will have improved outcomes are at best estimates of the causal relationships
- In the typically small clinical trials testing in SFA therapies, these devices are subject to variation in subject/vessel characteristics

Conclusions

- Stents are better than PTA (I think) for limited lesion length
- Long stents are worse than short stents
- Not all stent fractures are created equal
  - FESTO results not borne out in later trials
- Alternative therapies (photodynamic, adventitial injection, adjunctive atherectomy, etc.,) may be useful but as yet untested
- Drug-eluting balloon looks interesting in spite of lack of clear mechanism
- VIBRANT trial data will be interesting