Zilver PTX® - Technology & Single-Arm Study Results

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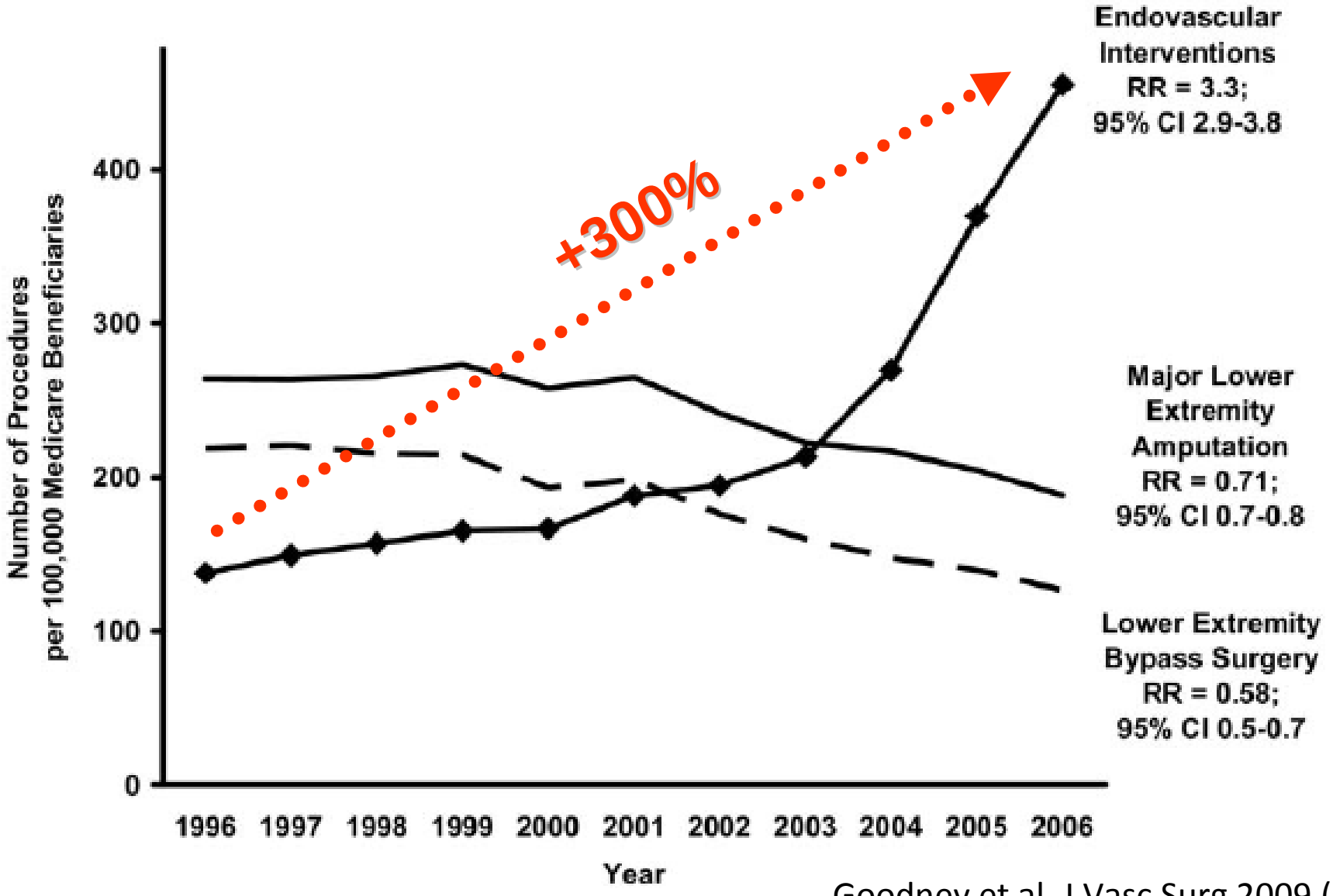
Overview

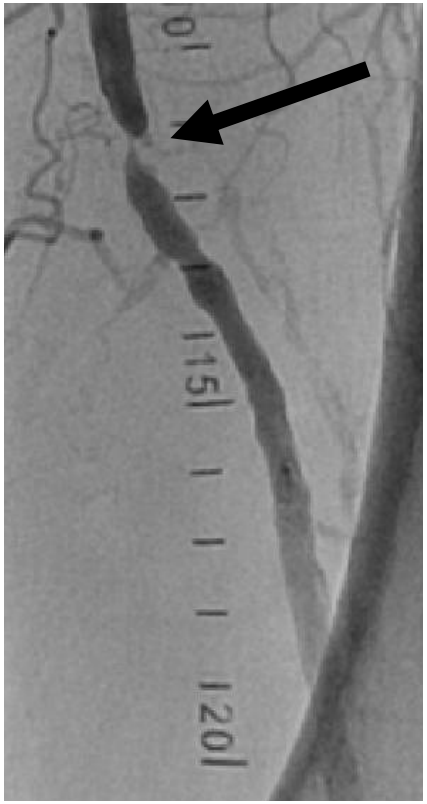
- Peripheral arterial disease (PAD) is increasing in prevalence and clinically important
- Limitation of endovascular treatment of complex disease
- Zilver PTX® technology
- Update on the **Zilver PTX® Single-Arm Study:**
  - Real-world patient population with complex disease
    - Stent fracture rate
    - Patency rates
    - Clinical benefits

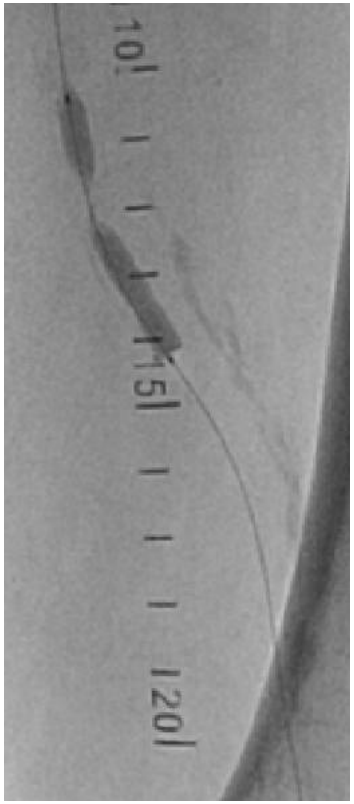
Changing Pattern of Revascularization

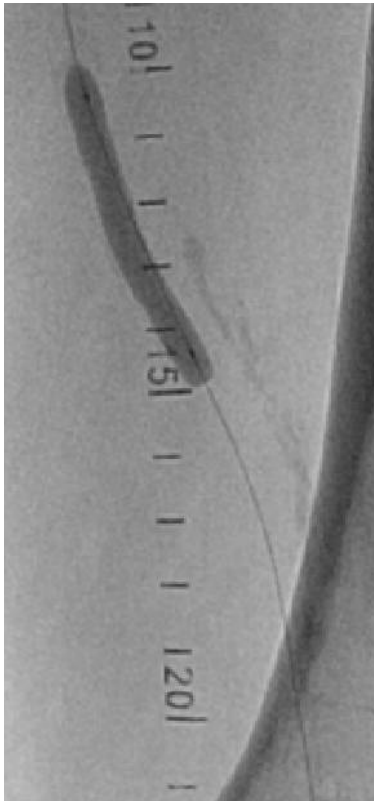


Goodney et al. J Vasc Surg 2009 (50)

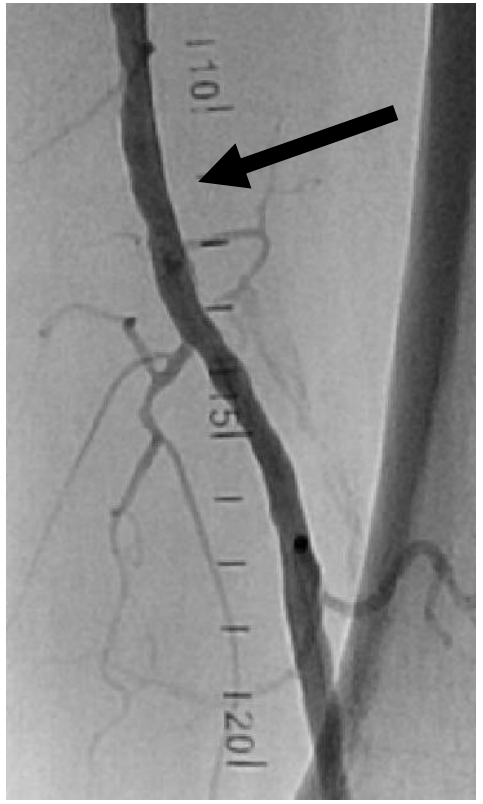
If all lesions were like this…







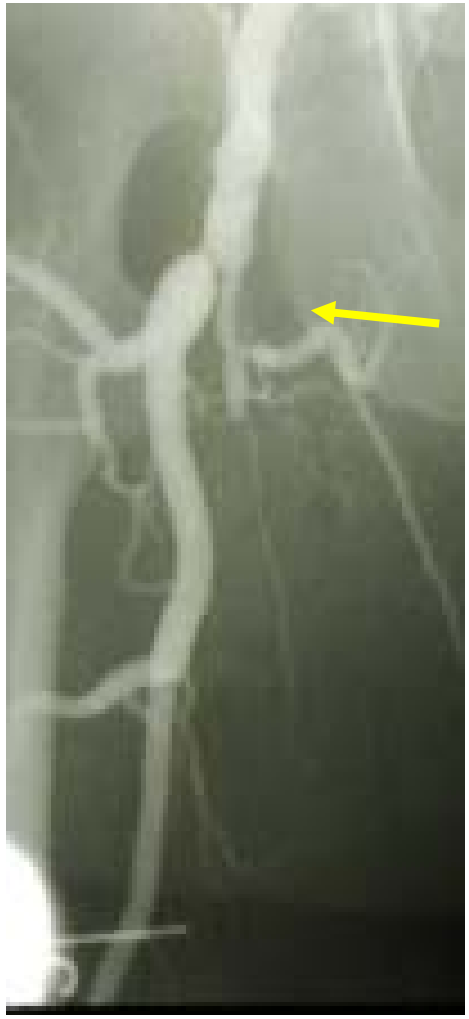
4cm Balloon

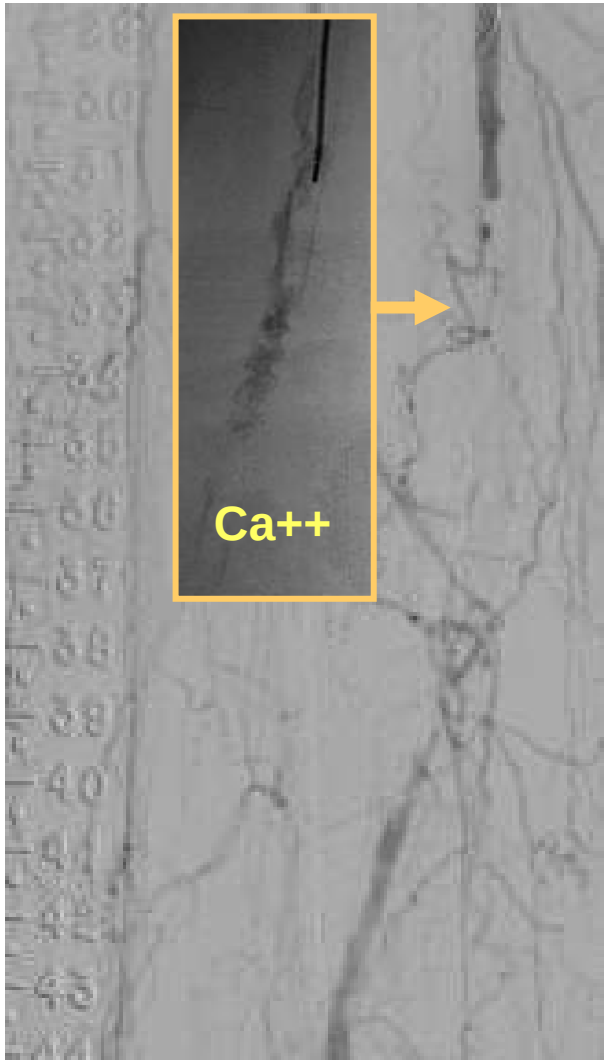


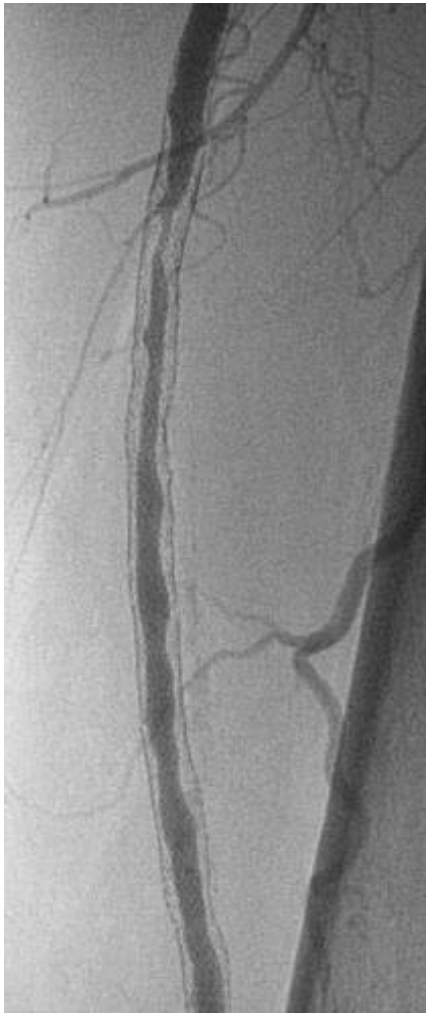
Post PTA

…but they are not!

..diffuse disease, long occlusions, heavy calcification, ISR...



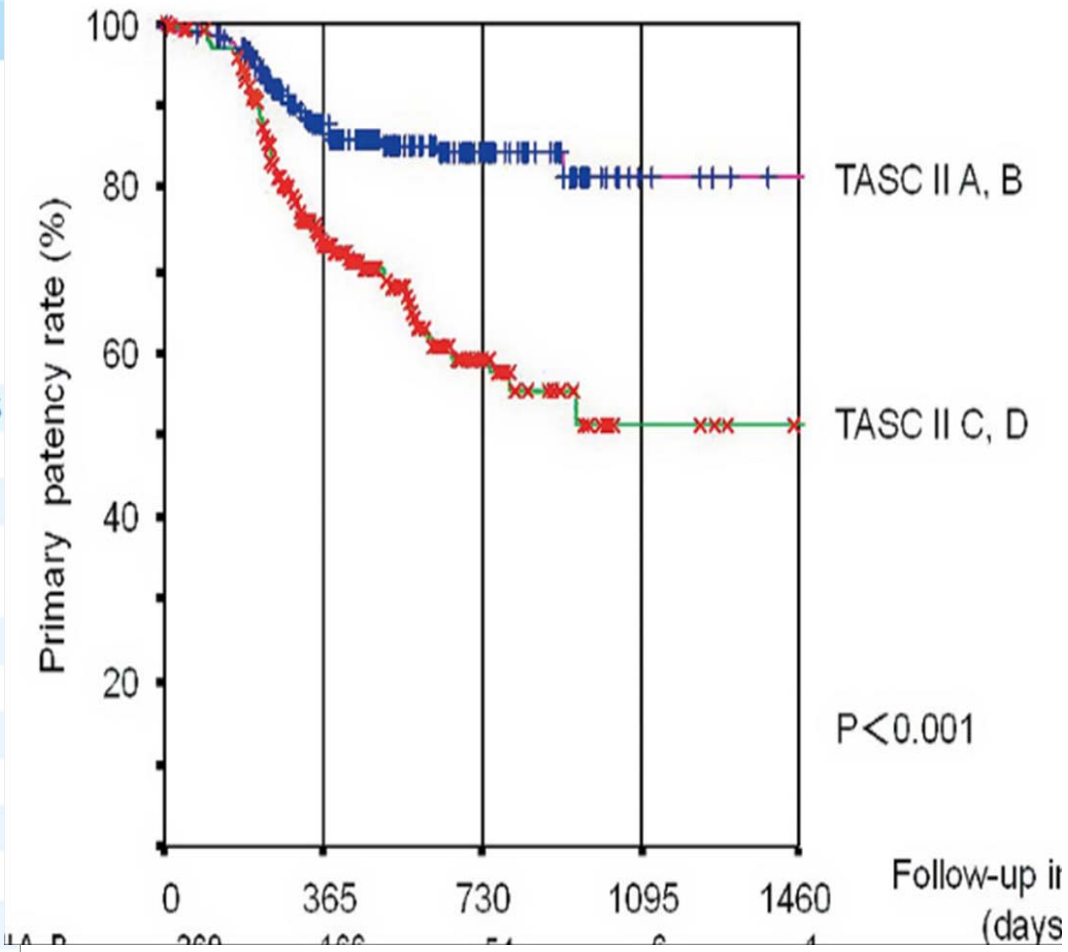




Real World Lesions

Table 2. Lesion Characteristics

	Total
n	528
De novo	528 (100)
Lesion length	15.7±8.1
CTO	297 (56)
Calcified lesion	195 (37)
Run-off vessel	
0/1/2/3	39/143/181/165
TASC II	
A, B	269 (51)
C, D	259 (49)
Stent diameter (mm)	
6	191 (36)
7	76 (14)
≥8	261 (49)
No. stent	
1	249 (47)
2	122 (23)
≥3	157 (30)
Cilostazol	361 (68)



Suzuki et al. Circ J. 2011

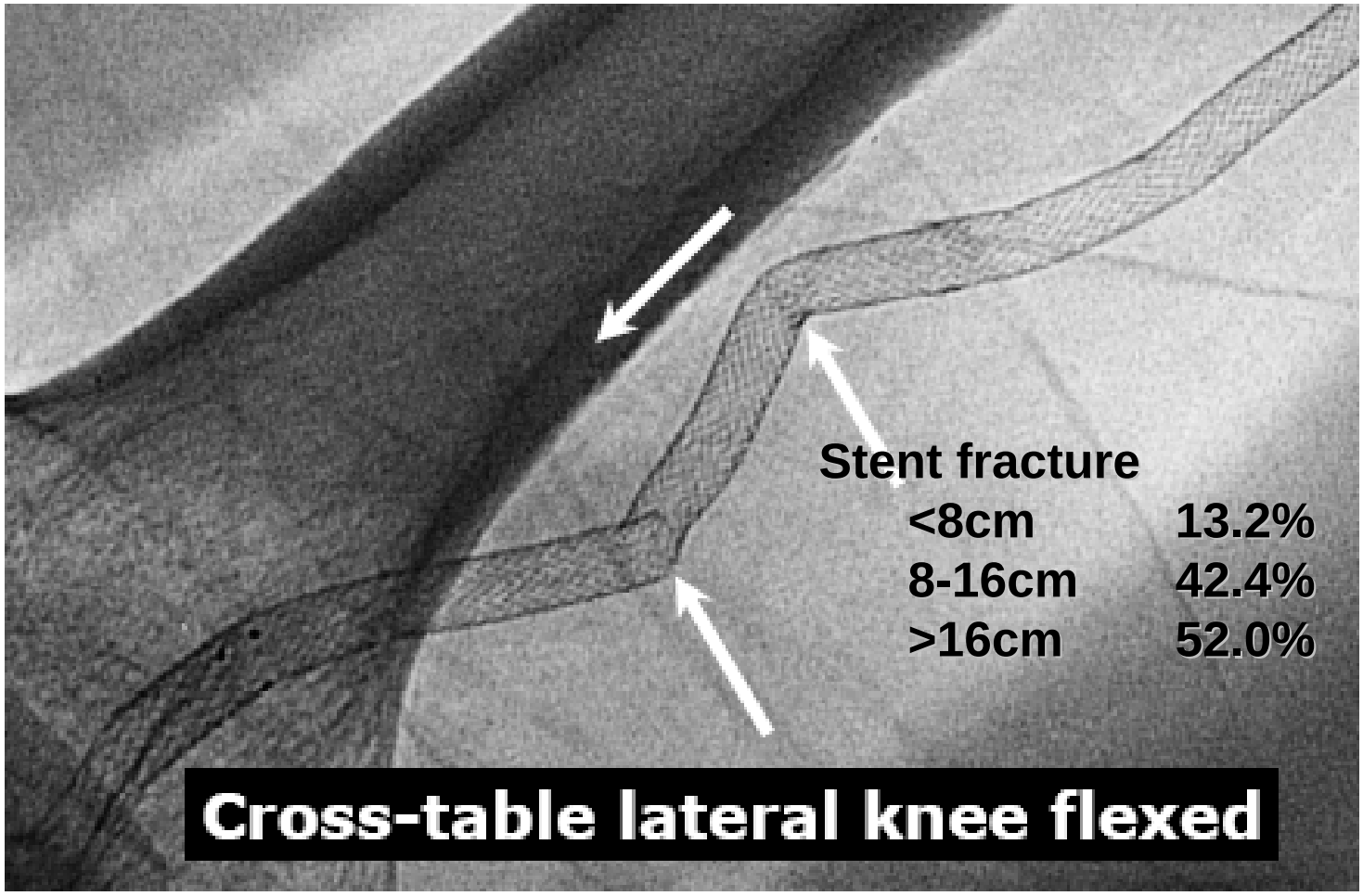
Big Questions in Percutaneous Treatment

- Should I open it?
- Can I open it?
- How can I keep it open?

SFA Treatment Overview

- **Medical therapy** – small population
- **Exercise** – effective when supervised; not reimbursed
- **Surgery** – invasive
- **PTA** – limited effectiveness (12-mo. patency rates ≈35%)
- **BMS** – more effective than PTA (12-mo. patency rates ≈70%)
- **Atherectomy** – no randomized data
- **Cryoplasty** – no randomized data
- **Previous DES (polymer-based, limus drug coatings)** – no sustained difference from BMS
- **Paclitaxel-coated balloons** – promising in short, simple lesions

SFA Compressive Forces: Stent Fracture



Overview

- Peripheral arterial disease (PAD) is increasing in prevalence and clinically important
- **Zilver PTX® technology**
- Update on the **Zilver PTX® Single-Arm Study:**

Drug-Eluting Stents

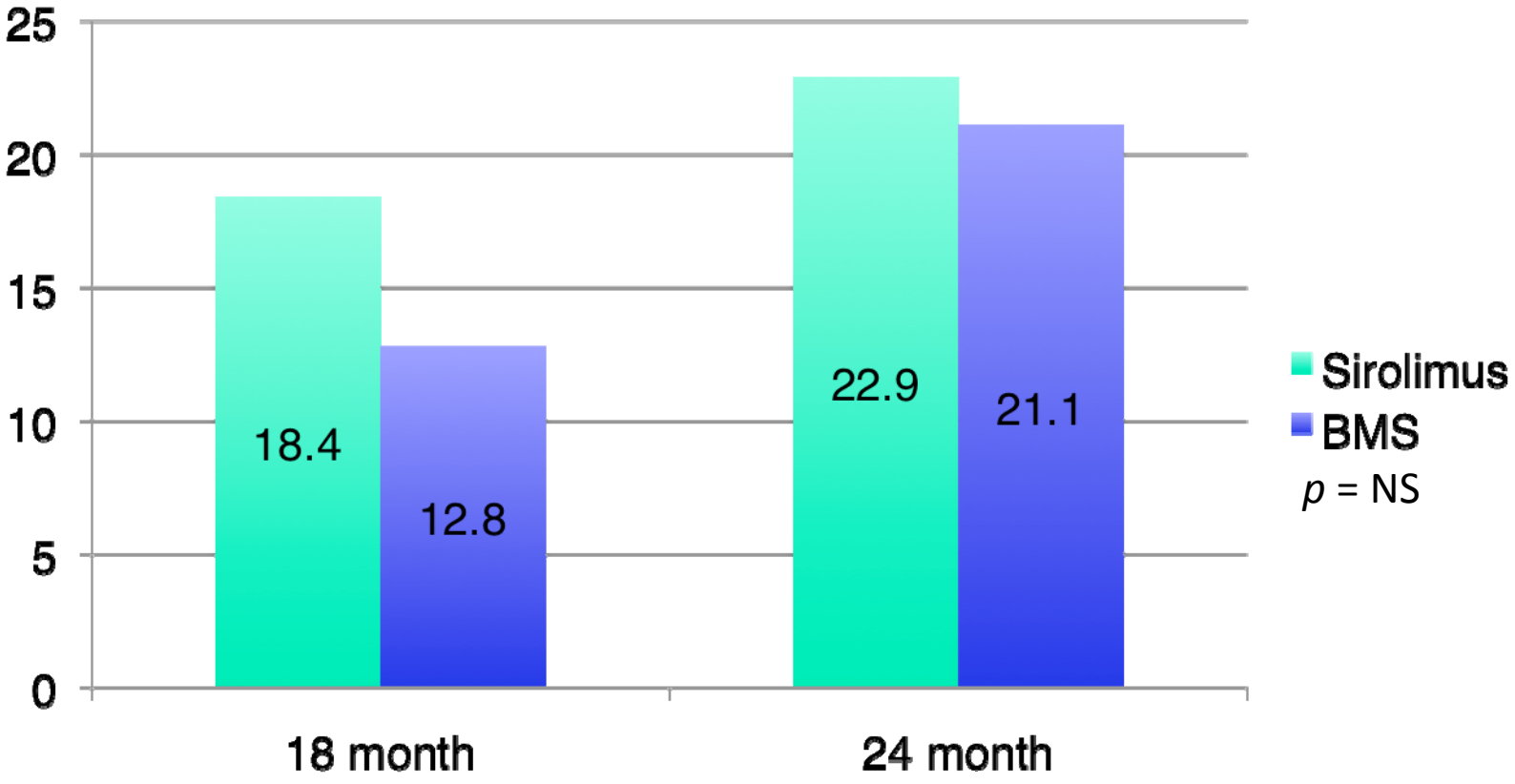
- The development of DES began with coatings to **inhibit stent thrombosis**
  - Classical example was heparin coatings
  - Heparin is extremely water soluble and requires a polymer or binder to prevent it from being washed off into the blood during tracking or immediately after implantation
- The evolution of DES progressed to **inhibiting in-stent restenosis**, and included an *assumption* that prolonged drug delivery, using polymers, was necessary. To a large extent, this assumption has persisted.
- Increasing evidence suggests that many polymers and binders may be a suboptimal component of DES (e.g., thrombogenic and inflammatory)

Drug-Eluting Stent Disappointments

- SIROCCO
  - SMART + polymer + sirolimus
- STRIDES
  - Dynalink-E + polymer + everolimus

SIROCCO: In-stent Restenosis

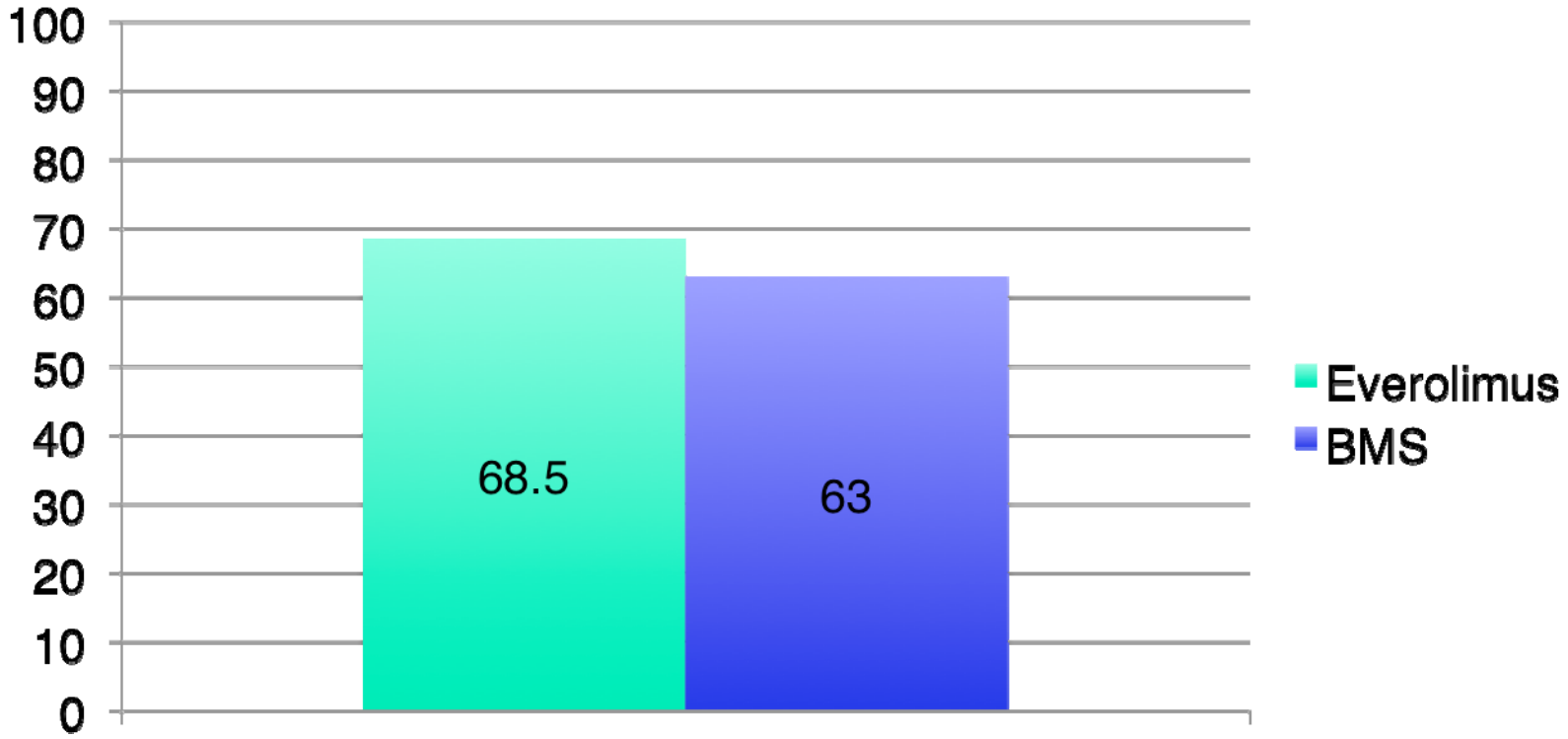
- **Duplex ultrasound**



Duda J Endovasc Ther 2006;13:701

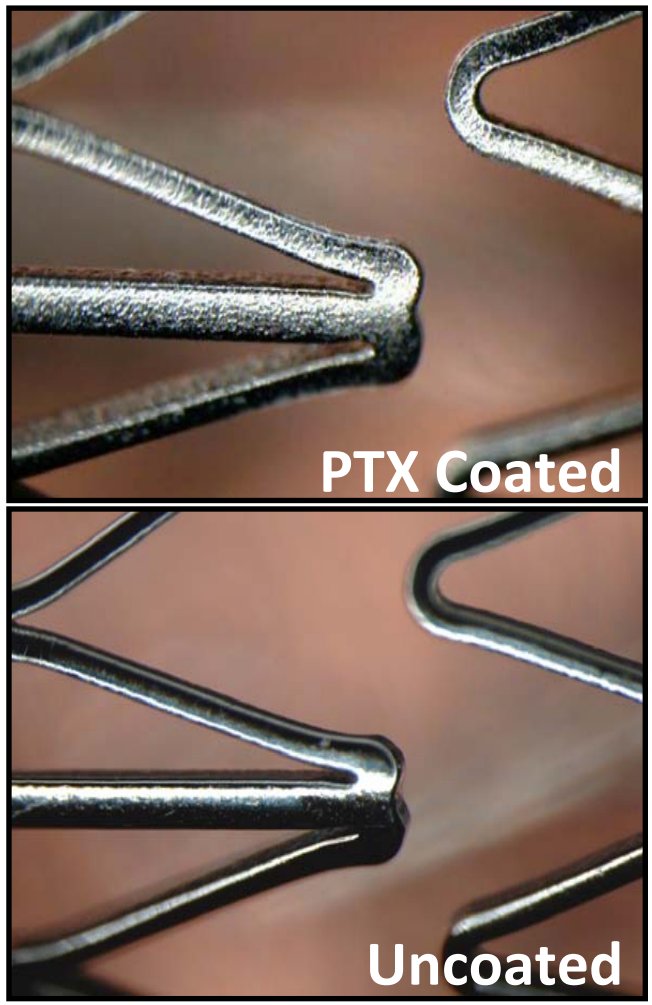
STRIDES: 12-Month Patency

- **Duplex ultrasound**



Zilver PTX® Drug-Eluting Stent

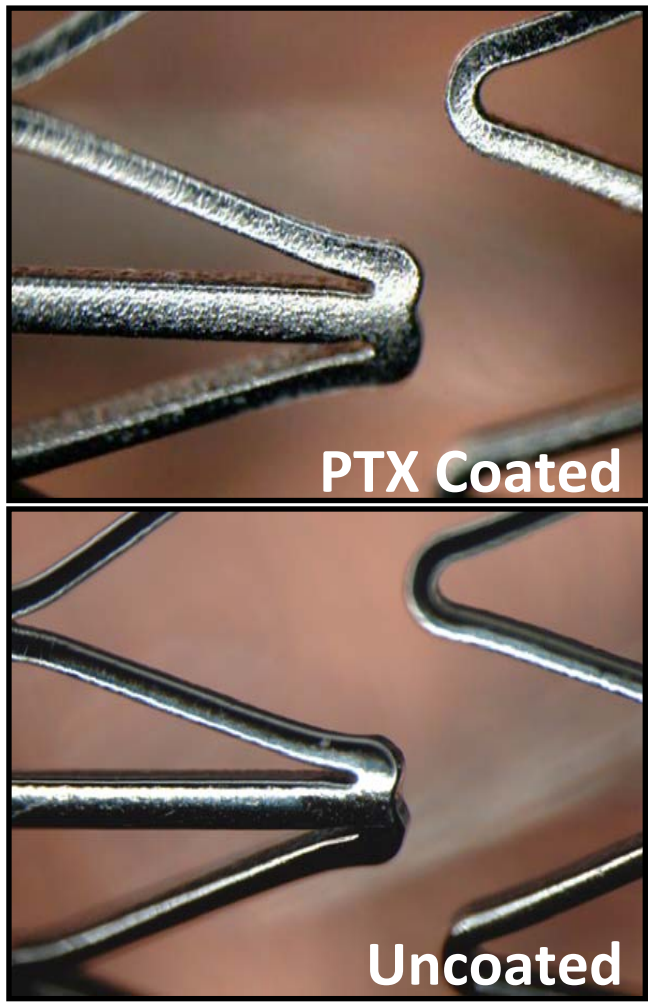
- Designed for the SFA
- CE Marked
  - Investigational in the US
- Paclitaxel only
  - No polymer or binder
  - 3 µg/mm2 dose density
- Zilver Flex® Stent Platform
- Sponsor: Cook Medical
- 7Fr compatible
- 4-10mm diameter
- Max 80mm length



Zilver PTX® Drug-Eluting Stent

- Designed for the SFA
- CE Marked
  - Investigational in the US
- Paclitaxel only
  - No polymer or binder
  - 3 µg/mm2 dose density
- Zilver Flex® Stent Platform
- Sponsor: Cook Medical
- 6 Fr compatible

- Max 120mm length

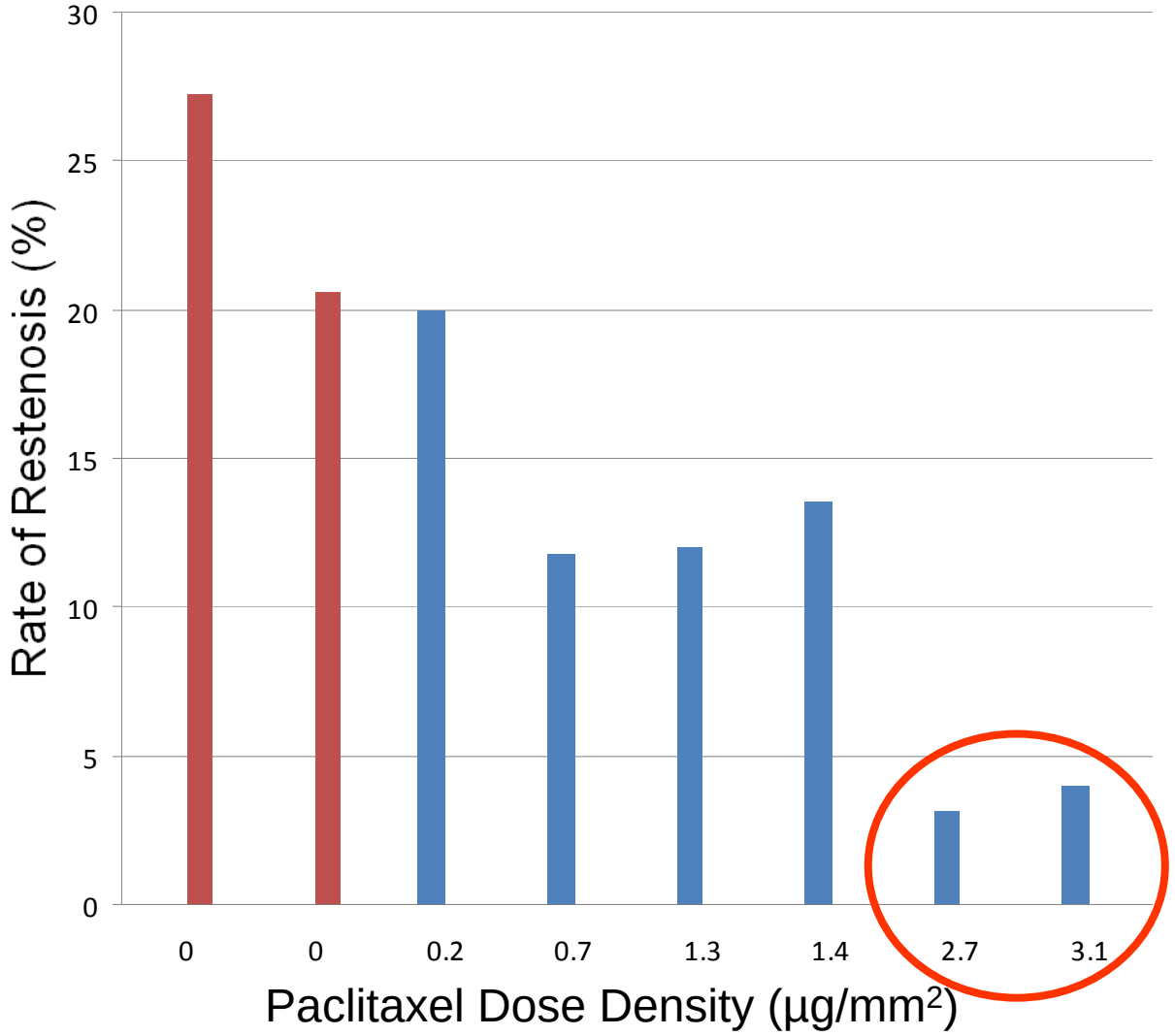


Paclitaxel Does not Require a Polymer

- Paclitaxel is approximately 200,000 times less soluble in water than heparin. Therefore, **a polymer is not needed to prevent PTX® wash off from stents during tracking or following implantation**.
- Paclitaxel (PTX®) is highly protein bound and lipophilic (approximately 10^{16} times so, as compared to heparin). This helps PTX® partition into the tissues of the vessel wall rather that into the bloodstream, and enhances cellular uptake and retention. Therefore, **a polymer is not needed for adequate PTX® delivery to the vessel wall**.

Drug	Water Solubility (µg/mL)	Lipophilicity (Octanol/Water Partition Coefficient)
Heparin	50,000	10^{-13}
PTX®	0.25	10^{3}
Comparison	200,000 times	10^{16} times

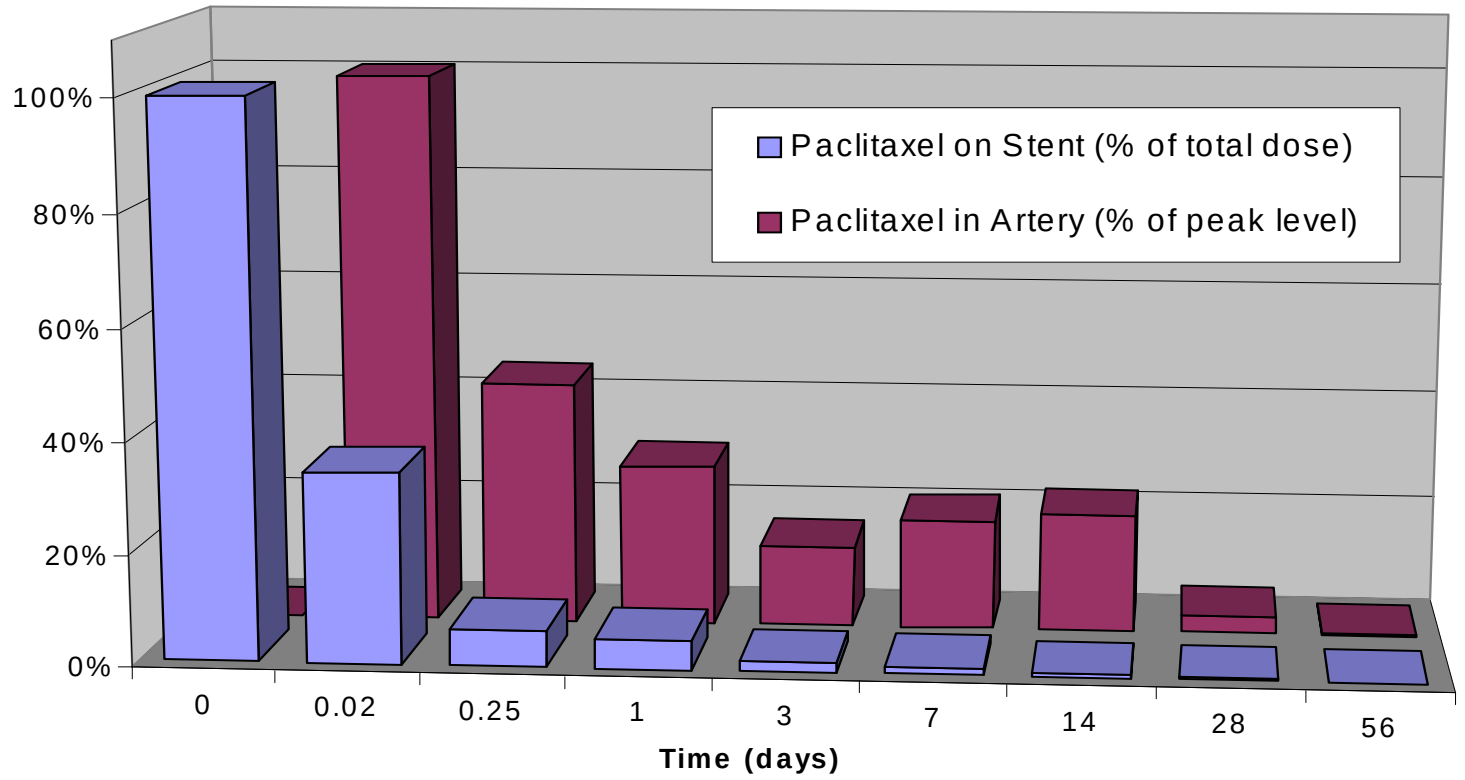
Dose Density: Polymer-free Paclitaxel Eluting Coronary Stents



Gershlick A *et al.*, Circulation. 2004;109:487-93. and Park SJ *et al.*, N Engl J Med. 2003;348:1537-45.

Zilver PTX® Pharmacokinetics

Animal studies have shown that the paclitaxel is rapidly delivered from the stent to the vessel wall but persists in the vessel wall for up to 56 days

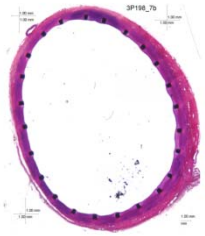


Time (days)

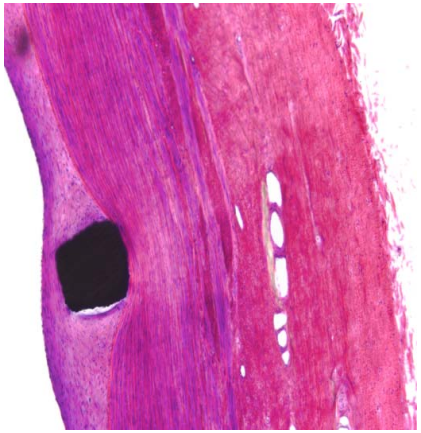
Vessel Healing with Zilver PTX®

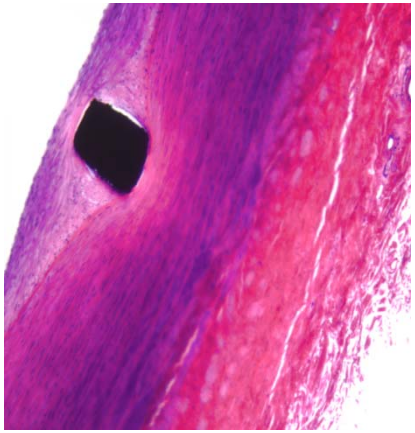
Animal studies have shown that vessel healing is complete (e.g., endothelialization, minimal inflammation) within 3 months

Bare Metal Zilver®



Zilver PTX®





Dake MD *et al.*, J Vasc Interv Radiol. 2011 Mar 16. [Epub ahead of print]

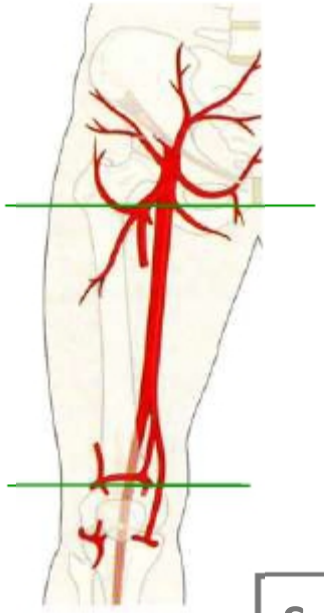
Overview

- Peripheral arterial disease (PAD) is increasing in prevalence and clinically important
- Zilver PTX® technology
- Update on the **Zilver PTX® Single-Arm Study:**
  - Real-world patient population with complex disease
    - 1.5% stent fracture rate through 12 months
    - 86.2% primary patency rate at 12 months
      - Diabetics: 86% patency through 12 months
      - Long lesion: 77% patency through 12 months
      - In-stent restenosis: 80% patency through 12 months
    - Freedom from TLR remains stable through 24 months
    - Sustained clinical benefit through 24 months

Zilver PTX Single-Arm Study

- **Prospective, nonrandomized, multinational study**
  - Largest study to date of endovascular treatment of SFA disease (787 patients, 900 lesions)
- **Real-world patient population**
  - Long lesions, in-stent restenosis, multiple overlapping stents
- **CEC and DSMB oversight with extensive data monitoring**
- **Stent fracture assessment**
  - Biplane X-ray at 6 and 12 months
- **Primary patency assessment**
  - Duplex ultrasonography at 6 and 12 months
- **Long-term clinical follow-up through 2 years**
  - Bilateral ABI, Rutherford class, walking scores

Anatomical Treatment Zone



55 sites in US, Japan and Germany

30 sites in Europe, Canada and Korea

Zilver PTX Randomized Trial

Primary Randomization

PTA
n = 238

Zilver PTX
n = 236

Suboptimal PTA
(>30% residual stenosis)
n = 120

Optimal PTA
n = 118

Secondary Randomization

Bare Zilver
n = 58

Zilver PTX
n = 61

Zilver PTX Single-Arm Study

Zilver PTX
n = 787

Studies are Complementary

* Maximum four per patient

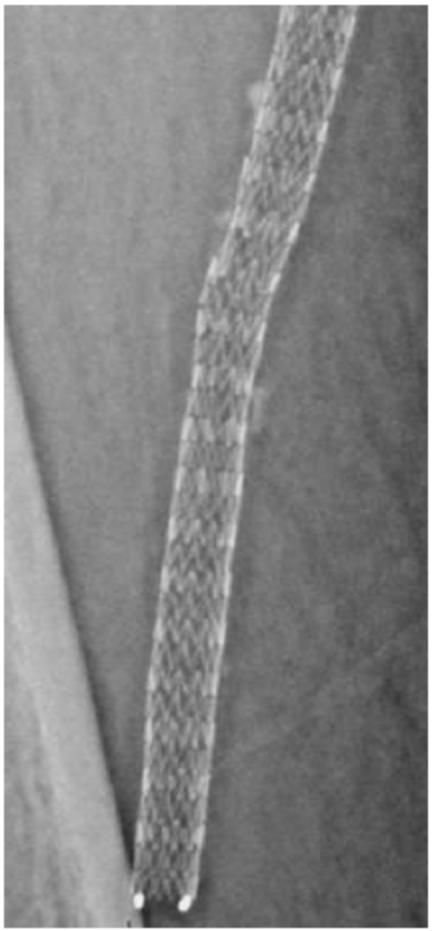
Zilver® PTX®	Single-Arm Study	Randomized Study
Protocol	Prospective, detailed case report forms, extensive monitoring	
Antiplatelets	Clopidogrel for 60 days, aspirin indefinitely	
Outcomes	Patency by ultrasound, stent integrity by X-ray, clinical benefit	
Control Group(s)	None	PTA with provisional BMS
Patients	Symptomatic PAD with Rutherford score > 2	
Lesions	*De novo* or restenotic, > 50% diameter stenosis,	
	Real-world: -Unlimited per limb -Included in-stent restenosis -Length not limited - Zilver® PTX® stents per lesion not limited*	**Controlled/Moderate:** -One lesion per limb -No prior stent in study vessel -Length ≤ 14 cm - Maximum 2 Zilver® PTX® stents per lesion
Imaging Analysis	Site-based	Core laboratories (duplex ultrasound, angiography, X-ray)
Primary Analysis	12 months	
Ongoing Follow-up	2 years	5 years

Baseline Lesion Characteristics

Lesions		900
Lesion length (mm)		100 ± 82
Diameter stenosis		85 ± 16%
TASC 2000 class	**A**	26%
	B	29%
	C	25%
	D	14%
Lesions > 7 cm		48%
Lesions > 15 cm		22%
Total occlusions		38%
Restenosis (all)		24%
In-stent restenosis (ISR)		14%

Low Stent Fracture Rate

Number of Stents Implanted	% of Lesions (n = 900)	% of Patients (n = 787)
1	50%	40%
2	22%	25%
3	13%	16%
4	14%	17%
>4	1%	2%
Average	**1.9 stents per lesion**	**2.2 stents per patient**



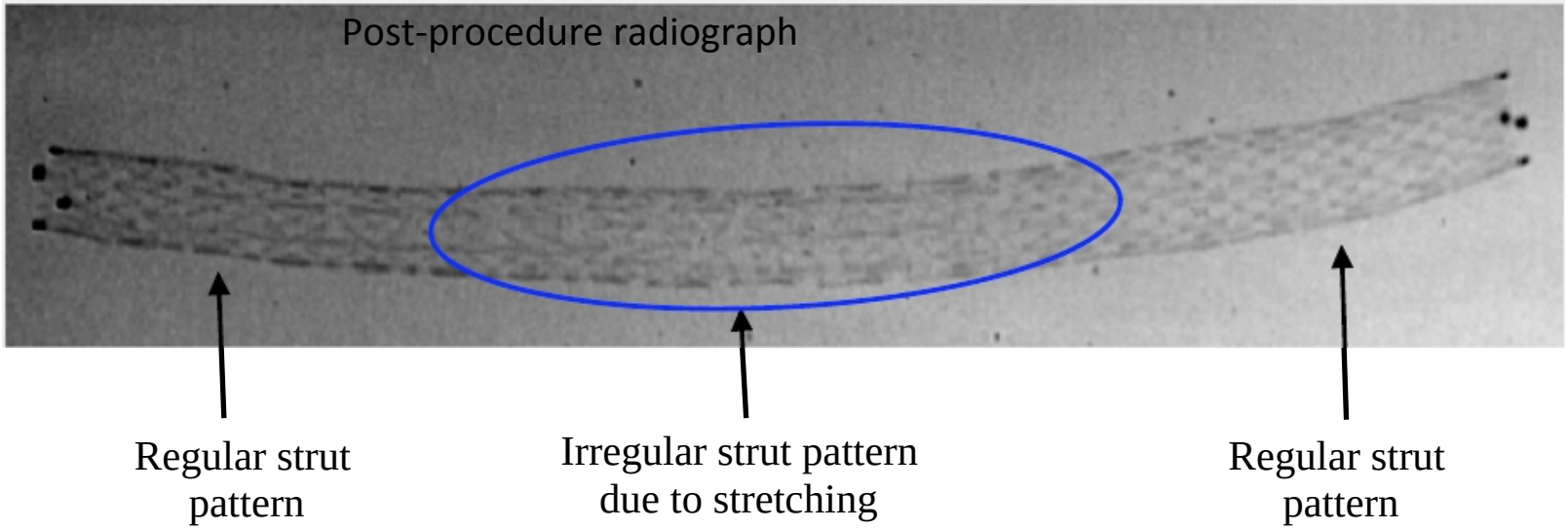
- 1,432 stents (82%) radiologically examined at 12M
  - 22 confirmed stent fractures
  - Almost all at stent overlap
  - Stent over-stretch associated with Type IV

1.5% stent fracture rate through 12 months

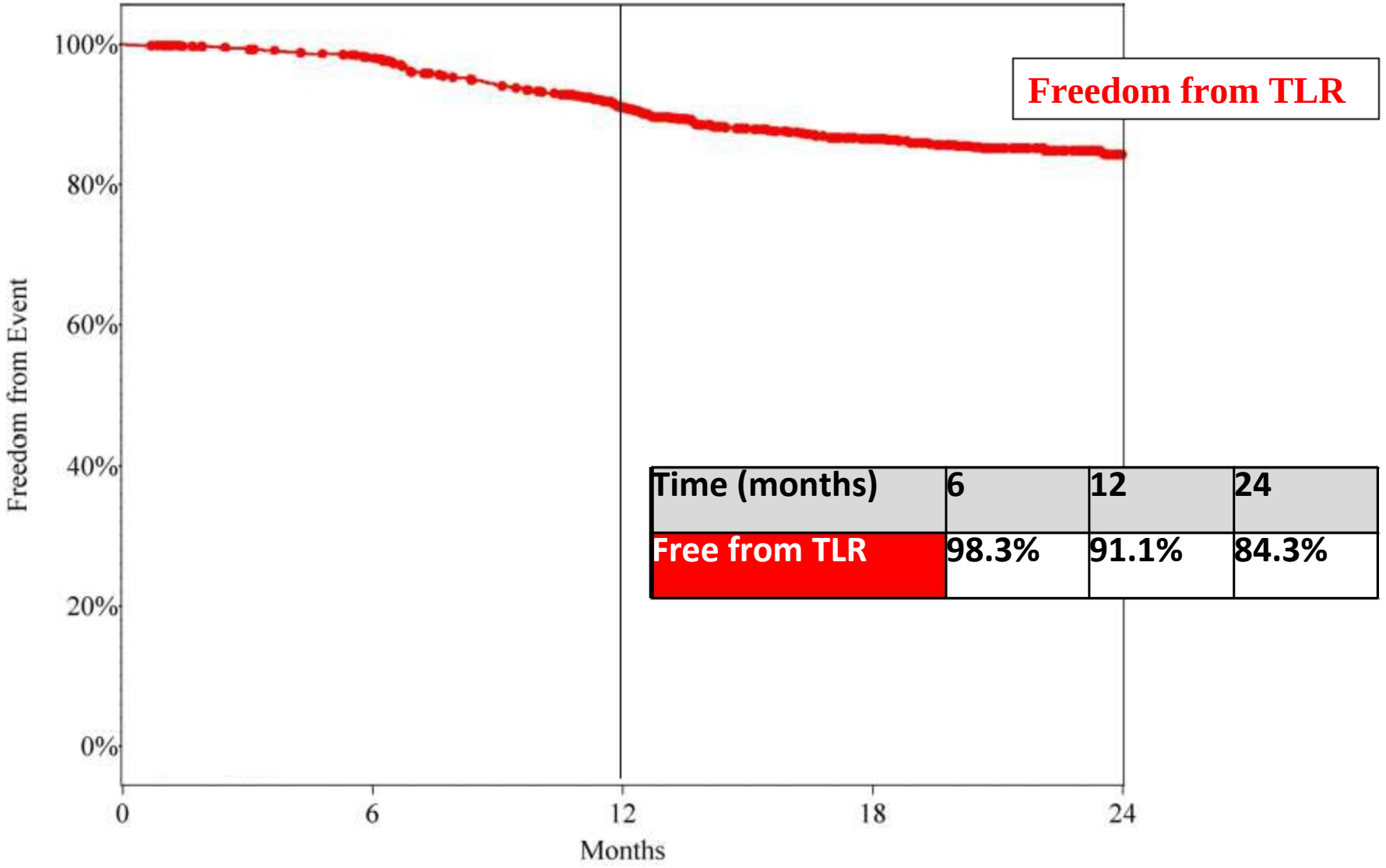
Stent Integrity

- Stent length stretched 20% during deployment:
  80 mm stent stretched to 96 mm

- Type IV fracture in the stretched region at 6 months

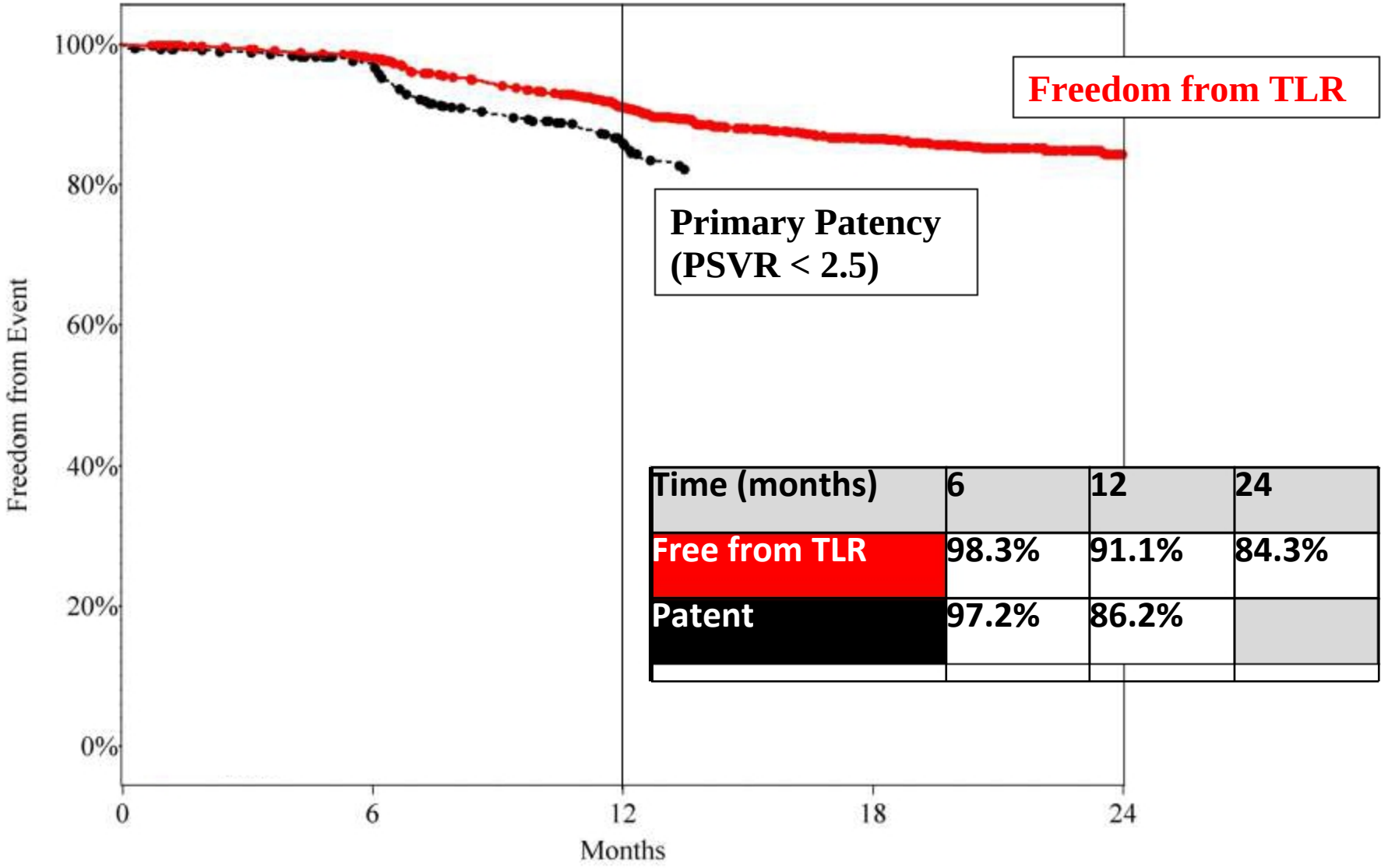


Long-term Effectiveness



Time (months)	6	12	24
Free from TLR	98.3%	91.1%	84.3%

Long-term Effectiveness



Time (months)	6	12	24
Free from TLR	98.3%	91.1%	84.3%
Patent	97.2%	86.2%	

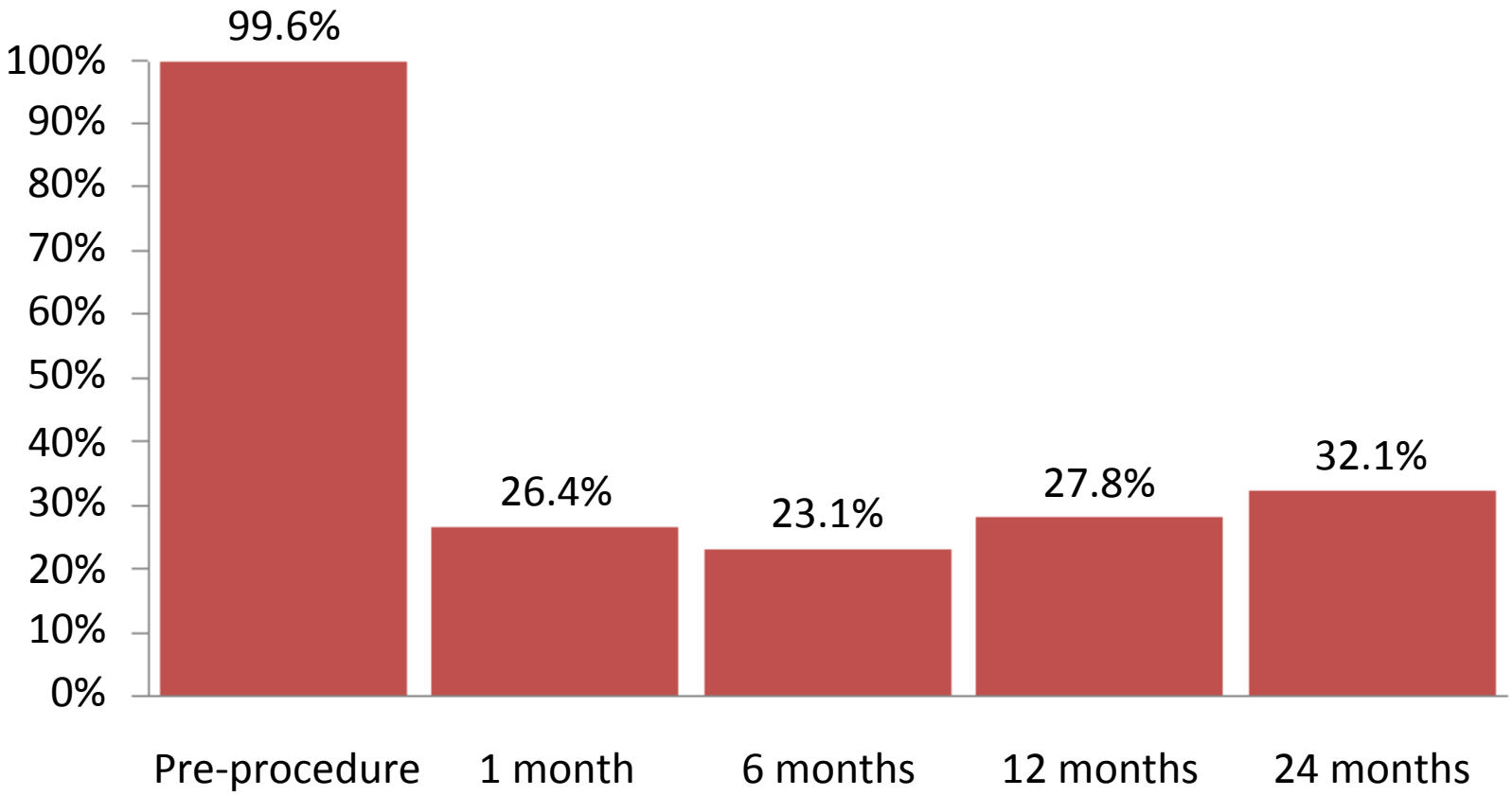
Freedom from TLR

Subgroup	12 Months	24 Months
Overall	89% (n = 818)	82% (n = 427)
De novo (all)	91%	88%
≤ 7 cm Lesions	94%	91%
> 7 cm to 15 cm Lesions	92%	86%
> 15 cm Lesions	84%	80%
TASC C and D*	87%	78%
Occlusions	86%	77%
Stenosis	90%	85%
Restenosis (all)	81%	70%
Restenosis (not ISR)	87%	73%
In-stent Restenosis (ISR)	78%	69%

*TASC 2000

[1] Dake M. Interim analysis of two-year clinical results for the Zilver PTX drug-eluting peripheral stent. Presented at: CIRSE 2009; September 21, 2009; Lisbon, Portugal.

Sustained Clinically Important Improvement



Time (months)	Pre-procedure	1	6	12	24
Median Rutherford	3	0	0	0	1
n (patients)	760	746	707	683	586

Zilver PTX® Effectiveness in Diabetics

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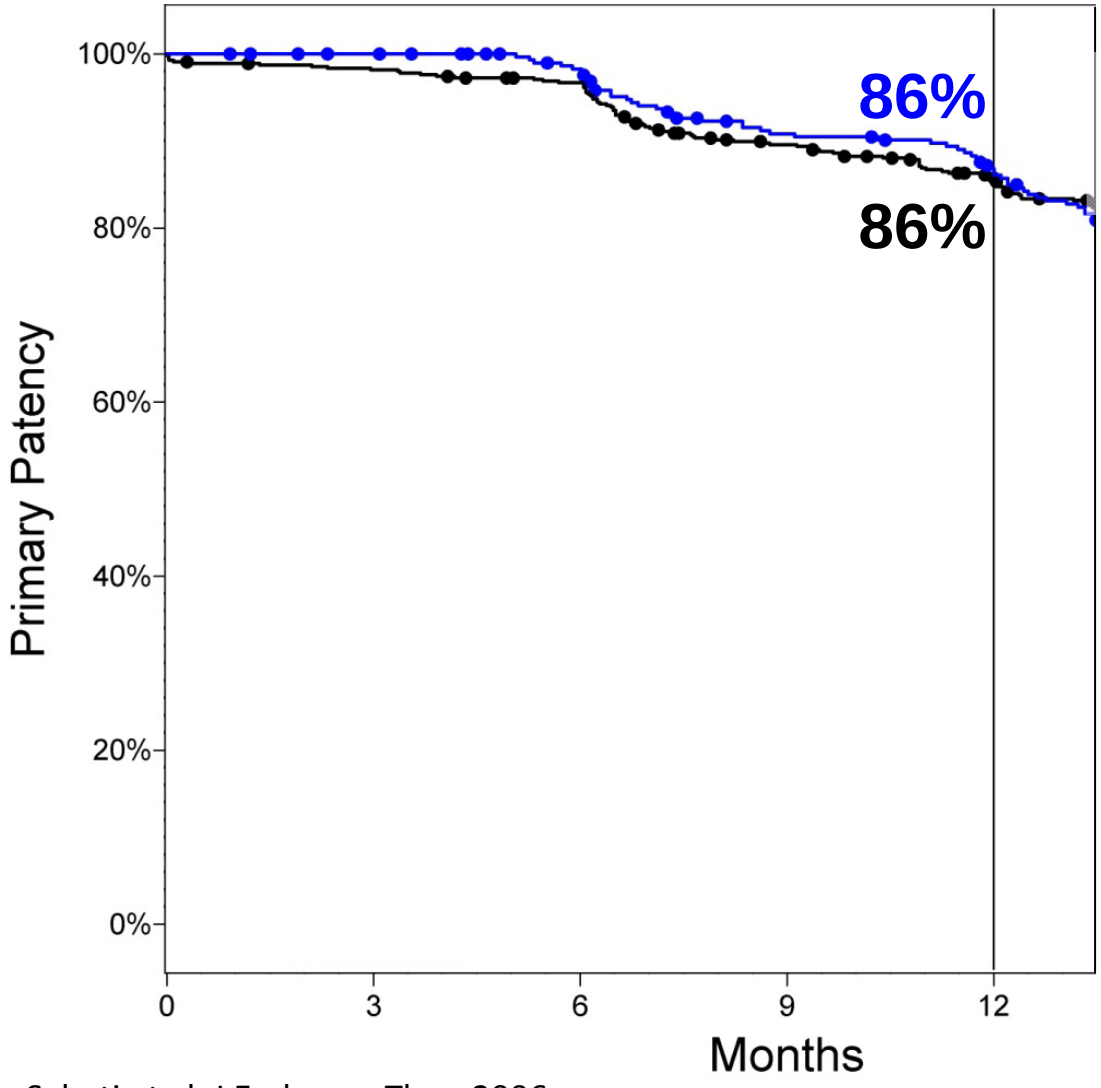
Baseline Lesion Characteristics

		Single-Arm Study: All Patients	Single-Arm Study: Diabetic Patients
Lesions		900	298
Lesion length (mm)		100 ± 82	98 ± 79
Diameter stenosis		85 ± 16%	81 ± 17%
TASC 2000 class	**A**	26%	29%
	B	29%	31%
	C	25%	31%
	D	14%	9%
Lesions > 7 cm		48%	51%
Lesions > 15 cm		22%	22%
Total occlusions		38%	30%
Restenosis (all)		24%	26%
In-stent restenosis (ISR)		14%	16%

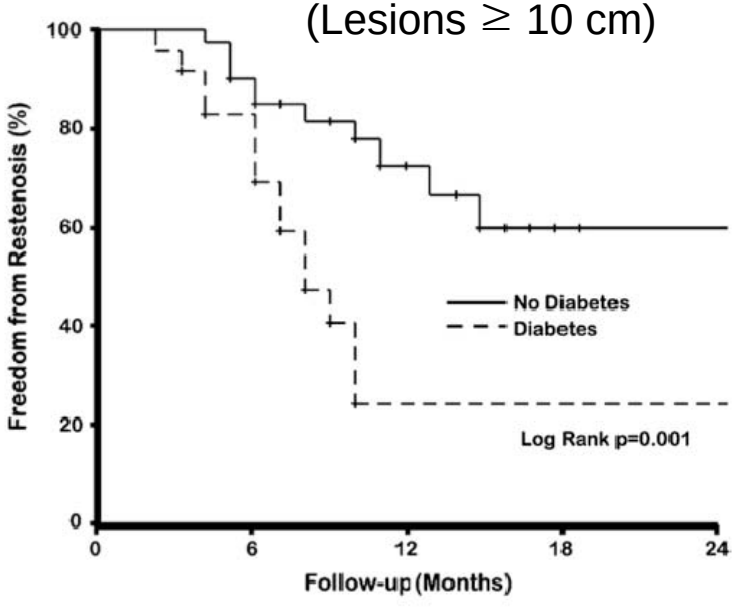
Zilver PTX® stenting is effective in diabetics Primary Patency (PSVR < 2.5)



Zilver PTX®
Diabetics

Zilver PTX®
Non-diabetics

Sabeti *et al.*
(Lesions ≥ 10 cm)



Sabeti et al, J Endovasc Ther, 2006

Zilver PTX® Effectiveness in long *de novo* SFA lesions

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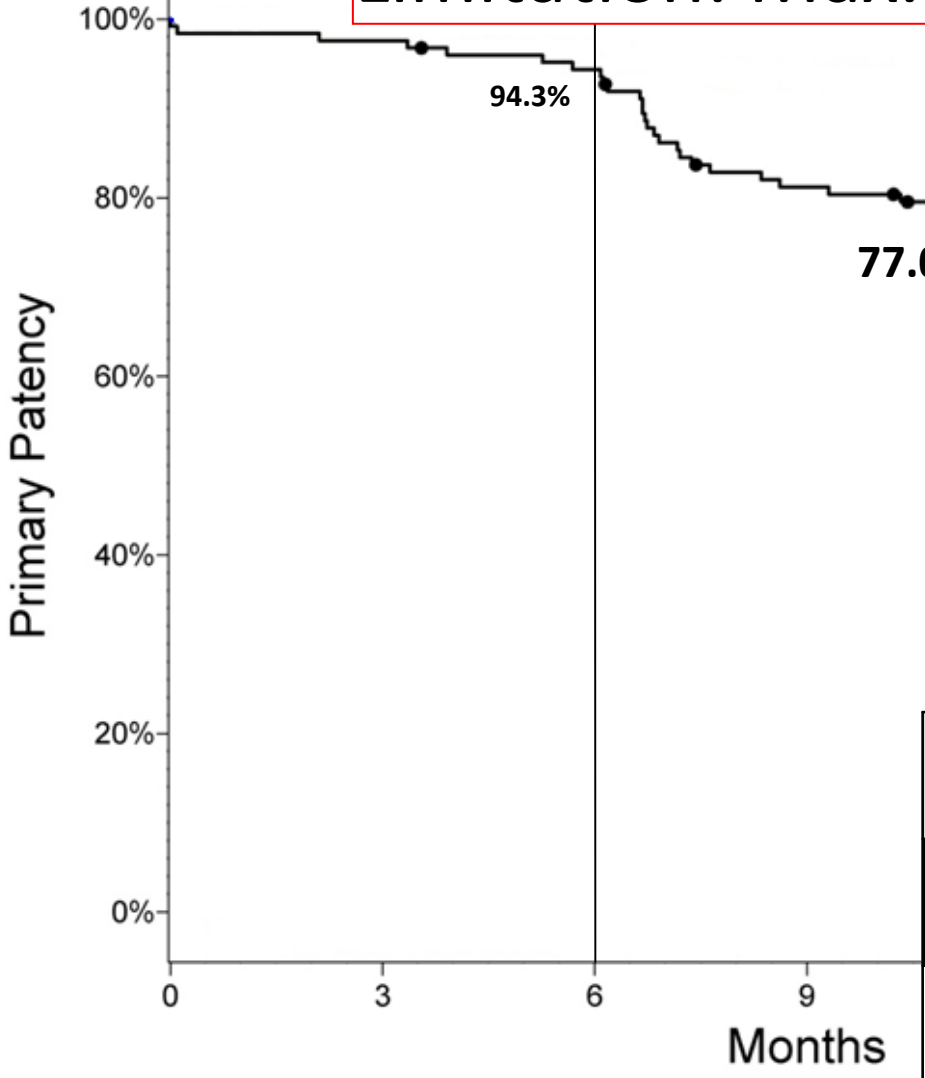
Baseline Lesion Characteristics

		Single-Arm Study: All Lesions	Single-Arm Study: *de novo* long lesions
Lesions		900	133
Lesion length (mm)		100 ± 82	226 ± 44
Diameter stenosis		85 ± 16%	97 ± 9%
TASC 2000 class	**A**	26%	3%
	B	29%	9%
	C	25%	46%
	D	14%	42%
Lesions > 15 cm		22%	100%
Total occlusions		38%	83%
Restenosis (all)		24%	0%
In-stent restenosis (ISR)		14%	0%

Zilver PTX® in long *de novo* lesions (> 15 cm) Primary Patency (PSVR < 2.5)[37]

Limitation: Max. Stent Length so far 8cm



Zilver PTX® stenting effectively treats long SFA lesions

Time	6 months	12 months
Primary patency	94.3%	77.0%
Lesions (at risk)	116	90

Zilver PTX® Effectiveness in In-stent Restenosis

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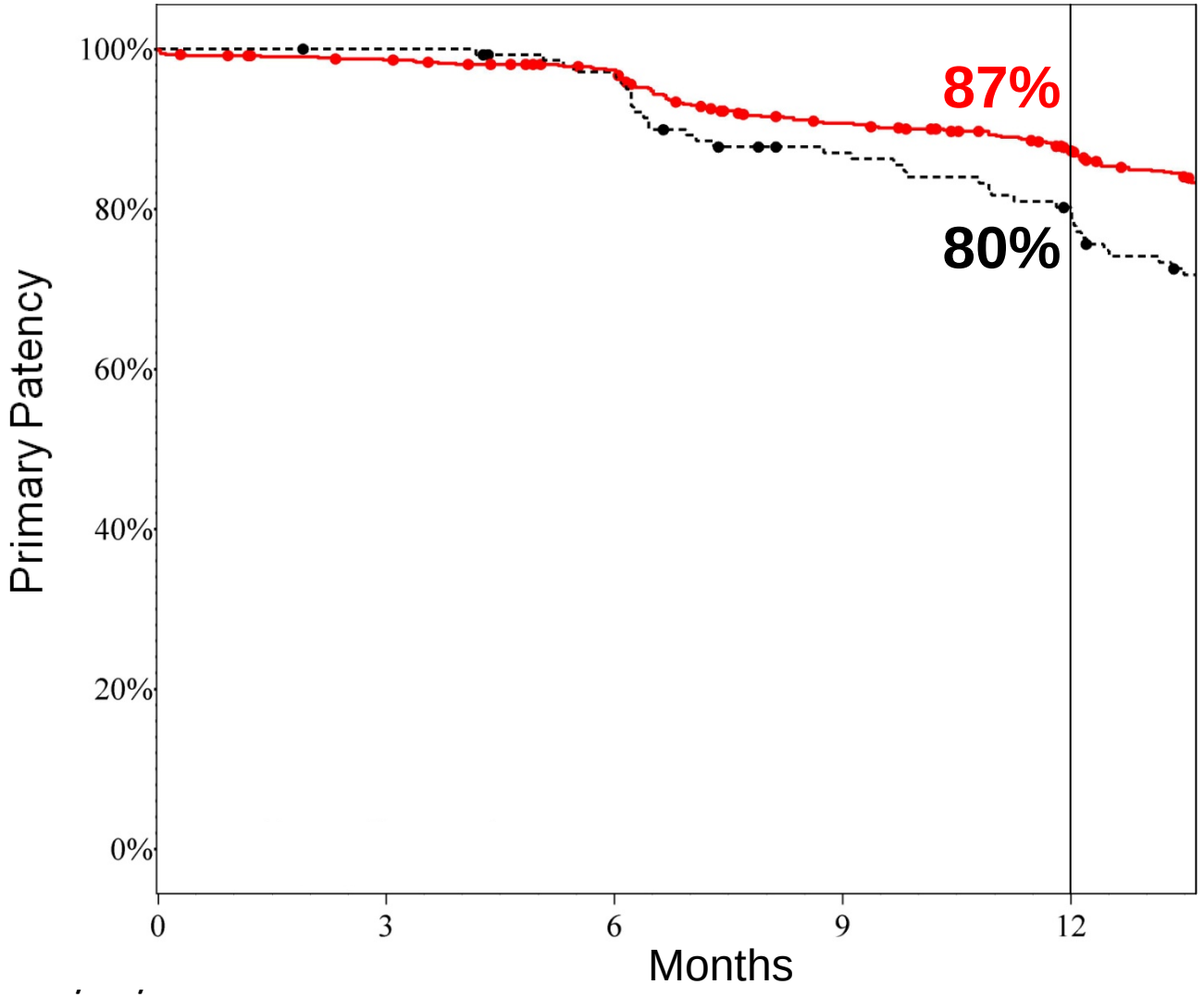
Data for Treating In-Stent Restenosis

Modality	Current Data
PTA	Dick et al (n=22, **27% PP**, 41% TLR at 6 months randomized trial to cutting balloon)
Cutting Balloon	Dick et al. (n=17, **35% PP**, 32% TLR at 6 months randomized trial to PTA)
Drug Coated Balloon	No peripheral data. PACCOCATH ISR (Coronary data for in-stent restenosis showed significant improvements in PP and TLR at 2yrs).
Brachytherapy	Pokrajac et al. (n=17/28, data not specific to in-stent, but entire population had restenosis **9, 28, 48%** at 1, 2, and 3 yrs)
Laser	No data. PATENT trial being done in Europe and IDE study in US.
Silverhawk	Zeller (n=43**, 54% PP** & 47% TLR 1yr, 49% PP & 49% TLR at 18 months)
Stent	None
Drug Eluting Stent	PTX Registry (n=65, 24% TLR at 1yr)
VIABAHN	Kazemi (n=20, **65% PP** 1yr), Ansel (n=27, 52% PP at 18 months)

Baseline Lesion Characteristics

		Single-Arm Study: All Patients	Single-Arm Study: Lesions with ISR
Lesions		900	142
Lesion length (mm)		100 ± 82	127 ± 90
Diameter stenosis		85 ± 16%	87 ± 12%
TASC 2000 class	**A**	26%	25%
	B	29%	30%
	C	25%	29%
	D	14%	16%
Lesions > 7 cm		48%	62%
Lesions > 15 cm		22%	33%
Total occlusions		38%	31%
In-stent restenosis (ISR)		14%	100%

Zilver PTX® effectiveness in treating ISR Primary Patency (PSVR < 2.5)



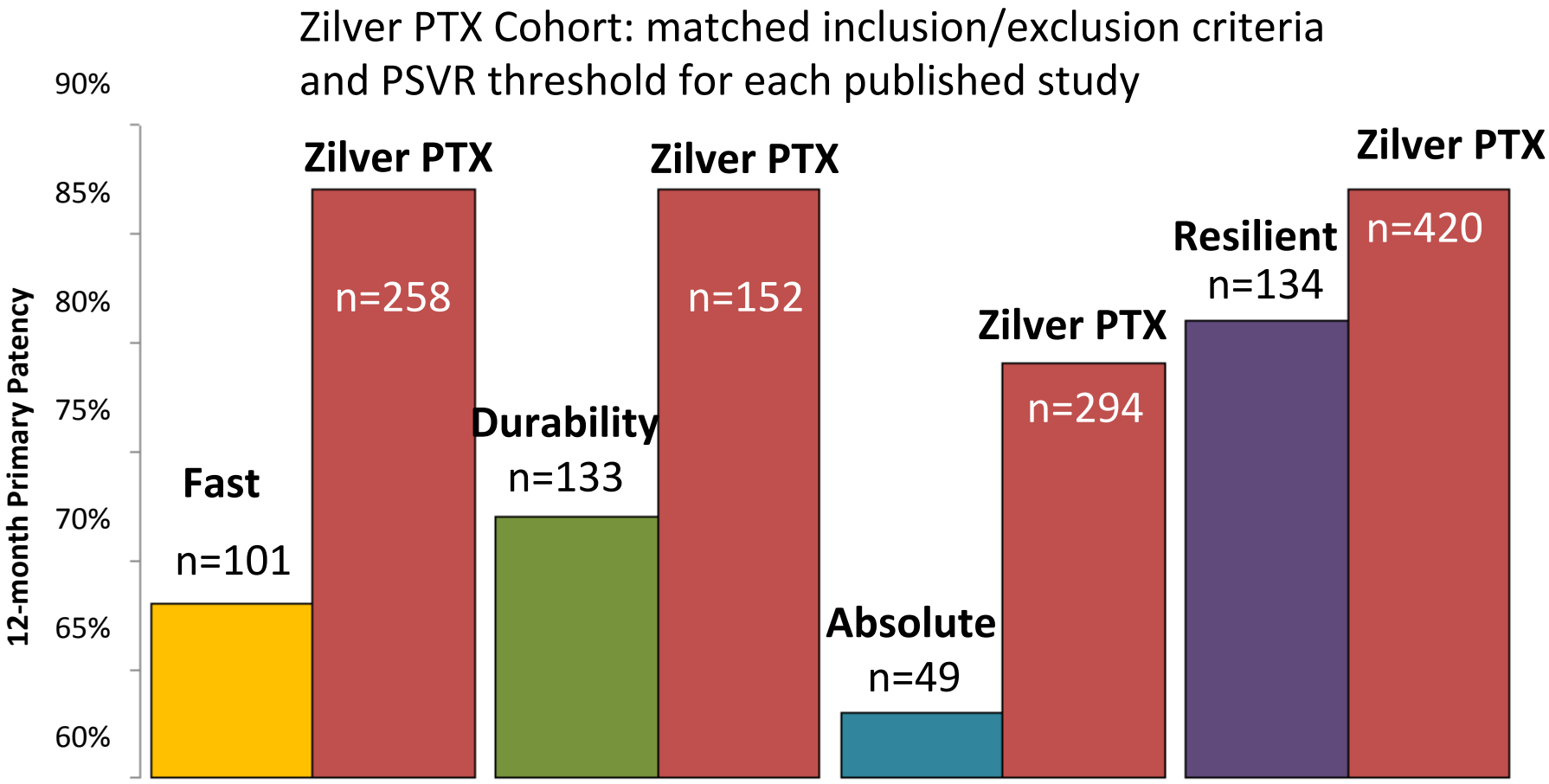
Zilver PTX®
No in-stent restenosis

Zilver PTX®
In-stent restenosis

Does Zilver PTX mean the end to bare metal stenting in the SFA?

- Expect to Parallel Coronary DES usage
  - DES rule rather than the exception
- May be disruptive to planned Drug eluting balloon development
  - Consistent angiographic and hemodynamic early result
  - Stent fractures appear rare with this platform
- Long-term bioabsorbable stents will be evaluated (7-10 yrs)

Zilver PTX Patency Compared to BMS



Zilver PTX stenting increases 12-month patency rates relative to BMS published literature

Literature Comparisons: TLR at 12 and 24 Months

Literature			Matching Registry Subset
Study	Inclusion Criteria	TLR	TLR
STRIDES: (Lammer 2009)*	• Single SFA lesion • No in-stent restenosis • Lesion length 3-17 cm • Rutherford 2-5	**Dynalink-E** everolimus-eluting stent **20% at 12 months (n = 104)**	**Zilver® PTX® 6% at 12 months (n = 315)**
		Dynalink-E everolimus-eluting stent **24 months Pending**	**Zilver® PTX® 11% at 24 months (n=115)**

*Lammer, J., et al. First-in-human clinical trial of a nitinol self-expanding everolimus-eluting stent for prevention of restenosis following infrainguinal endovascular intervention: the STRIDES trial, CIRSE 2009

Hypothetical Cost Effectiveness of Zilver PTX
TASC A & B Lesions

Non-DES		
100 index intervention (1.4 stents/case)	100*1.4*US$1300	182,000
30 re-intervention (12M PP ~70%)	30*US$1300	39,000
TOTAL		US$221,000
DES		
100 index intervention (1.4 stents/case)	100*1.4*US$1800	252,000
10 re-intervention (12M PP ~90%)	10*US$1800	18,000
Total		US$270,000

Incremental Cost Per Re-intervention Avoided = US$2450

Hypothetical Cost Effectiveness of Zilver PTX
TASC C & D Lesions

Bypass		
100 index intervention + hospitalization	100*US$6300†	630,000
15 endovascular re-intervention (12M PP ~85%)	15*US$1300	19,500
TOTAL		US$649,500
DES		
100 index intervention (**3.7** stents/case)	100***3.7***US$1800	666,000
100 hospitalization (average 1.5 days)	100*1.5*US$650	97,500
15 re-intervention (12M PP ~85%)	15*US$1800	27,000
Total		US$790,500

† Forbes et al. J Vasc Surg. 2010 May;51(5 Suppl):43S-51S

Incremental Cost Per Patient = US$1410

Hypothetical Cost Effectiveness of Zilver PTX
TASC C & D Lesions

Bypass		
100 index intervention + hospitalization	100*US$6300†	630,000
15 endovascular re-intervention (12M PP ~85%)	15*US$1300	19,500
TOTAL		US$649,500
DES		
100 index intervention (**2.7** stents/case)	100***2.7***US$1800	**486,000**
100 hospitalization (average 1.5 days)	100*1.5*US$650	97,500
15 re-intervention (12M PP ~85%)	15*US$1800	27,000
Total		**US$610,500**

† Forbes et al. J Vasc Surg. 2010 May;51(5 Suppl):43S-51S

Incremental Cost Per Patient = US$390

Conclusion:
Promising Treatment of Real World PAD

- Zilver PTX® is an effective treatment for patients with complex disease
  - Complementary to RCT
  - Low 1.5% stent fracture rate through 12 months
  - 86.2% primary patency rate at 12 months
    - Diabetics: 86% patency through 12 months
    - Long lesion: 77% patency through 12 months
    - In-stent restenosis: 80% patency through 12 months
- Freedom from TLR remains stable through 24 months
- Sustained clinical benefit through 24 months
- Potentially cost-effective treatment strategy for SFA disease