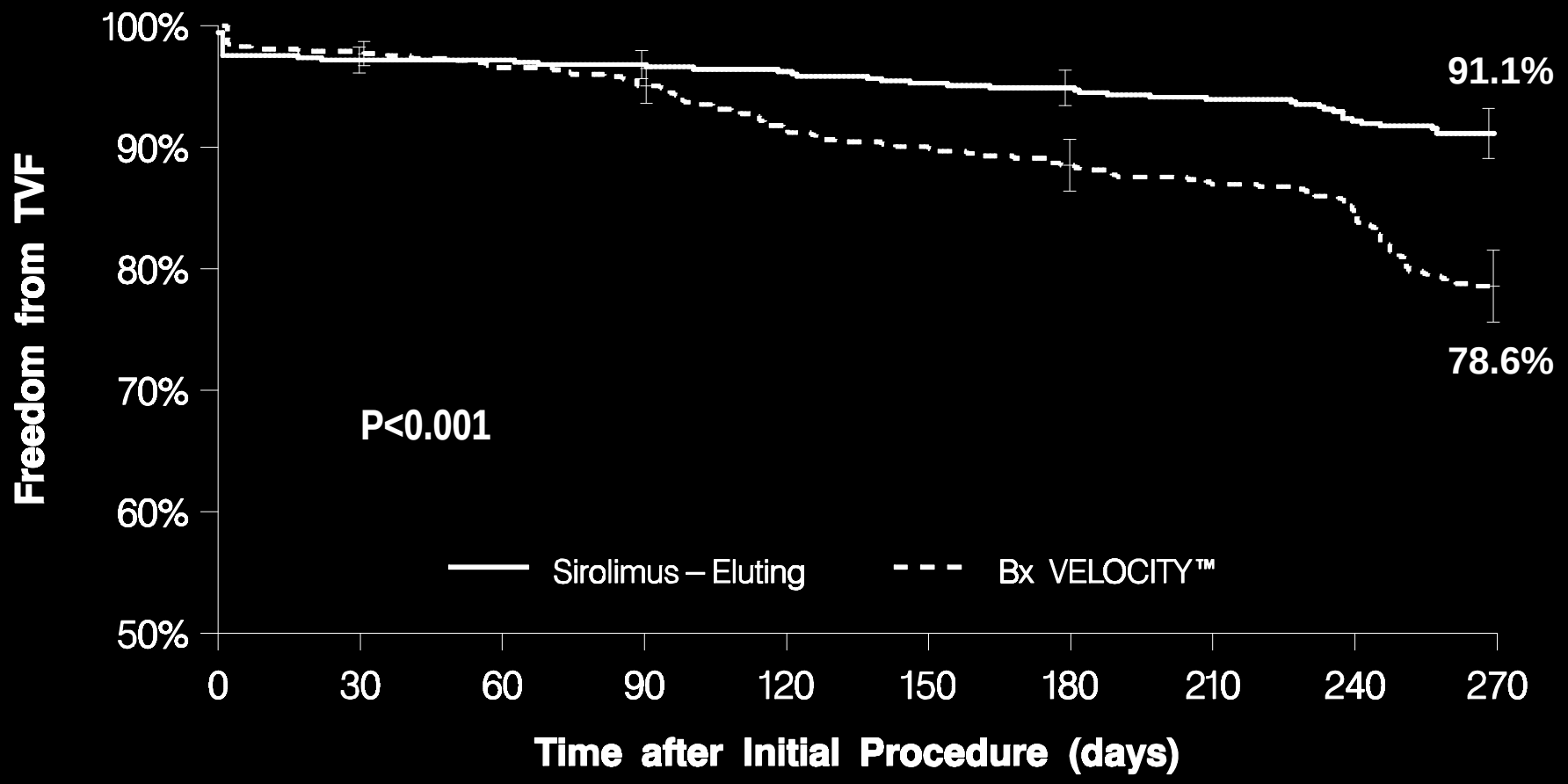
SIRIUS: Clinical Events
All Events (To 9 Months)

Events	Sirolimus % n=533	Control % n=525	p-value
Death	0.9 (5)	0.6 (3)	0.726
MI (all)	2.8 (15)	3.2 (17)	0.723
Q-wave	0.8 (4)	0.4 (2)	0.687
Non Q-wave	2.1 (11)	2.9 (15)	0.433
TLR (clinically driven)	4.1 (22)	16.6 (87)	<0.001
TVR (non-TL)	3.2 (17)	4.8 (25)	0.210
MACE	7.1 (38)	18.9 (99)	<0.001
TVF (1° endpoint)	8.6 (46)	21.0 (110)	<0.001

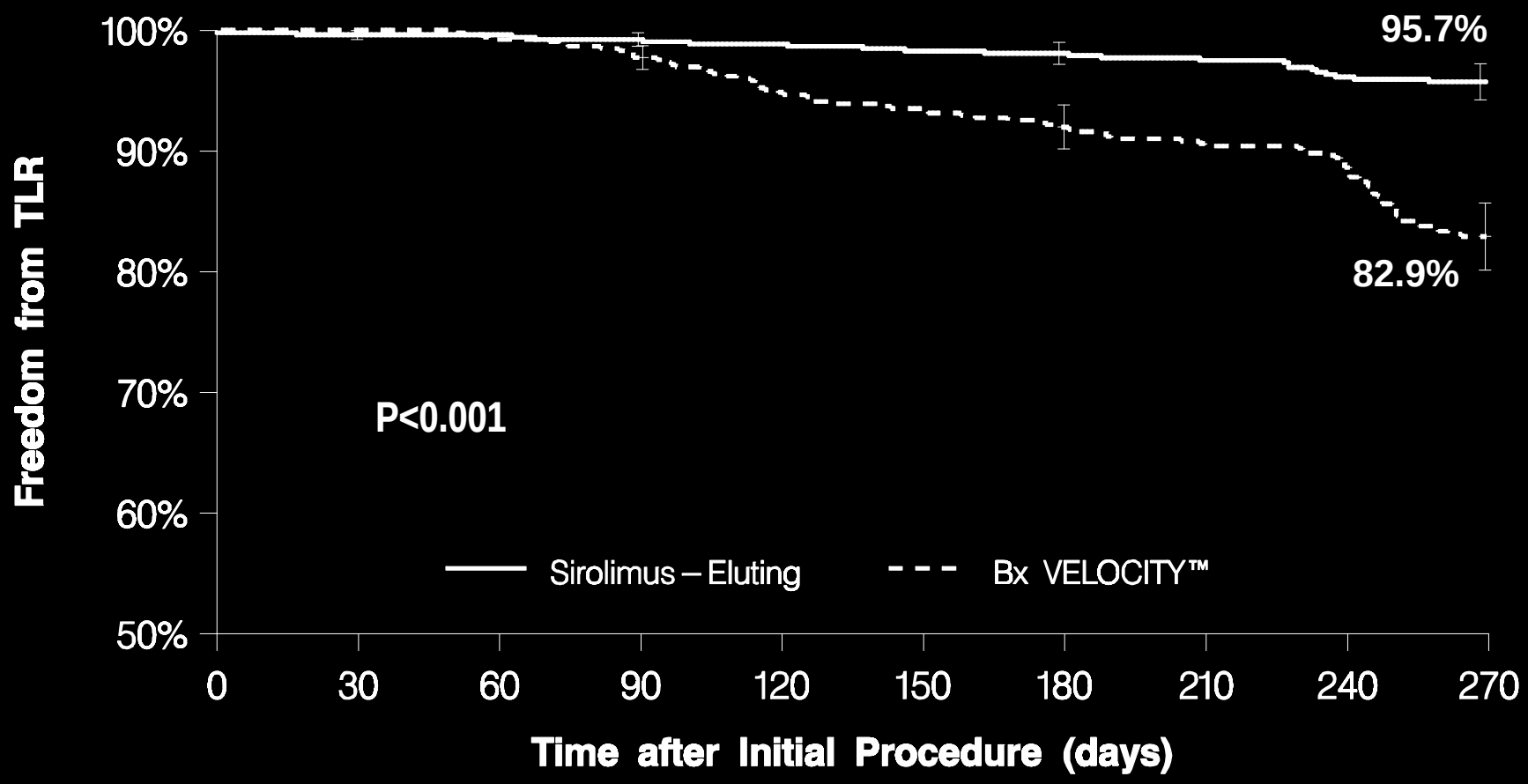
SIRIUS: Deaths in Sirolimus Eluting-stent Group

1. 53 year-old female. Successful index procedure on 7/31/01 of the mid LAD. Five hours post-procedure experienced respiratory arrest and was intubated. CT scan revealed large **brain hematoma**. Patient expired one day post procedure. (Cardiac)
2. 83 year-old female. Successful index procedure on 7/15/01 of the proximal CFX. On 12/15/01 she was admitted with unresponsiveness. Patient developed urinary tract infection, liver dysfunction, renal failure, OVT, pneumonia and CHF. Patient expired 1/19/02 **due to heart failure**. (Cardiac)
3. 67 year-old male. Successful index procedure on 5/4/01 of the 1st OM. On 5/22/01, CT scan revealed right kidney tumor with "spot" on lung, stomach and left shoulder. On 9/8/01, patient expired due to metastatic renal cell **carcinoma**. (Non-cardiac)
4. 73 year-old male. Successful index procedure on 7/27/01 of the R-PDA. On 3/23/02, patient slipped on ice and suffered a **subdural hematoma** and expired. (Non-cardiac)
5. 84 year-old female. Successful index procedure on 5/21/01 of mid RCA. On 8/12/01 she developed seizures. A CT scan revealed an **acute intracranial hemorrhage**. The patient expired on 8/20/01 due to a CVA. (Non-cardiac)

SIRIUS: Event Free Survival Curves
TVF - Death, MI, TVR

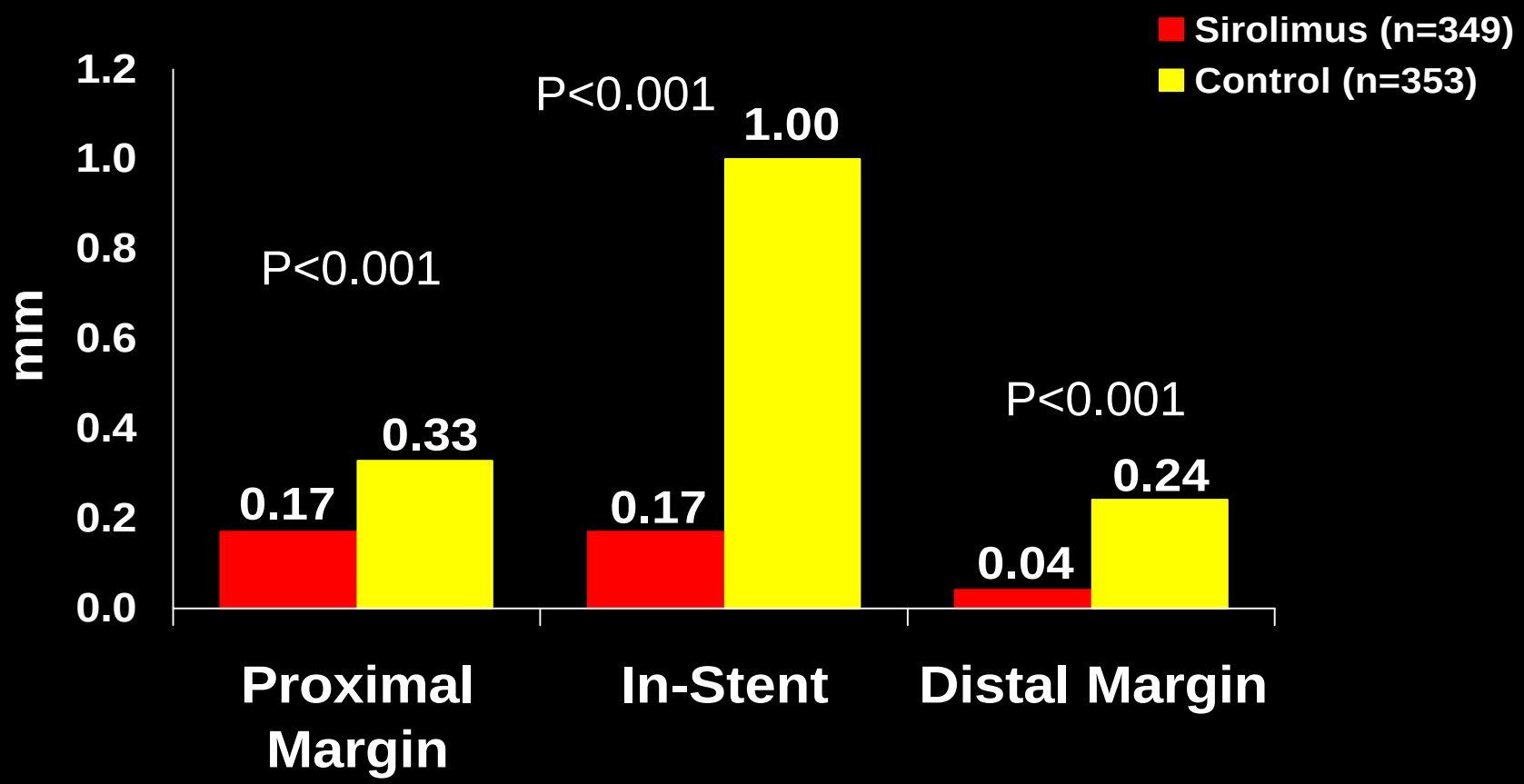


SIRIUS: Event Free Survival Curves TLR - TL-CABG, TL-PTCA



SIRIUS: QCA Stent and Stent Margins Analysis

Late Loss (mm)



Additional Safety Assessments

- Overlapping Stents
- Stent Thrombosis
- Aneurysms
- Incomplete Apposition
- Polymer and Sirolimus Dose

SIRIUS: Overlapping Stents Clinical Outcomes

	Sirolimus % n=176	Control % n=168	p-value
In-hospital MACE	4.5	4.2	>0.999
Stent Thrombosis			
Subacute	0.6	0.6	>0.999
Late	0	0	---
MACE at 9 months	8.5	22.6	<0.001
TLR at 9 months	4.5	17.9	<0.001

Stent Thrombosis

	Sirolimus (%)	Control (%)
RAVEL Total (1-365 Days) (60 Day Antiplatelet Therapy)	0 (120)	0 (118)
SIRIUS Total (90 Day Antiplatelet Therapy)	0.4 (2/533)	0.8 (4/525)
Subacute (1-30 Days)	0.2 (1)	0.2 (1)
Late (31–270 Days)	0.2 (1)	0.6 (3)

No statistically significant differences between groups

Aneurysms

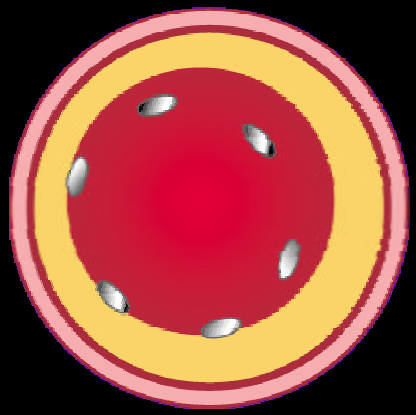
	Sirolimus	Control
RAVEL (6 Months)	0/109	0/107
SIRIUS (8 Months)	2/346 (0.6%)	4/356 (1.1%)

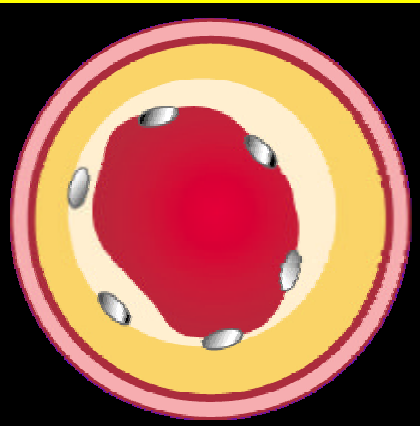
NOTE: No adverse events related to aneurysms

$$\text{Aneurysm} = \frac{\text{treatment site diameter}}{\text{normal reference vessel}} \geq 1.2$$

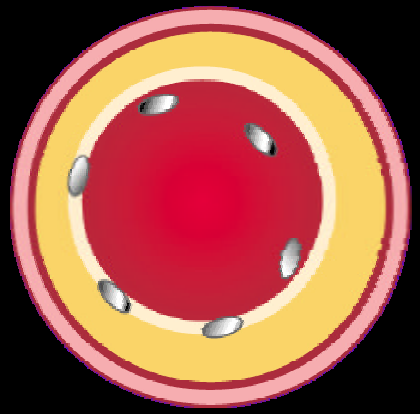
Fates of Incomplete Apposition (IA)

Baseline
Incomplete Apposition





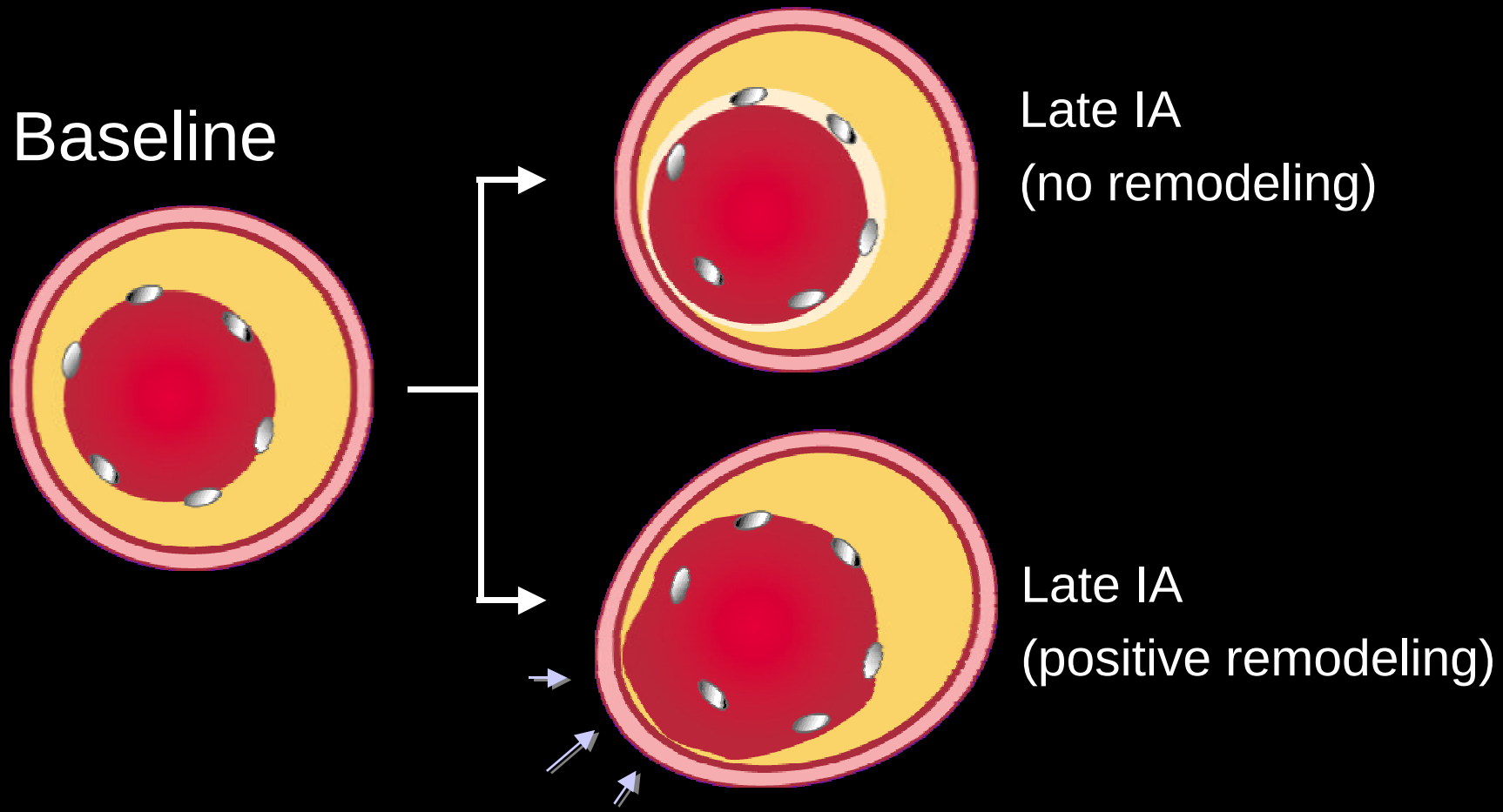
Healed/Resolved
Incomplete Apposition



Preserved
Incomplete Apposition

Definition: Separation of one or more struts from vessel wall with evidence of blood speckles behind the stent strut

Follow-up IA


Baseline
Late IA
(no remodeling)
Late IA
(positive remodeling)

Association of Late IA with Bare Stents

Vivek M. Shah, MS; Gary S. Mintz, MD; Sue Apple, DNSc; Neil J. Weissman, MD*

- Baseline and 6-month IVUS evaluation of 206 bare stent patients
- 4.4% (9) incidence of late IA
- All 9 patients had positive remodeling
- No clinical events

*Circulation 2002; 106: 1753-1755

RAVEL: Incomplete Apposition

IVUS follow-up at 6 months

	Sirolimus	Control	p-value
Incomplete Apposition	(10/48) 20.8%	(2/47) 4.3%	0.027

IVUS follow-up at 18 months on 9 out of 10 sirolimus patients

- IA remained in all 9 patients
- No adverse events reported in these10 patients
- 1 aneurysm noted; asymptomatic. Intramural hemorrhage noted in area of aneurysm on earlier IVUS

Data submitted but not reviewed by the FDA

SIRIUS: Incomplete Apposition

	Sirolimus	Control	p-value
Post procedure	15/105 (14.3%)	14/94 (14.9%)	>0.999
8 Month Follow-Up	18/96 (18.7%)	7/76 (9.2%)	0.085
Matched pair analysis			
Resolved	6/72 (8.3%)	3/55 (5.4%)	0.731
Persistent	6/72 (8.3%)	6/55 (10.9%)	0.762
Late	7/72 (9.7%)*	0/55 (0.0%)	0.019

- No late IA occurred in the area of overlapping sirolimus stents
- None of the sirolimus patients with late IA reported an adverse event

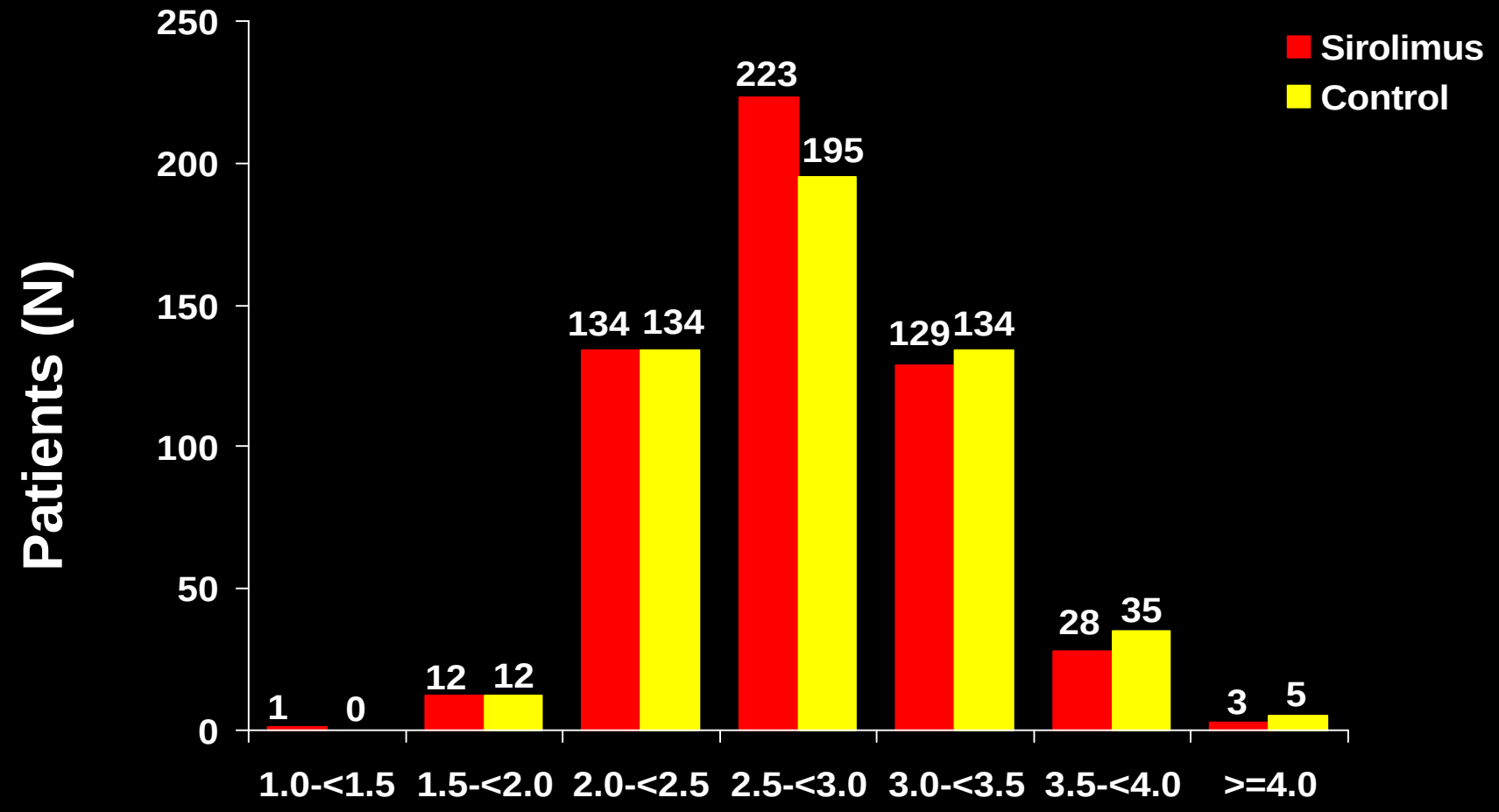
* 3 patients with positive remodeling: >20% increase EEM area

Data submitted but not reviewed by the FDA

Summary: Late Incomplete Apposition

- 4-5% incidence with bare metal stents
- Unlike brachytherapy, there is complete endothelialization
- Effect is similar to side branch jail
- Not related to overlapping stents
- No increase in stent thrombosis despite being off antiplatelet therapy for 6-16 months

Frequency of Patients by Treatment Group and RVD



* Stent sizes available 2.5-3.5 mm

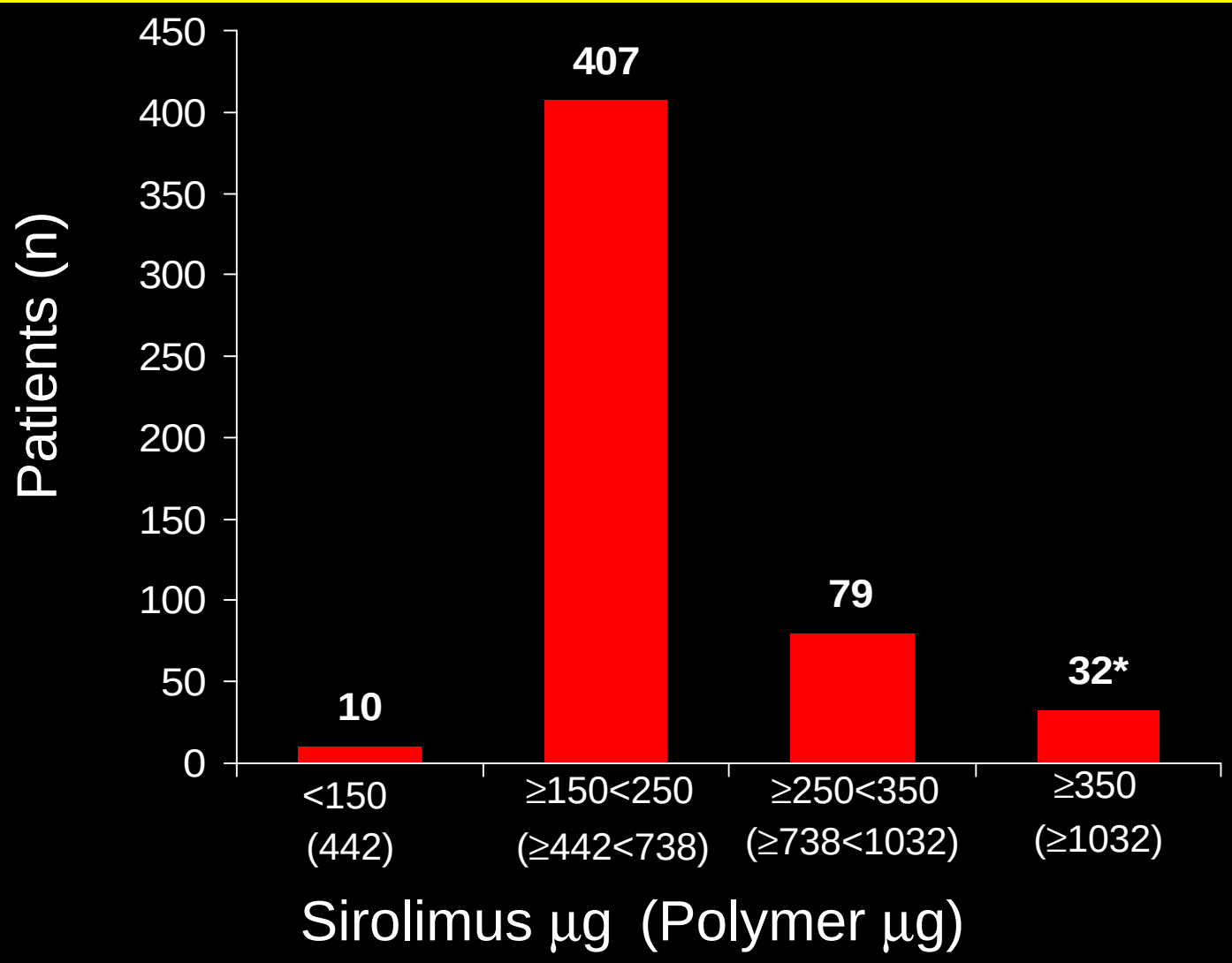
Frequency of Patients by Stent Length

Proposed Sirolimus-eluting Matrix and Drug Content

Stent Diameter (mm)	Stent Length					
	8mm	13mm	18mm	23mm	28mm	33mm
2.25	71µg	111µg	150µg	190µg	229µg	268µg
2.5	71µg	111µg	150µg	190µg	229µg	268µg
2.75	71µg	111µg	150µg	190µg	229µg	268µg
3.0	71µg	111µg	150µg	190µg	229µg	268µg
3.5	83µg	129µg	175µg	221µg	268µg	314µg
4.0	83µg	129µg	175µg	221µg	268µg	314µg
4.5	105µg	164µg	223µg	281µg	340µg	399µg
5.0		164µg	223µg	281µg	340µg	399µg

94% of patients treated with CYPHER™ stent(s) received a dose up to 350µg sirolimus

SIRIUS: Distribution of Drug and Polymer



* MACE - 2 periprocedural MI's and 3 TLR's, no aneurysms, 1 late IA

SIRIUS: Secondary Analysis

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Financial Disclosures

- No equity or consulting relationship
- Harvard Clinical Research Institute, a non-profit research center at Harvard Medical School, is the CRO for the SIRIUS trial
- Cordis provides an educational grant to the Department of Medicine, Brigham and Women's Hospital, for fellowship training in clinical trials
- Travel expenses will be reimbursed

SIRIUS: Multivariable Predictors*

For all major angiographic and clinical endpoints…

- Reference vessel size
- Lesion length/stent length
- Diabetes

*** for both control and sirolimus groups**

Data in this presentation have been submitted but have not been reviewed by the FDA

SIRIUS: Determinants of TLR to 270 Days

	Coefficient	Standard Error	Odds Ratio	p-value
RVD (per mm)	-0.8687	0.2442	0.419	0.0004
Lesion Length (per mm)	0.0459	0.0165	1.047	0.0053
Diabetes	0.5404	0.2205	1.717	0.0143
Treatment Assignment	-1.5655	0.2509	0.209	0.0001

SIRIUS: Determinants of In-Segment Restenosis

	Coefficient	Standard Error	Odds Ratio	p-value
RVD (per mm)	-0.8729	0.2287	0.418	0.0001
Lesion Length (per mm)	0.0351	0.0163	1.036	0.0316
Diabetes	0.8707	0.2102	2.389	0.0001
Treatment Assignment	-1.8677	0.2270	0.154	0.0001

Predicted Angiographic Restenosis Rates

Post-Procedure In-Stent MLD	Lesion Length 10 mm	15 mm	20 mm	25 mm
Non-Diabetics				
2.5 mm	27%	30%	33%	37%
3.0 mm	17%	19%	22%	25%
3.5 mm	10%	12%	14%	16%
4.0 mm	6%	7%	8%	10%
Diabetics				
2.5 mm	35%	39%	43%	46%
3.0 mm	23%	26%	30%	33%
3.5 mm	15%	17%	19%	22%
4.0 mm	9%	10%	12%	14%

Ho KKL, Senerchia C, Rodriguez O, Chauhan MS, Kuntz RE. Predictors of angiographic restenosis after stenting: pooled analysis of 1197 patient with protocol-mandated angiographic follow-up from 5 randomized stent trials. *Circulation* 1998; 98:I-362.

SIRIUS: Multivariable Predictors
In-Segment Restenosis - Control

Non–Diabetic

Ref Diam	Lesion Length <12mm	12-15mm	>15mm
>3.0mm	18.7%	20.9%	25.0%
2.5-3.0mm	27.7%	30.6%	35.7%
<2.5mm	36.8%	40.1%	45.7%

Diabetic

Ref Diam	Lesion Length <12mm	12-15mm	>15mm
>3.0mm	35.4%	38.7%	44.3%
2.5-3.0mm	47.8%	51.3%	57.0%
<2.5mm	58.1%	61.5%	66.8%

SIRIUS: Multivariable Predictors
TLR - Control

Non–Diabetic

Ref Diam	Lesion Length <12mm	12-15mm	>15mm
>3.0mm	7.4%	8.7%	11.4%
2.5-3.0mm	11.7%	13.7%	17.7%
<2.5mm	16.7%	19.4%	24.6%

Diabetic

Ref Diam	Lesion Length <12mm	12-15mm	>15mm
>3.0mm	12.0%	14.1%	18.2%
2.5-3.0mm	18.5%	21.5%	27.0%
<2.5mm	25.6%	29.3%	35.9%

SIRIUS: Multivariable Predictors
In-Segment Restenosis - Sirolimus

Non–Diabetic

Ref Diam	Lesion Length <12mm	12-15mm	>15mm
>3.0mm	3.4%	3.9%	4.9%
2.5-3.0mm	5.6%	6.4%	7.9%
<2.5mm	8.2%	9.4%	11.5%

Diabetic

Ref Diam	Lesion Length <12mm	12-15mm	>15mm
>3.0mm	7.8%	8.9%	10.9%
2.5-3.0mm	12.4%	14.0%	17.0%
<2.5mm	17.7%	19.8%	23.7%

SIRIUS: Multivariable Predictors
TLR - 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: Δ In-Segment Restenosis
Between Control and Sirolimus

Non–Diabetic

Ref Diam	Lesion Length <12mm	12-15mm	>15mm
≥3.0mm	15.2%	17.0%	20.1%
2.5-3.0mm	22.1%	24.2%	27.8%
<2.5mm	28.5%	30.7%	34.2%

Diabetic

Ref Diam	Lesion Length <12mm	12-15mm	>15mm
≥3.0mm	27.6%	29.8%	33.3%
2.5-3.0mm	35.4%	37.3%	40.0%
<2.5mm	40.5%	41.7%	43.1%

SIRIUS: Δ TLR
Between Control and Sirolimus

Non–Diabetic

Ref Diam	Lesion Length <12mm	12-15mm	>15mm
≥3.0mm	5.7%	6.8%	8.8%
2.5-3.0mm	9.0%	10.5%	13.4%
<2.5mm	12.7%	14.6%	18.2%

Diabetic

Ref Diam	Lesion Length <12mm	12-15mm	>15mm
≥3.0mm	9.2%	10.8%	13.7%
2.5-3.0mm	14.0%	16.1%	19.8%
<2.5mm	18.9%	21.3%	25.4%

SIRIUS: In-Segment Restenosis Treatment Effect Between Control and Sirolimus

Non–Diabetic

Ref Diam	Lesion Length <12mm	12-15mm	>15mm
≥3.0mm	81.7%	81.2%	80.4%
2.5-3.0mm	79.8%	79.2%	77.9%
<2.5mm	77.6%	76.6%	74.8%

Diabetic

Ref Diam	Lesion Length <12mm	12-15mm	>15mm
≥3.0mm	78.0%	77.0%	75.3%
2.5-3.0mm	74.1%	72.7%	70.2%
<2.5mm	69.6%	67.8%	64.5%

SIRIUS: TLR Treatment Effect
Between Control and Sirolimus

Non–Diabetic

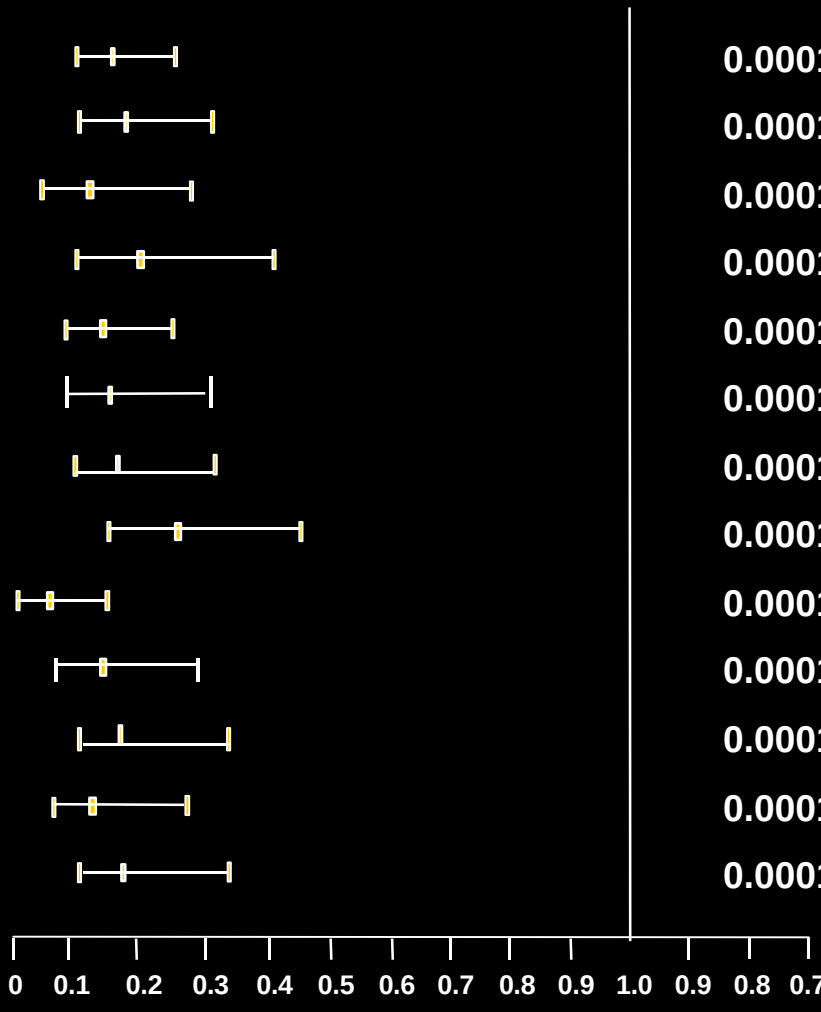
Ref Diam	Lesion Length <12mm	12-15mm	>15mm
≥3.0mm	77.8%	77.6%	77.0%
2.5-3.0mm	77.0%	76.6%	75.7%
<2.5mm	75.9%	75.3%	74.1%

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%

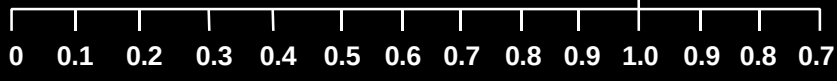
SIRIUS: Odds Ratio Subgroup Analysis TLR

	Sirolimus	Control	p-value	# events prevented per 1,000 patients
Overall	8.9	36.3	0.0001	274
Male	9.1	34.3	0.0001	251
Female	8.1	42.9	0.0001	347
Diabetes	17.6	50.5	0.0001	328
No Diabetes	6.1	31.2	0.0001	251
LAD	10.1	41.6	0.0001	315
Non-LAD	8.0	32.7	0.0001	247
Small Vessel (<2.75)	14.9	39.9	0.0001	250
Large Vessel	2.9	33.2	0.0001	303
Short Lesion	8.0	36.1	0.0001	282
Long Lesion (>13.5)	9.9	36.8	0.0001	269
Overlap	8.8	43.5	0.0001	347
No Overlap	8.9	33.6	0.0001	247

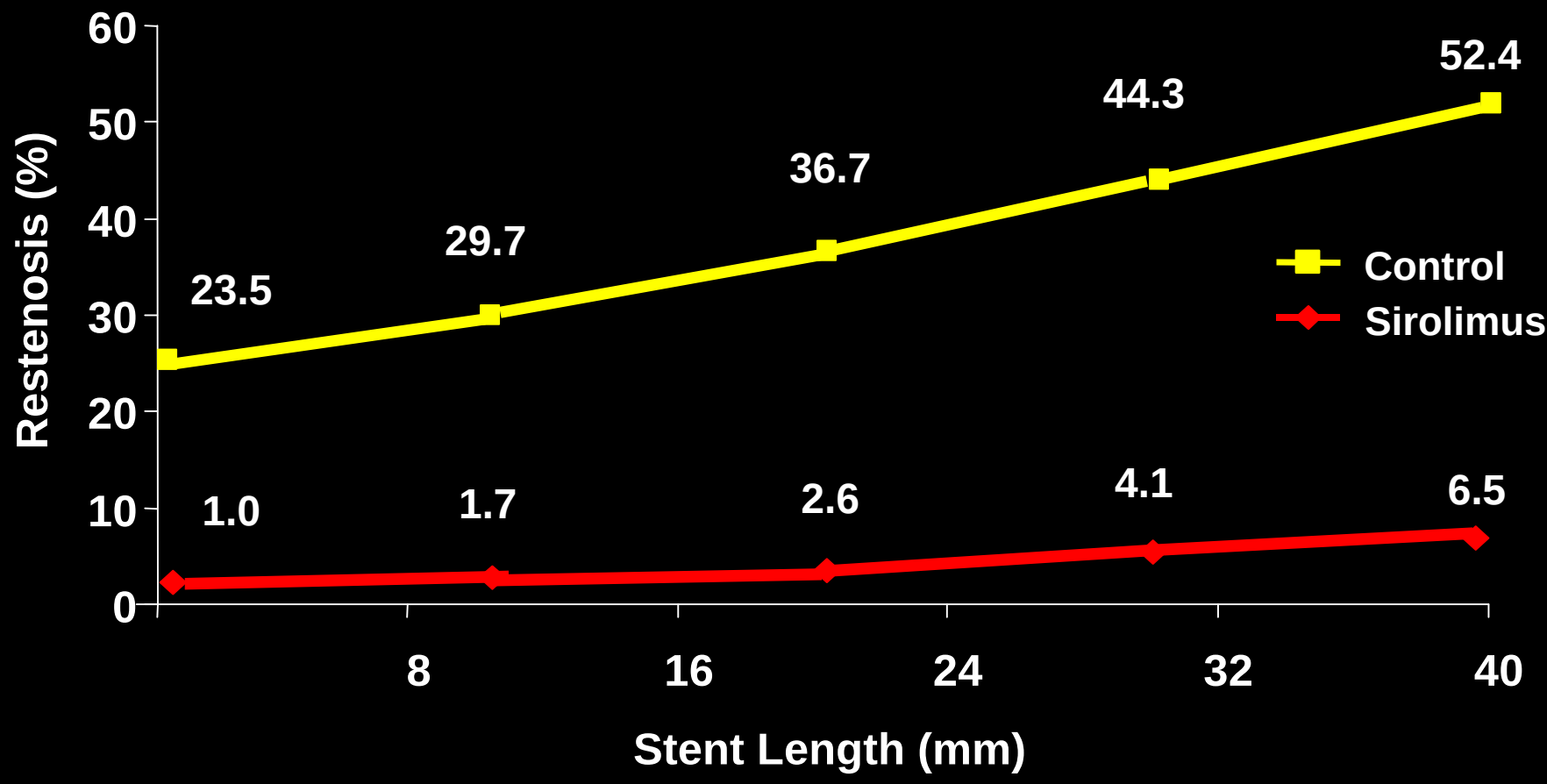


SIRIUS: Odds Ratio Subgroup Analysis In-Segment Restenosis

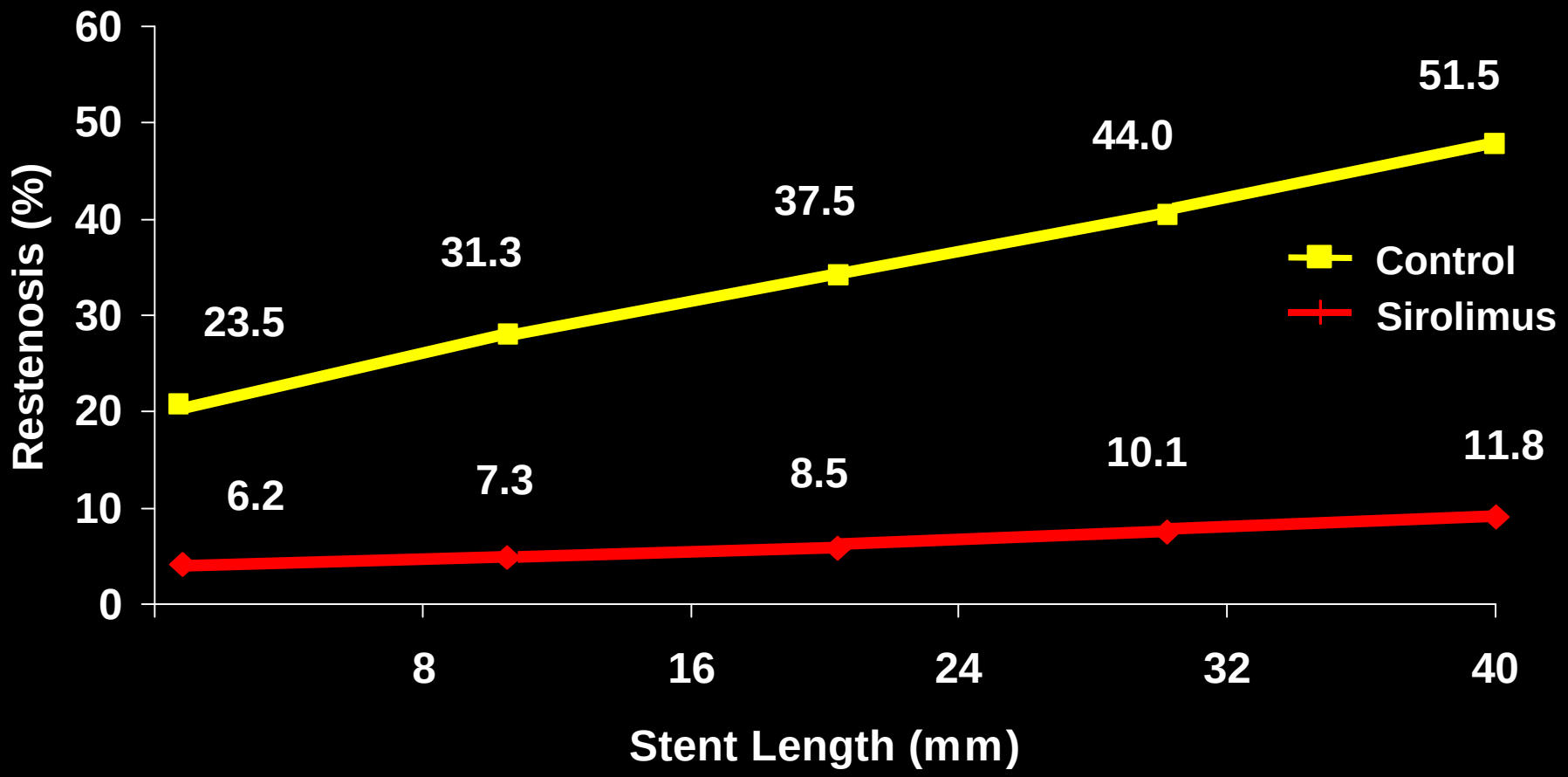
	Sirolimus	Control	p-value	# events prevented per 1,000 patients
Overall	4.1	16.6	0.0001	124
Male	4.4	16.6	0.0001	122
Female	3.4	16.5	0.0007	130
Diabetes	6.9	22.3	0.0006	154
No Diabetes	3.2	14.3	0.0001	111
LAD	5.1	19.8	0.0001	147
Non-LAD	3.4	14.3	0.0001	109
Small Vessel (<2.75)	6.3	18.7	0.0001	125
Large 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



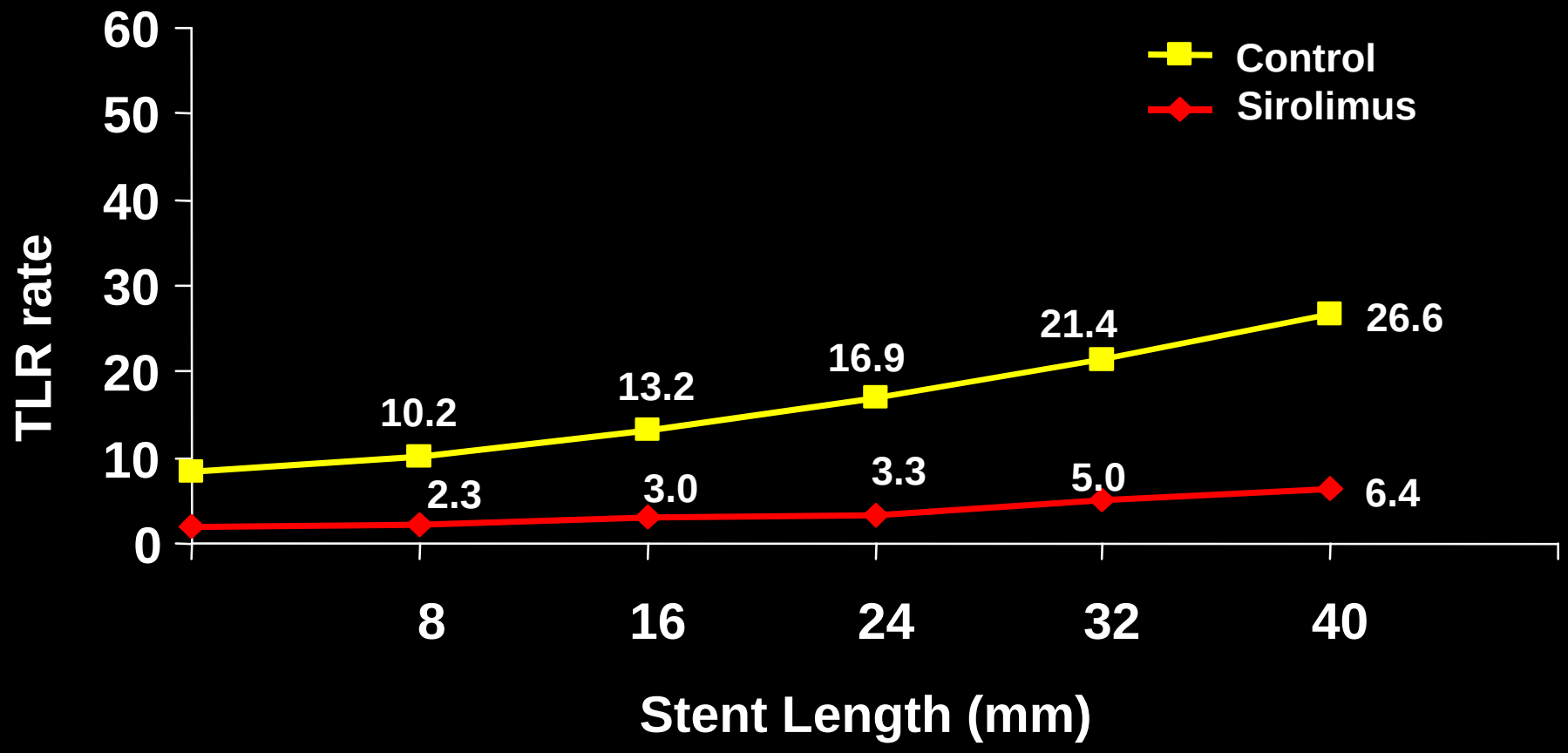
SIRIUS: Restenosis vs. Stent Length In-Stent



SIRIUS: Restenosis vs. Stent Length In-Segment



SIRIUS: TLR vs. Stent Length



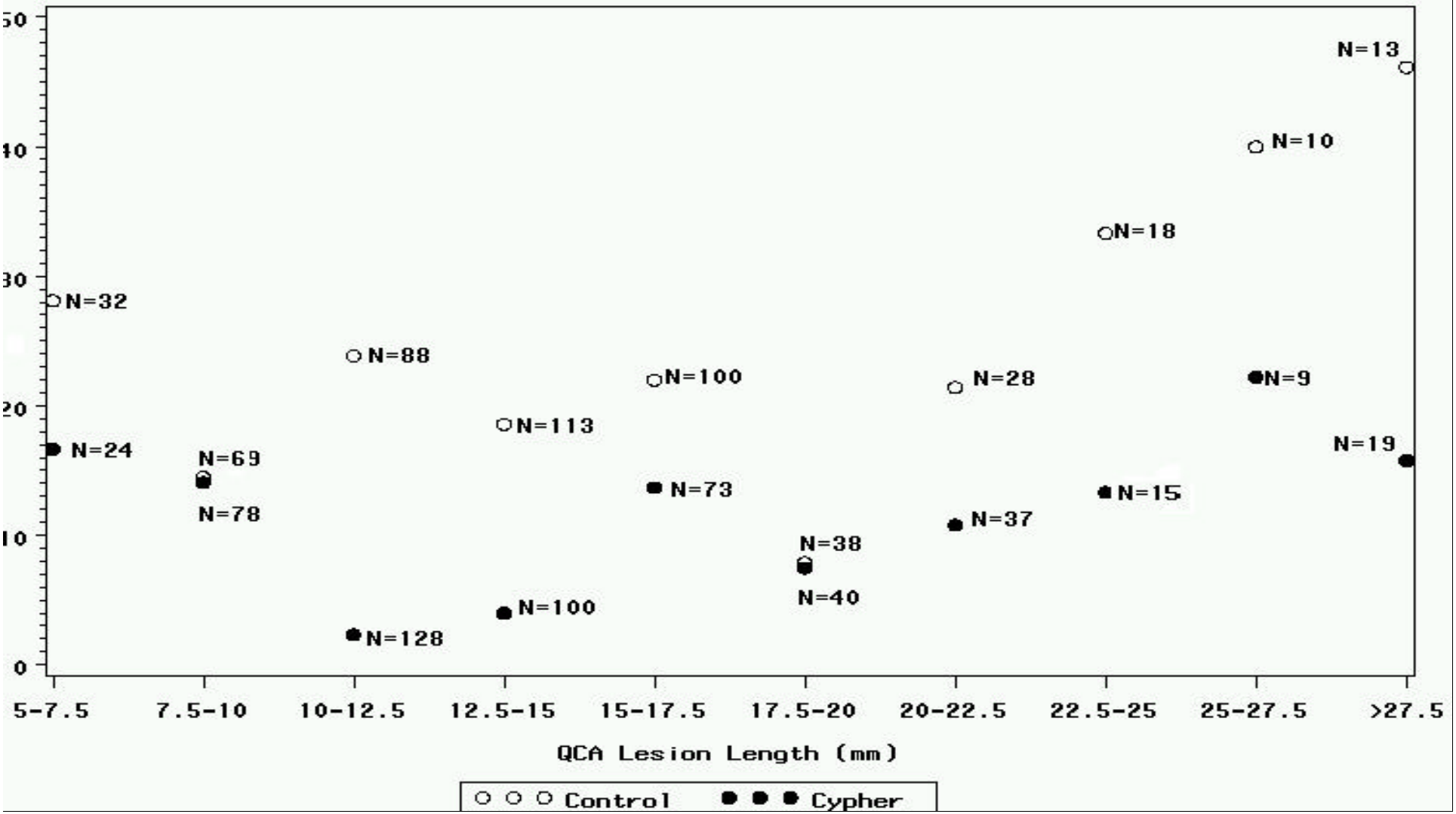
Treatment Interaction Evaluation (1)

- FDA analysis suggests no treatment effect on TVF for sirolimus in lesions ≥ 20 mm
- FDA evaluated the treatment effect on TVF within subsets of lesions binned to 5 mm increments
  - Assessment based on overlapping of confidence intervals of treatment TVF rates within lesion length bins
- In addition to multiple sub-segment analyses, FDA used nonlinear regression models to suggest no treatment benefit for sirolimus in lesions ≥20 mm
  - It appears that separate formulas for a combination of third order (cubic) terms were fitted to the two arms of the SIRIUS trial
  - No formulas or goodness-of-fit data were provided for interpretation of the models

Treatment Interaction Evaluation (2)

- Our analysis of TVF also showed statistical differences remained for the subsets of short and long lesions (<15 mm v. =15 mm, <20 mm v. =20 mm)
  - Study not powered to show significance in 5 mm increments, but we also calculated odds ratios for TVF by 5 mm increment; most were significant
- 3 logistic regression models listed below on $\geq$20 mm length subgroup (n=149) adjusting for diabetes found significant treatment effect ($p<0.03$)
  - linear length term
  - linear and quadratic length terms
  - linear, quadratic and cubic terms
- Our analysis also detected no interactions between lesion length and treatment assignment, reference vessel size and treatment assignment, or diabetes and treatment assignment for the 4 common restenosis dependent variables: in-segment, ISR, TLR, and TVF
  - With the exception of RVD and treatment interaction for in-segment restenosis only
    - The interaction was a quantitative interaction, in which there was no difference in direction of effect, only a difference in magnitude of effect
    - A statistically significant difference between treatment arms remained across the RVD subgroups
    - For example, graph shows unadjusted TVF rate is always lower for sirolimus than control regardless of lesion length

Unadjusted 9-Month TVF Rates by Lesion Category



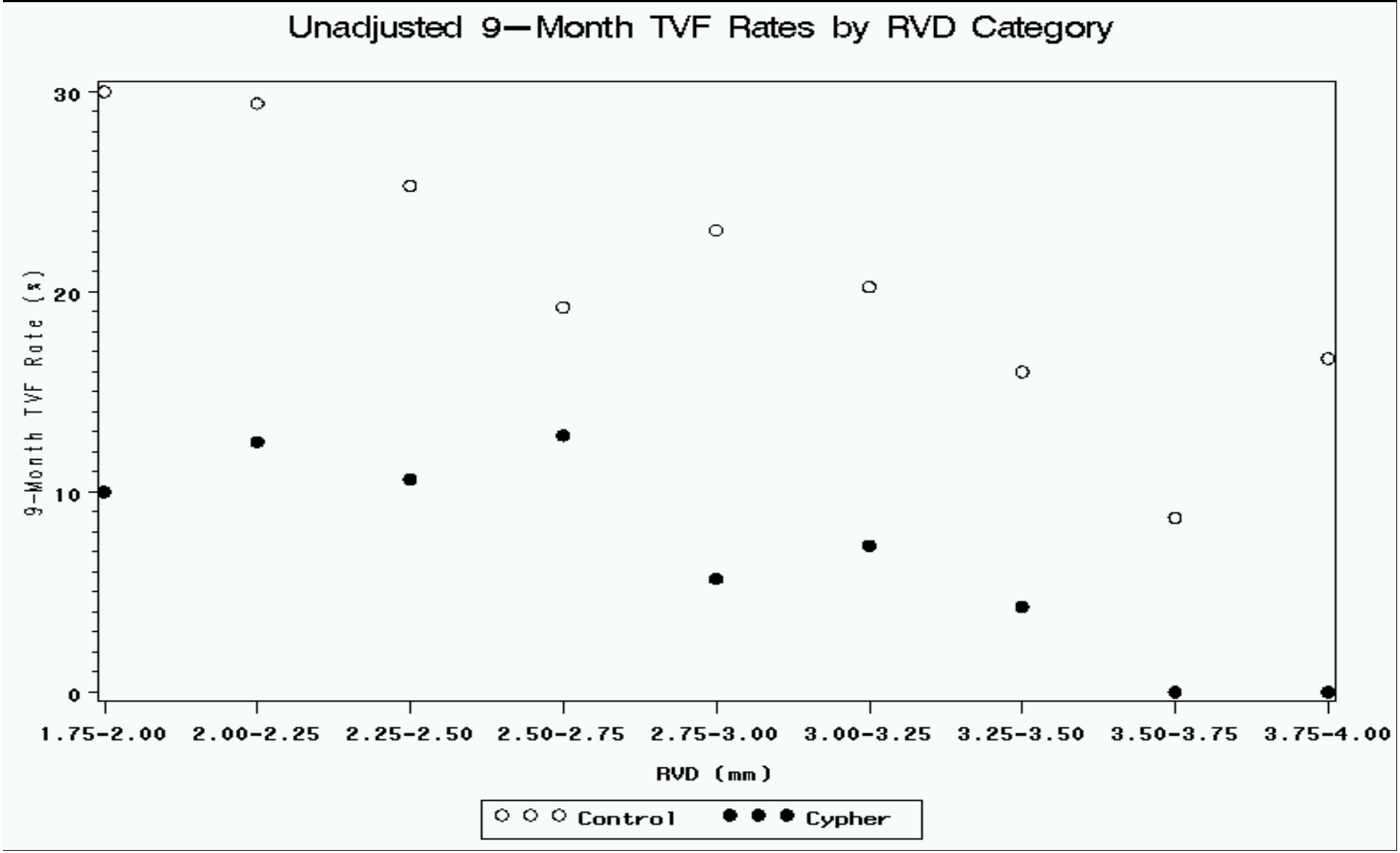
TVF vs. Lesion Length

- Our analyses showed that there was no compelling need to utilize quadratic or cubic regression over linear regression
  - No statistically significant non-linear (quadratic or cubic) main effects were found, based on TVF logistic model either ≥20 mm length subgroup or over entire length spectrum
  - No statistically significant interactions of treatment with length (linear, quadradic or cubic) were found, based on TVF logistic model (all p>0.19) either ≥20 mm length subgroup or over entire length spectrum
  - No marked improvements in discrimination or calibration were seen with non-linear modeling
- Unadjusted odds ratio for control vs. sirolimus 2.9 [1.3 - 6.7] in ≥20 mm patient subgroup
- Same subgroup analyses above repeated on length ≥15 mm (n=400) with similar, if not more significant results
- These analyses suggest that sirolimus is effective for lesion lengths =30 mm

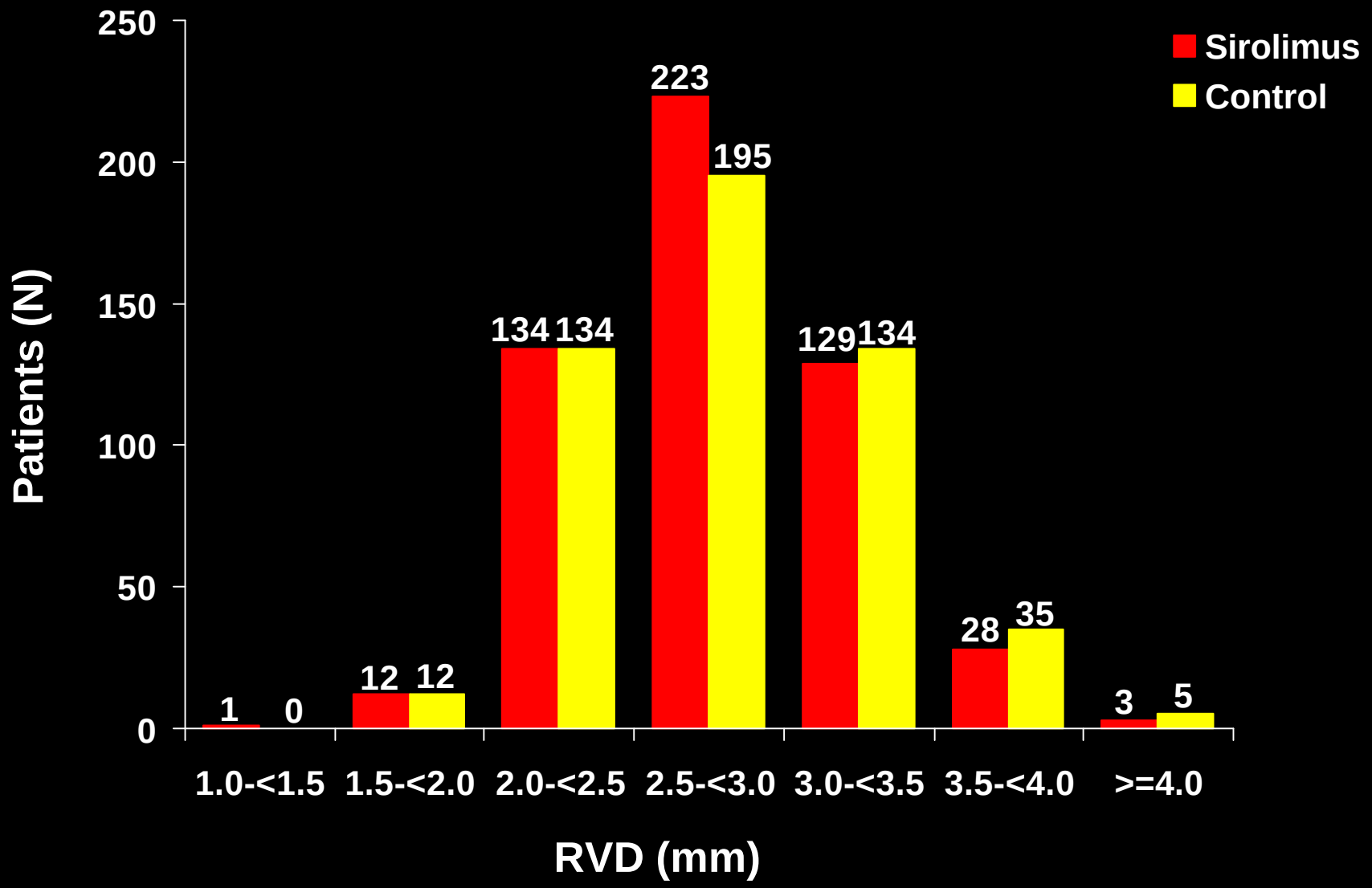
TVF vs. Reference Vessel Diameter (RVD)

- FDA used nonlinear regression models and multiple sub-segment analyses to suggest no treatment benefit for sirolimus at <2 mm and >3.7 mm RVD
- Graph shows unadjusted TVF rate is always lower for sirolimus than control regardless of RVD between >1.75 and 4.0 mm
- No statistically significant interactions of treatment with RVD
- In a logistic model the quadratic effect for RVD is highly non-significant ($p>0.4$) for both groups combined and by treatment group

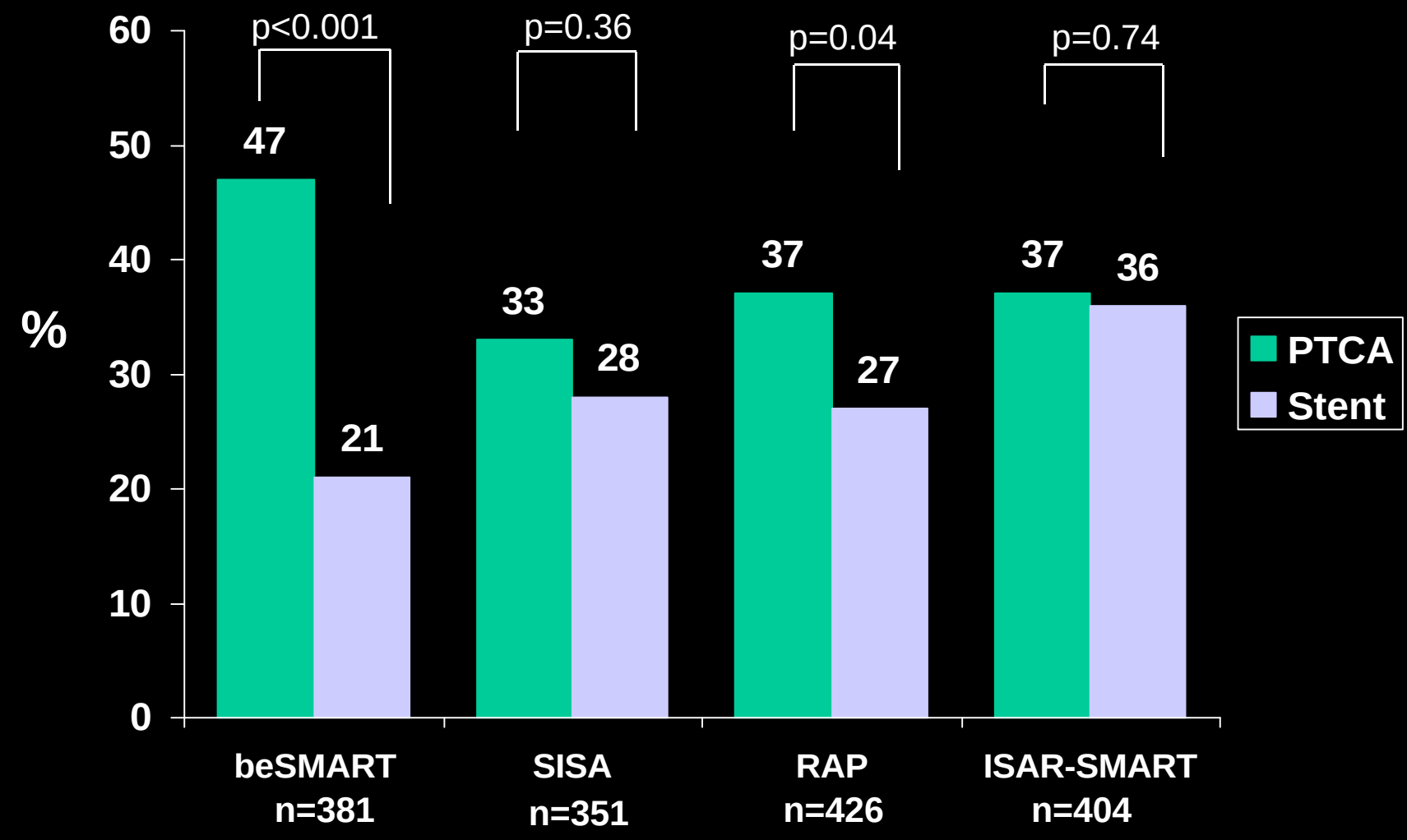
Unadjusted 9-Month TVF Rates by RVD Category



Frequency of Patients by Treatment Group and RVD

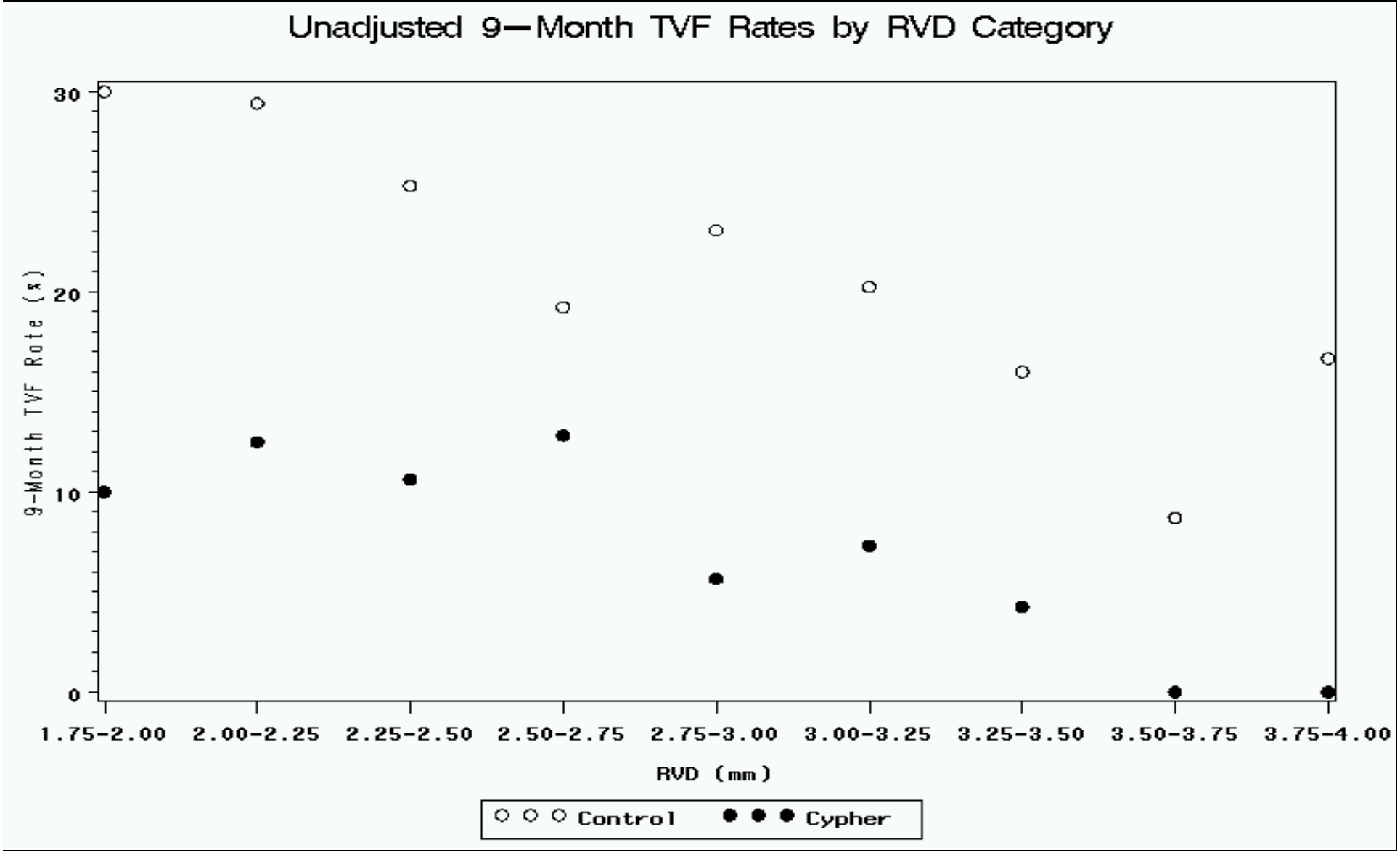


Restenosis Rates in Randomized Trials of Small-Vessel Stenting vs. Balloon PTCA*



* Columbo A, Stankovic G, Moses J. Selection of Coronary Stents. *J Am Coll Cardiol.* 2002;40:1021-33

Unadjusted 9-Month TVF Rates by RVD Category



TVF vs. Reference Vessel Diameter (RVD)

- There is good evidence for substantial treatment effect of sirolimus compared with placebo over a range of vessel sizes from 2.0 – 4.0 mm

- While there is no consistent evidence in small vessels (<2.75 mm) that coronary stenting reduces restenosis rates compared with balloon angioplasty, 4 RCTs demonstrated that stenting is as good or better than balloon angioplasty (but not worse)

  – The consistent treatment effect for vessels >2.0 mm suggests strongly that sirolimus is more effective than balloon angioplasty for small vessels

Overall Safety Conclusions

- Death and MI rates for sirolimus are similar to control
- The risk of stent thrombosis for sirolimus is similar to control
- The incidence of aneurysms for sirolimus is similar to control
- Sirolimus stents can be overlapped safely
- Data have been generated across a sirolimus dose range that supports the safety of stents up to 33 mm in length and >4.0 mm in diameter
- Late IA is more frequently observed with sirolimus
  - However, it does not appear to be related to any adverse outcomes
  - Long-term follow up is ongoing (yearly to 5 years)

Overall Efficacy Conclusions

- The superiority of the sirolimus-eluting stent is clearly demonstrated in two double-blind, randomized trials across all angiographic, IVUS and clinical endpoints
- Detailed angiographic analyses do not demonstrate evidence of an “edge effect”
- Efficacy is maintained across all lesion lengths (8-40 mm) and vessel diameters (2.0-4.0 mm) tested.
  - There are limited data for vessel diameters above 4.0 mm, however, since efficacy has been maintained across all other diameters it is anticipated that it will be maintained for vessels >4.0 mm.
- The 2-year angiographic and clinical data from the FIM trial as well as the 1-year clinical follow up in the RAVEL trial show sustained benefit with no evidence of “catch up” effect

Overall Conclusions

- The data demonstrate a clinically significant therapeutic benefit to patients over a bare metal stent
- The clinical benefit does outweigh the potential risks
- The data support the requested indication:

"The CYPHER™ Sirolimus-eluting stent is indicated for improving coronary luminal diameter in patients with symptomatic ischemic disease due to discrete do novo lesions (length ≤ 30 mm) in native coronary arteries with a reference vessel diameter of 2.25 - 5.00 mm"