Zilver PTX (Paclitaxel-Coated Stent): Transparency, Data, and Patient Safety

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COI Disclosure
First Author : Hiroyoshi Yokoi

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2.Stock ownership/ Profit : none
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Overview

- Device design and Study results
- Safety results through 5 years
  - Mortality issue
- Prediction model for freedom from TLR from a multi-study analysis

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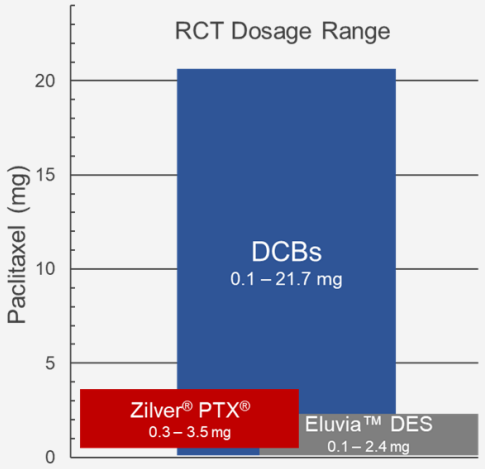
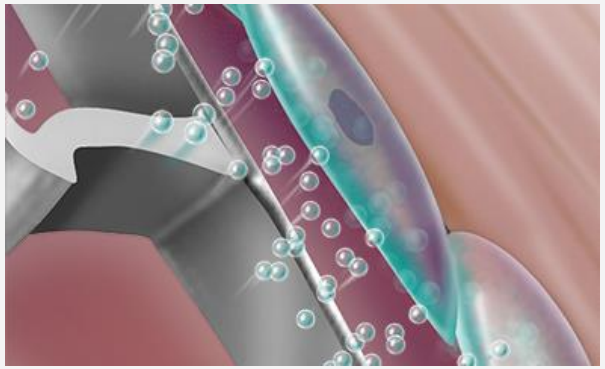
Zilver PTX Stent Overview



Coating

Low dose, amorphous coating with no polymer or excipient



Local Drug Delivery

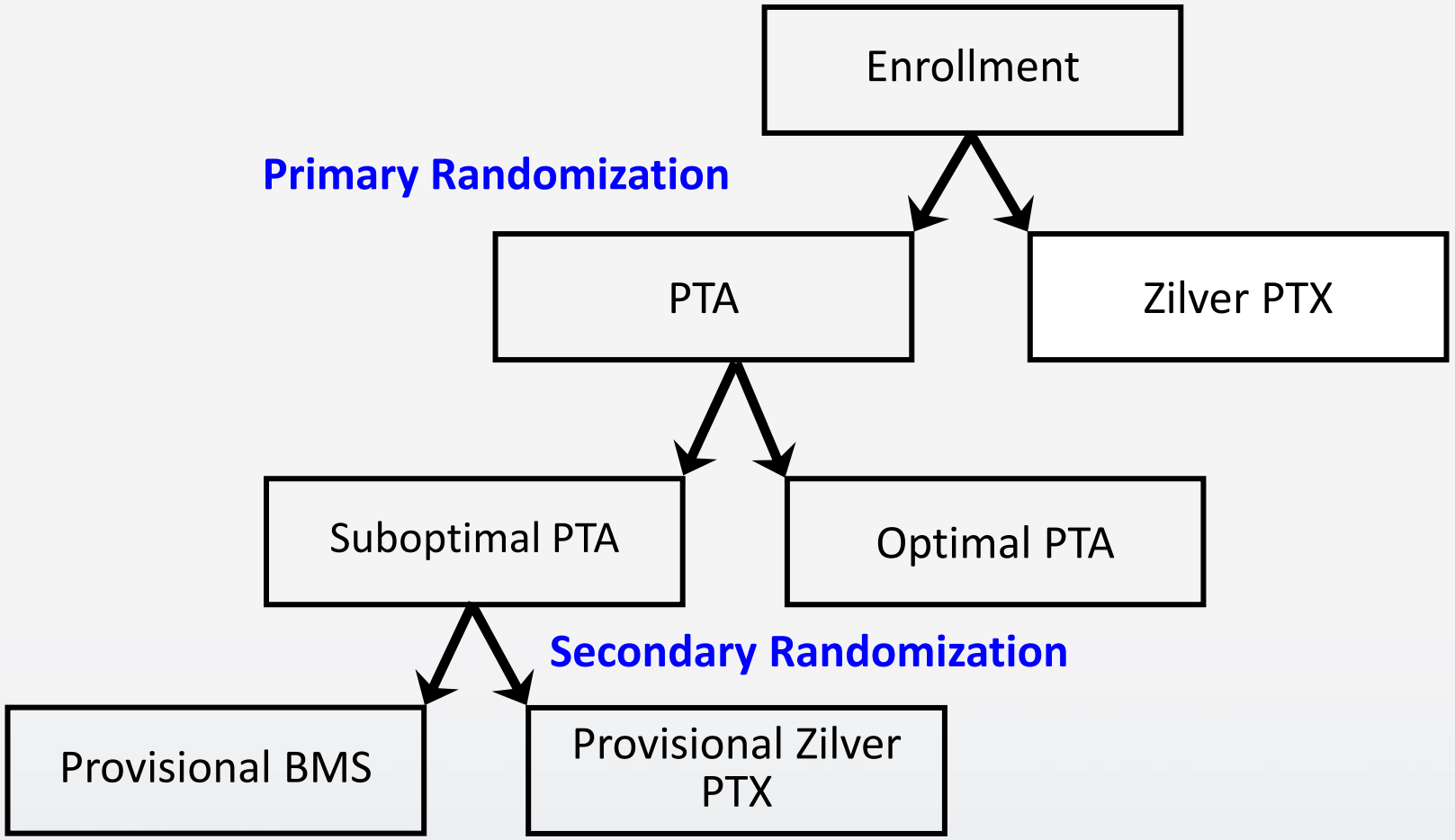
Short-term drug delivery, no long-term paclitaxel exposure, only BMS remains

5 YEARS

Long-term data

Only peripheral DES with long-term safety data

Zilver PTX Study Design



Patient Demographics and Comorbidities

	PTA	Zilver PTX	*p*-value
Patients	238	236	
Age (years)	68 ± 11	68 ± 10	0.88
Male	64%	66%	0.70
Height (in)	66 ± 4	67 ± 4	0.55
Weight (lbs)	179 ± 44	180 ± 40	0.62
Diabetes	42%	50%	0.11
High cholesterol	70%	76%	0.12
Hypertension	82%	89%	0.02*
Past/current smoker	84%	86%	0.70

* Statistically significant

Baseline Lesion Characteristics

		PTA	Zilver PTX	*p*-value
Lesions		251	247	
Normal-to-normal lesion length (mm)		63 ± 41	66 ± 39	0.36
Stenosed lesion length (mm)[1,2]		53 ± 40	55 ± 41	0.71
Diameter stenosis (%)[1]		78 ± 17	80 ± 17	0.38
Total occlusions		27%	33%	0.20
***De novo* lesions**		94%	95%	0.68
Lesion calcification[1]	**None**	5%	2%	< 0.01*
	Little	38%	26%	
	Moderate	22%	35%	
	Severe	35%	37%	

[1] Angiographic core lab assessment
[2] Region with > 20% diameter stenosis
* Statistically significant

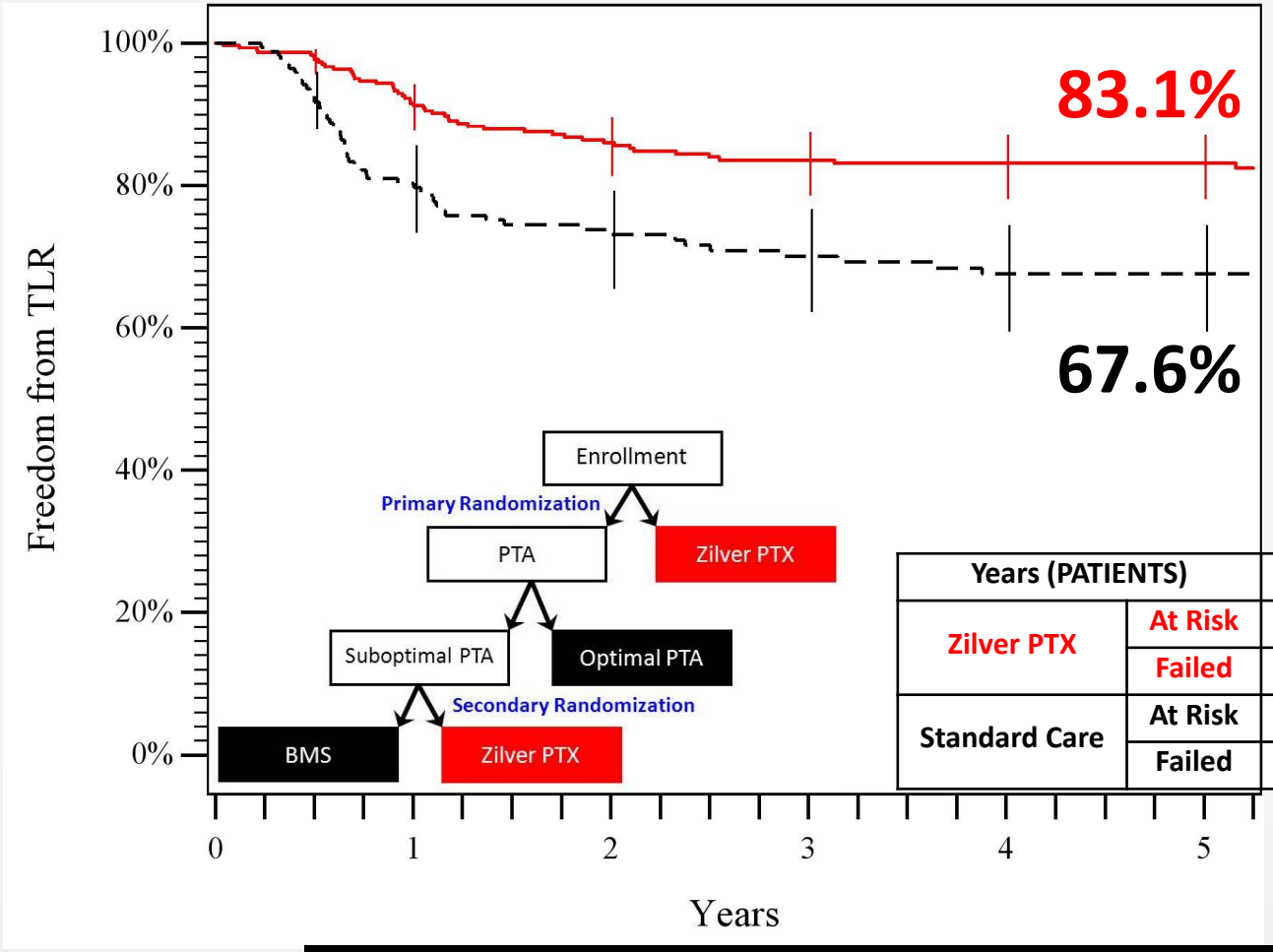
5-year Stent Integrity

Study Period	Number of New Events	Fracture Rate[1]
Enrollment	0	0.0%
1-year	4	0.9%
3-year	3	1.9%
5-year	0	1.9%

[1] Kaplan-Meier estimates

Zilver PTX has excellent durability in challenging SFA environment

5-year Freedom from TLR
Zilver PTX vs. Standard Care

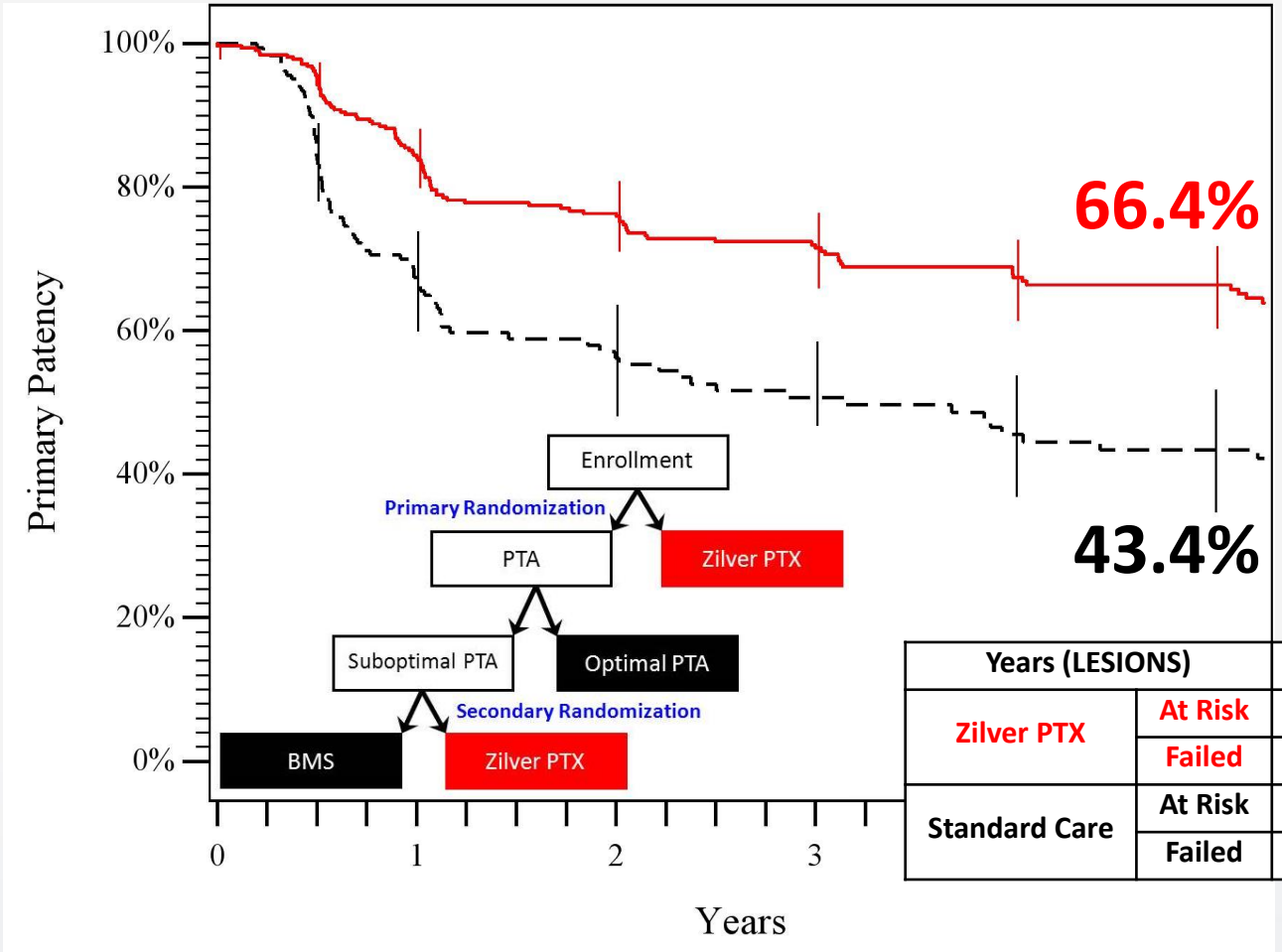


$p < 0.01$
log-rank

Years (PATIENTS)		0	1	2	3	4	5
Zilver PTX	At Risk	305	260	220	187	164	133
	Failed	0	25	40	46	47	47
Standard Care	At Risk	172	125	106	88	78	69
	Failed	0	33	44	48	51	51

At 5 years, Zilver PTX demonstrates a 48% reduction in reintervention compared to standard care

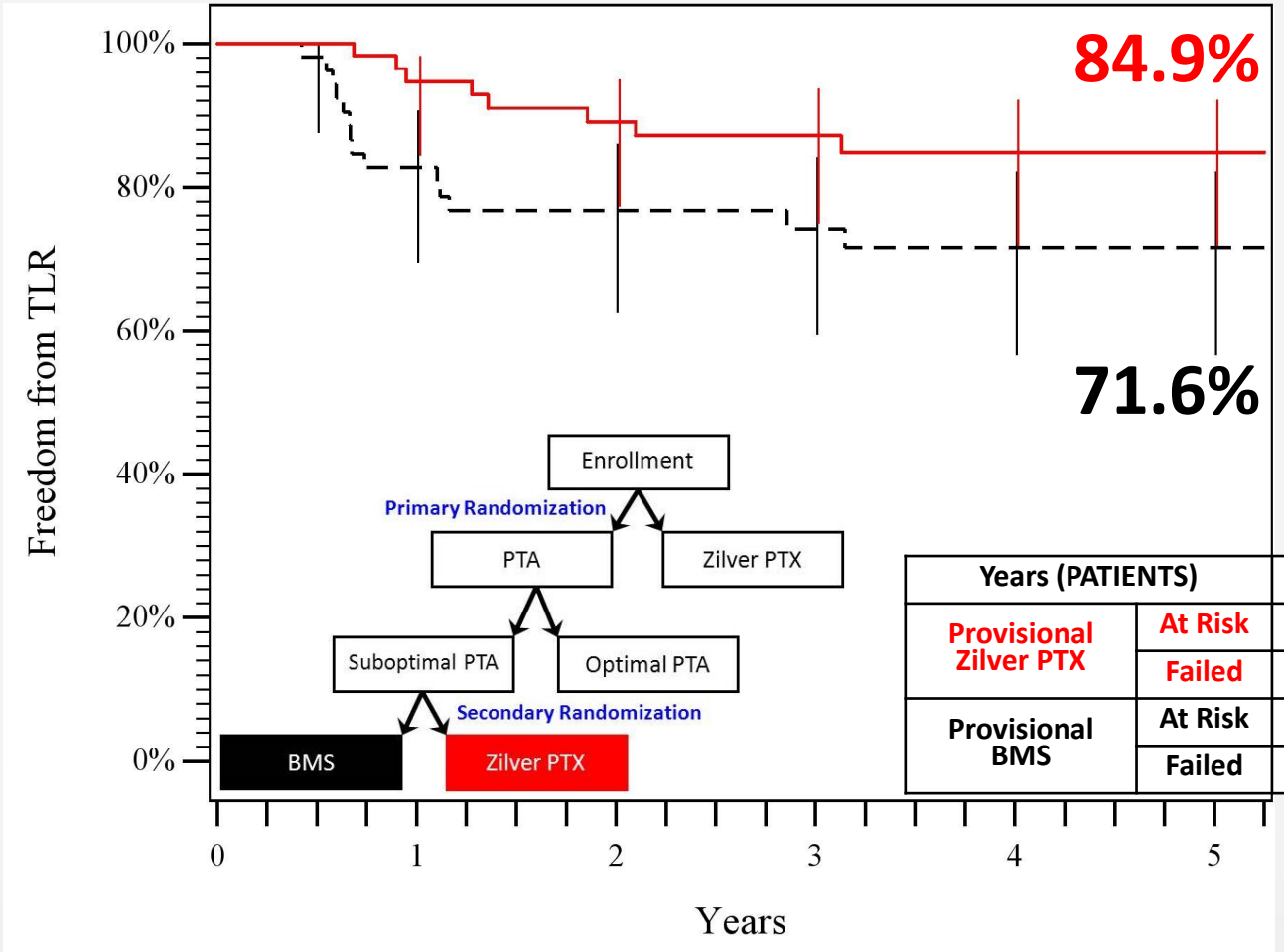
5-year Primary Patency (PSVR < 2.0)
Zilver PTX vs. Standard Care



Years (LESIONS)		0	1	2	3	4	5
Zilver PTX	At Risk	318	246	199	163	137	109
	Failed	1	48	71	83	92	94
Standard Care	At Risk	183	108	64	52	44	38
	Failed	0	57	73	79	84	86

At 5 years, Zilver PTX demonstrates a 41% reduction in restenosis compared to standard care

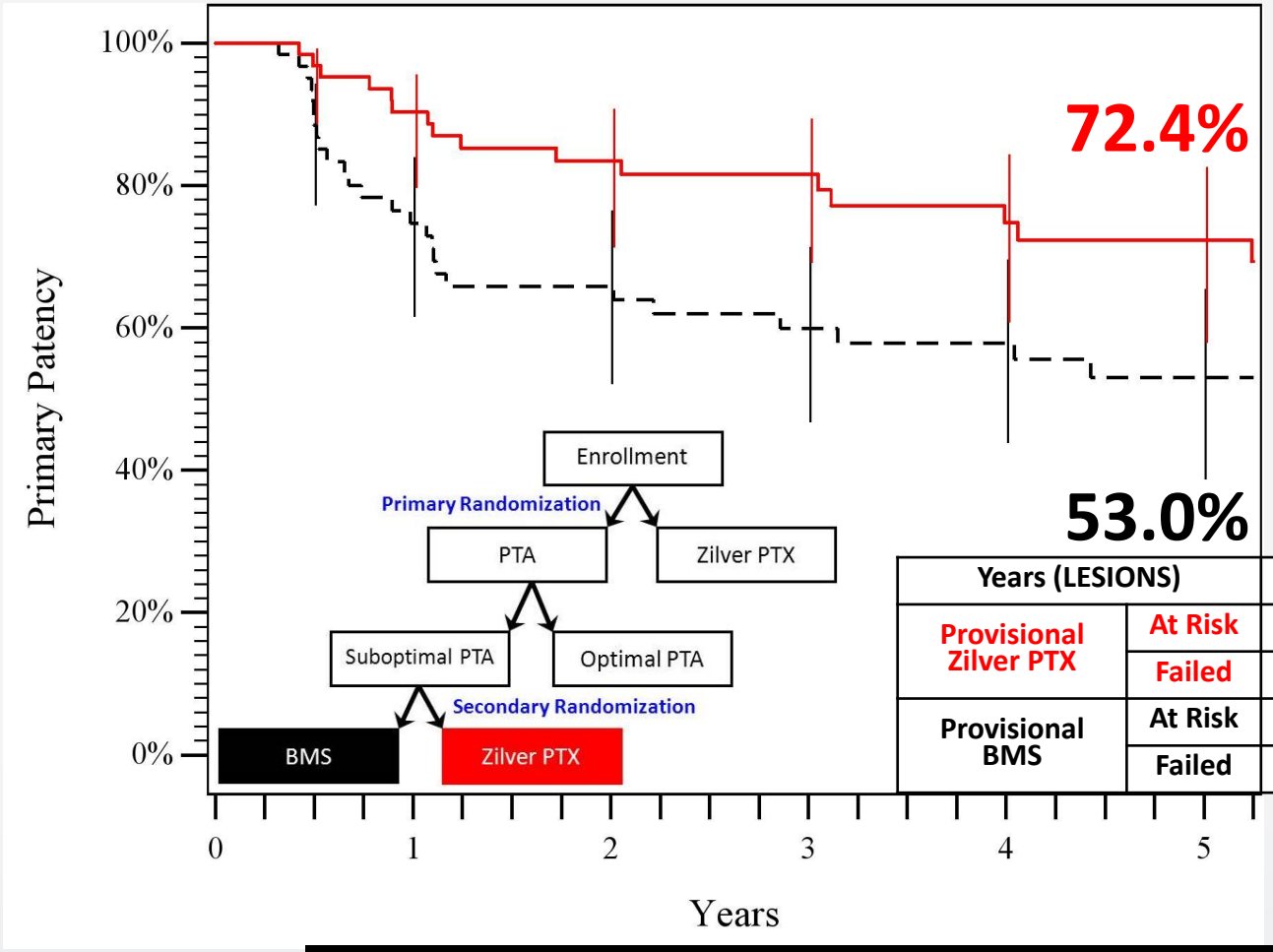
5-year Freedom from TLR
Provisional Zilver PTX vs. BMS



Years (PATIENTS)		0	1	2	3	4	5
Provisional Zilver PTX	At Risk	60	53	47	39	34	31
	Failed	0	3	6	7	8	8
Provisional BMS	At Risk	54	41	36	29	27	23
	Failed	0	9	12	13	14	14

At 5 years, Zilver PTX demonstrates a 47% reduction in reintervention compared to BMS

5-year Primary Patency (PSVR < 2.0)
Provisional Zilver PTX vs. BMS



72.4% Provisional Zilver PTX

53.0% Provisional BMS

$p = 0.03$ log-rank

Years (LESIONS)		0	1	2	3	4	5
Provisional Zilver PTX	At Risk	63	55	46	38	31	25
	Failed	0	6	10	11	14	15
Provisional BMS	At Risk	62	42	35	29	26	19
	Failed	0	15	20	23	24	26

At 5 years, Zilver PTX demonstrates a 41% reduction in restenosis compared to BMS

Overview

- Device design and Study results

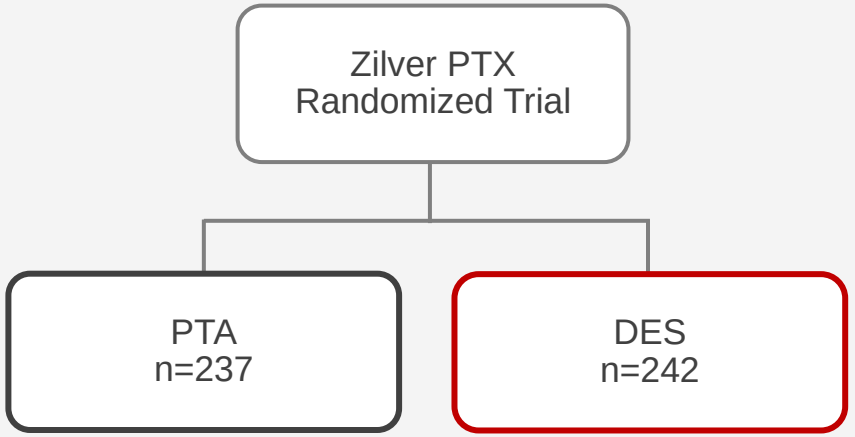
- Safety results through 5 years
  - Mortality issue

- Prediction model for freedom from TLR from a multi-study analysis

TRIAL DESIGN

Primary Randomization

DES Group
PTA / BMS Group

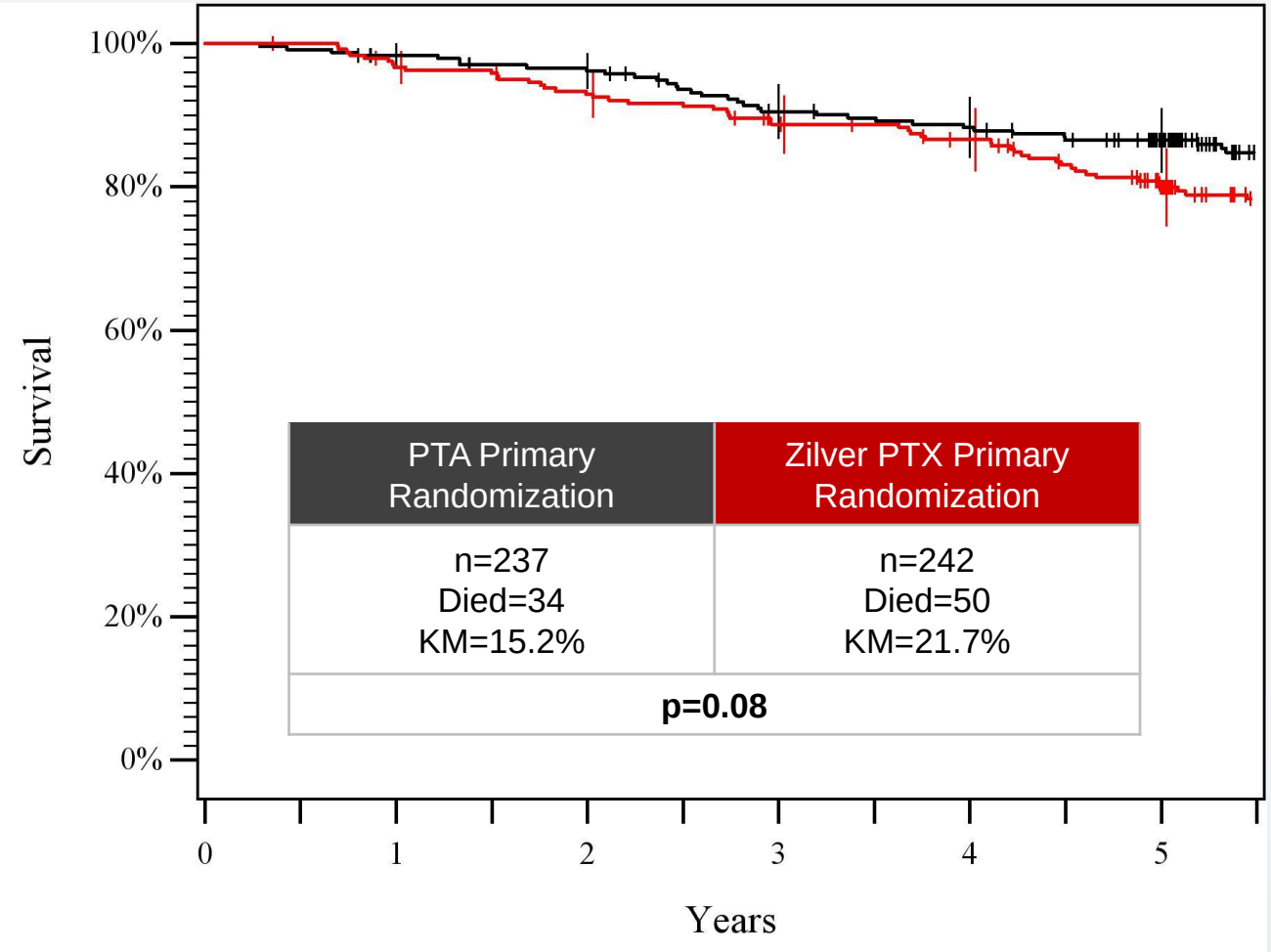


Randomization

- RCTs are not designed to ensure balance across numerous baseline risk factors
- Randomization was stratified only by lesion length
  - Stratification by lesion length does not ensure balance across multiple patient comorbidities and demographics

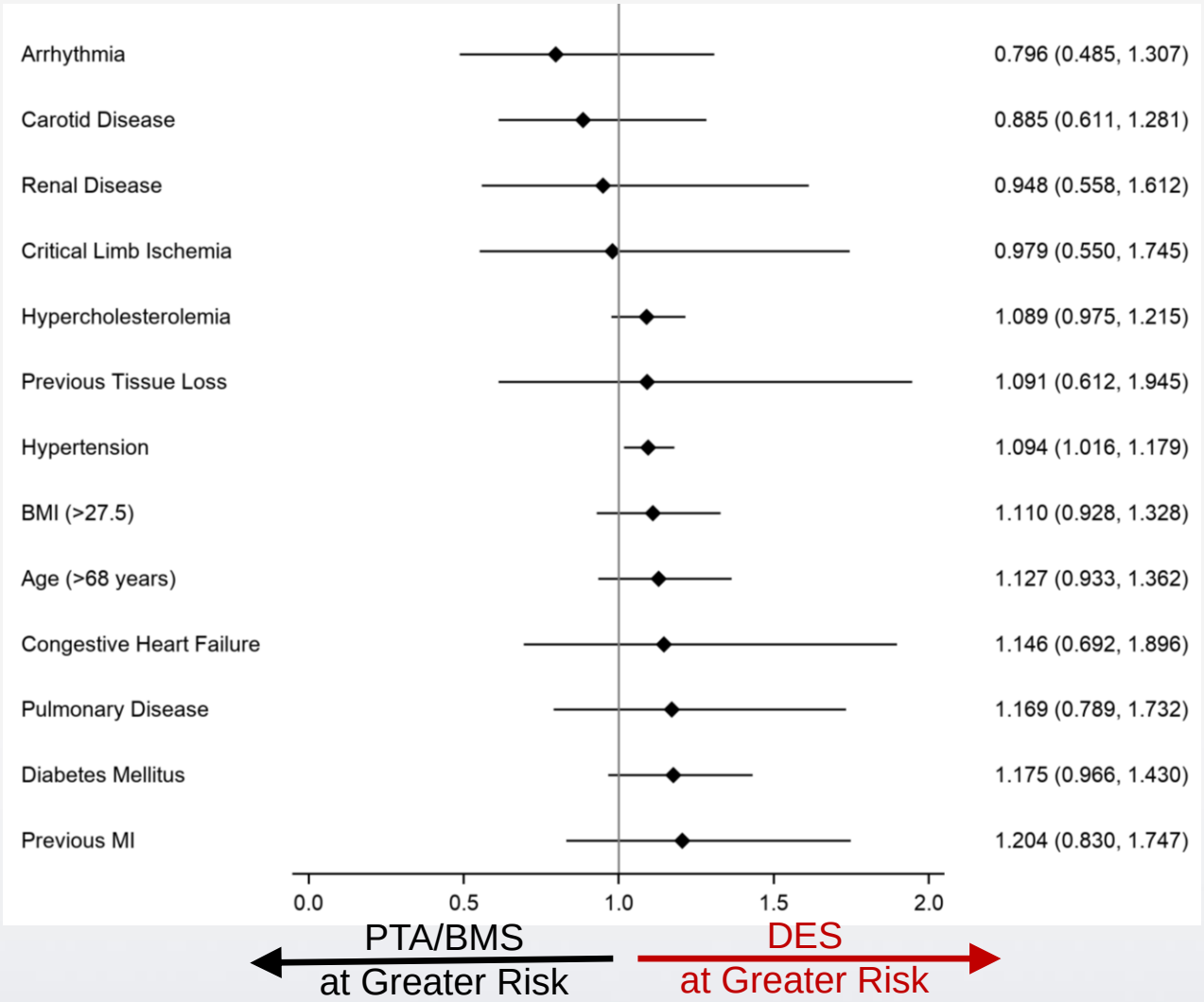
INTENT-TO-TREAT

Mortality Analysis



- 5-year vital status for 94% of patients
- DES patients included in PTA group
- Not significant
- Difference may be due to imbalance of risk factors

Baseline Mortality Risk Factors

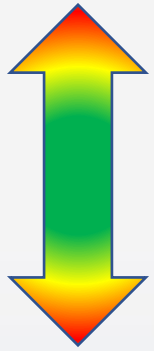


- Risk factors common in PAD patients may collectively contribute to overall patient prognosis
- Imbalance of risk factors, despite randomization

Baseline Patient Risk Factors for Mortality

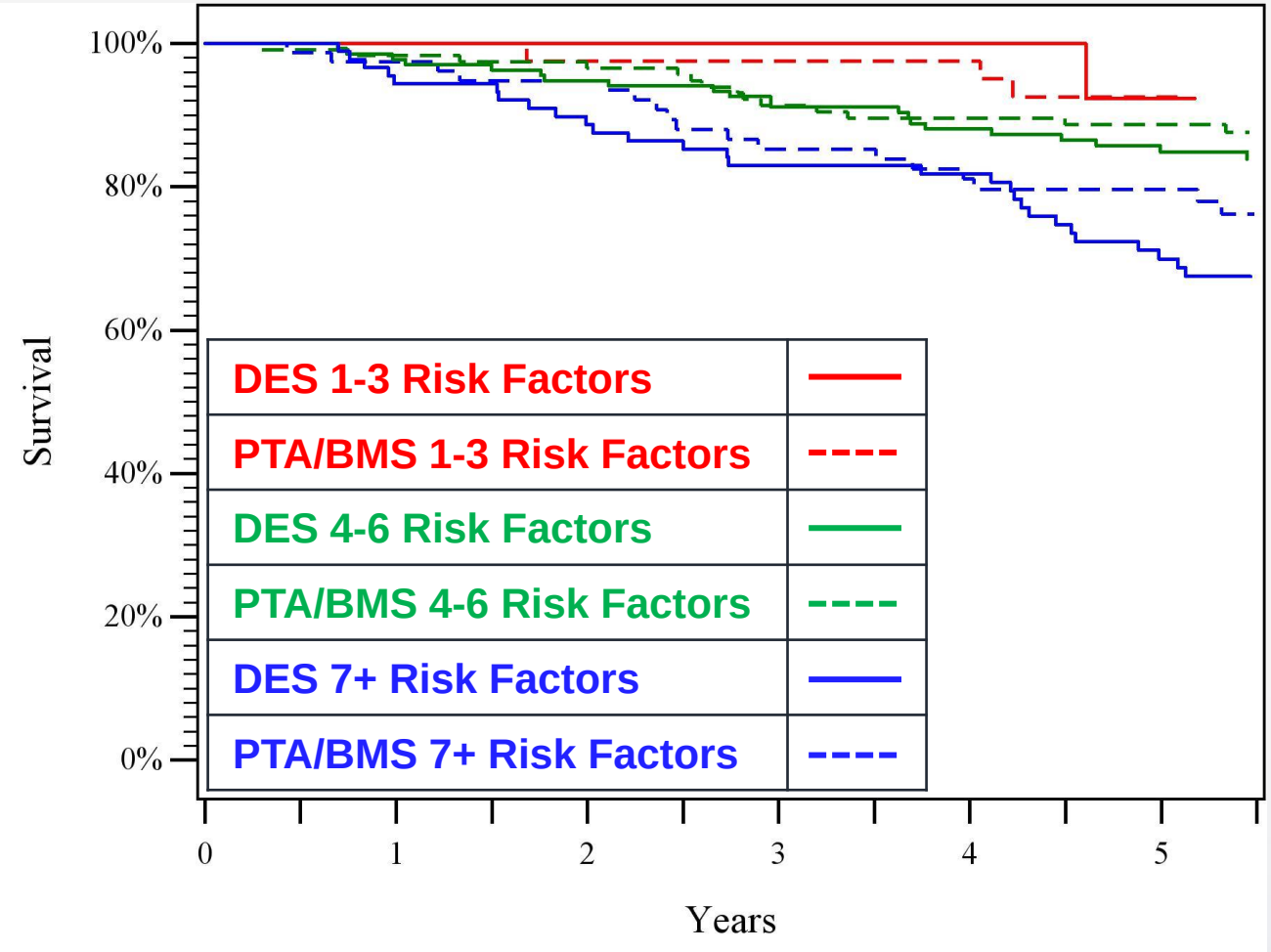
- Combinations of risk factors more prevalent in Zilver PTX primary randomization group ($p<0.01$)

Risk Factors	PTA Primary Randomization	Zilver PTX Primary Randomization
1-3	18%	7%
4-6	50%	56%
7+	33%	37%



INTENT-TO-TREAT

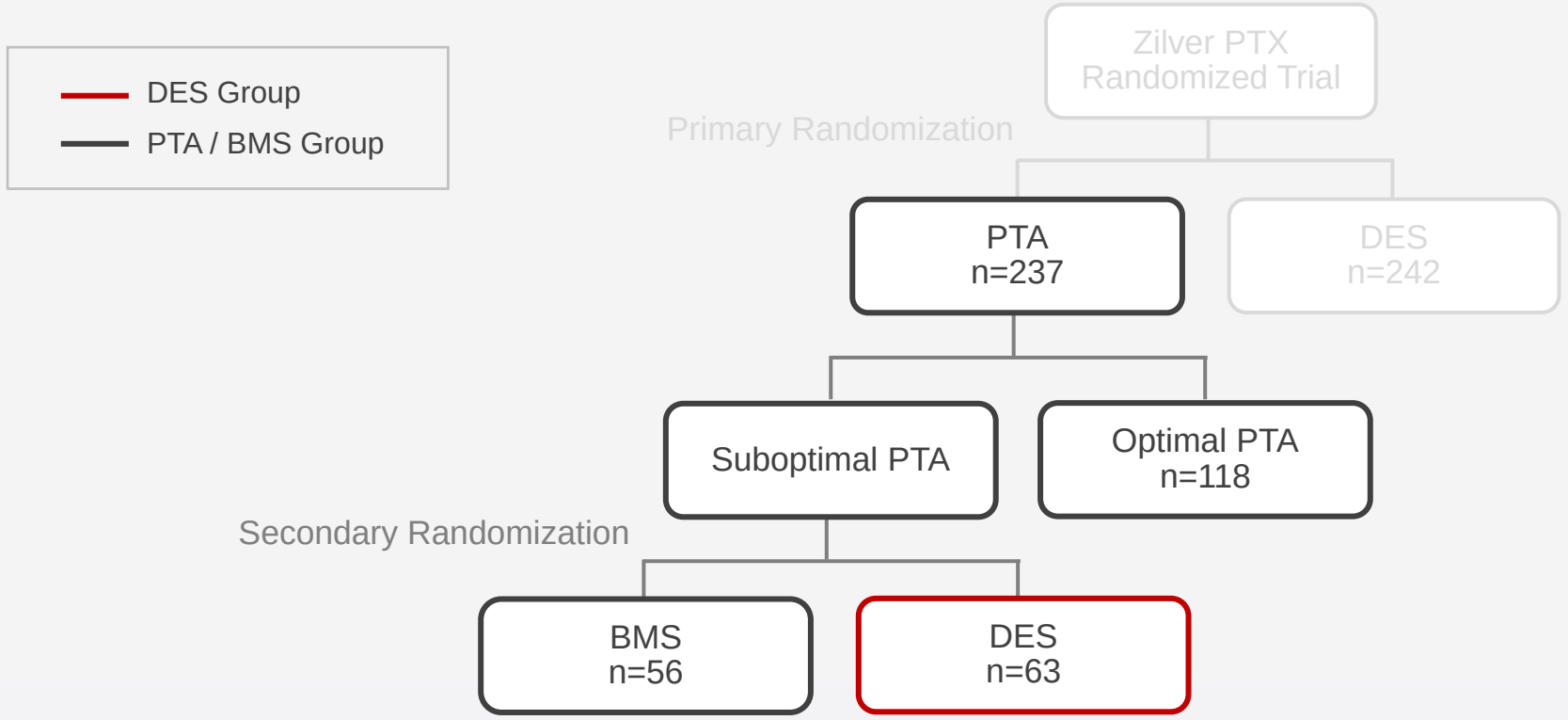
Risk Factor Mortality Analysis



- Mortality rate decreases with fewer risk factors

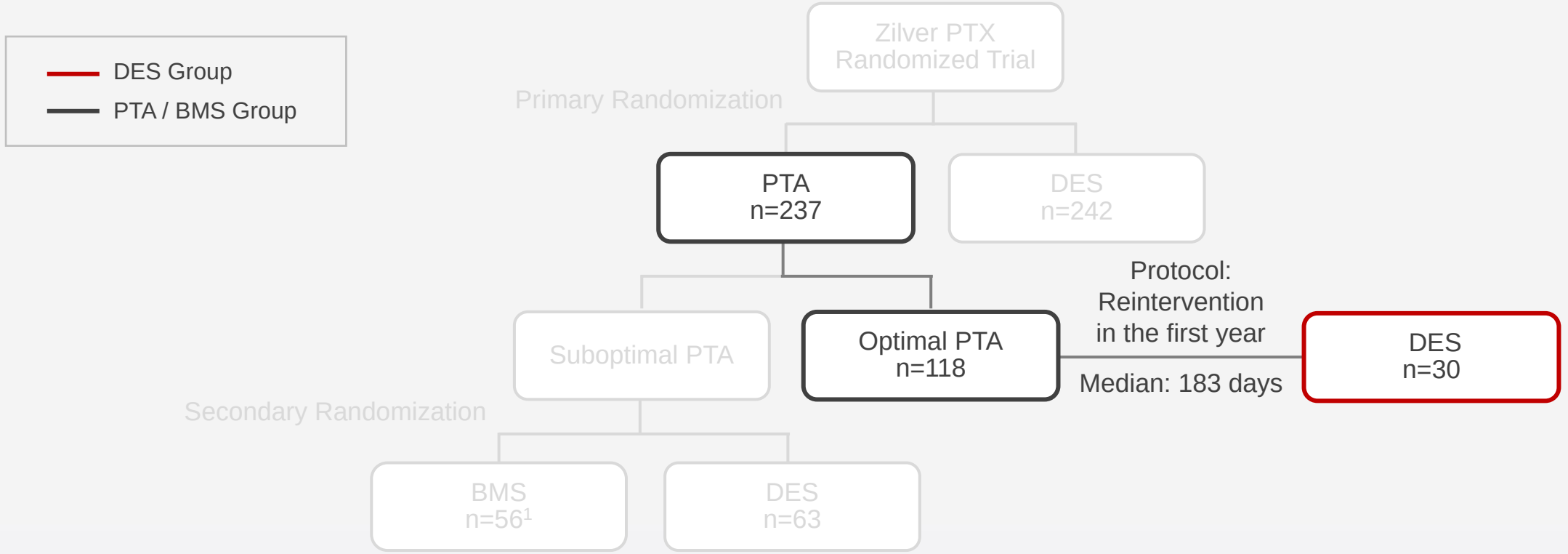
TRIAL DESIGN

Secondary Randomization



TRIAL DESIGN

Early Crossover

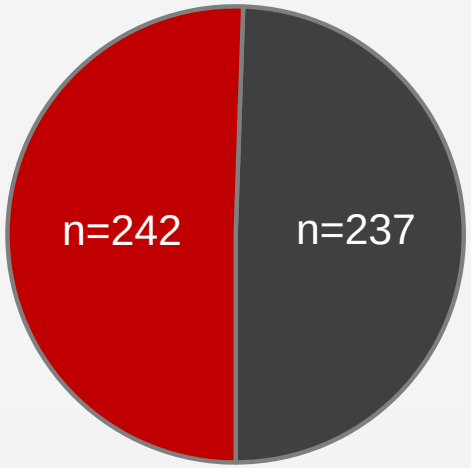


[1] One BMS patient received a DES during reintervention within the first year

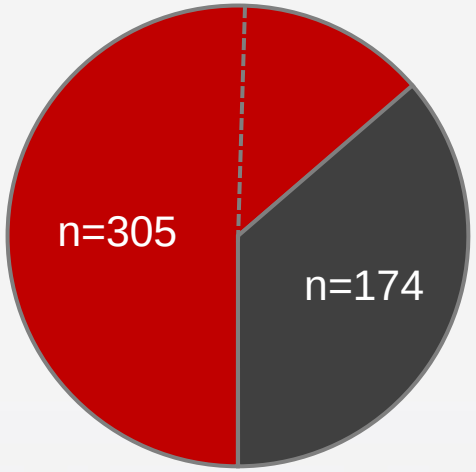
Treatment Results

DES
PTA / BMS

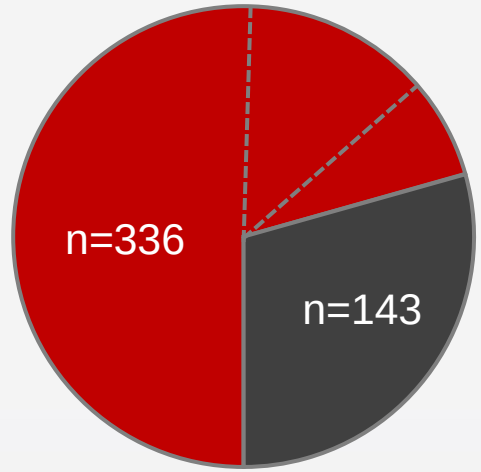
Primary Randomization



Primary + Secondary Randomization



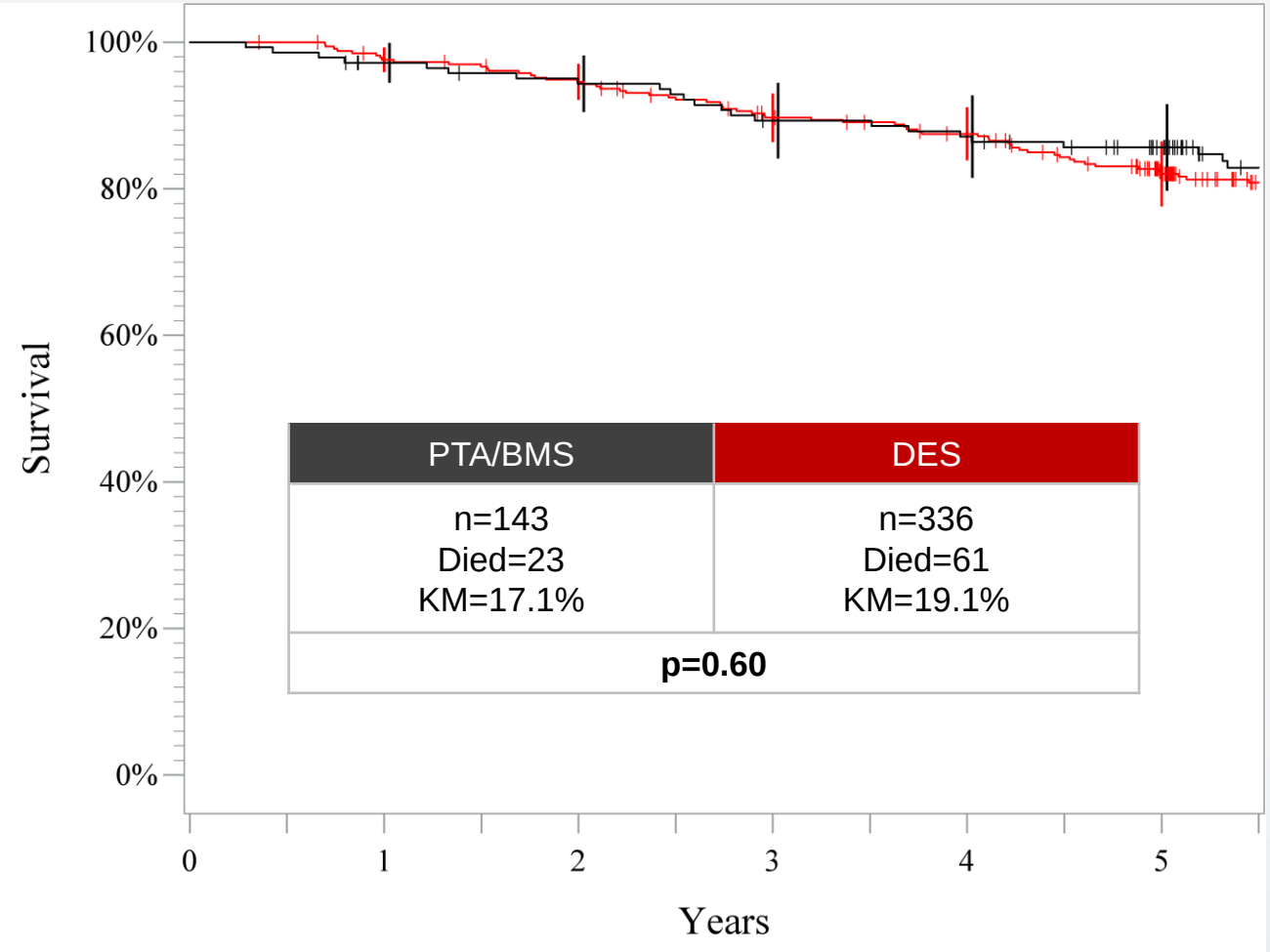
Actual Treatment = Primary + Secondary + Crossover



40% of patients initially randomized to PTA were actually treated with DES

ACTUAL TREATMENT

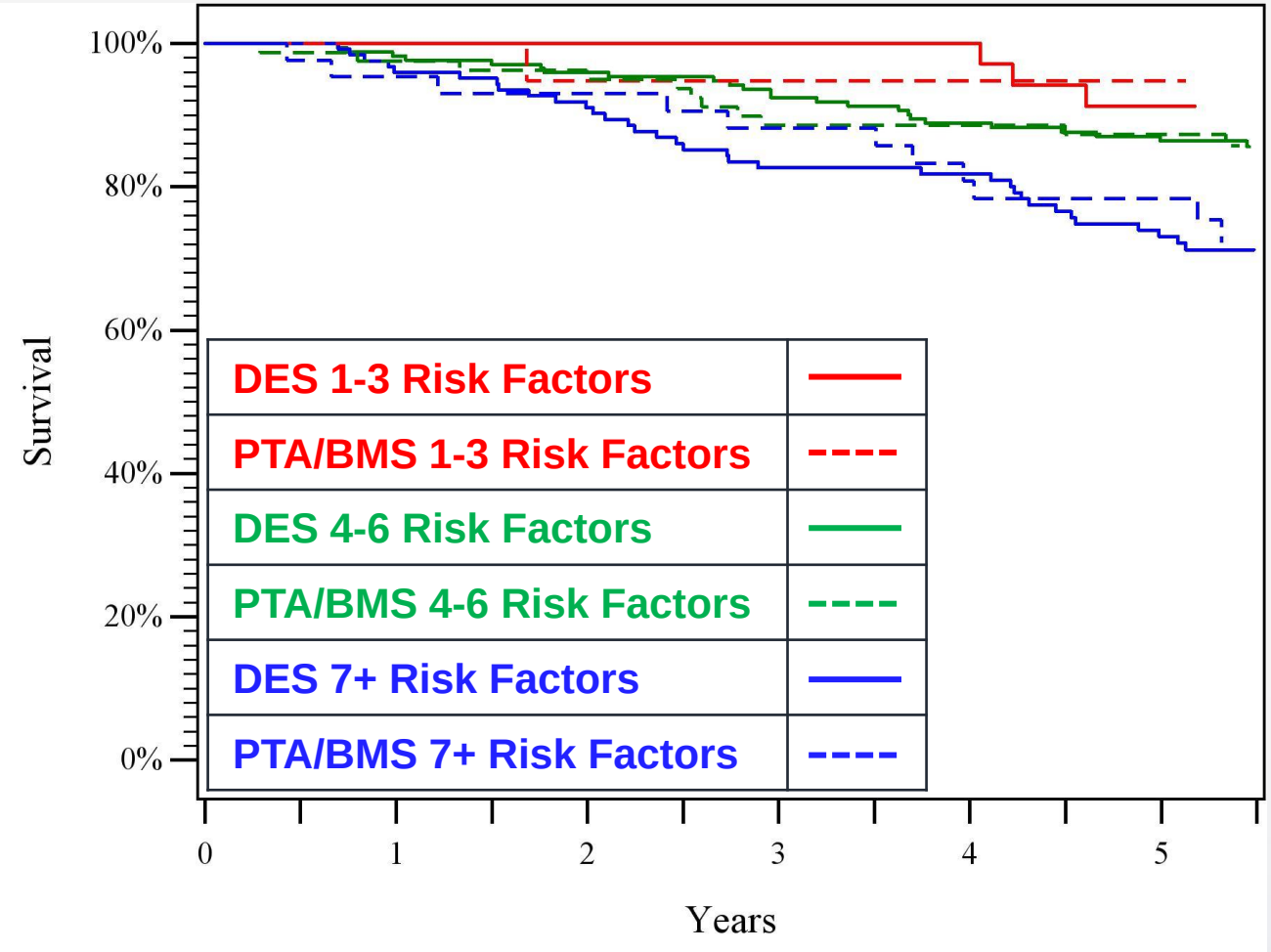
Mortality Analysis



- All patients analyzed by actual treatment
- No mortality signal

ACTUAL TREATMENT

Risk Factor Mortality Analysis



- Mortality rate decreases with fewer risk factors
- No mortality signal for actual treatment

MD Dake

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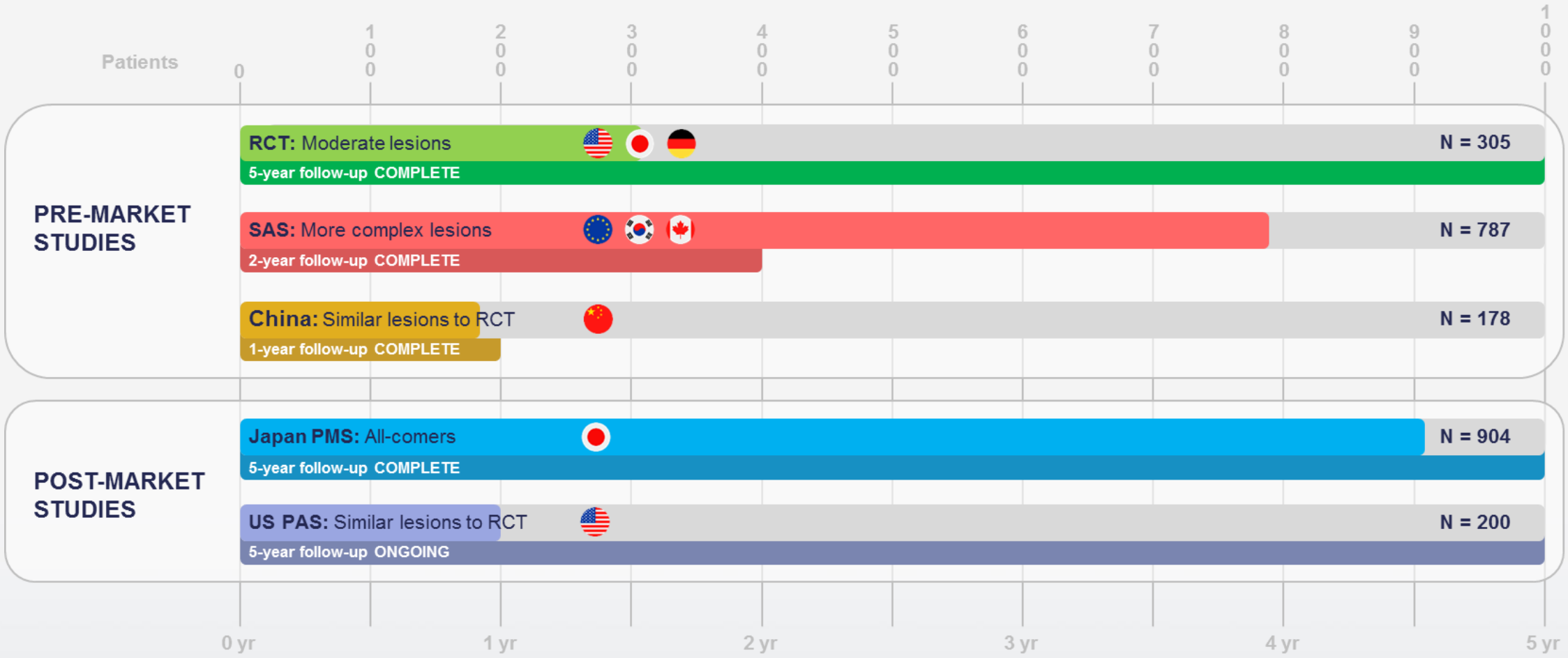
Global Clinical Program



2374 patients treated with the Zilver PTX DES

Aim

- Develop a prediction model to determine the impact of patient and lesion factors on freedom from TLR through 5 years for patients who are candidates for Zilver PTX treatment for femoropopliteal lesions

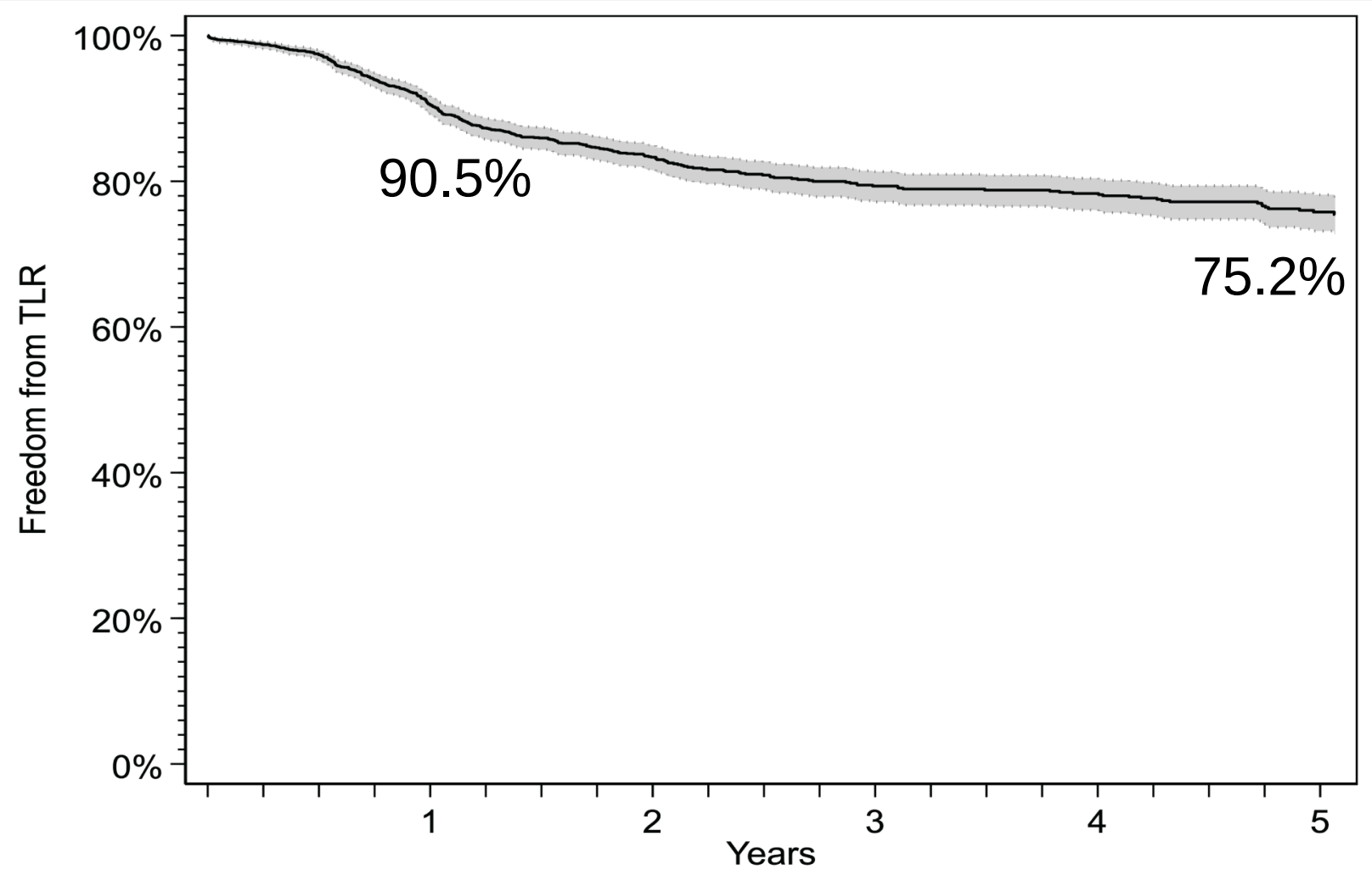
Study Characteristics

	RCT	SAS	China	US PAS	Japan PMS
Study design	Prospective, multicenter, RCT	Prospective, multicenter, single-arm study	Prospective, multicenter, single-arm study	Prospective, multicenter, single-arm study	Prospective, multicenter, single-arm study
Number of DES patients	305	787	178	200	904
Prior stent in SFA	No	Yes (ISR)	No	No	No exclusion criteria All patients treated with the DES enrolled (up to enrollment limit)
Lesion length	≤ 140 mm	No exclusion	≤ 140 mm	≤ 140 mm	
Renal exclusion	Serum creatinine > 2.0, renal failure, or dialysis	No exclusion	Chronic renal failure[a] or dialysis	No exclusion	
Core laboratory	Angiography Duplex Ultrasound X-Ray	X-Ray[b]	Angiography Duplex Ultrasound	Angiography Duplex Ultrasound X-Ray	X-Ray[b]

[a] eGFR < 30 mLs/ min/1.73m^2

[b] In the event a stent fracture was reported by an investigative site, an independent core laboratory reviewed the imaging, confirmed the fracture, and classified the fracture by type (I-IV).

Results of Combined Studies



- 2227 cases (94%) with complete data used to generate the model
- 2 years median follow-up time
- Freedom from TLR
  - 90.5% at 1 year
  - 75.2% at 5 years

Factors Included in Prediction Model

Patient Demographics	Lesion Characteristics
Sex	Lesion length
Age	RVD
Diabetes	Popliteal involvement
Hypertension	Total occlusion
Hypercholesterolemia	Calcification
Renal disease	Prior interventions
Smoking status	Number of patent runoff vessels
Rutherford classification	

Multivariate Model Results

Characteristic		Hazard Ratio	p-value
Male		0.760	**0.022***
Age	65-74	0.734	**0.002***
	75-84	0.637	
	>85	0.398	
Diabetes		1.033	0.766
Hypertension		0.927	0.596
Hypercholesterolemia		1.126	0.296
Renal disease		1.072	0.578
Smoking status	Past	0.825	0.187
	Current	1.020	
Rutherford	CLI	1.429	**0.010***
Lesion length (mm)	50-99	1.443	**<0.001***
	100-149	2.066	
	150-199	2.205	
	200-249	2.847	
	250-299	2.899	
	>300	3.454	
RVD (mm)	≥5	0.727	**0.006***
Popliteal involvement		1.042	0.815
Total occlusion		1.406	**0.004***
Calcification	Mild/moderate	0.994	0.845
	Severe	1.078	
Prior interventions		1.815	**<0.001***
Number of runoff vessels	≥2	0.958	0.719

- Risk factors common in PAD patients may collectively contribute to overall patient prognosis
- As expected, CLI, lesion length, and total occlusion have a significant impact on TLR
  - Other factors such as diabetes and calcification did not have a significant impact on TLR

Zilver® PTX® Predictability Model

Disclaimer

The Dataset includes data collected from Cook-sponsored studies, including pre-market data, post-approval data, and real-world data collected as a requirement of approval. The model generates predictions for freedom from target lesion revascularization based on the Dataset. The model outcomes resulting from the Dataset are provided for transparency and as part of ongoing scientific exchange regarding clinical evidence associated with the Zilver® PTX® stent.

Terms and Conditions

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Patient Demographics

Sex	◉ Male	○ Female		
Age (yrs)	◉ <65	○ 65-74	○ 75-84	○ 85+
Diabetes	◉ No	○ Yes		
Hypertension	◉ No	○ Yes		
Hypercholesterolemia	◉ No	○ Yes		
Renal Insufficiency	◉ No	○ Yes		
Smoking	◉ Never	○ Current	○ Past	
Limb Status	◉ Claudicant	○ CLI		

Visit the interactive web-based tool to see how Zilver PTX might help your patients

https://cooksfa.z13.web.core.windows.net

Patient Demographics

Sex	◉ Male	○ Female		
Age (yrs)	◉ <65	○ 65-74	○ 75-84	○ 85+
Diabetes	◉ No	○ Yes		
Hypertension	◉ No	○ Yes		
Hypercholesterolemia	◉ No	○ Yes		
Renal Insufficiency	◉ No	○ Yes		
Smoking	◉ Never	○ Current	○ Past	
Limb Status	◉ Claudicant	○ CLI		

Lesion Characteristics

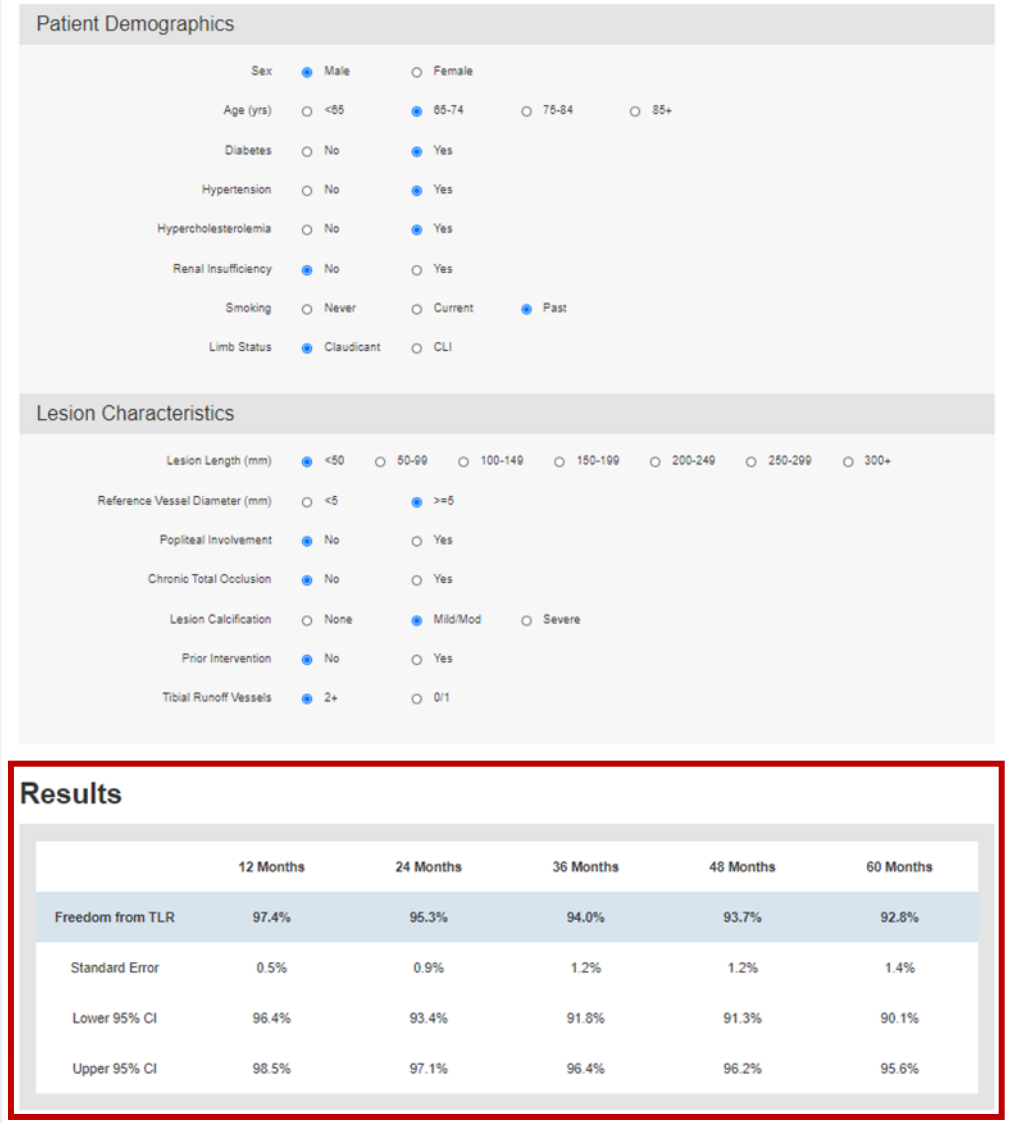
Lesion Length (mm)	◉ <50	○ 50-99	○ 100-149	○ 150-199	○ 200-249	○ 250-299	○ 300+	
Reference Vessel Diameter (mm)	○ <5	◉ >=5						
Popliteal Involvement	◉ No	○ Yes						
Chronic Total Occlusion	◉ No	○ Yes						
Lesion Calcification	○ None	◉ Mild/Mod	○ Severe					
Prior Intervention	◉ No	○ Yes						
Tibial Runoff Vessels	◉ 2+	○ 0/1						

Results

	12 Months	24 Months	36 Months	48 Months	60 Months
Freedom from TLR	97.4%	95.3%	94.0%	93.7%	92.8%
Standard Error	0.5%	0.9%	1.2%	1.2%	1.4%
Lower 95% CI	96.4%	93.4%	91.8%	91.3%	90.1%
Upper 95% CI	98.5%	97.1%	96.4%	96.2%	95.6%

Prediction for Example Patient Profile #1

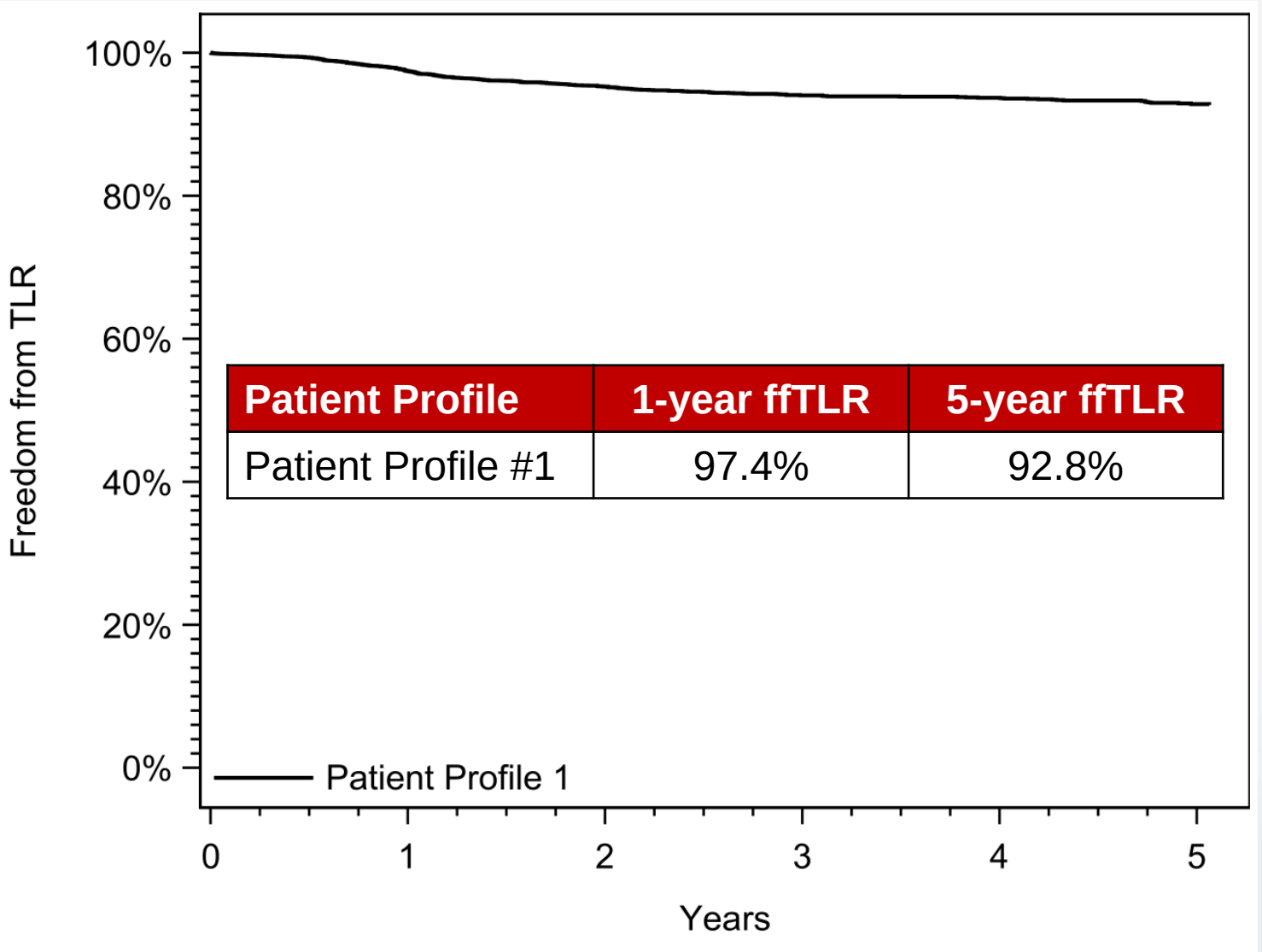
Factor	Patient Profile #1
Sex	Male
Age	65-74
Diabetes	Yes
Hypertension	Yes
Hypercholesterolemia	Yes
Renal disease	No
Smoking status	Past smoker
Rutherford classification	Claudicant
Lesion length	<50 mm
RVD	≥5 mm
Popliteal involvement	No
Occlusion	No
Calcification severity	Mild/moderate
Prior interventions	No
Number of runoff vessels	2+



FREEDOM FROM TLR

Prediction for Example Patient Profile #1

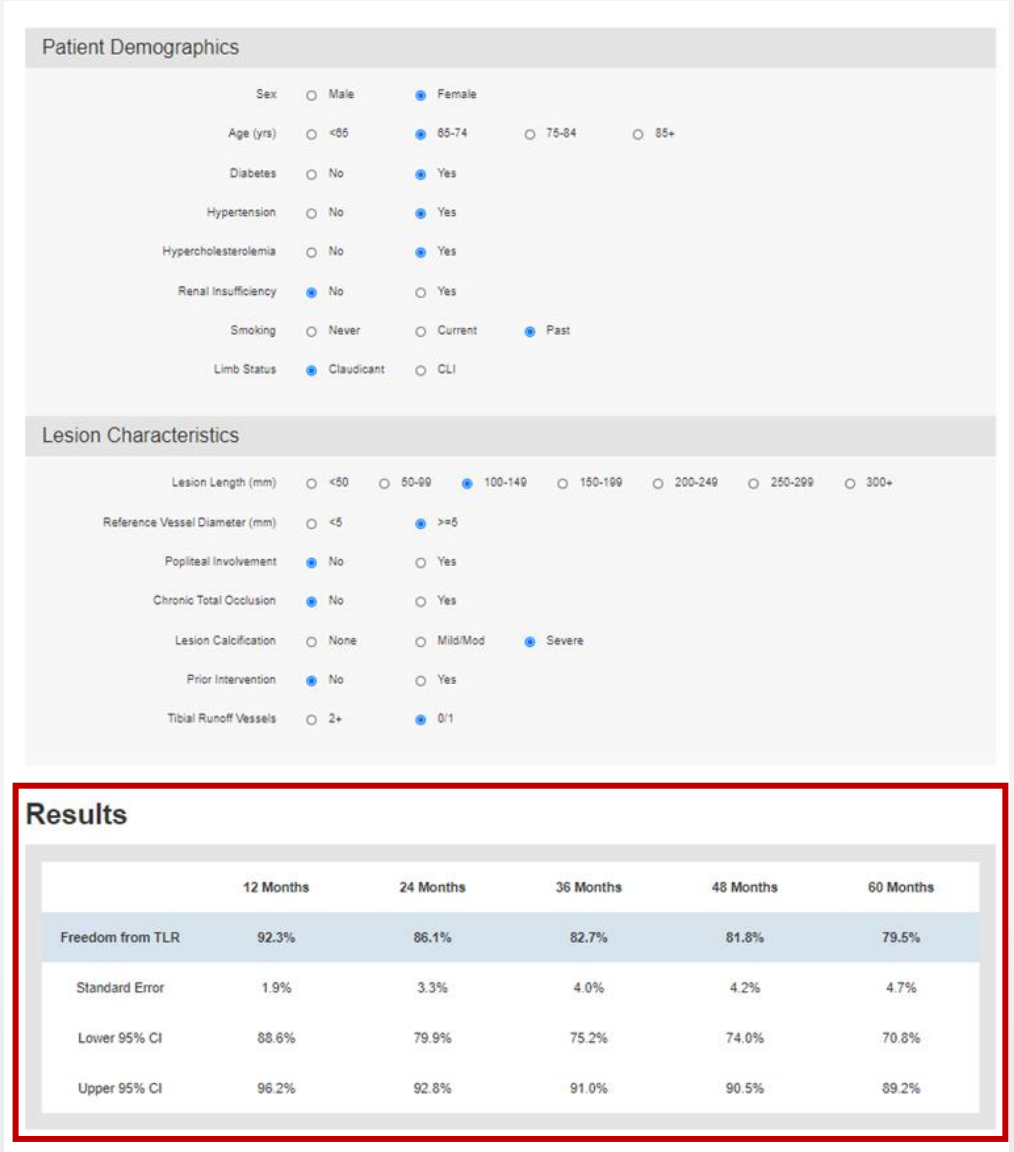
Factor	Patient Profile #1
Sex	Male
Age	65-74
Diabetes	Yes
Hypertension	Yes
Hypercholesterolemia	Yes
Renal disease	No
Smoking status	Past smoker
Rutherford classification	Claudicant
Lesion length	<50 mm
RVD	≥5 mm
Popliteal involvement	No
Occlusion	No
Calcification severity	Mild/moderate
Prior interventions	No
Number of runoff vessels	2+



Patient Profile	1-year ffTLR	5-year ffTLR
Patient Profile #1	97.4%	92.8%

Prediction for Example Patient Profile #2

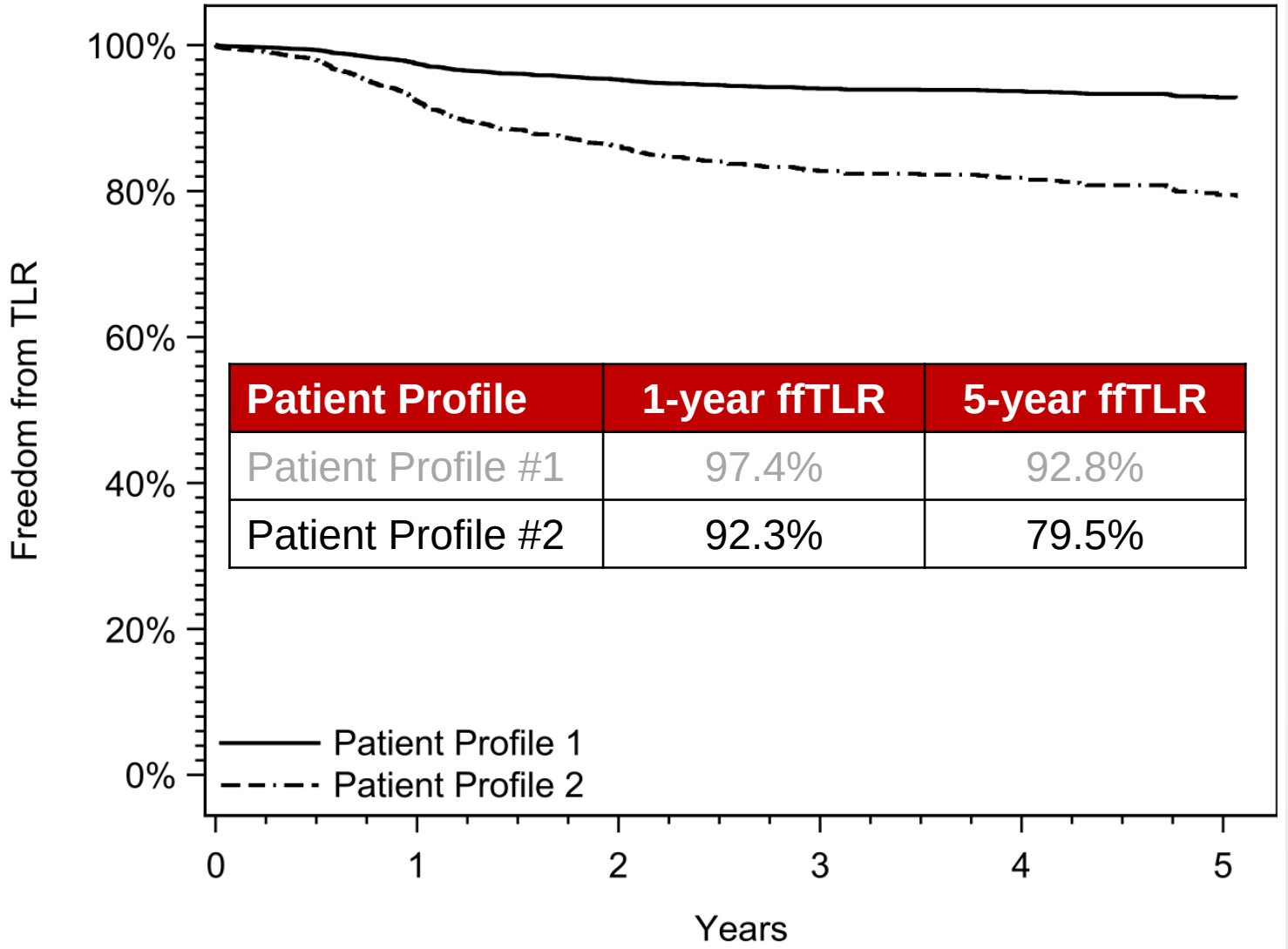
Factor	Patient Profile #2
Sex	Female
Age	65-74
Diabetes	Yes
Hypertension	Yes
Hypercholesterolemia	Yes
Renal disease	No
Smoking status	Past smoker
Rutherford classification	Claudicant
Lesion length	100-149 mm
RVD	≥5 mm
Popliteal involvement	No
Occlusion	No
Calcification severity	Severe
Prior interventions	No
Number of runoff vessels	0 or 1



FREEDOM FROM TLR

Prediction for Example Patient Profile #2

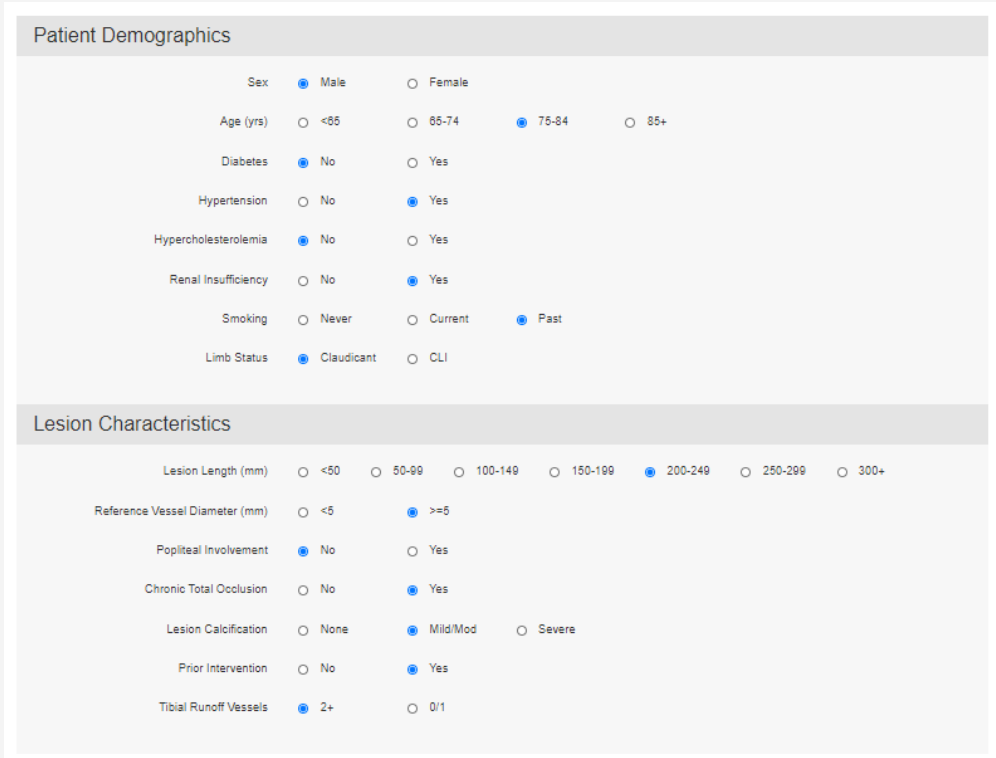
Factor	Patient Profile #2
Sex	Female
Age	65-74
Diabetes	Yes
Hypertension	Yes
Hypercholesterolemia	Yes
Renal disease	No
Smoking status	Past smoker
Rutherford classification	Claudicant
Lesion length	100-149 mm
RVD	≥5 mm
Popliteal involvement	No
Occlusion	No
Calcification severity	Severe
Prior interventions	No
Number of runoff vessels	0 or 1



Patient Profile	1-year ffTLR	5-year ffTLR
Patient Profile #1	97.4%	92.8%
Patient Profile #2	92.3%	79.5%

Prediction for Example Patient Profile #3

Factor	Patient Profile #3
Sex	Male
Age	75-84
Diabetes	No
Hypertension	Yes
Hypercholesterolemia	No
Renal disease	Yes
Smoking status	Past smoker
Rutherford classification	Claudicant
Lesion length	200-249 mm
RVD	≥5 mm
Popliteal involvement	No
Occlusion	Yes
Calcification severity	Mild/moderate
Prior interventions	Yes
Number of runoff vessels	2+



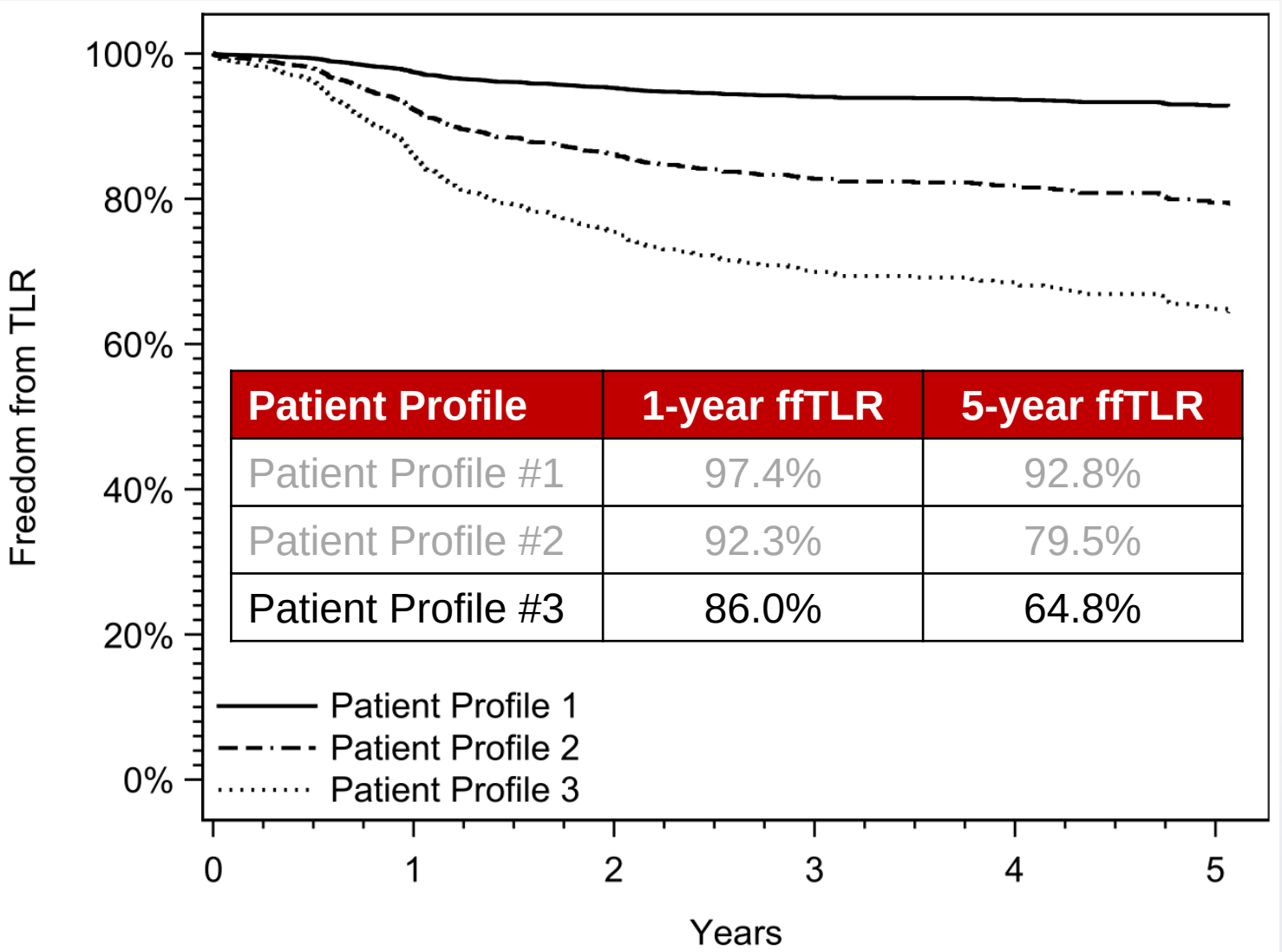
Results

	12 Months	24 Months	36 Months	48 Months	60 Months
Freedom from TLR	86.0%	75.4%	69.9%	68.5%	64.8%
Standard Error	3.2%	5.2%	6.1%	6.3%	6.8%
Lower 95% CI	79.9%	65.9%	59.0%	57.2%	52.7%
Upper 95% CI	92.5%	86.3%	82.9%	82.0%	79.7%

FREEDOM FROM TLR

Prediction for Example Patient Profile #3

Factor	Patient Profile #3
Sex	Male
Age	75-84
Diabetes	No
Hypertension	Yes
Hypercholesterolemia	No
Renal disease	Yes
Smoking status	Past smoker
Rutherford classification	Claudicant
Lesion length	200-249 mm
RVD	≥5 mm
Popliteal involvement	No
Occlusion	Yes
Calcification severity	Mild/moderate
Prior interventions	Yes
Number of runoff vessels	2+



Patient Profile	1-year ffTLR	5-year ffTLR
Patient Profile #1	97.4%	92.8%
Patient Profile #2	92.3%	79.5%
Patient Profile #3	86.0%	64.8%

Conclusions

- **5-year results confirm long-term superiority of Zilver PTX versus standard of care**
  - Greater than 40% reduction in reintervention and restenosis
  - Superior clinical benefit
  - These benefits increase with time – results with Zilver PTX continue to diverge from standard care over 5 years with no late catch-up

- **No safety concerns regarding paclitaxel**
  - No significant difference in mortality; vital status through 5 years for 94% of patients
  - Imbalance in risk factors ($p<0.01$), despite randomization
  - 40% of patients in PTA primary randomization group treated with Zilver PTX
  - No mortality signal

- **Patient and lesion factors from 5 global clinical studies used to develop a prediction model for freedom from TLR**
  - Data from over 2200 patients used to create the model
  - Based on unique patient profile, model provides expected patient outcomes following treatment with the Zilver PTX DES
  - May assist in defining treatment algorithms for patients as the value of population management is increasingly recognized